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Emerging Developments Using Nitrogen−Heteroatom Bonds as Amination Reagents in the Synthesis of Aminoarenes

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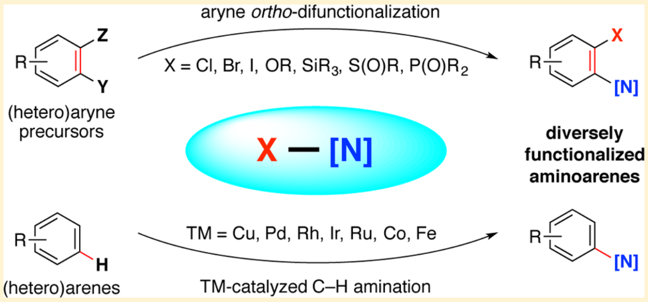
ABSTRACT: Aminoarenes constitute valuable building blocks in organic synthesis and an essential skeleton ubiquitously found in ligands, agrochemicals, and pharmaceuticals. This Synopsis presents recent amination methods using nitrogen−heteroatom bonds as a powerful and versatile platform to rapidly synthesize diverse aminoarenes, with a focus on aryne amino functionalization and transition-metal-catalyzed arene C−H amination.

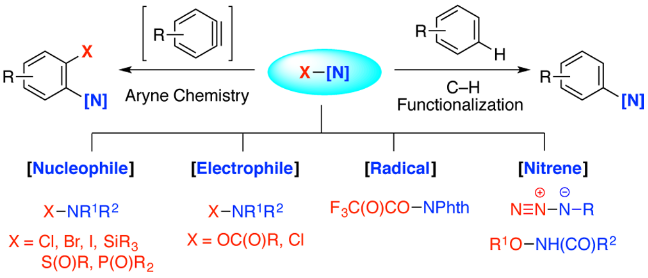


INTRODUCTION

Aminoarenes are prominent features in functionally important molecules such as ligands,[1] agrochemicals,[2] and pharmaceuticals.[3] Synthesis of aminoarenes, traditionally relying on nitroarene reduction and S_NAr amination methods, has received great advancement in the past two decades, largely through transition-metal-catalyzed cross coupling reactions of amine nucleophiles (N−H) with prefunctionalized arene electrophiles (Buchwald−Hartwig reaction[4]) or nucleophiles (Chan−Lam reaction[5]). Recently, nitrogen−heteroatom (N−X) bonds have emerged as versatile precursors for the synthesis of aminoarenes via new amination strategies that are complementary to classic methods. These recent developments employing N−X bonds provide valuable access to complex aminoarene scaffolds and to unexplored chemical space and structural diversity, presenting a promising impact on medicinal chemistry.[6]

Innovation in this field builds upon the versatile reactivity of N−X bonds, serving as nitrogen nucleophiles, radicals, electrophiles, or nitrene equivalents (Scheme 1). Though diverse reactive modes of these reagents have been recognized for over a century in C−N bond formation reactions,[7] N−X bonds were not extensively studied as a platform for the synthesis of aminoarenes until recently. For example, the Johnson group reported the pioneering copper-catalyzed cross coupling of arylzinc nucleophiles using *O*-benzoylhydroxylamines for aryl amination in 2004.[8] Since then, diverse N−X bonds have been exploited to design novel approaches to complex aminoarenes by harnessing the different modes of nitrogen reactivity. These efforts aspire to advance N−X bond-mediated amination beyond the reach of traditional methods, allowing access to more diverse and complex aminoarene scaffolds, especially those that were difficult to achieve previously. This Synopsis will focus on these recent developments employing N−X bonds to construct functionalized aminoarenes using aryne chemistry and C−H functionalization (Scheme 1).

Scheme 1. Diverse Reactive Modes of Nitrogen−Heteroatom Bonds in Arene Amination



INSERTION OF NITROGEN−HETEROATOM BONDS BY ARYNES FOR THE RAPID SYNTHESIS OF *ORTHO*-AMINO-FUNCTIONALIZED ARENES

Arynes are not only a feature of classic organic chemistry but also greatly valued for their synthetic utility as reactive intermediates.[9] The strained electrophilic π-bond enables simultaneous functionalization of two adjacent carbon atoms to construct diverse and complex aryl derivatives with myriad reaction partners. Advancement in aryne chemistry has been accelerated by the available approaches to generate this class of highly reactive intermediates, most successfully by fluoride-mediated elimination of commercially available and readily synthesized *o*-trimethylsilyl aryltriflates.[10] In particular, this mild aryne formation platform has facilitated the development of new transformations between arynes and sensitive reaction partners, such as nitrogen−heteroatom bonds, as a novel and effective strategy for the synthesis of aminoarenes.

