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Substitution-type Electrophilic Amination Using Hydroxylamine-Derived Reagents

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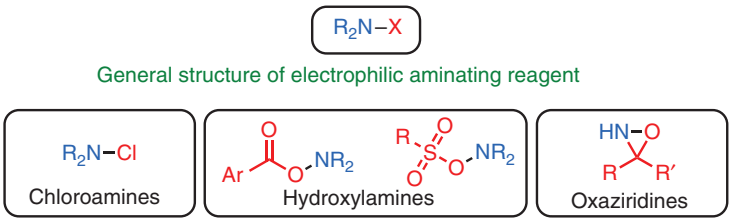
1.1 Introduction

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).

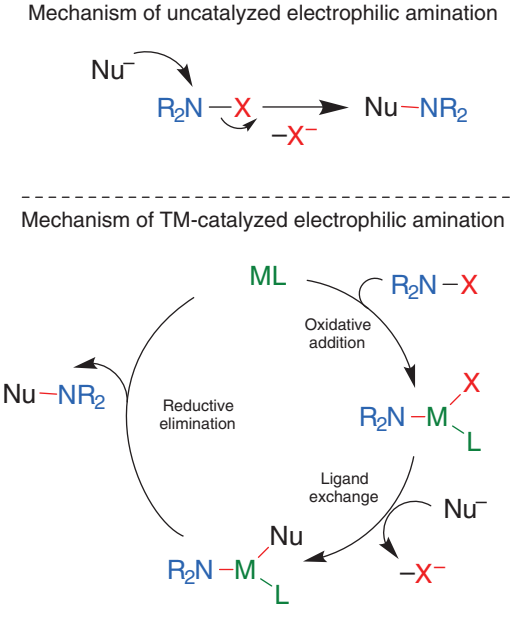
Substitution-type electrophilic amination reactions can operate under either uncatalyzed or catalyzed conditions. The majority of catalytic substitution-type electrophilic amination reactions are catalyzed by complexes of transition metals (TMs). In the uncatalyzed reactions, the carbon nucleophile directly 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.

Methodologies in Amine Synthesis: Challenges and Applications, First Edition.
Edited by Alfredo Ricci and Luca Bernardi.



Scheme 1.1 General structure of electrophilic aminating reagent.

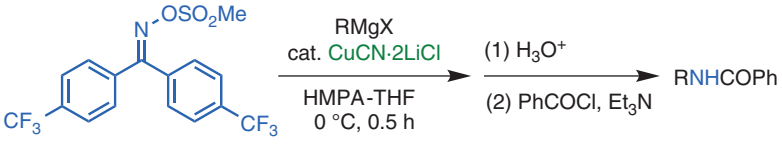


Scheme 1.2 Mechanisms of two main types of electrophilic amination.

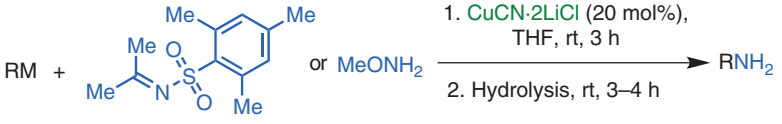
1.2 Cu-Catalyzed Reactions

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]



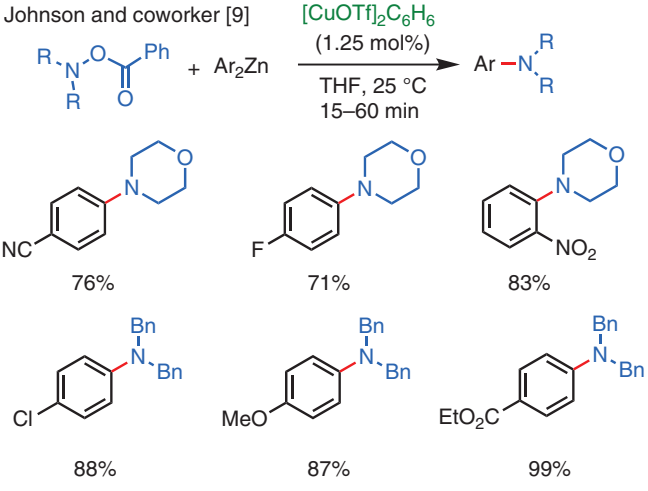
Erdik et al. [7,8]



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].

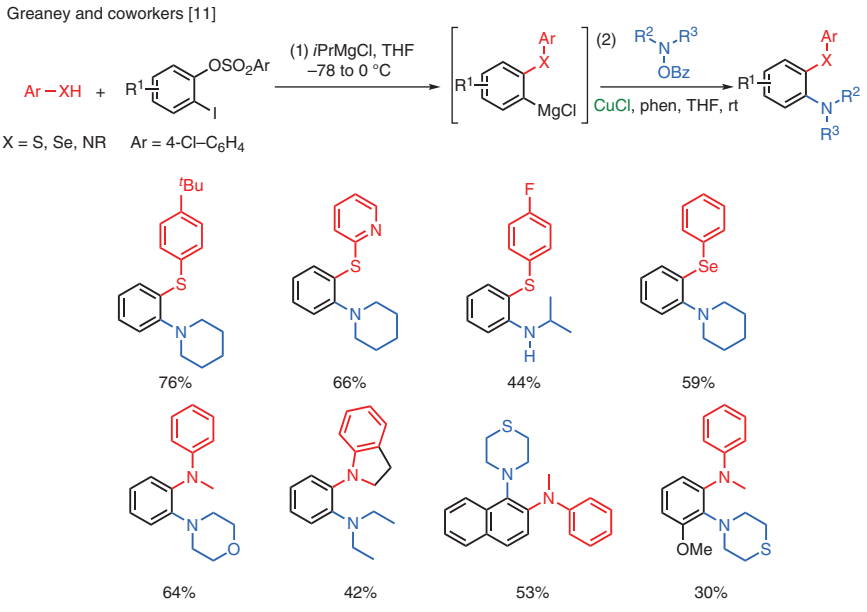
Johnson and coworker [9]



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].



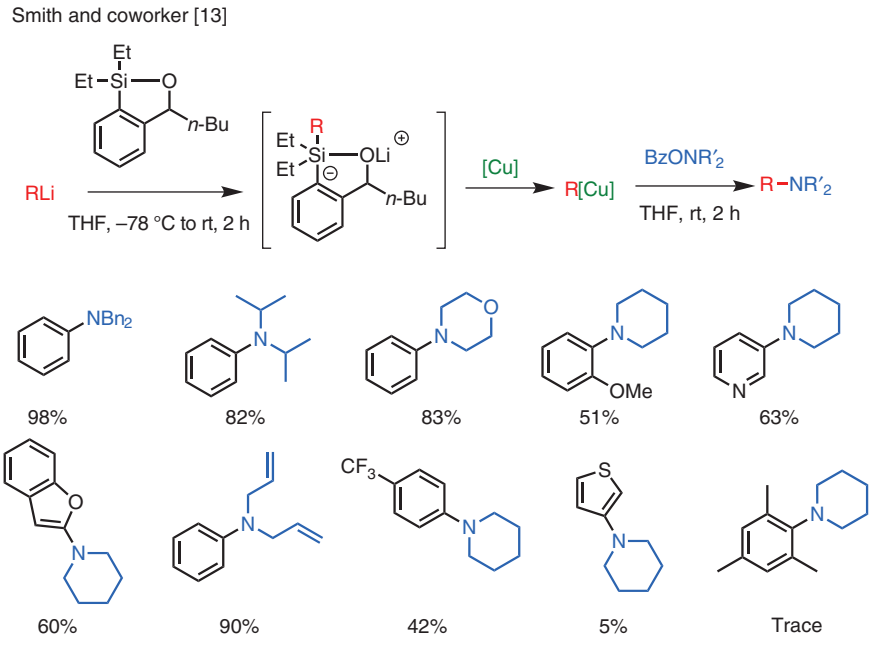
Scheme 1.5 Cu-catalyzed electrophilic amination via aryne intermediate.

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

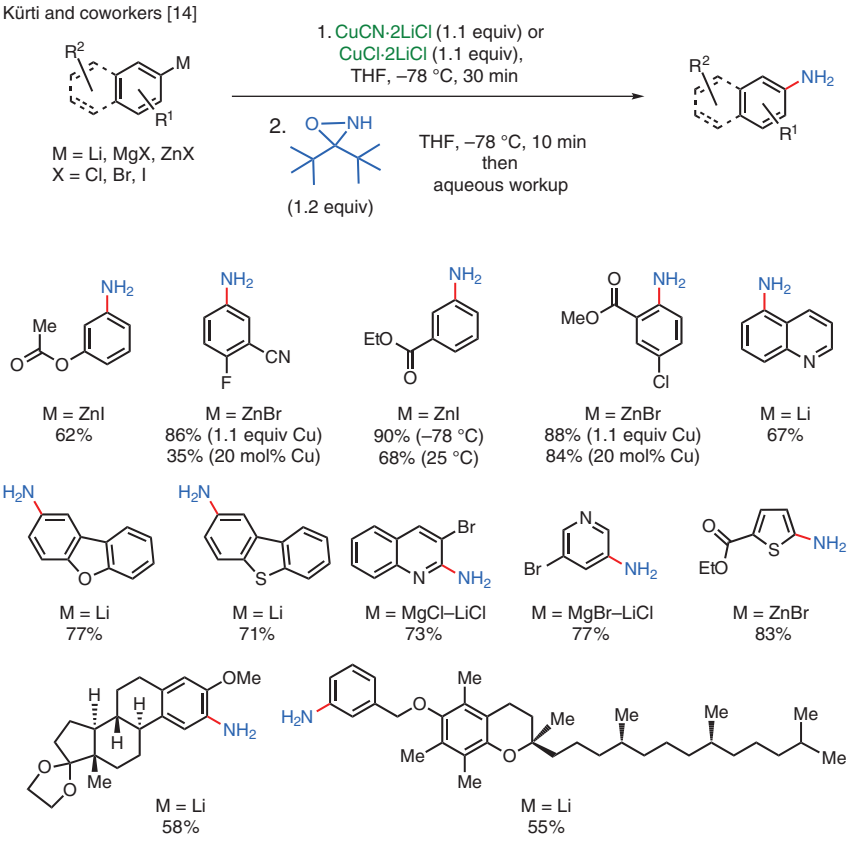


Scheme 1.6 Cu-catalyzed electrophilic amination of organolithium reagents.

