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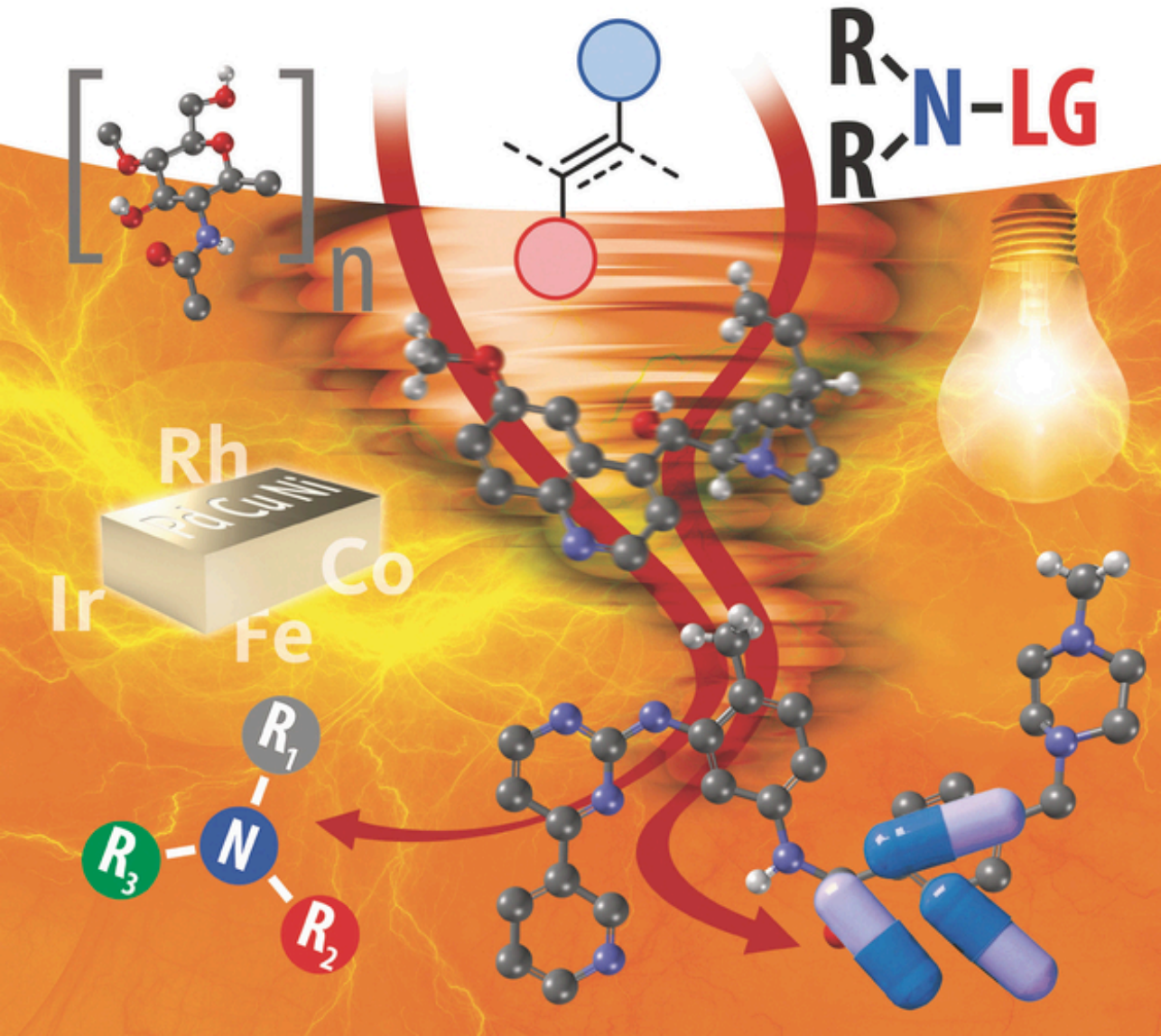
Alfredo Ricci and Luca Bernardi

Methodologies in Amine Synthesis

Challenges and Applications



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Preface

The books "Modern Amination Methods" and "Amino Group Chemistry – From Synthesis to the Life Sciences" edited by one of us for Wiley-VCH in 2000 and in 2007, respectively, were intended to provide the reader with exhaustive overviews of the most advanced methodologies for the C—N bond formation and with the role played by the amino function in those processes that are closely related to the life sciences.

These books were well received by the chemical community and highlighted the importance of keeping scientists to be continuously aware of the progress in the field of amino group chemistry. In 2018, setting up to discuss the prospect of coediting a new book on amino group chemistry, we asked ourselves if the past decade witnessed sufficient breakthroughs to make such update worth to be read by academicians or industrialists. It did not take too much time to convince ourselves that such endeavor would have been worthwhile and timely. In the past years, most of the breakthrough discoveries in synthetic organic chemistry embed efficient preparations of nitrogen-containing compounds. Arguably, amino group chemistry lies at the core of recent methodological trends. Furthermore, the disclosure of new materials, from medicine to nanoscience, has often been grounded on nitrogen derivatives. Thus, we embarked in this adventure, approaching the selection of the topics with an unbiased and wide-range attitude. In this new book, we aimed at providing not only an overview over specific aspects of amino chemistry but also a unique journey through modern chemistry.

With the very useful insights into the topic selection provided by Wiley anonymous reviewers, we commenced to approach several prospective authors. We have been very lucky to find contact authors among the most authoritative of their fields, who, together with their coworkers, assembled chapters characterized by clear structures, schemes, mechanisms, and figures accompanying the text together with exhaustive and up-to-date reference sections.

Throughout the 10 chapters of the book, amines are discussed with respect to the most advanced methodologies for their preparation, from design to scope surveys to applications to biologically active targets or precursors thereof, including large-scale industrial settings. Because the pharmaceutical and agrochemical industries are nowadays mostly away from the development of racemic compounds, several of the book chapters refer to enantioselective synthesis of chiral amines. It is worth noting that the contributions to this book present interlinks that, as a fil rouge crossing the whole book, allow the reader to face some of the topics under different perspectives.

The book starts with a topic that constitutes a continuum between the 2000s monographies and this one: electrophilic amination. Indeed, substitution-type electrophilic amination has gained a tremendous progress in the decade. This unconventional, yet synthetically appealing approach to C—N bond formation is nowadays performed under transition metal (TM)- and metal-free catalysis aiming to employ bench-stable and easily obtainable reagents for forging new C—N bonds. In this context, Chapter 1 summarizes the most recent achievements complying with the requirements for an ideal simple and versatile synthetic methodology.

The following part of the book brings the reader in the domain of nitrogen radicals as reactive intermediates, a reactivity stream displaying high complementarity to classical ionic and TM mediated processes. The use of photo- and electrochemical induced catalytic strategies is widely discussed (Chapters 2 and 3), overviewing the recent dramatic advances enabling to couple challenging C–H activation processes with C—N bond forming events. Although aminations with high enantioselectivity are yet rarely accessed, these radical methodologies targeting the synthesis of a wide range of heterocyclic systems and an array of complex N-containing structures outline a new and highly promising frontier.