Nitrogen−halide bonds, such as chloro-, bromo-, and iodoamines, have been investigated for direct difunctionaliza-

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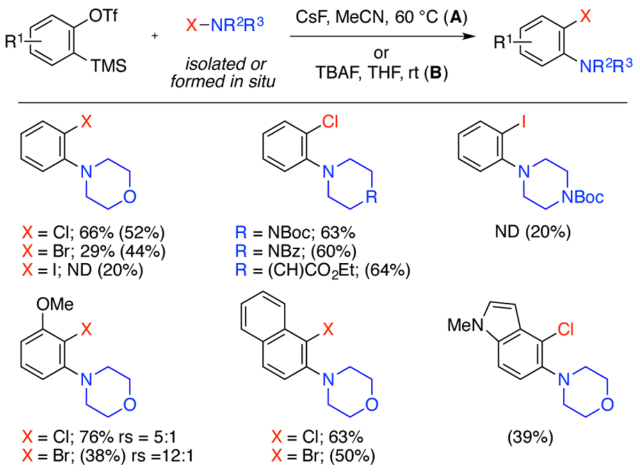
tion of arynes, successfully affording *o*-haloaminoarenes in a single step (Scheme 2).[11] In this study, two complementary protocols for the in situ formation of arynes were established by treating *o*-trimethylsilyl aryltriflates with either cesium fluoride (CsF) at elevated temperatures or tetrabutylammonium fluoride (TBAF) at room temperature. Notably, the formation of *N*-haloamines could be performed in situ by initial treatment of amines with *N*-halosuccinimides, enabling the participation of otherwise unstable *N*-halide bonds such as *N*-iodoamines in this transformation. Generally, the reactions with electron-deficient *N*-chloramines were more efficient using CsF at elevated temperatures, whereas electron-rich and more reactive substrates, such as *N*-chloropiperidines, *N*-bromoamines, and *N*-iodoamines, performed better with more soluble TBAF at room temperature. The insertion of arynes into the N−X bond is chemoselective in the presence of carbamates, amides, and esters. The reactions also demonstrated a high level of regioselectivity with 3-methoxybenzyne, 1,2-naphthylyne, and even 4,5-indolyne. The observed regioselectivity provides mechanistic insight by means of aryne distortion theory,[12] with the nitrogen of the N−X bond retaining nucleophilic character rather than participating as an *umpolung* nitrogen equivalent. A mechanistically similar insertion of *N*-silylamines has been reported[13] and revisited recently.[14]

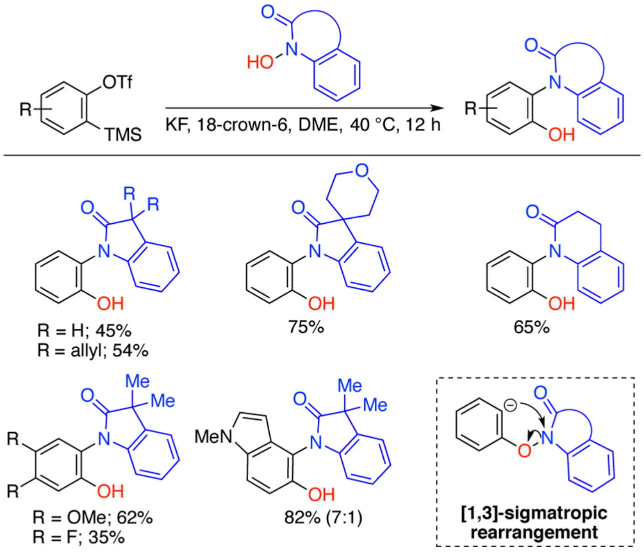
Scheme 2. Aryne Insertion into N−Cl, N−Br, and N−I Bonds[a]



[a] Isolation yields shown from method A (method B), respectively. ND = not detected. rs = regioselectivity. Major isomer shown.