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.

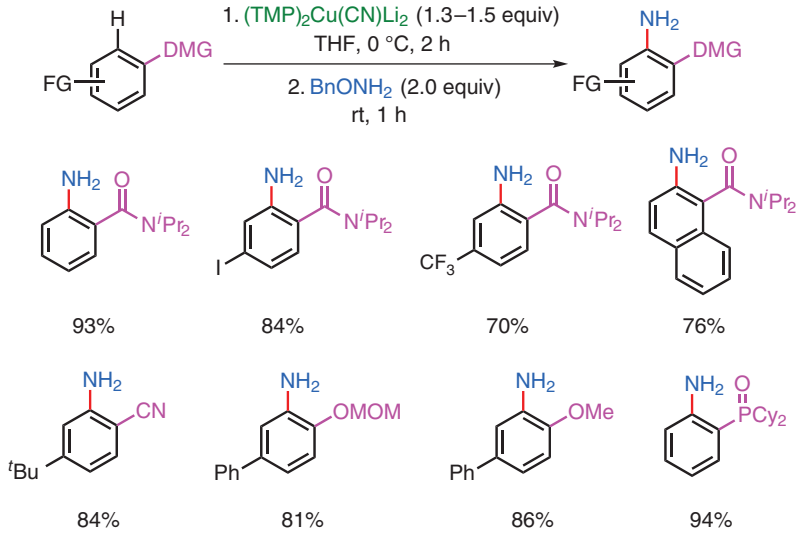


Scheme 1.7 Electrophilic amination of arylcuprates using a NH-oxaziridine.

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.

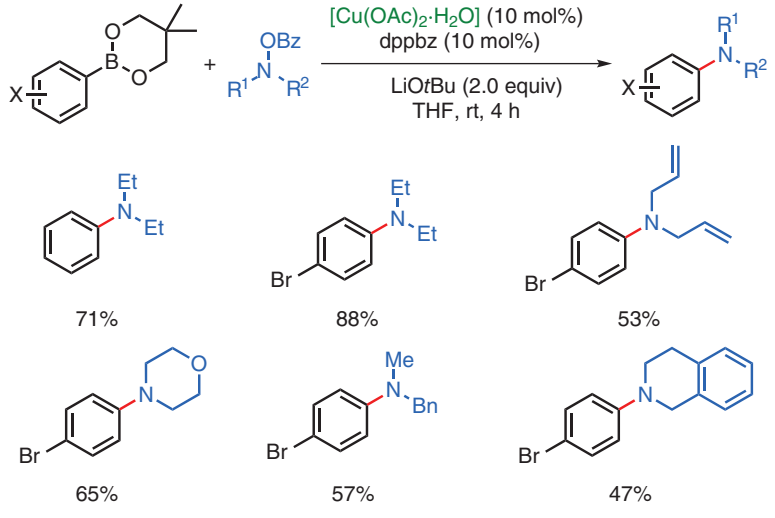
The instability of organometallic reagents used in the aforementioned reactions imposes limits on their widespread utilization, especially in an industrial setting. Efforts have been made to replace the air- and moisture-sensitive organometallic reagents with more stable alternatives that can be conveniently 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]

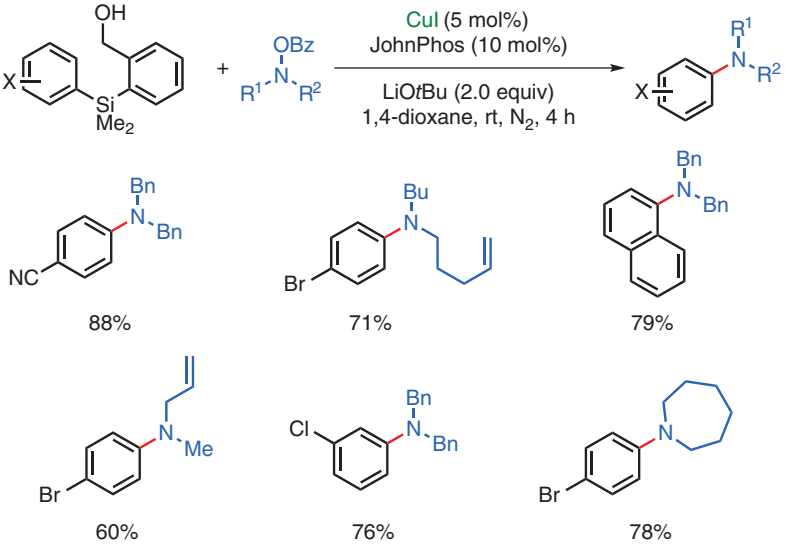


Scheme 1.9 Cu-catalyzed electrophilic amination of arylboronates.

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.

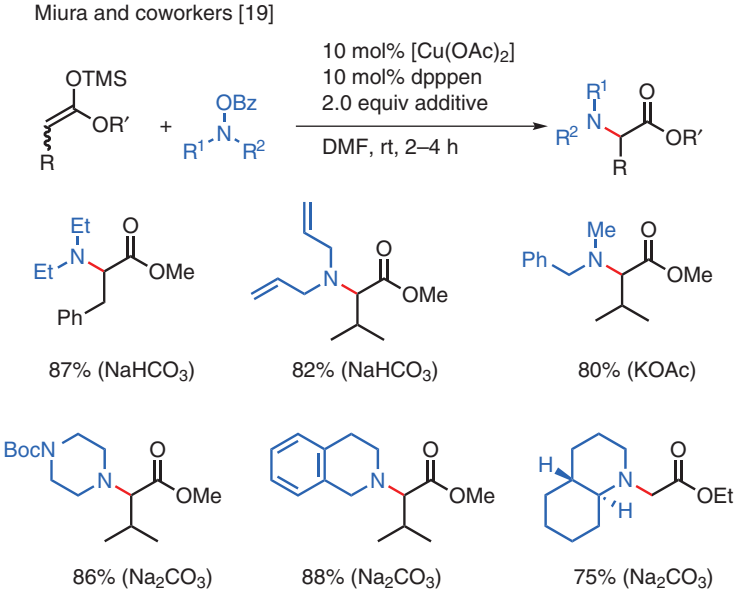
Weak nucleophiles such as styrenes and some electron-deficient heterocycles can also participate in Cu-catalyzed electrophilic amination reactions.

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.

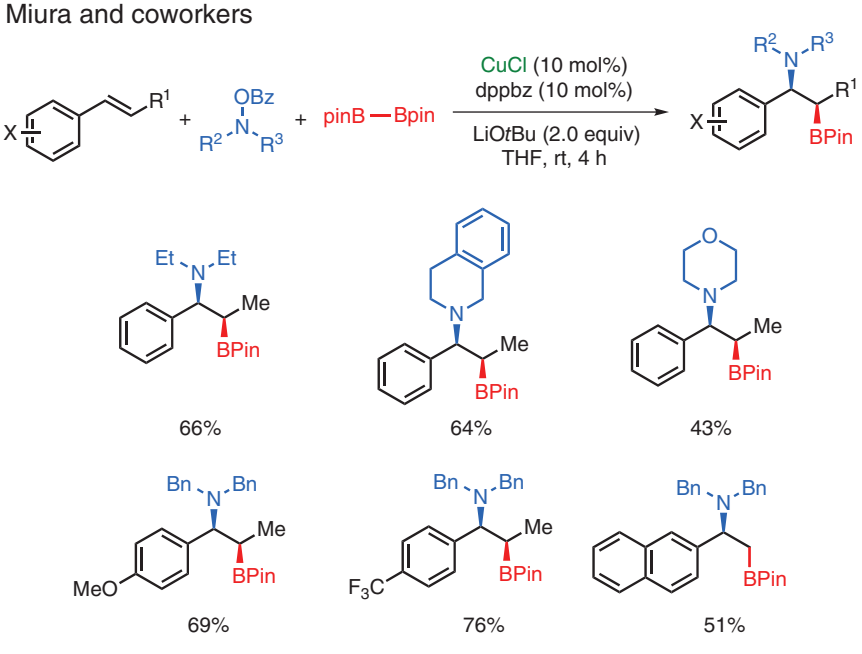
When polymethylhydrosiloxane (PMHS) is used instead of bis(pinacolato)diboron, hydroamination products can be obtained under similar reaction conditions (Scheme 1.13). In these cases, it is proposed that the reaction proceeds with an initial CuH addition across the C—C bond of the olefins, followed by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