As an enabling methodology, the development and application of asymmetric catalysis is now an integral part of the work of any major research unit in academia and industry. In the past decade, organo- and biocatalysis have flanked TM catalysis as key players for the enantioselective synthesis of chiral amino compounds, as overviewed in the ensuing Chapters 4–7. Worth noting is the possibility that these various catalytic approaches might concur toward attaining the same targets. This is exemplified in Chapter 4 devoted to the synthesis of chiral propargylamines. Many of these compounds possessing pharmaceutical properties have found applications in the treatment of diseases and can be considered among the most efficient building blocks for the synthesis N-containing heterocycles.

The relevance of high atom efficiency and very limited waste production (high atom economy) is of paramount importance for the development of methodologies with industrial prospects. Reactions such as TM-catalyzed asymmetric hydroamination, reductive amination, and hydroaminomethylation, reported in Chapter 5, meet these goals, an additional advantage being the simplicity and the easy availability of the starting materials, which is only partially counterbalanced by the complexity of the used ligands. Because of their relevance, these reactions are occasionally mentioned elsewhere in this book, although in the frame of different contexts, thus providing the reader with an exhaustive set of complementary information.

In the following chapters, metal-free stereoselective catalytic methodologies at the service of amine synthesis, represented by organo- and biocatalysis, are treated with a greater focus on industrial applications reflecting the dynamic nature of these catalytic streams. The central goal of organocatalysis (Chapter 6) is herein addressed to the emerging utilization of this methodology as an exceedingly useful synthetic tool for the large-scale preparation of active pharmaceutical ingredients (APIs) in industrial settings. An emphasis is placed on three case studied in which organocatalysis stands out with respect to other enantioselective strategies, for its versatility and potential for scale-up. The revolutionary approach of enzyme engineering, in the context of oxidoreductase enzymes applied to the synthesis of N-containing biologically relevant intermediates and products, is described in Chapter 7.

The intrinsic selectivity of enzymes provides an obvious advantage in the key challenge of developing new synthetic platforms amenable to industrialization.

The following two chapters stand out for their uniqueness, targeting topics that were not even touched in the previous two books on amino chemistry but of exceptional prominence and timeliness. Chapter 8 deals with the use of amines in the synthesis, stabilization, and functionalization of organic–inorganic hybrid nanomaterials, highlighting through a large number of case studies the pivotal role played by the amino group to unlock practical applications in the fields of biology, medicine, and energy production. Conversely, the synthesis of a number of valuable amino compounds is reported in Chapter 9, from the transformation of renewable biomass resources that already incorporate the amino groups such as chitin, chitosan, and amino acids or by modifying bio-based compounds, followed by amination. Rare aminosugars, precursors of medicinal compounds, and a wide range of heterocycles are obtained avoiding the use of fossil-based feedstocks, thus providing a remarkable step forward in the ongoing shift from depleting to renewable resources.

The final Chapter 10 addresses current applications of TM-catalyzed aromatic amination in industrial settings by discussing a large number of case studies related to the manufacturing process of pharmaceutical compounds. In addition, with reference to the seminal work by Ullmann, Buchwald, and Hartwig, this contribution points on new concepts still at academic level, but either further extending the applicability of new methodologies, or on the brink of being industrially used. Also approaches with a focus on process intensification and sustainability (flow chemistry and catalyst immobilization) are presented, together with a view of the accompanying questions when applying the methodology of aromatic amination in the pharmaceutical industry. To make aware the reader about these challenges, themes such as the control of elemental impurities, the TM accounting, and the metal recycling are treated as well. Besides being a highly useful and up-to-date source of information on the TM-catalyzed aromatic amination in industry, this contribution will hopefully provide inspiration for academic research in developing new methodologies amenable to industrialization.

We warmly thank all the distinguished scientists and their coauthors for their rewarding and highly instructive contributions. Without their effort, even more valuable considering it partially coincided with a difficult period at the international level, this volume would have not been possible. Grateful acknowledgments are also addressed to the Wiley-VCH editorial staff, and in particular to Anne Brennführer, Aruna Pragasam, Elke Maase, and Katherine Wong, who encouraged us at project outset and helped us in a very competent manner in all the phases of the preparation of this book.

Bologna
07 April 2020

Alfredo Ricci and Luca Bernardi

1

Substitution-type Electrophilic Amination Using Hydroxylamine-Derived Reagents

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1.1 Introduction

Electrophilic amination is a class of organic reactions where C—N bonds are formed via the use of electrophilic aminating reagents [1–4]. Depending on the specific reaction pathway, electrophilic amination reactions can be classified either as substitution or addition. This chapter focuses on substitution reactions. Aminating reagents for the substitution-type electrophilic aminations are essentially NR_2^+ synthons, and the electrophilicity on the nitrogen atom is generally achieved by attaching a more electronegative functionality (X) to the nitrogen atom that can serve as a leaving group. Common structural motifs for this class of reagents include chloramines, hydroxylamines, and oxaziridines (i.e. cyclic hydroxylamine derivatives). Because of the safety hazards associated with the use of chloramines, recent developments in this area have been focused on the use of more stable hydroxylamine-type reagents (Scheme 1.1).

Substitution-type electrophilic amination reactions can operate under either uncatalyzed or catalyzed conditions. The majority of catalytic substitution-type electrophilic amination reactions are catalyzed by complexes of transition metals (TMs). In the uncatalyzed reactions, the carbon nucleophile directly attacks the electrophilic nitrogen atom and a new C—N bond is formed. In the TM-catalyzed reactions, the transition metal first enters into the N—X bond via an oxidative addition, and the new C—N bond is formed after sequential ligand exchange and reductive elimination (Scheme 1.2). The major difference between TM-catalyzed substitution-type electrophilic amination reactions and TM-catalyzed C–N cross-coupling reactions (i.e. Buchwald–Hartwig coupling) is the role of the nitrogen source: it acts as an electrophile in the former while as a nucleophile in the latter.

The majority of the literature in this area concerns the TM-catalyzed versions of substitution-type electrophilic amination. Therefore, they will be discussed first in this chapter.

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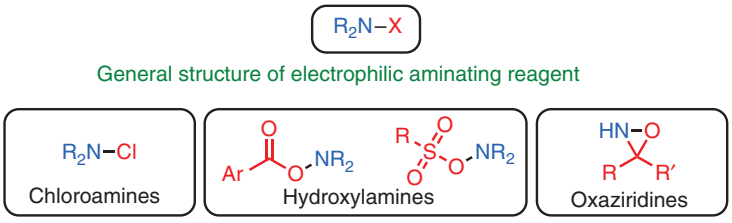
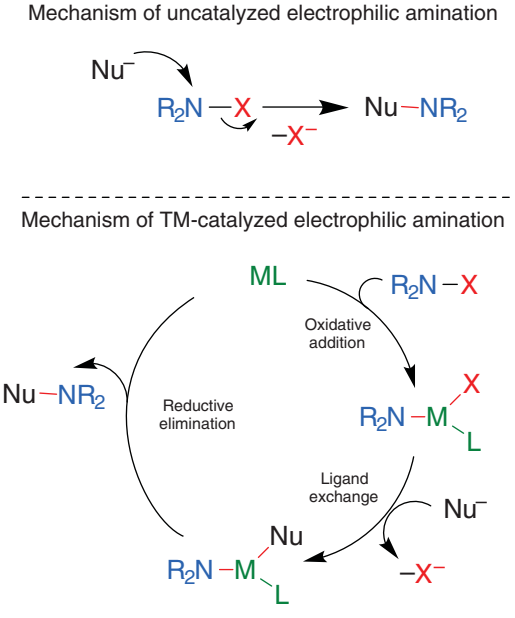


Scheme 1.1 General structure of electrophilic aminating reagent.