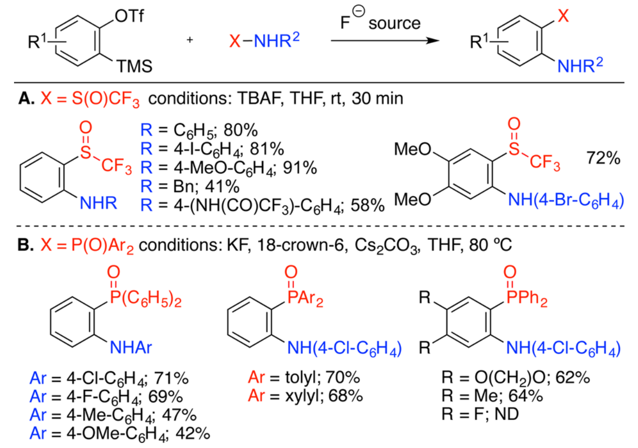
Interestingly, in an analogous formation of *o*-hydroxyamidoarenes, hydroxyindolinones and -quinolinones display umpolung nitrogen reactivity in the formal N−O insertion reaction with arynes and heteroarynes (Scheme 3).[15] The hydroxyamidation reaction of *o*-trimethylsilyl aryltriflates was achieved in the presence of potassium fluoride (KF) and 18-crown-6 on variously substituted hydroxyindolinones and hydroxyquinolinones, with higher efficacy on electron-rich aryne substrates. Good regioselectivity was also observed in the reaction of 4,5-indolyne with 4-amido-5-hydroxyindole as the major product. The influence of electronics and regioselectivity can be explained by the proposed mechanism that involves initial nucleophilic *O*-arylation followed by a selective [1,3]-sigmatropic rearrangement of the resultant *o*-hydroxylamine aryl carbanion.

Scheme 3. Formal Aryne Insertion into the N−O Bond of Hydroxyindolinones



Aryne insertion into nitrogen−sulfur bonds has also been achieved (Scheme 4A).[16] Reactions with different secondary aryl trifluoromethylsulfinamides occurred in good to excellent yields. Both electron-withdrawing aryl halides and electron-donating aryl ether functionalities were well tolerated. Selective sulfinamide insertion was observed in the presence of a trifluoromethyl amide. Benzyne insertion into *N*-benzylsulfonamide was reported as an example of an *N*-alkyltrifluoromethylsulfonamide substrate, yet in a much lower 41% yield. Mechanistically, this transformation is presumed to be initiated by nucleophilic addition of the nitrogen followed by anionic aza-thia-Fries rearrangement to release the aniline functionality, analogous to *α*-carbonyl insertion with amides or enolates.[17] Note that sulfilimines are also known to undergo aryne aminothiolation with nitrogen as the nucleophile.[18]

Scheme 4. Aryne Insertion into N−S and N−P Bonds



Similar aryne insertion into the N−P bond of *N*-arylphosphoryl amides has been studied, providing aminophosphinylation products in moderate to good yields (Scheme 4B).[19] Substituents on the nitrogen were highly influential, with electron-withdrawing *N*-aryl groups providing substantially higher yields, while varied methyl substitutions of the aryl group on the phosphine oxide group had minimal effects.

Among the different arynes examined, electron-deficient substrates failed to afford the desired product, possibly due to side reactions resulting from their increased reactivity. The reaction is proposed to proceed through nucleophilic nitrogen addition, as implied by the need for cesium carbonate as a base, followed by aryl phosphorylation of the resultant aryl carbanion. Electron-deficient *N*-aryl groups potentially facilitate the phosphorylation step by further stabilizing the anionic aniline product.