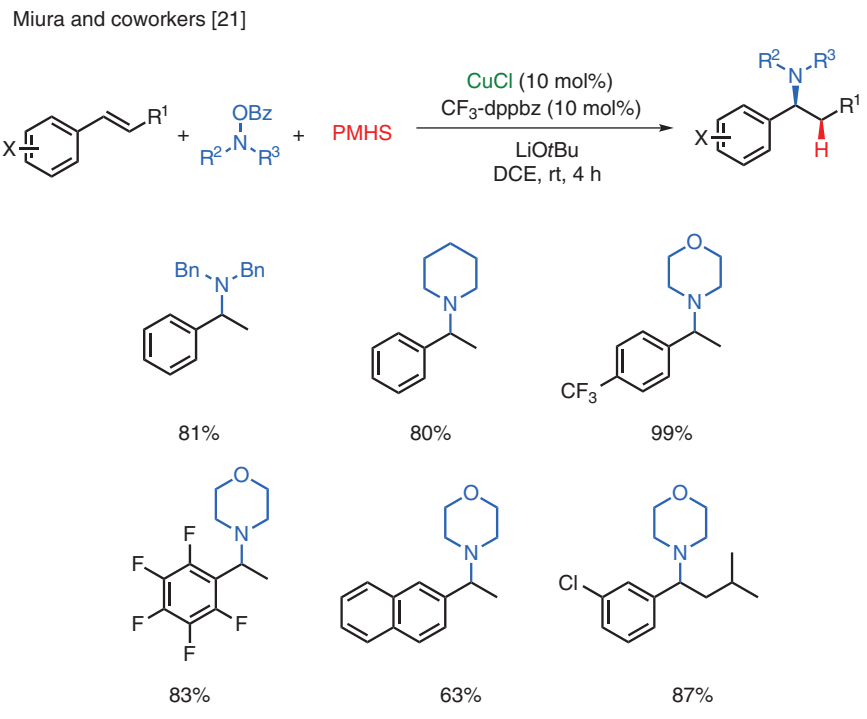
Buchwald and coworkers have also reported the hydroamination of aryl acetylenes. The reaction is highly stereoselective, giving *E*-enamines as the major products. The enamine products can be further reduced to give alkyl amines, which are important building blocks in organic synthesis (Scheme 1.16)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



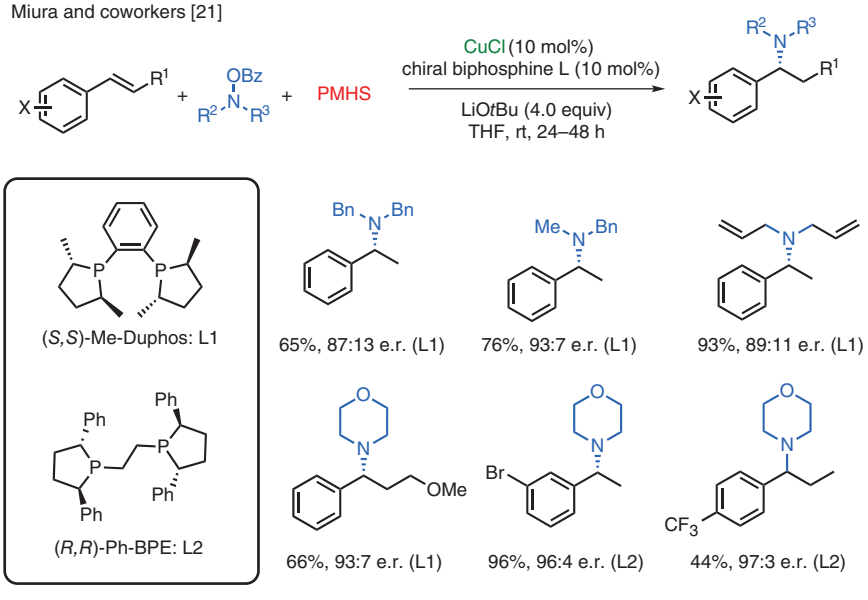
Scheme 1.11 Cu-catalyzed electrophilic amination of silyl enol ethers. Source: Modified from Matsuda et al. [19].



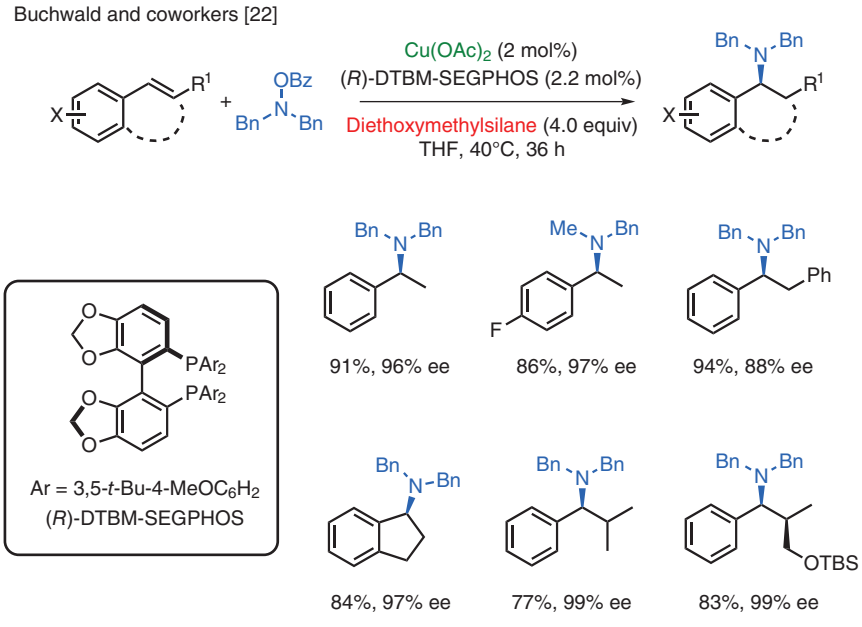
Scheme 1.12 Cu-catalyzed electrophilic catalyzed aminoboration of styrenes. Source: Modified from Matsuda et al. [20].



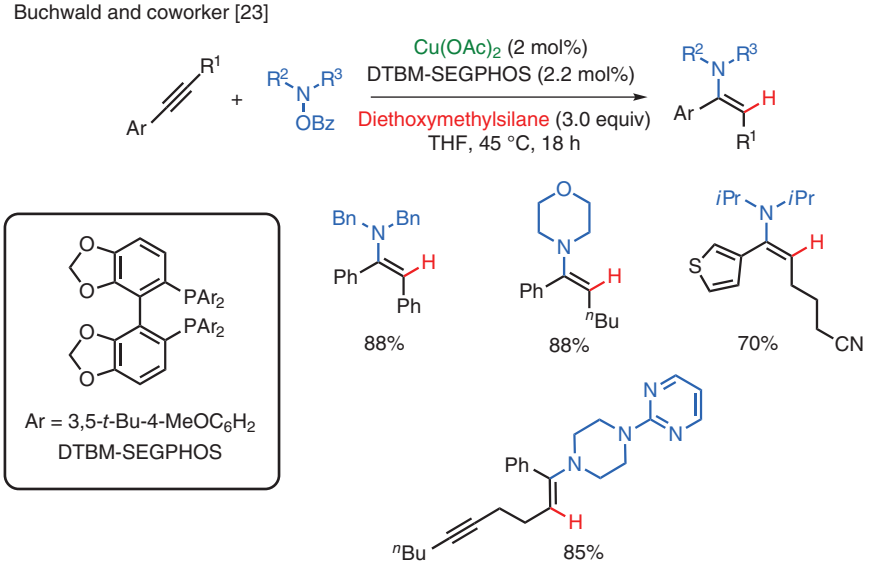
Scheme 1.13 Cu-catalyzed electrophilic hydroamination of styrenes. Source: Modified from Miki et al. [21].



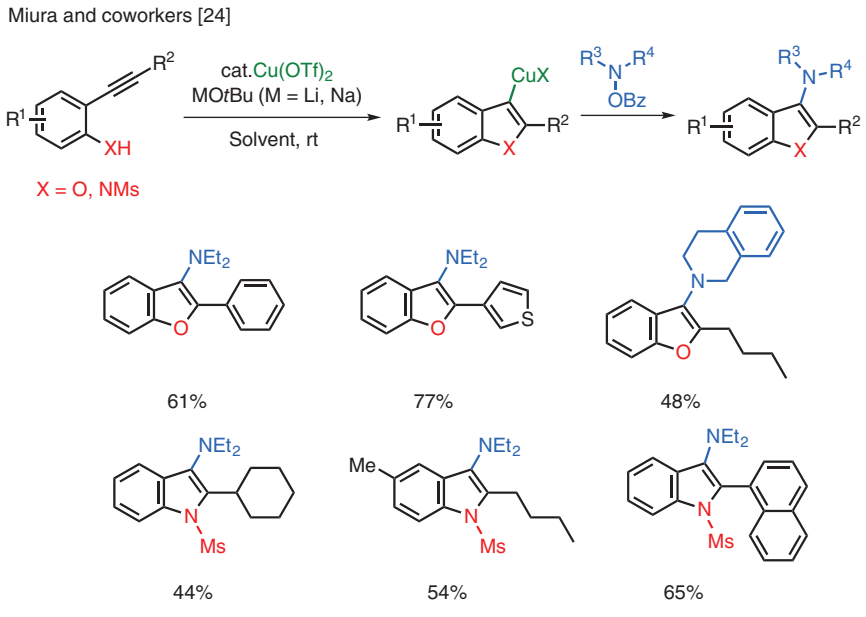
Scheme 1.14 Enantioselective Cu-catalyzed electrophilic hydroamination of styrenes. Source: Miki et al. [21].



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].



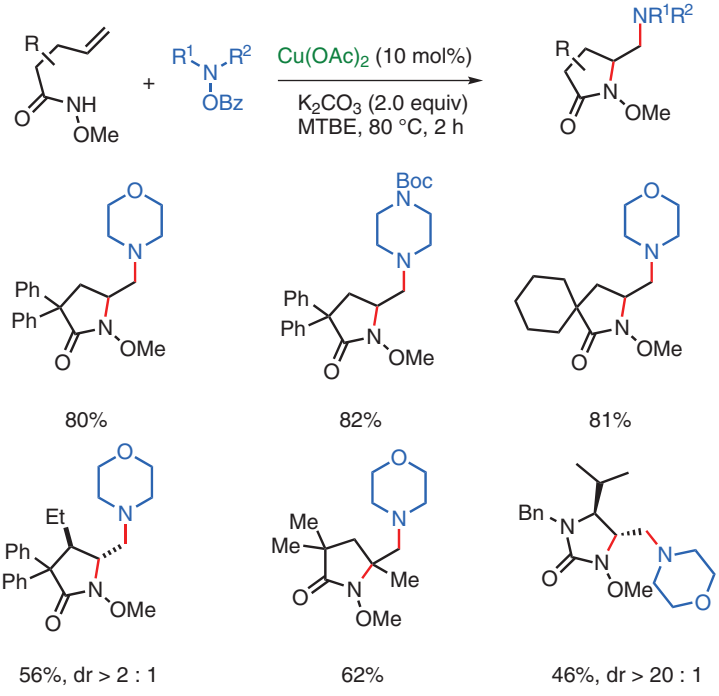
Scheme 1.17 Cu-catalyzed annulative electrophilic amination. Source: Modified from Matsuda et al. [24].