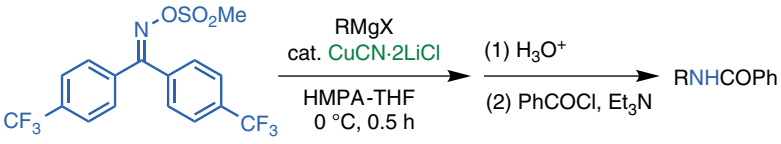


Scheme 1.2 Mechanisms of two main types of electrophilic amination.

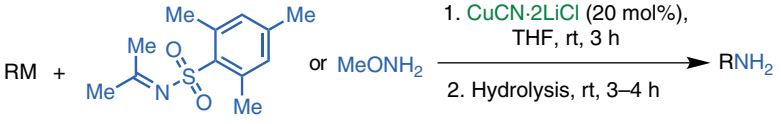
1.2 Cu-Catalyzed Reactions

Narasaka and coworkers reported an early iteration of Cu-catalyzed substitution-type electrophilic amination of Grignard reagents utilizing *O*-sulfonyloximes as aminating reagents. The reactions can also give products without copper catalysis, albeit with much lower yields. Because of the nature of the aminating reagents, subsequent acidic hydrolysis is needed to convert the imine products to the desired amines [5, 6]. A similar amination process of organozinc reagents was reported by the Erdik group around the same time. In this case, in addition to the *O*-sulfonyloximes, the authors showed that the reaction can also proceed with methoxyamine when excess of the organometallic reagent was used (Scheme 1.3) [7, 8]. These early reactions have several drawbacks that affect their utilizations, including a very limited substrate scope, low conversion rate due to many side reactions, and, most importantly, the need to use a strong acid to hydrolyze the initial imine

Narasaka et al. [5,6]



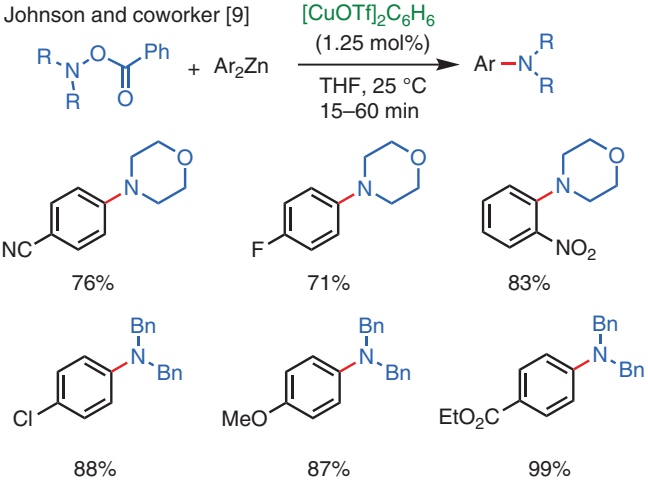
Erdik et al. [7,8]



M = ZnCl, ZnBr, 1/2 Zn, 1/3 ZnMgBr

Scheme 1.3 Early examples of Cu-catalyzed electrophilic amination. Source: Erdik and Ay [2] and Tsutsui et al. [5].

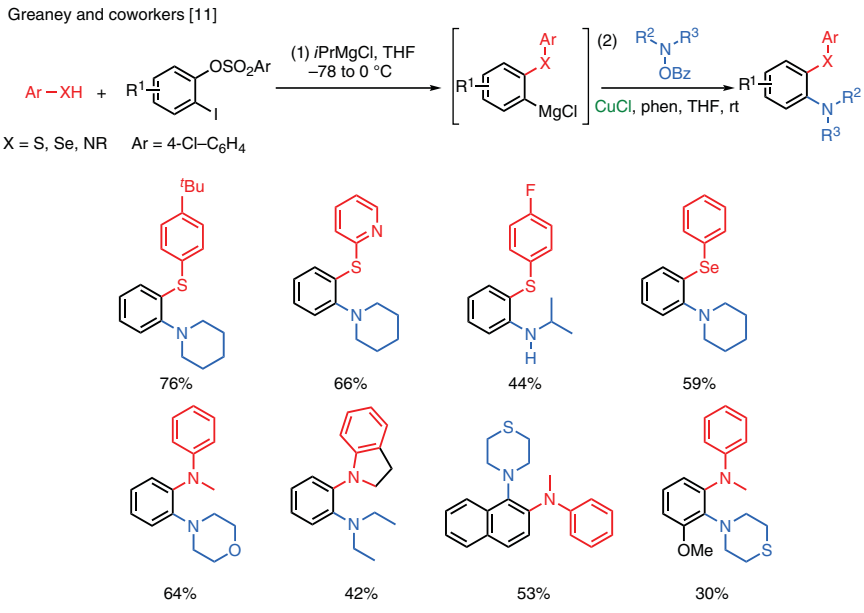
Johnson and coworker [9]



Scheme 1.4 Cu-catalyzed electrophilic amination of organozinc reagents.

products. The use of strong acidic conditions in the hydrolysis makes these procedures unsuitable for substrates containing acid-labile functionalities.

In 2004, the Johnson group at UNC reported the Cu-catalyzed electrophilic amination of diorganozinc reagents using acyl hydroxylamines as aminating reagents [9]. This is the first report of Cu-catalyzed electrophilic amination reactions that give tertiary amines as products (Scheme 1.4). Compared to the *O*-sulfonyloximes, *O*-acyl hydroxylamines are more synthetically accessible and have better atom economy. A limitation, however, is that the nitrogen must be fully substituted (i.e. no acidic N—H bond is tolerated). In place of the diorganozinc substrate, this reaction can also use a Grignard reagent as the nucleophile, which is arguably more accessible and convenient to use [10].