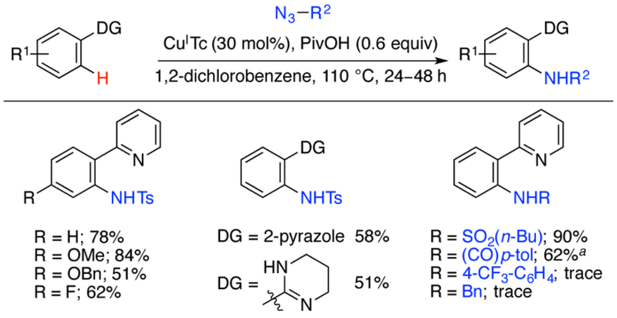
As demonstrated in the vicinal amino functionalization reactions above with N−halide, N−O, N−S, and N−P bonds, aryne insertions with N−X bonds enable the preparation of *ortho*-functionalized aminoarenes in a single transformation. Expediting access to diverse aryne precursors, such as complex *o*-trimethylsilyl aryltriflate motifs, will provide a gateway to solving the synthetic challenges in the application of aryne intermediates. Meanwhile, expanding this approach to harness the reactivity of a wider range of N−X bonds will broaden this strategy toward the synthesis of more complex and diverse aminoarene scaffolds.

■ TRANSITION-METAL-CATALYZED ARENE C−H AMINATION USING NITROGEN−HETEROATOM BONDS

Nitrogen−heteroatom bonds have been exploited in aminoarene synthesis by coupling reactions with various organometallic species. Since the original work on copper-catalyzed amination reaction of arylzinc intermediates,[8] electrophilic amination using hydroxylamine derivatives has been extended to other organometallic nucleophiles, such as lithium,[20] magnesium,[21] aluminum,[22] boron,[23] silicon,[24] and tin[23a] reagents. *N*-Chloramines have also been used in copper-,[25] nickel-,[26] or palladium-catalyzed[27] electrophilic aminations. Even in the absence of a catalyst, the amination of arylzinc and Grignard reagents was also realized with suitable additives.[28] In comparison to traditional amination reactions between organometallic species and nucleophilic amines under oxidative conditions, methods using nitrogen−heteroatom bonds eliminate the need for an exogenous oxidant. This approach avoids problematic side reactions, such as undesired homocoupling,[5] as detailed in recent reviews.[29] Herein, this synopsis will highlight emerging developments using *N*-heteroatom bonds as electrophilic nitrogen equivalents in recent syntheses of aminoarenes, with a focus on transition-metal-catalyzed C−H amination and *o*-amino functionalization of arenes.

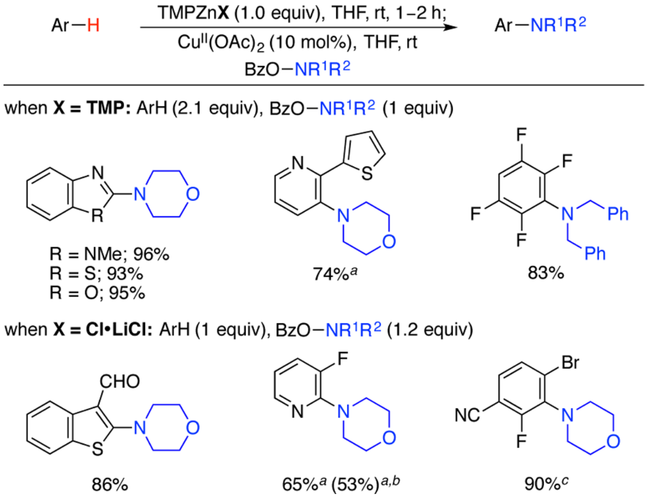
Copper-catalyzed *ortho*-sulfonamidation of aromatic C−H bonds has been achieved in the presence of a strong directing group using tosyl azide electrophiles (Scheme 5).[30] For example, different 2-pyridylarenes all provided *ortho*-sulfonamidated arenes smoothly. Cyclic amidine and pyrazole were also effective, but less efficient, directing groups in promoting the *ortho*-sulfonamidation. Alkylsulfonyl azides were excellent precursors for alkylsulfonamide products, and acyl azides were compatible as amide precursors despite requiring a stoichiometric amount of copper catalyst. Aryl and alkyl azides were not effective, however, providing only trace amounts of aniline products. The mechanism is proposed to proceed via a reactive Cu(III) species, generated by oxidative addition to the acid-activated sulfonyl azide with concomitant release of nitrogen gas. This reactive intermediate would promote the challenging *ortho*-directed deprotonative aryl cupration, followed by sulfonamidation.