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]

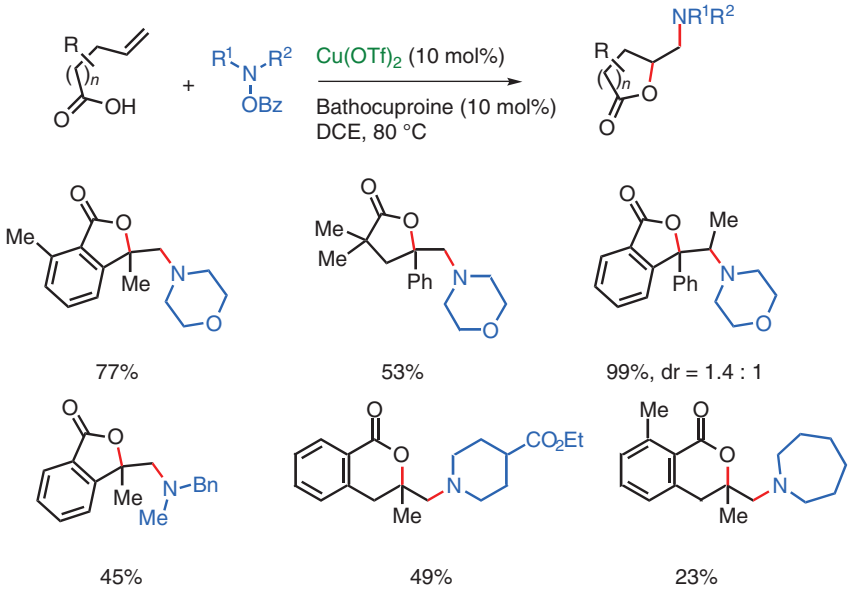


Scheme 1.18 Cu-catalyzed electrophilic diamination. Source: Modified from Shen and Wang [25].

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.

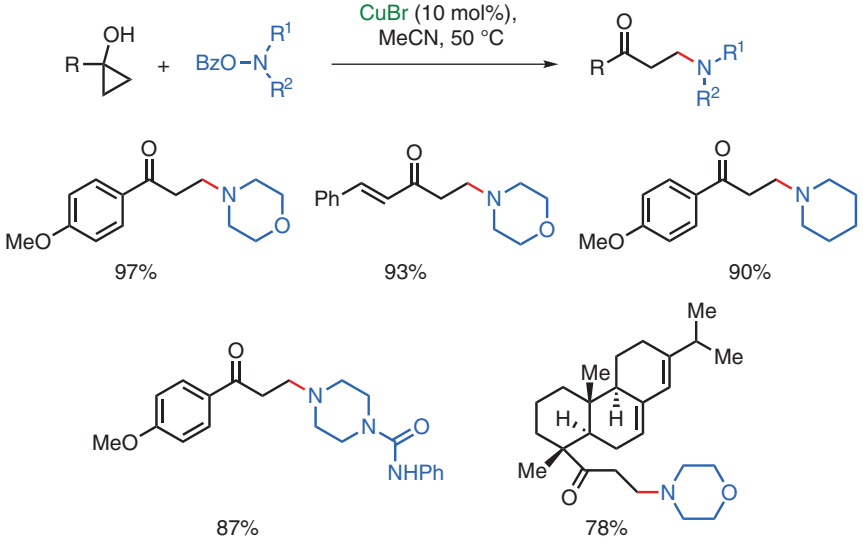
With electron-deficient arenes, direct C–H amination is also possible. Miura and coworkers have reported the Cu-catalyzed direct C–H amination using benzoyl hydroxylamines as aminating reagents (Scheme 1.21) [28]. Electron-deficient aromatic substrates such as fluoroarenes, oxadiazoles, and thiazoles 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]

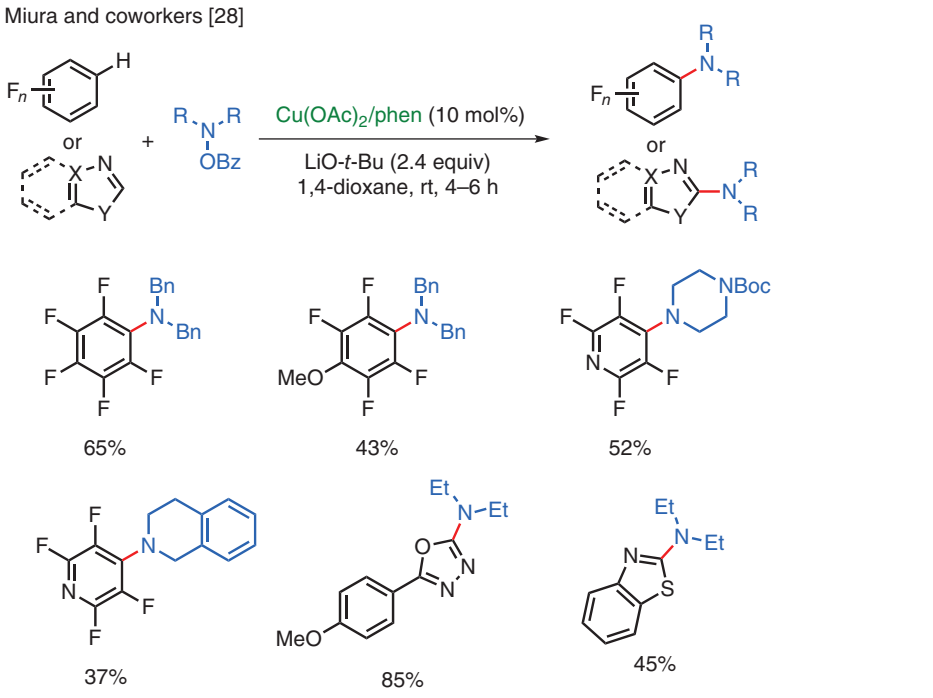


Scheme 1.19 Cu-catalyzed electrophilic amino-lactonization. Source: Modified from Hemric et al. [26].

Dai and coworkers [27]



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



Scheme 1.21 Cu-catalyzed C–H amination of heterocycles. Source: Matsuda et al. [28].

1.3 Electrophilic Amination Reactions Catalyzed by Other Transition Metals

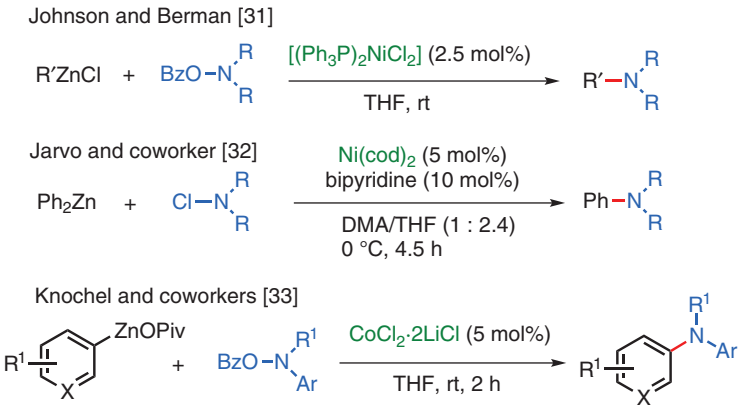
Although the current focus of TM-catalyzed electrophilic amination is copper catalysis, other transition metal complexes are also capable of serving as catalysts in these reactions.

Complexes of both Ni and Co can catalyze the electrophilic amination of organozinc reagents. The reaction mechanism is similar to the Cu-catalyzed reactions; that is, the N—O or N—Cl bond of the aminating reagent undergoes cleavage when the metal enters into it via oxidative addition. The Johnson [31], Jarvo [32], and Knochel [33] groups reported their findings in several publications (Scheme 1.22).

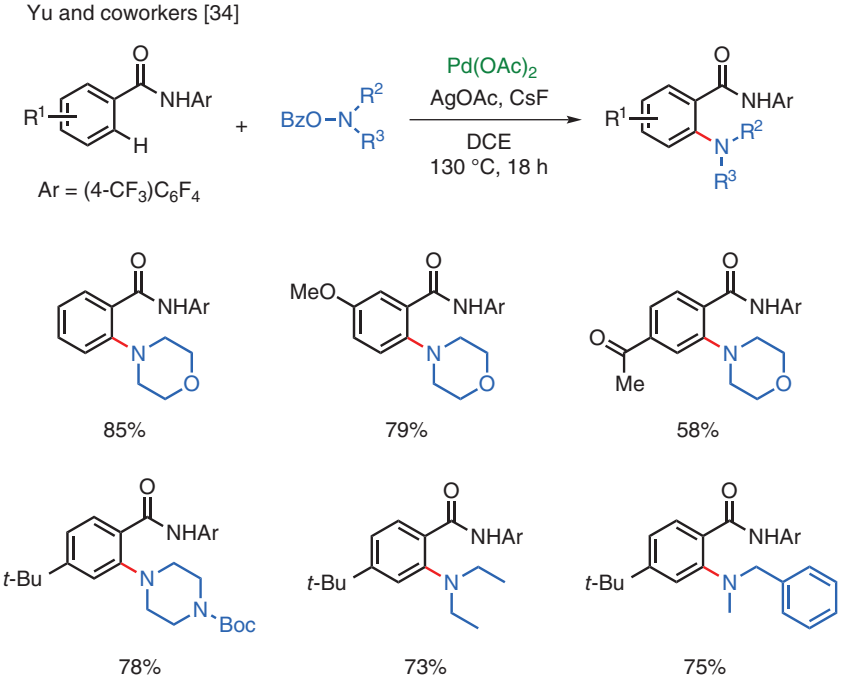
J.-Q. Yu and coworkers (The Scripps Research Institute) have successfully combined the Pd-catalyzed C–H activation and electrophilic amination. Both sp^2 (Scheme 1.23) and sp^3 (Scheme 1.24) C—H bonds can be aminated with this process. Mechanistically, these reactions proceed via a Pd(II)/Pd(IV) cycle: after the C–H activation, the resulting Pd(II) complex oxidatively inserts into the N—O bond of the aminating reagent, which is followed by a reductive elimination to form the new C—N bond. In some cases, it is necessary to add a Ag(I) salt as a sacrificial oxidant to help establish the catalytic cycle [34, 35].