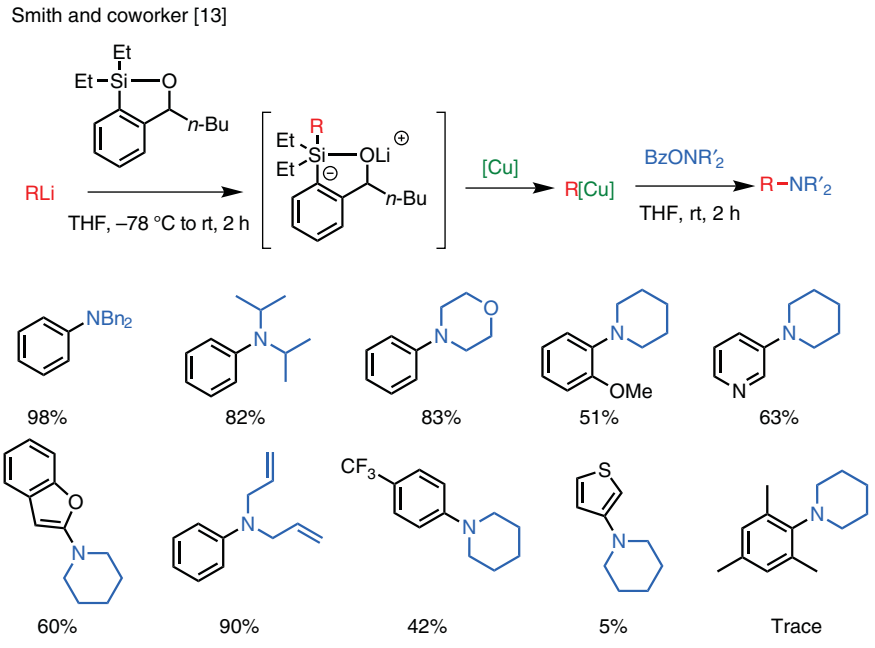
Scheme 1.5 Cu-catalyzed electrophilic amination via aryne intermediate.

After the initial disclosure of Johnson and coworkers, subsequent research showed that other organometallic reagents can also serve as the nucleophile.

A unique reaction was reported by Greaney and coworkers at the University of Manchester in the UK [11]. In this case, an aryne intermediate is first generated in situ via iodine–magnesium exchange, followed by elimination. A nucleophile subsequently attacks the aryne, and the resulting arylmetal undergoes Cu-catalyzed electrophilic amination with the hydroxylamine-derived electrophilic aminating reagent to furnish aryl amines as the final products (Scheme 1.5). This reaction gives access to unique aromatic products with a 1,2-bis substitution pattern. The nucleophiles that can be used in this reaction include arylamines, thiophenols, and arylselenols. The overall transformation exhibits excellent regioselectivity; however, the isolated yield is lowered in those cases in which the reactants are sterically encumbered.

One important consideration in these types of reactions is that the nucleophile has to be able to coexist with the aminating reagent in order for the catalytic cycle to be established. Otherwise, the nucleophile may directly react (i.e. protonation and/or uncatalyzed nucleophilic attack) with the aminating reagent and may lead to the formation of undesired by-products. This puts limitations on both the nucleophilicity and basicity of the organometallic nucleophiles. Organozinc compounds, Grignard reagents, and organoaluminum [12] reagents have been shown to be suitable nucleophiles for these types of reactions, while organolithium reagents are generally unsuitable because of their strong basicity and tendency to participate in side reactions that involve electron transfer pathways.

To address this issue and provide a solution for the direct electrophilic amination of organolithium reagents via copper catalysis, the group of A. B. Smith III (University of

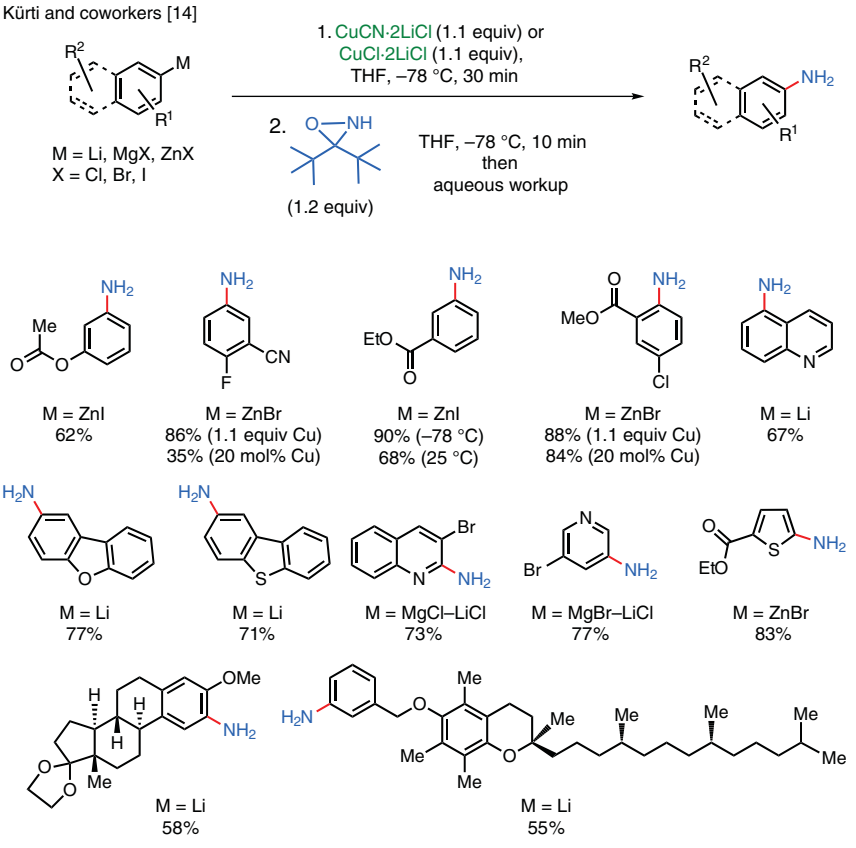


Scheme 1.6 Cu-catalyzed electrophilic amination of organolithium reagents.

Pennsylvania, 2013) developed a protocol in which a siloxane transfer reagent is used to modulate the reactivity of the organolithium reagents (Scheme 1.6) [13]. The siloxane reagent acts as an "attenuator" for the more reactive organolithium reagents and lowers its reactivity by forming a less basic complex that can more readily participate in the catalytic cycle and, in the meantime, prevents the direct attack on the aminating reagent by the organolithium.

This type of C—N bond-forming reaction can also take place directly between cuprates and electrophilic aminating reagents. One reason to justify the use of stoichiometric amounts of a copper salt (i.e. full transmetalation) is that the low basicity of the resulting cuprate can tolerate the presence of N–H protons in the aminating reagent, thereby enabling the synthesis of primary and secondary amine products without the use of excess organometallic reagent. The Kürti group has demonstrated this possibility with the use of sterically hindered N–H oxaziridines (Scheme 1.7) [14]. Compared to the tertiary amines, unprotected primary amines are more versatile building blocks for further functionalization.

These sterically hindered N–H oxaziridines can be readily synthesized on multigram scale from the corresponding N–H imines and *meta*-chloroperbenzoic acid (*m*CPBA). The N–H oxaziridines are bench-stable compounds and can also be readily purified via flash column chromatography and using regular silica gel as the stationary phase. The steric hindrance created by the bulky alkyl groups reduces the kinetic acidity of the oxaziridine N—H bond, thus allowing the cuprates to be aminated as opposed to suffering unproductive proton transfer.