Scheme 5. *Ortho*-Amidation of Arenes with Tosyl Azides



[a] 1.0 equiv of CuTc used. Tc = thiophene-2-carboxylate

Scheme 6. Copper-Catalyzed Amination of Arenes and Heteroarenes with *O*-Benzoylhydroxylamines via H−Zn Exchange

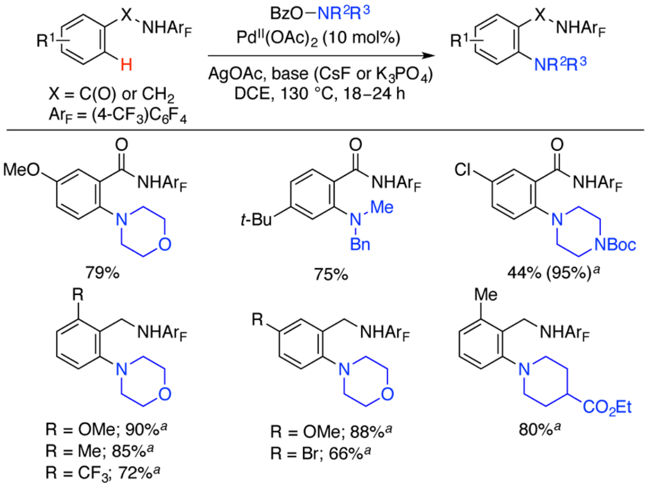


[a] Amination run at 50 °C. [b] Yield on 50 mmol scale. [c] Zincation step at 65 °C. TMP = 2,2,6,6-tetramethylpiperidide.

In 2014, a more general copper-catalyzed arene amination was achieved via an alternative C−H zincation with subsequent electrophilic amination of *O*-benzoylhydroxylamines under mild conditions (Scheme 6).[31] A variety of azoles readily underwent net C−H amination, including difficult substrates for previous amination protocols, such as *N*-alkylbenzimidazoles.[32] Similarly, activated pyridines and arenes were aminated in generally good yields although elevated temperatures were required in some cases. Functional group tolerance was found to be excellent, with aldehydes, aryl bromides, and nitriles left untouched. Furthermore, this reaction was demonstrated to be reliable even on a multigram scale without loss of efficiency.[31b] In this transformation, stoichiometric formation of either diarylzinc or arylzinc chloride nucleophiles—by direct zincation of arenes in situ with strong, non-nucleophilic bases[33] Zn(TMP)$_2$ or (TMP)ZnCl·LiCl, respectively—circumvents the stringent directing group requirements in previous *ortho*-directed aminations. In 2016, a related arene amination reaction for the preparation of primary anilines was reported using the zincate base Zn(*t*-Bu)$_2$(TMP)Li to achieve C−H zincation step followed by copper-catalyzed amination using *O*-benzylhydroxylamine as an NH$_2$ synthon.[34] Though the mechanism remains to be elucidated, it is proposed that upon transmetalation with organozinc intermediates the resulting arylcopper species mediates coupling with the amine electrophile.

Palladium-catalyzed *ortho*-directed C−H amination of arenes has been also studied with *O*-benzoyldialkylhydroxylamine electrophiles (Scheme 7).[35] Critical to this system is the use of *N*-perfluoroaryl benzamide and benzylamine as effective and readily cleavable directing groups for C−H palladation. The use of an electron-rich pyridyl ligand was found to be advantageous for electron-deficient *N*-perfluoroaryl benzamides and benzylamines. The selectivity of monoamination was remarkably high and generally occurs at the more sterically accessible position. Diverse amine electrophiles could be employed, including cyclic and acyclic precursors bearing functional groups such as esters and carbamates. The amination reaction is suggested to proceed via a Pd(II)/Pd(IV) two-electron mechanism by *ortho*-directed carbopalladation of the Pd(II) catalyst, oxidative addition into the weak N−O bond resulting in a Pd(IV) species, and finally reductive elimination. The involvement of a high-valent Pd(IV) intermediate species is supported by recent computational efforts.[36]

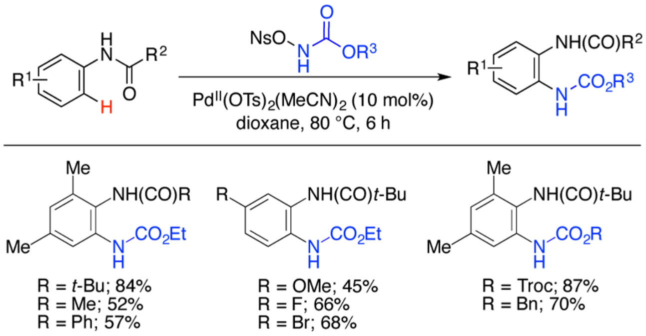
Scheme 7. Palladium-Catalyzed Arene *Ortho*-Amination with *O*-Benzoylhydroxylamines



[a] 2,4,6-Trimethoxypyridine used as a ligand.