The Yu group also demonstrated that rhodium and ruthenium complexes can also catalyze these types of reactions via similar mechanisms (Scheme 1.25) [36].

Apart from using a directing group in the C–H functionalization process, Catellani-type reactions can also achieve directed C–H activation without the use of amide-type directing



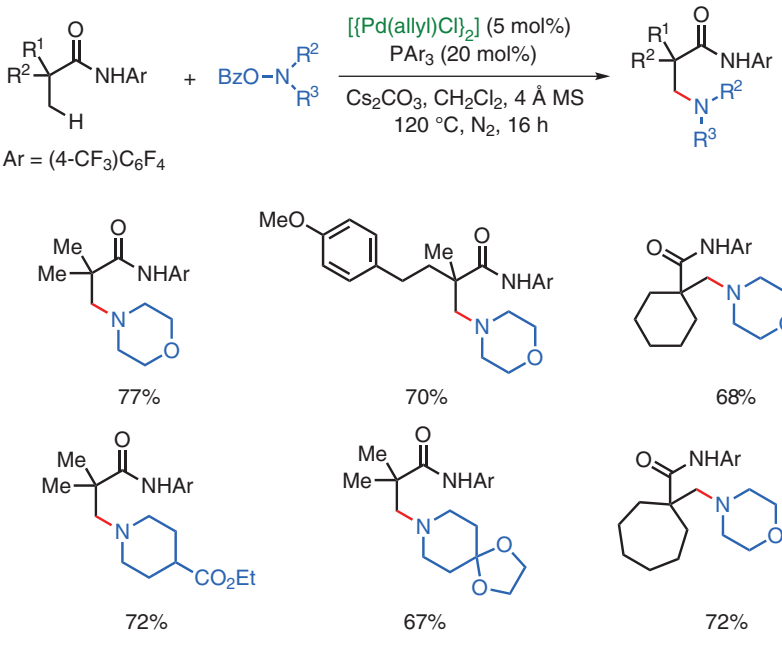
Scheme 1.22 Electrophilic amination catalyzed by other transition metals. Source: Johnson and Berman [31], Barker and Jarvo [32], and Lutter et al. [33].



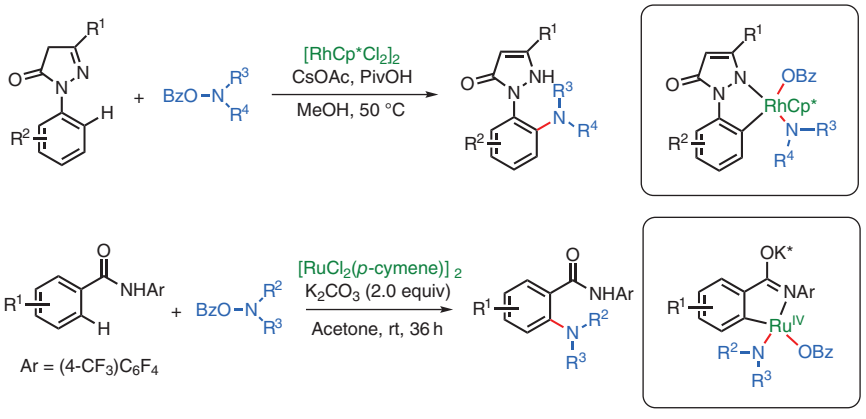
Scheme 1.23 Pd-catalyzed aromatic C–H amination via electrophilic amination. Source: Modified from Yoo et al. [34].

groups. Dong and coworkers applied this strategy in the development of Pd-catalyzed electrophilic amination reactions (Scheme 1.26) [37]. The main difference between this transformation and the standard Buchwald–Hartwig protocol is that the C–H group adjacent to the aryl halide moiety (i.e. the ortho position) gets aminated, while in the Buchwald–Hartwig reactions, the C—X bond itself gets aminated (i.e. the ipso position).

Yu and coworkers [35]



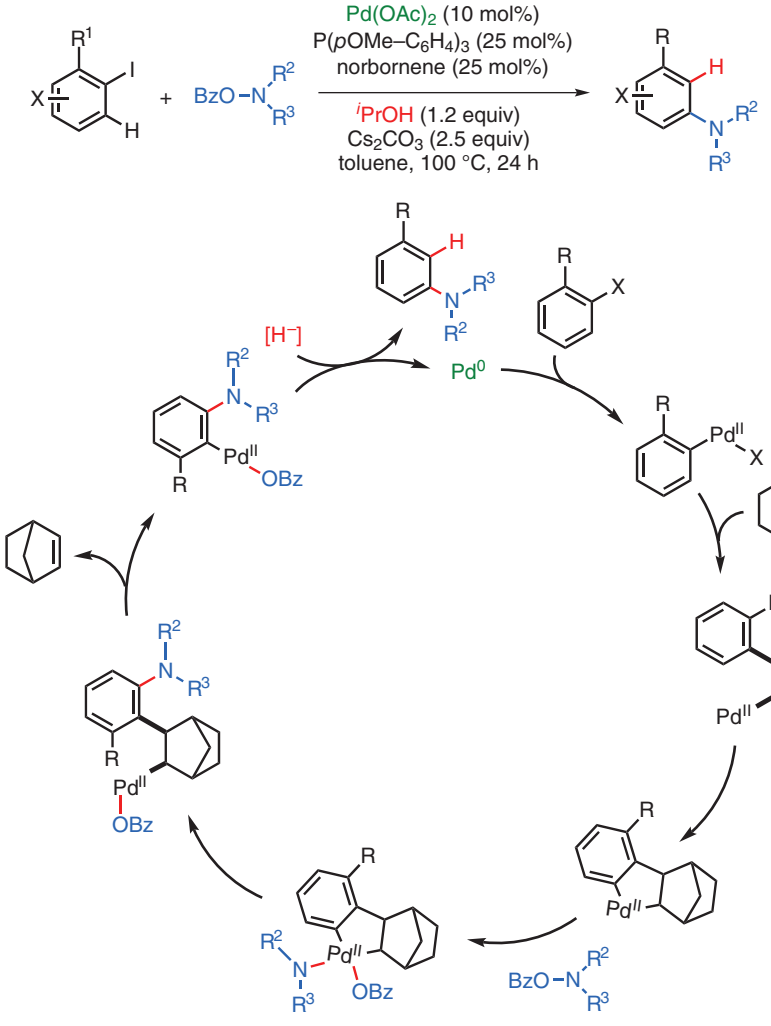
Scheme 1.24 Pd-catalyzed aliphatic C–H amination via electrophilic amination. Source: Modified from He et al. [35].



Scheme 1.25 Ru-catalyzed C–H amination. Source: Modified from Shang et al. [36].

A unique Fe-catalyzed reaction was reported by the Yang group in which styrenes undergo formal hydroamination to afford tertiary amines with Markovnikov regioselectivity [38]. In this case, an organoferrates initially formed from a Grignard reagent and the iron(II) catalyst. This organoferrate intermediate engages the styrene substrate to form a hydride complex, which hydrometallates the styrene double bond and subsequently undergoes electrophilic amination (Scheme 1.27).

Dong and Dong [37]



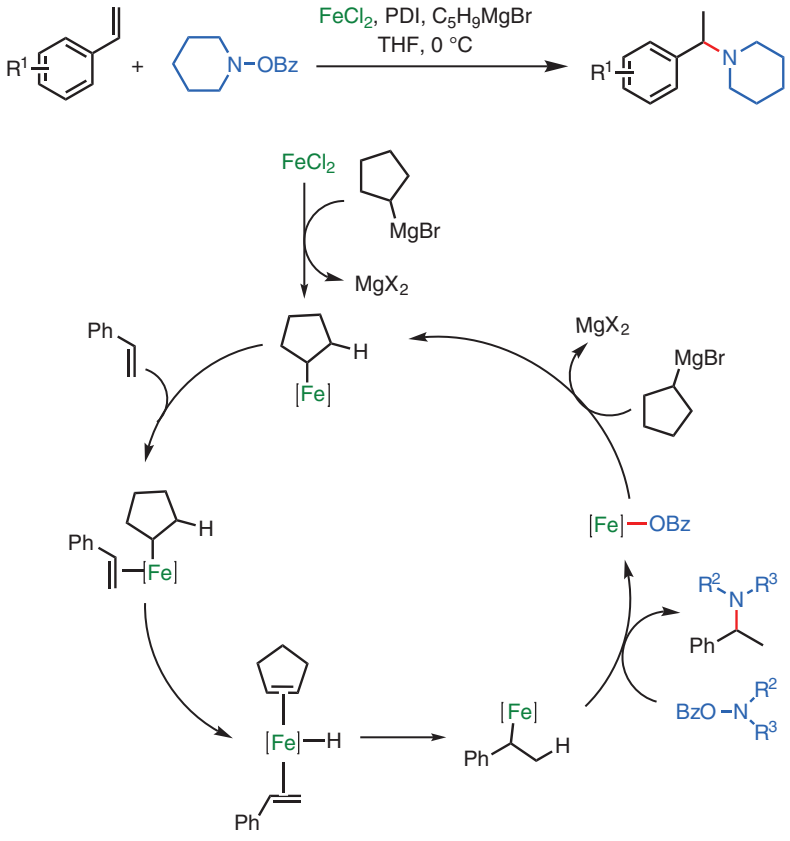
Scheme 1.26 Pd-catalyzed Catellani-type C–H electrophilic amination. Source: Modified from Dong and Dong et al. [37].