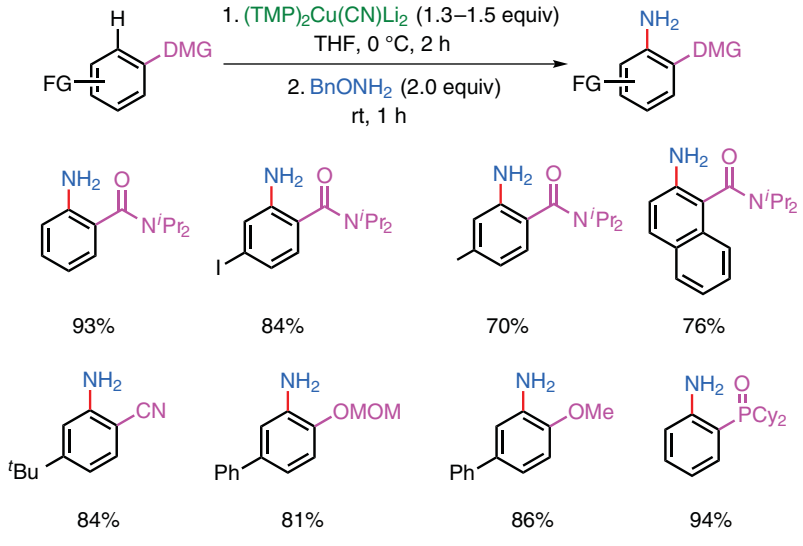


Scheme 1.7 Electrophilic amination of arylcuprates using a NH-oxaziridine.

Since the advent of direct C–H cupration of arenes, it is now also possible to utilize cuprate nucleophiles without first going through a separate transmetalation step. Uchiyama and coworkers (at RIKEN, Japan) showed that it was indeed possible to directly aminate aryl cuprates with *O*-benzyl hydroxylamine. The directed C–H cupration of arenes was achieved using a strong base $(TMP)_2Cu(CN)Li_2$, which can selectively deprotonate at the ortho position of the amide directing group. The resulting aryl cuprates can be directly primary aminated with benzyl hydroxylamine (Scheme 1.8) [15]. The hygroscopic nature of *O*-benzyl hydroxylamine necessitates its use as a stock solution in an organic solvent.

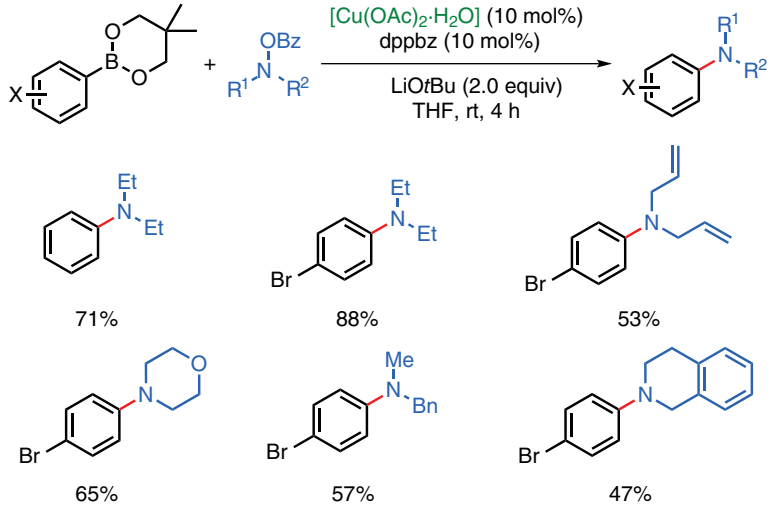
The instability of organometallic reagents used in the aforementioned reactions imposes limits on their widespread utilization, especially in an industrial setting. Efforts have been made to replace the air- and moisture-sensitive organometallic reagents with more stable alternatives that can be conveniently stored and used. Miura and coworkers (Osaka University, Japan) have shown that both arylboronates (Scheme 1.9) [16] and arylsilanes (Scheme 1.10) [17] can serve as starting materials in Cu-catalyzed electrophilic amination reactions. These reactions can proceed under ambient temperature and furnish the corresponding anilines in good to excellent isolated yields. The enhanced stability of arylboronates and arylsilanes reduces the complexity of the operation and, at the same

Uchiyama and coworkers [15]



Scheme 1.8 Electrophilic amination via directed C–H cupration.

Miura and coworkers [16]

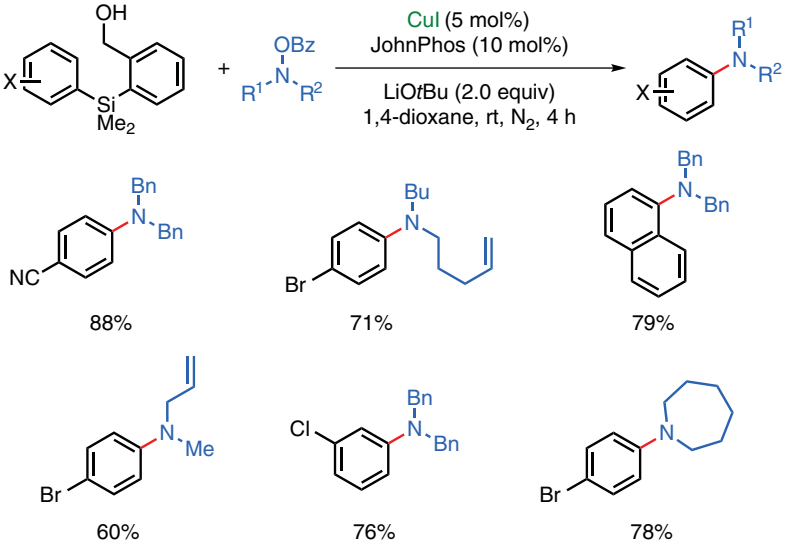


Scheme 1.9 Cu-catalyzed electrophilic amination of arylboronates.

time, the wide commercial availability of arylboronates also adds convenience to these types of reactions.

Hirano and Miura discovered that ambident nucleophiles such as silyl ketene acetals are also suitable nucleophiles for the Cu-catalyzed electrophilic amination reactions. These reactions result in the formation of alpha-amino esters as products. The first generation of this reaction uses chloramines as aminating reagents [18], while the second generation

Miura and coworkers [17]



Scheme 1.10 Cu-catalyzed electrophilic amination of aryl silanes. Source: Modified from Miki et al. [17].

can proceed with the more stable and much safer *O*-benzoyl hydroxylamines (Scheme 1.11) [19]. This method provides a potential route for the syntheses of unnatural as well as modified natural amino acids.

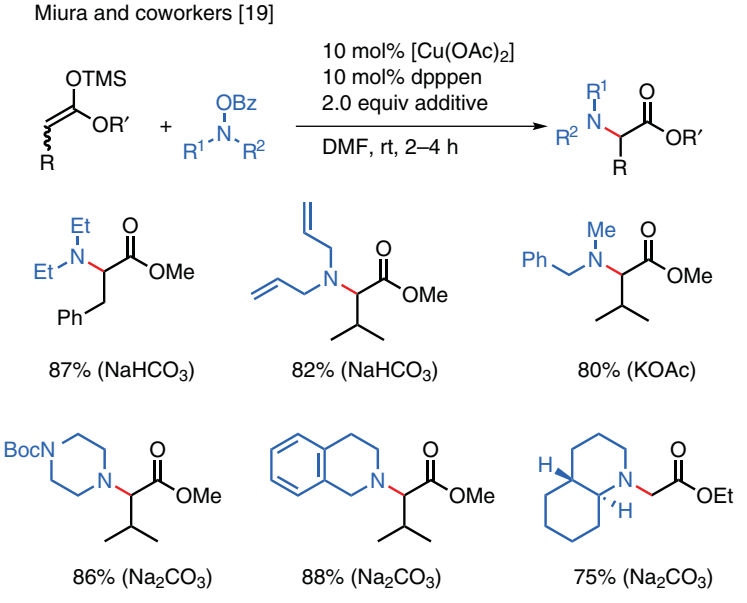
Weak nucleophiles such as styrenes and some electron-deficient heterocycles can also participate in Cu-catalyzed electrophilic amination reactions.

In the case of styrenes, the substrates can undergo hydroamination or aminoboration depending on the specific reaction conditions. Hirano, Miura, and coworkers have demonstrated that styrenes can be stereoselectively functionalized with benzoyl hydroxylamine and bis(pinacolato)diboron under Cu catalysis (Scheme 1.12) [20]. The resulting products can further participate in transition-metal-catalyzed cross-coupling reactions.

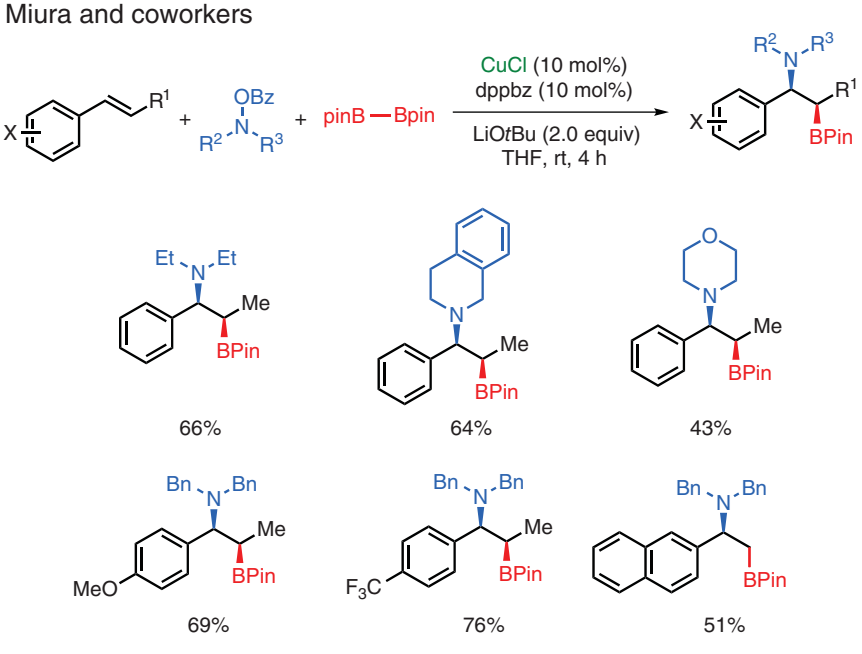
When polymethylhydrosiloxane (PMHS) is used instead of bis(pinacolato)diboron, hydroamination products can be obtained under similar reaction conditions (Scheme 1.13). In these cases, it is proposed that the reaction proceeds with an initial CuH addition across the C—C bond of the olefins, followed by the electrophilic amination of the resulting cuprates [21].

With chiral ligands, the hydroamination reactions can give enantiomerically enriched products. Both the Miura (Scheme 1.14) and Buchwald (Scheme 1.15) groups have developed conditions using chiral phosphine ligands [21, 22].

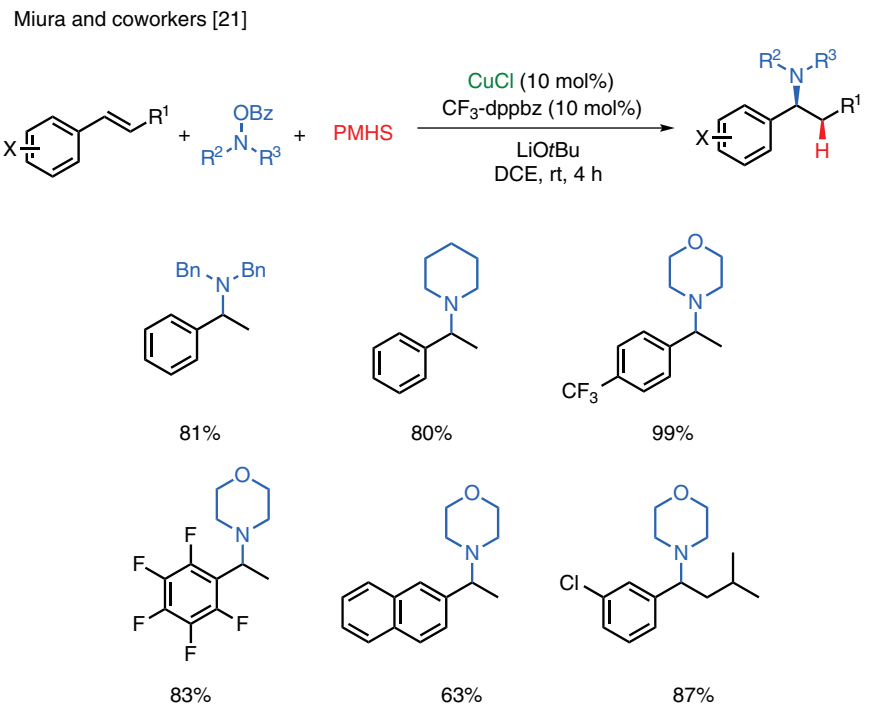
Buchwald and coworkers have also reported the hydroamination of aryl acetylenes. The reaction is highly stereoselective, giving *E*-enamines as the major products. The enamine products can be further reduced to give alkyl amines, which are important building blocks in organic synthesis (Scheme 1.16) [23].



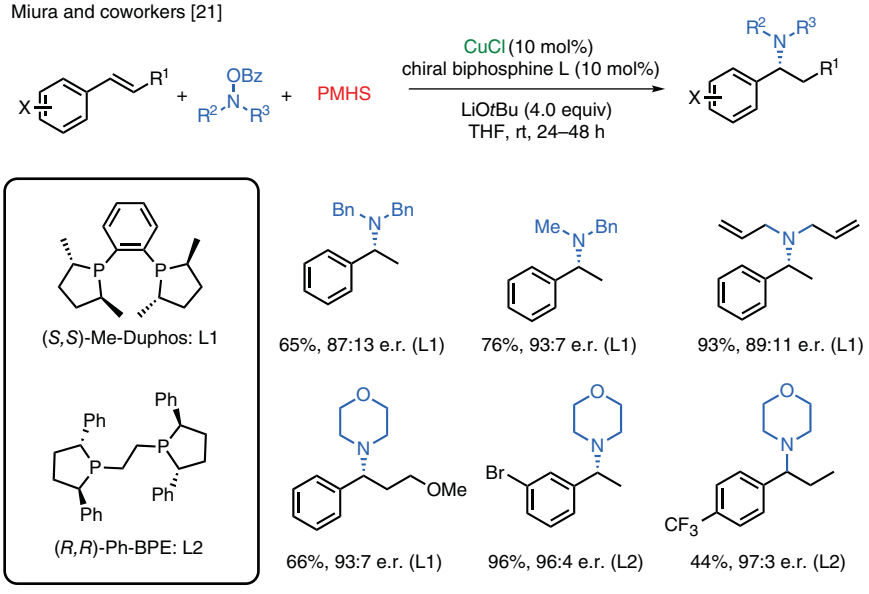
Scheme 1.11 Cu-catalyzed electrophilic amination of silyl enol ethers. Source: Modified from Matsuda et al. [19].