1.4 Electrophilic Amination with Hydroxylamine-derived Metallanitrenes

A nitrene is the nitrogen analog of a carbene, which is a six-electron electron-deficient species. Although it is formally uncharged and univalent, it can be considered to be an electrophile because of the unsatisfied octet. These highly reactive intermediates are involved in many chemical reactions, including electrophilic aminations [39–41].

Nitrene intermediates can be generated from various precursors. Pioneering studies by Khan and Kwart in the 1960s showed that elemental copper can catalyze the decomposition

Yang and coworkers [38]

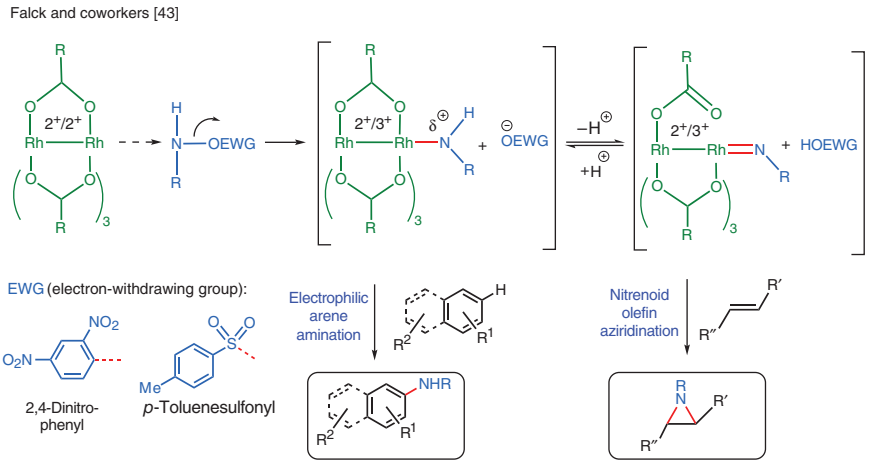


Scheme 1.27 Fe-catalyzed electrophilic amination of styrenes. Source: Modified from Huehls et al. [38].

of a sulfonyl azide, and the resulting reaction mixture can aminate cyclohexene and give aziridine as one of the products [42]. This result is consistent with the participation of metallanitrene intermediates. However, because of the instability and toxicity of organic azides, this procedure is not widely adapted by the organic chemistry community. In later years, (*N*-(sulfonyl)imino)phenyliodinane was found to be a suitable alternative nitrogen source. In addition to Cu, Mn and Fe are also capable of catalyzing the formation of metallanitrenes. These "tamed" nitrenes are more stable and have longer lifetimes, making them uniquely suitable for synthetic studies. However, the *N*-sulfonyl groups are hard to remove, limiting the usefulness of the resulting products.

Recently, studies have shown that hydroxylamines can also serve as the nitrogen sources for metallanitrenes. Using hydroxylamines, it is now possible to generate N–H and N–alkyl amine products without sulfonyl groups. This section focuses on reactions that involve hydroxylamine-derived metallanitrenes.

Metallanitrenes are generated from O-activated hydroxylamines, in which the nitrogen atom bears a strong leaving group and a transition metal catalyst. In 2014, Kürti, Falck,



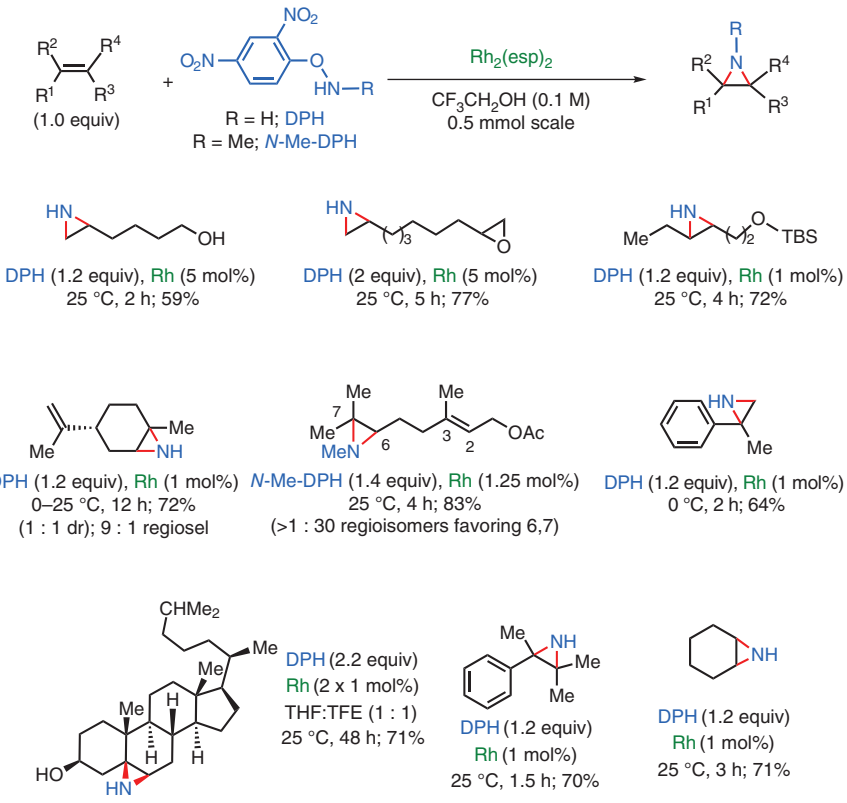
Scheme 1.28 Rh-catalyzed formation of metallanitrenes.

and coworkers developed an N–H aziridination procedure for unactivated olefins using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) as the nitrogen source and a dirhodium carboxylate catalyst. Computational studies conducted by the Ess group support the intermediacy of a Rh–nitrene pathway (Scheme 1.28) [43].

As the smallest nitrogen-containing heterocycles, aziridines are important synthetic building blocks for the synthesis of amines. Recently, it has been shown that natural product analogs containing aziridine functionalities can possess improved biological activities than their natural counterparts [44]. Despite their importance, the majority of literature has focused on the synthesis of aziridines bearing electron-withdrawing sulfonyl groups on the nitrogen atom (i.e. *N*-tosylaziridines). The stability of the sulfonyl group renders the deprotection and functionalization of these aziridines difficult. In comparison, unprotected N–H aziridines can be further functionalized with relative ease.

The transformation is operationally simple as neither the aminating reagent nor the catalyst is air- or moisture-sensitive. The functional group tolerance is excellent as hydroxyl groups, epoxides, and esters in the substrates are unaffected. The NH-aziridination is stereospecific and no scrambling of the olefin stereochemistry is observed even in sensitive styrene-type substrates. When more than one C—C double bond is present in the substrate, the more electron-rich one undergoes aziridination preferentially. The aziridination of terminal double bonds requires a slightly higher catalyst loading. The triple bond of alkynes and electron-deficient double bonds (i.e. α,β-unsaturated carbonyl compounds) remain unchanged under the reaction conditions. The choice of solvent is important because the presence of trifluoroethanol is required for aziridination.

The first iteration of this reaction uses the nitro group-containing DPH as the aminating reagent (Scheme 1.29). Because of its thermal instability, there were some concerns about its safety in industrial-scale settings. To address this issue, the Kürti group developed an improved version of this reaction in 2017 [45]. Instead of the nitro-containing DPH, the new version can proceed with the stable and inexpensive hydroxylamine-*O*-sulfonic acid (HOSA) (Scheme 1.30). Because HOSA is a zwitterionic compound, its solubility in

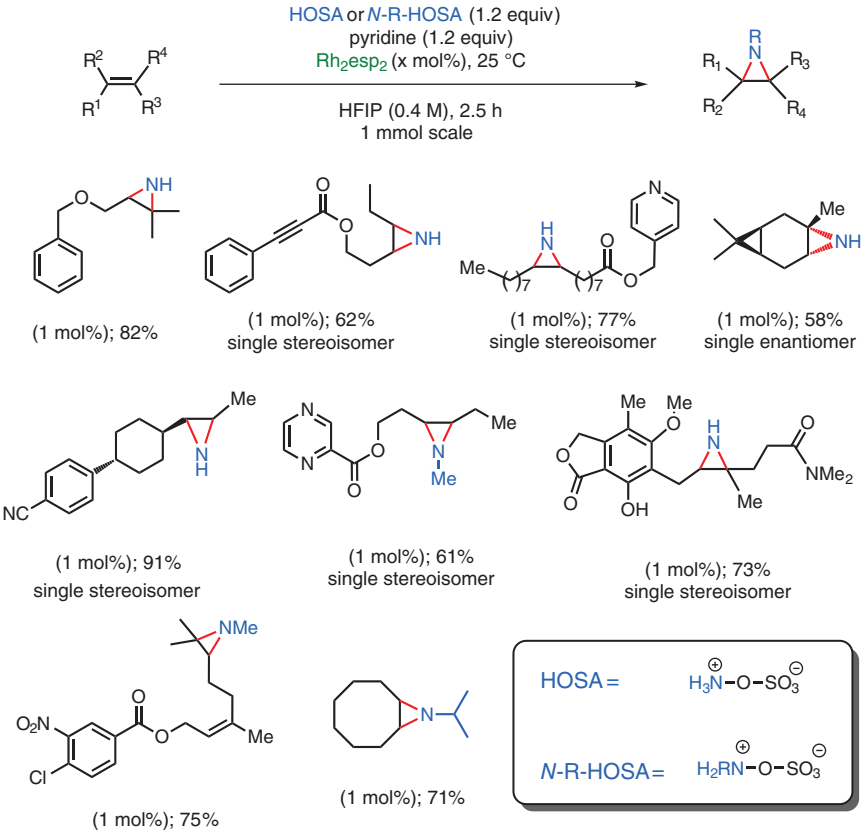


Scheme 1.29 Rh-catalyzed NH-aziridination of unactivated olefins using DPH.

common organic solvents is very low. However, through the addition of an equivalent of a mild base (i.e. pyridine), HOSA can be solubilized. Hexafluoroisopropanol (HFIP) was identified as the optimal solvent, and under these modified conditions, the olefin aziridination reaction can proceed at room temperature and with generally higher rates compared to the original DPH process. The scope of substrates is further expanded and now includes nitrogen heterocycles with basic nitrogen atoms. A further advantage is that the inorganic sulfate by-product is water-soluble and nontoxic, which greatly simplifies the purification.