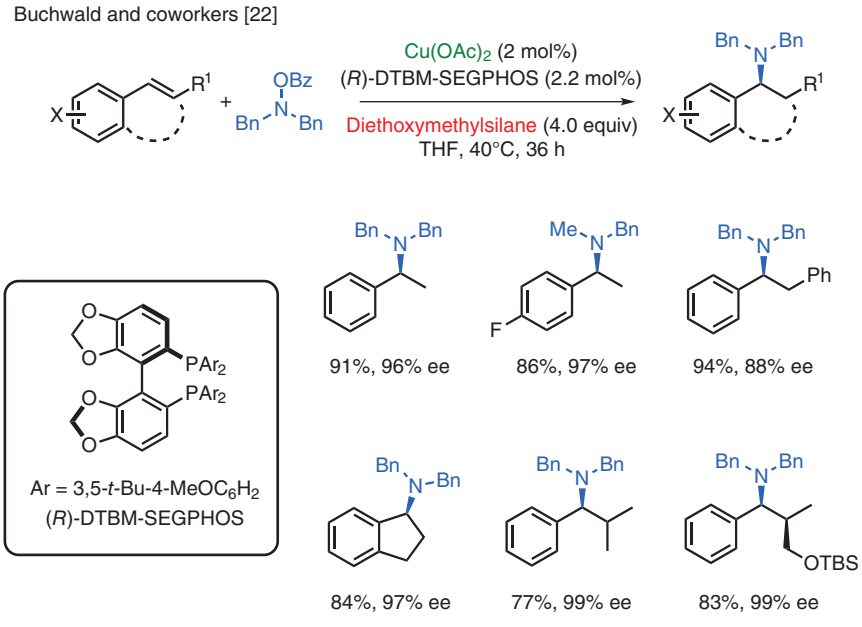
Scheme 1.12 Cu-catalyzed electrophilic catalyzed aminoboration of styrenes. Source: Modified from Matsuda et al. [20].



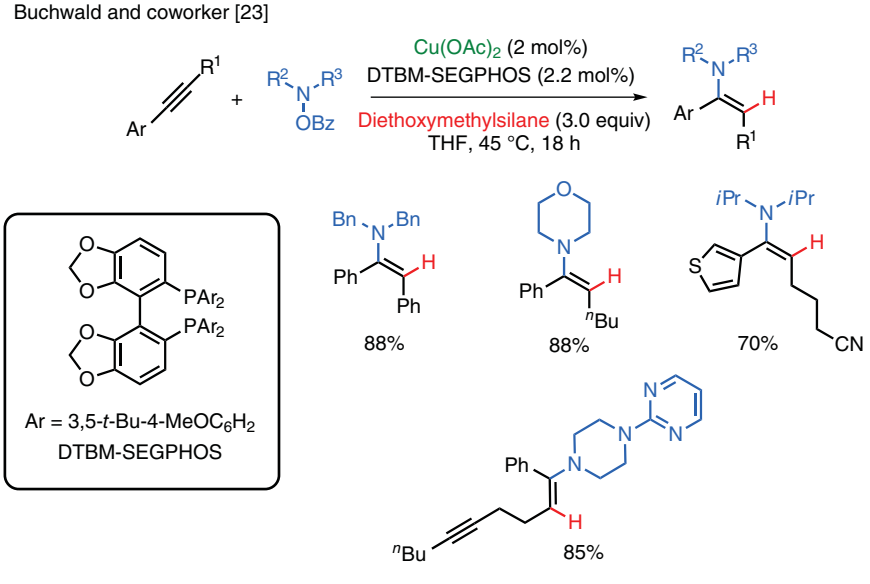
Scheme 1.13 Cu-catalyzed electrophilic hydroamination of styrenes. Source: Modified from Miki et al. [21].



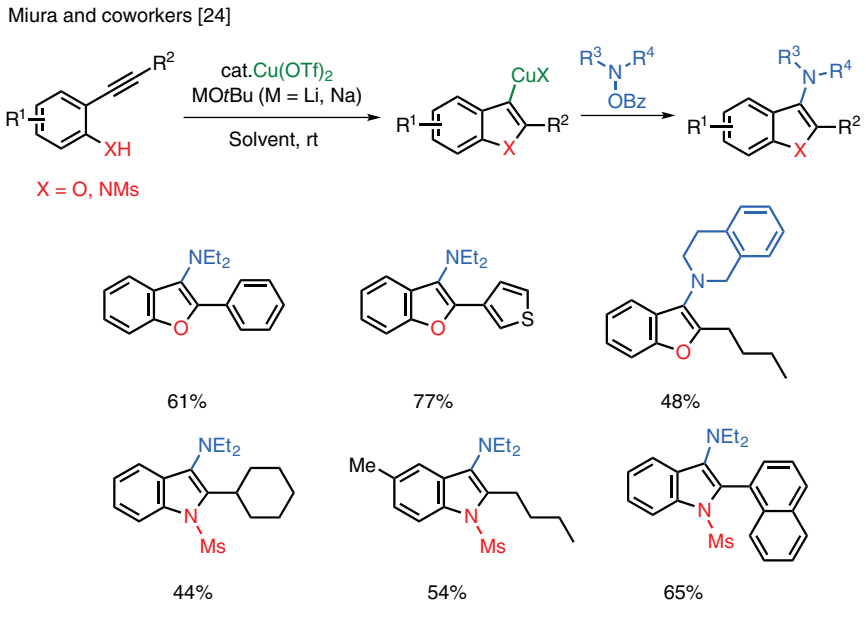
Scheme 1.14 Enantioselective Cu-catalyzed electrophilic hydroamination of styrenes. Source: Miki et al. [21].



Scheme 1.15 Enantioselective Cu-catalyzed electrophilic hydroamination of styrenes. Source: Modified from Zhu et al. [22].



Scheme 1.16 Cu-catalyzed electrophilic amination of alkynes. Source: Shi and Buchwald [23].