Because *N*-alkyl HOSA derivatives can be readily prepared on multigram scale [46], it was demonstrated that *N*-Me as well as *N*-isopropyl units could be stereospecifically transferred to olefins, leading to the corresponding *N*-alkylaziridines.

Further studies on this catalytic system by the three groups showed that the Rh–nitrene intermediate can also facilitate the C–H amination of electron-rich aromatic rings (Scheme 1.31) [47]. In 2016, the Falck, Kürti, and Ess groups published the direct C–H amination of arenes. By using a more reactive aminating reagent and modifying the acidity of the reaction, Rh–nitrene intermediate can be directly inserted into the aromatic π-system of electron-rich arenes. Using this protocol, both inter- and intramolecular arene C–H amination can be achieved.



Scheme 1.30 Rh-catalyzed NH-aziridination of unactivated olefins using HOSA.

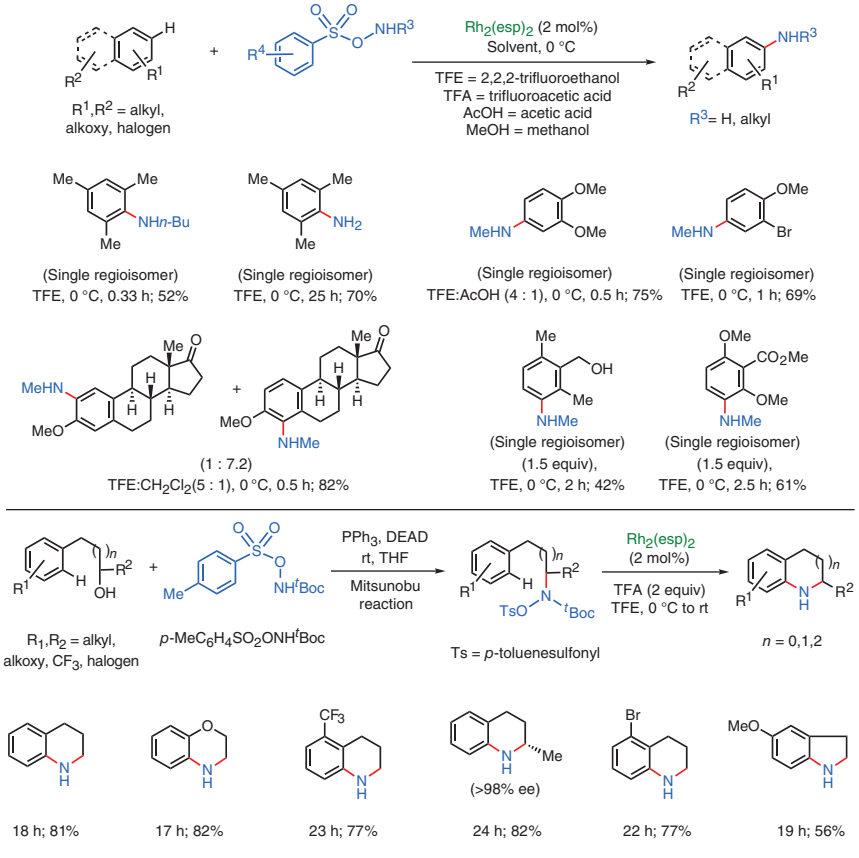
1.5 Transition-Metal-Free Electrophilic Amination Reactions

Although the mechanism of uncatalyzed electrophilic amination reactions seems straightforward, in practice, these uncatalyzed reactions often suffer from poor efficiency and low yields. A common issue with uncatalyzed electrophilic amination is the side reaction between the nucleophile and the highly reactive aminating reagent. It is especially difficult to directly synthesize primary or secondary amines under uncatalyzed conditions because the unmasked NH protons will usually quench the strongly basic nucleophiles used in the reactions (Scheme 1.32).

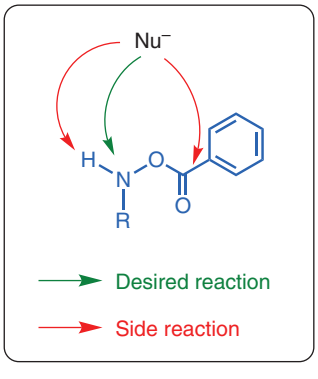
In recent years, several approaches have been developed to address these issues and finally achieve practical TM-free electrophilic aminations.

One approach is to use a mild nucleophile to avoid quenching and/or side reactions. In 2012, the Kürti group reported a TM-free primary amination of arylboronic acids (Scheme 1.33) [48].

This strategy exploits the fact that hydroxylamines can act as both electrophiles and nucleophiles. The nitrogen atom in the DPH aminating reagent first acts as a nucleophile to attack the boronic acid, and subsequently, it acts as an electrophile to accept an

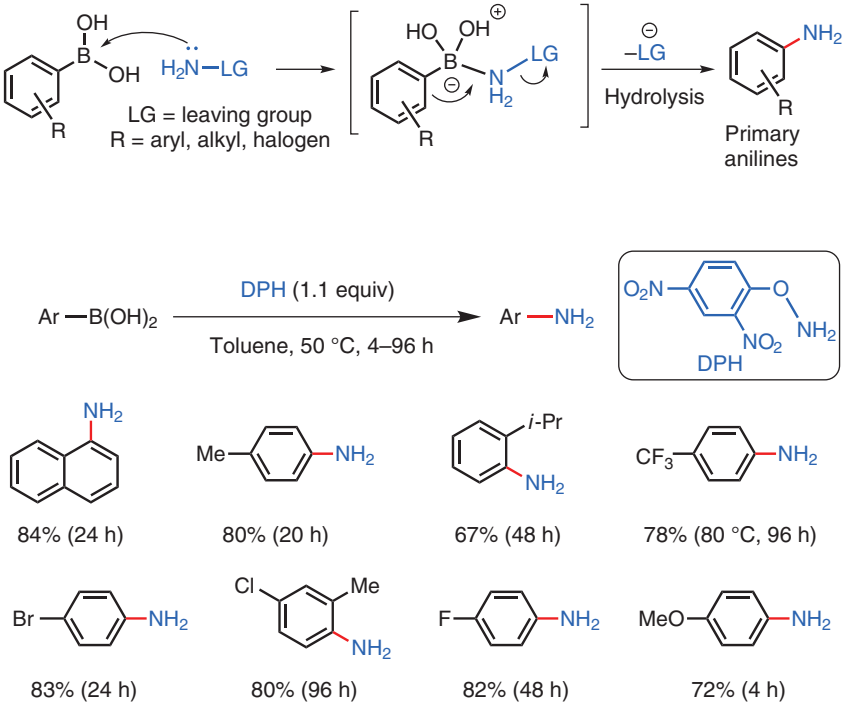


Scheme 1.31 Rh-catalyzed aromatic C–H amination. Source: Modified from Paudyal et al. [47].



Scheme 1.32 Problems with uncatalyzed electrophilic amination.

Kürti and coworkers [48]

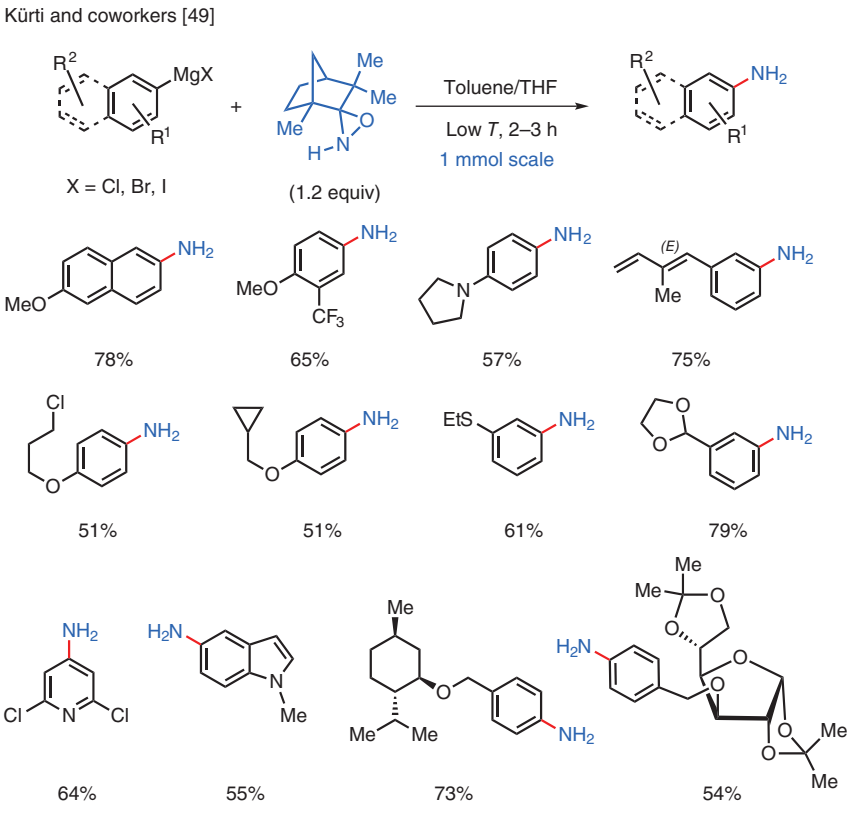


Scheme 1.33 TM-free electrophilic amination of arylboronic acids. Source: Modified from Zhu et al. [48].

intramolecular nucleophilic attack to furnish the aniline products. Before this method, the direct conversion of arylboronic acids to the corresponding primary arylamines under mild conditions was not possible. Now, even halogenated primary arylamines may be readily prepared under transition-metal-free conditions.

Another approach to achieve TM-free electrophilic amination while avoiding undesired quenching of the nucleophile is to modify the structure of the aminating reagent. In 2017, the Kürti group reported the use of sterically hindered oxaziridines to achieve the TM-free direct primary amination of aryl Grignard reagents and aryl lithiums (Scheme 1.34) [49]. Subsequent studies carried out in the Kürti group successfully expanded the substrate scope to include alkyl organometallic reagents [50].

The backbone of these aminating reagents can be readily recovered and reused for the preparation of more reagents (i.e. NH-oxazirdines). Remarkably, the N—H bond does not undergo deprotonation as this pathway is sterically inhibited (i.e. because of the kinetic decrease of the N—H bond acidity). It is intriguing that the *N*-alkyl derivatives of these oxaziridines transfer the oxygen atom to aryl and alkyl Grignard reagents at low temperatures with complete chemoselectivity (i.e. no N-transfer occurs with these reagents). Both the direct primary amination and hydroxylation of Grignard reagents are currently considered to be still extremely challenging, and they represent unmet synthetic needs. The camphor-derived *N*-benzyl oxaziridine is significantly less reactive and considerably more

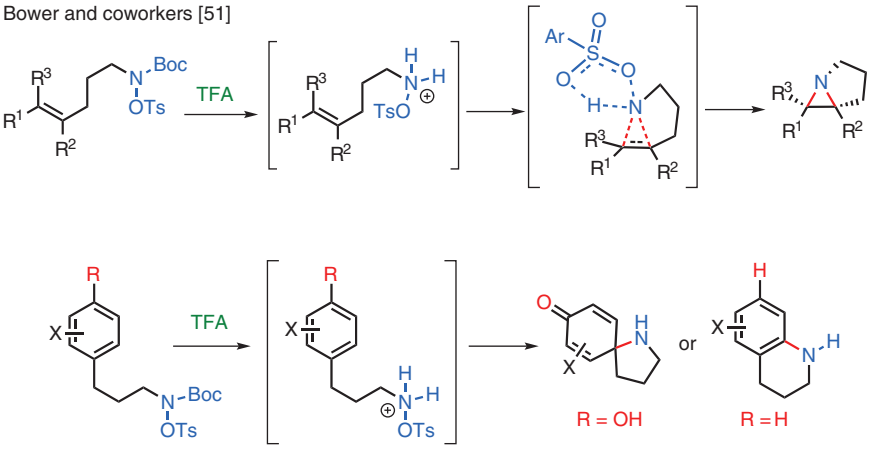


Scheme 1.34 TM-free electrophilic amination of arylmetals using NH-oxaziridines. Source: Modified from Gao et al. [49].

stable than Davis's oxaziridine; thus, it allows for highly chemoselective hydroxylations in the presence of multiple sensitive functionalities such as sulfides, amines, and alkenes.

For weaker nucleophiles such as olefins and arenes, successful TM-free electrophilic aminations rely on highly reactive aminating reagents. Pioneering works in this area by the Bower group have shown that it is possible to achieve TM-free intramolecular electrophilic amination using highly reactive sulfonyl hydroxylamines under acid catalysis (Scheme 1.35). The unprotected tosylhydroxylamines are too unstable to be isolated, so they are instead generated *in situ* from the Boc-protected precursors under acidic conditions. These reactions are proposed to proceed via the "Butterfly Mechanism" akin to the Prilezhaev reaction [51].

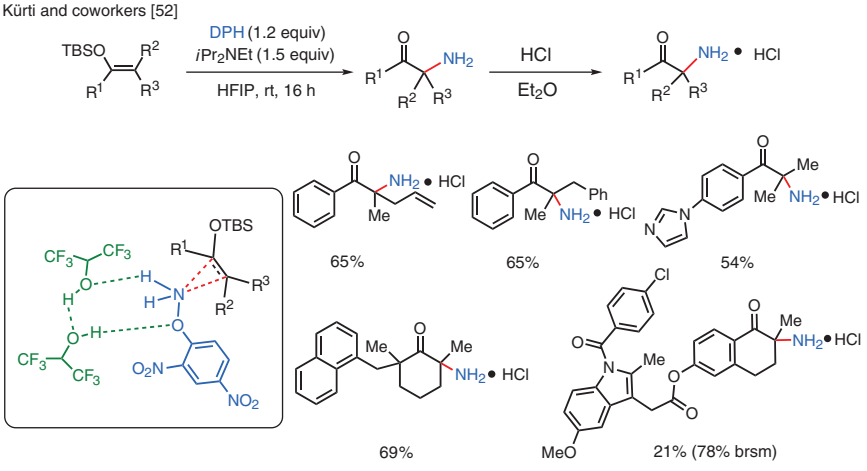
The α-aminoketone moiety is commonly found in biological molecules, natural products, and active pharmaceutical ingredients. Despite their apparent importance, synthetic access to these compounds is not always straightforward. This is especially evident when the desired amino ketones have a primary amino group attached to a fully substituted α-carbon atom. The most common strategy for synthesizing these compounds involves a two-step approach, in which either an azido, a nitro, or a hydroxylamino group is first installed at the α-position. A subsequent hydrogenation, usually catalyzed by a transition



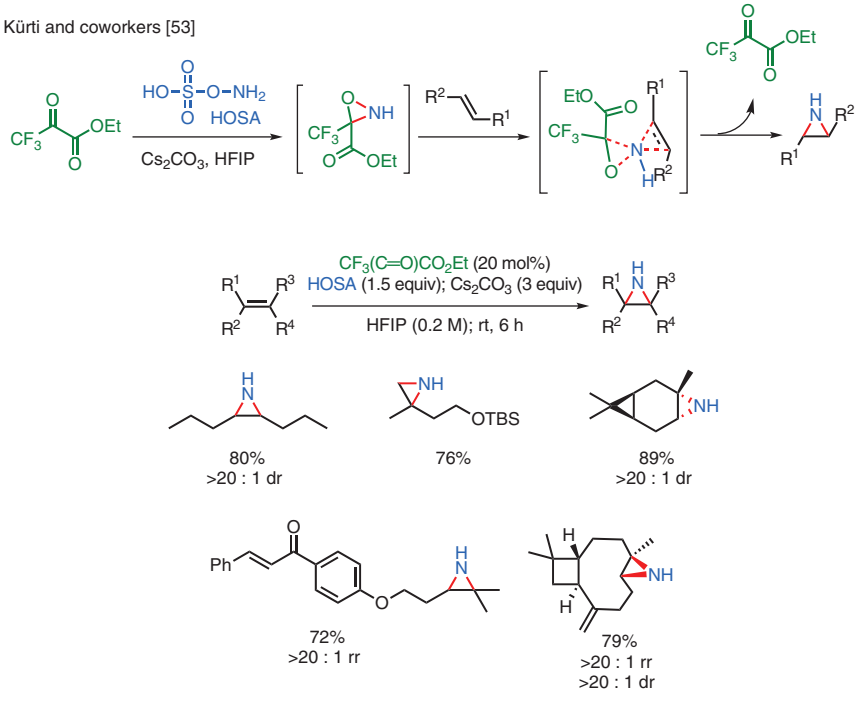
Scheme 1.35 TM-free Prilezhaev reaction. Source: Modified from Farndon et al. [51].

metal such as Pd, Pt, or Raney Ni, is then carried out to obtain the corresponding primary α-aminoketone. Aside from the added steps, this approach also has limitations such as the lack of chemoselectivity during the reduction and the potential instability of the azido- or nitro-intermediates.

In 2019, the Kürti group reported the intermolecular TM-free Aza-Rubottom reaction [52]. Electron-rich silyl enol ethers can be directly converted to the corresponding α-primary amino ketones in one step. This reaction also proceeds via the "Butterfly Mechanism," and the reactivity of the hydroxylamine aminating reagent is enhanced by cooperative hydrogen bonding interactions provided by the HFIP solvent molecules (Scheme 1.36).



Scheme 1.36 TM-free Rubottom oxidation.



Scheme 1.37 TM-free NH-aziridination of unactivated olefins. Source: Modified from Cheng et al. [53].

Two sets of conditions for the synthesis of primary α-aminoketones from silyl enol ethers were developed. Electron-rich substrates can be α-aminated without transition metal catalysis, while substrates bearing electron-withdrawing substituents can undergo α-amination with the help of Rh or Cu catalysts.

Further studies in the Kürti group have shown that it is possible to achieve TM-free NH-aziridination of unactivated olefins with highly reactive NH-oxaziridines via the "Butterfly Mechanism" [53]. These unique NH-oxaziridines bear one or more strongly electron-withdrawing group(s), which greatly enhance the electrophilicity of the nitrogen atom. With the further enhancement provided via the hydrogen bonding interactions by the HFIP solvent molecules, these highly reactive intermediates are capable of TM-free transfer of the NH onto the unactivated olefins (Scheme 1.37).

However, because of their high reactivities, these highly electron-deficient NH-oxaziridines cannot be isolated. The Kürti group solved this issue by forming these intermediates *in situ* from HOSA and ketones bearing electron-withdrawing groups. Mass spectrometric studies confirmed the existence of the highly reactive oxaziridine intermediates.

By using a chiral nonracemic ketone as the organocatalyst, the reaction can give enantiomerically enriched products.

1.6 Conclusion

In the past two decades, a number of C—N bond-forming reactions have been developed that take advantage of hydroxylamine-based electrophilic aminating agents as sources of nitrogen. A great deal of structural diversity has been achieved in terms of the products. Olefins, substituted aromatic systems, as well as organometallic compounds have been successfully aminated. Although the vast majority of reported methods utilize transition metal complexes as catalysts, metal-free and even organocatalytic methods have also emerged during the past decade. The two emerging trends are to incorporate unprotected amino groups directly and to use inexpensive and nontoxic transition metal catalysts such as iron complexes. We are confident that during the next decade, we will see further innovation in electrophilic amination chemistries.

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