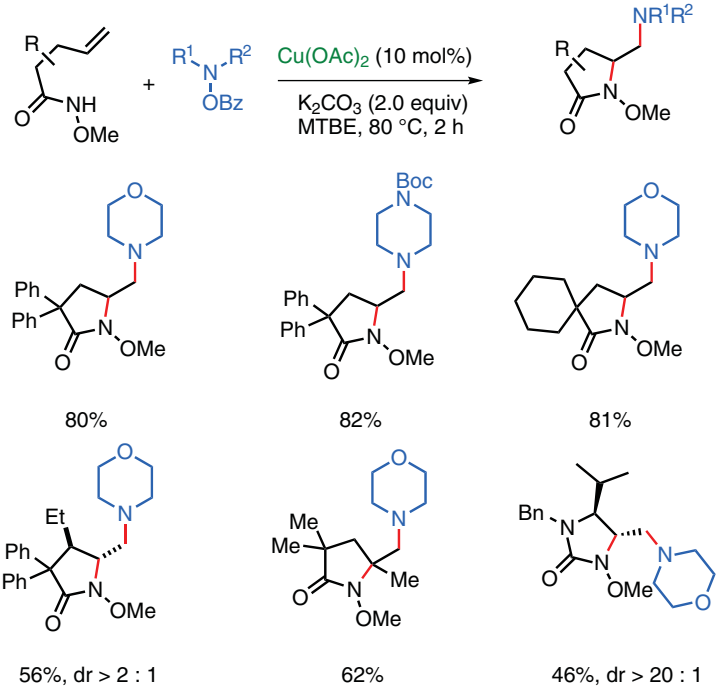
Scheme 1.17 Cu-catalyzed annulative electrophilic amination. Source: Modified from Matsuda et al. [24].

ortho-Alkynyl phenols and anilines can also undergo annulative amination with electrophilic aminating reagents under Cu catalysis. Miura and coworkers have developed conditions for the synthesis of aminated benzofurans and indoles (Scheme 1.17) [24]. The transformation is operationally simple and proceeds at room temperature. The mechanism was probed and the authors concluded that the most plausible pathway is a nonradical electrophilic amination of the heteroarylcuprate species in the C—N bond-forming step.

Similar intramolecular reactions can also take place with substrates containing unactivated terminal alkenes. In 2015, the Wang group (Duke University) reported the copper-catalyzed vicinal diamination of unactivated alkenes with hydroxylamines that is both regio- and stereoselective. The first iteration of this reaction takes place on unsaturated amides and gives 4-amino-2-pyrrolidones as the products (Scheme 1.18) [25]. This transformation is considered to be the first metal-catalyzed alkene 1,2-diamination that enables the direct incorporation of an electron-rich amino group.

In 2016, Wang and coworkers successfully expanded the substrate scope to include unsaturated carboxylic acids, which undergo amino-lactonization under the reaction conditions (Scheme 1.19) [26]. The overall transformation allows the practitioner to access quickly and efficiently a wide range of amino-substituted γ- and δ-lactones as well as 1,2-amino alcohol derivatives, which are of significant value in the synthesis of natural products and active pharmaceutical ingredients.

Wang [25]

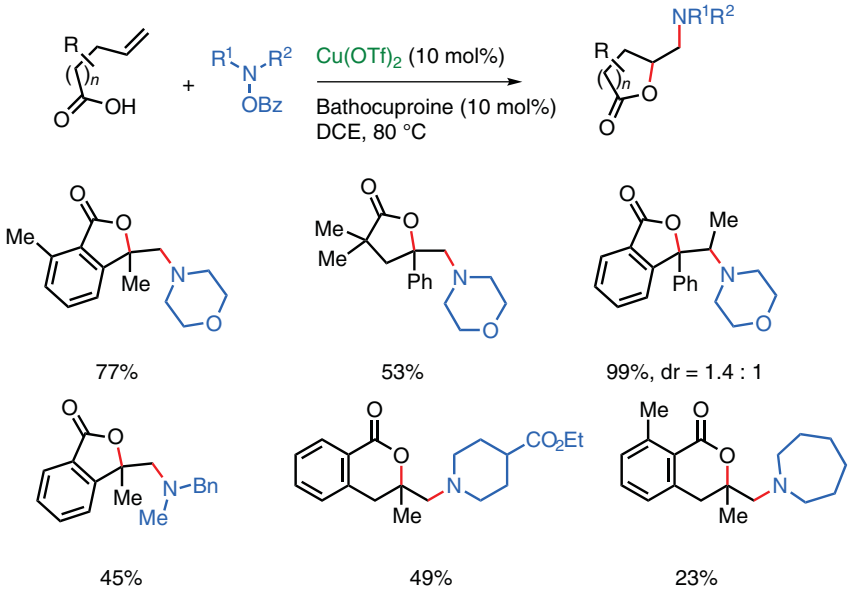


Scheme 1.18 Cu-catalyzed electrophilic diamination. Source: Modified from Shen and Wang [25].

An unusual case of ring-opening amination of cyclopropanols has been reported by the Dai group [27]. In this reaction, a base-initiated ring-opening of cyclopropanol generates a carbanion nucleophile, which participates in the Cu-catalyzed electrophilic amination and affords β-aminoketones as products (Scheme 1.20). The catalytic cycle involves the oxidation of the Cu(I) complex to the corresponding Cu(III) species by the hydroxylamine reagent. Next, the Cu(III) intermediate promotes the ring-opening of the cyclopropanol substrate and the resulting copper-homoenolate undergoes reductive elimination to form the new C—N bond and to regenerate the catalytically active Cu(I) species. Overall, the transformation proceeds under mild reaction conditions and it is also compatible with a number of sensitive functionalities such as esters, epoxides, and unsaturated carbonyl compounds.

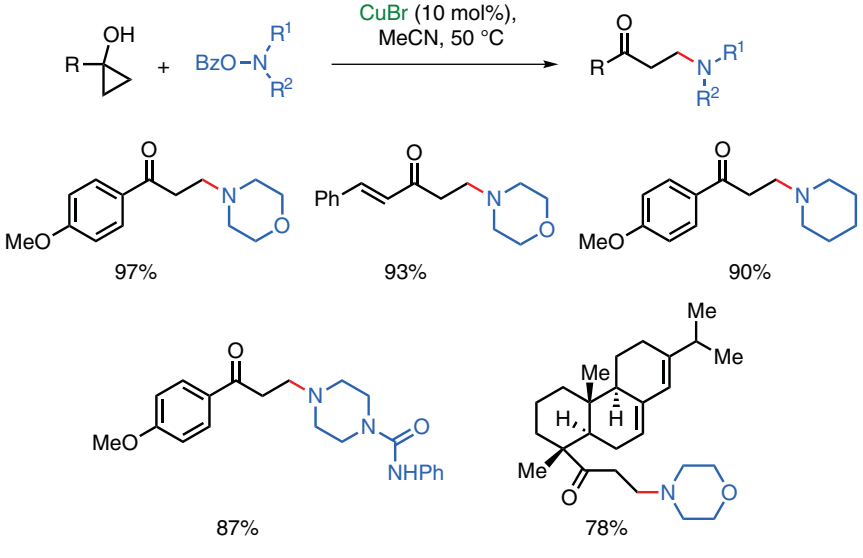
With electron-deficient arenes, direct C–H amination is also possible. Miura and coworkers have reported the Cu-catalyzed direct C–H amination using benzoyl hydroxylamines as aminating reagents (Scheme 1.21) [28]. Electron-deficient aromatic substrates such as fluoroarenes, oxadiazoles, and thiazoles can be directly aminated to furnish the corresponding aryl and heteroaryl amines. The Yotphan group later expanded the substrate scope to include benzoxazoles [29], while the Li group applied the reaction to enable the C–H amination of quinoline *N*-oxide [30].

Wang and coworkers [26]



Scheme 1.19 Cu-catalyzed electrophilic amino-lactonization. Source: Modified from Hemric et al. [26].

Dai and coworkers [27]



Scheme 1.20 Cu-catalyzed ring-opening amination. Source: Modified from Ye and Dai [27].