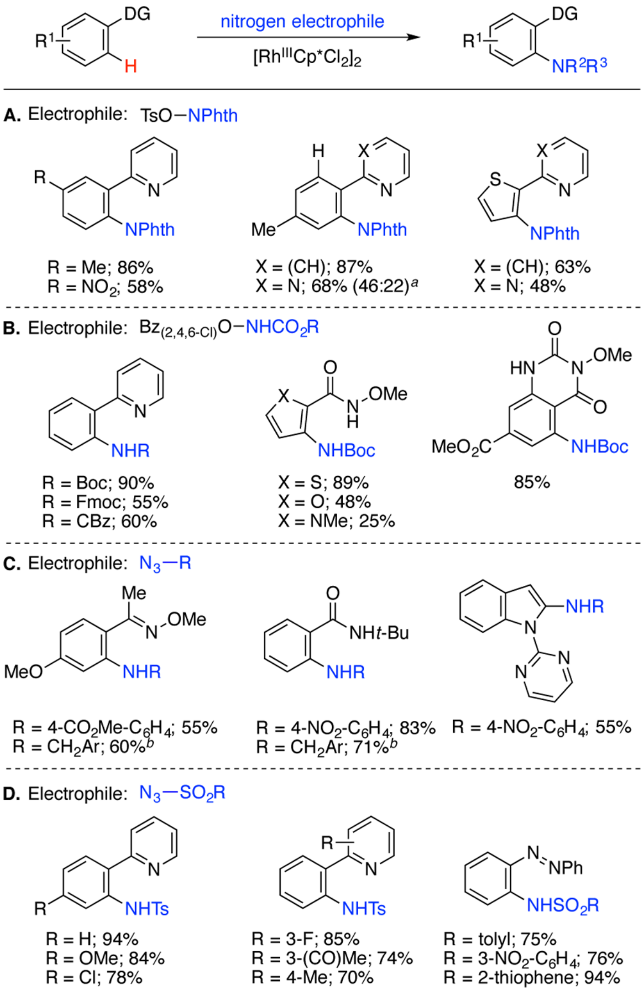
Besides the synthesis of *o*-carbonyl aminoarenes, palladium-catalyzed *ortho*-amidation was achieved with isomeric anilides as directing groups using *O*-nosylhydroxamic acids (Scheme 8).[37] The *O*-nosyl group of the carbamate electrophiles was important in this reaction as the competitive amide complexation of the palladium catalyst often presents a challenge in amidation reactions.[38] Among different anilide directing groups, sterically hindered *N*-pivaloylamide proved to be most efficient, although less hindered primary and secondary anilides could also be employed with slightly reduced efficiency. The reaction exhibited good regioselectivity for the more sterically accessible *ortho*-position and favored electron-deficient arene substrates. The protocol is modular for the formation of secondary carbamates, including generation of Troc- and benzyl-protected products. The mechanism is proposed to involve C−H palladation and subsequent coordination of the secondary hydroxamic acid electrophile prior to elimination of the *O*-nosyl leaving group, forming a palladium nitrene species suitable for C−N bond formation.

Scheme 8. Palladium-Catalyzed Arene *Ortho*-Amidation Using *O*-Sulfonylhydroxymates



Exceptionally active in *ortho*-directed C−H amination, rhodium catalysts have been investigated extensively with various nitrogen electrophiles. Direct imidation of arenes and heteroarenes was achieved using *O*-tosylhydroxyphthalimide (Scheme 9A).[39] The 2-pyridyl directing group provided superior yields and chemoselectivity, yielding monofunctionalized arylimides regioselectively. Other heteroarenes, such as pyrimidine and thiophene, as well as sensitive nitro groups

Scheme 9. Rhodium(III)-Catalyzed *Ortho*-Amination of Arenes Using Various Nitrogen Electrophiles

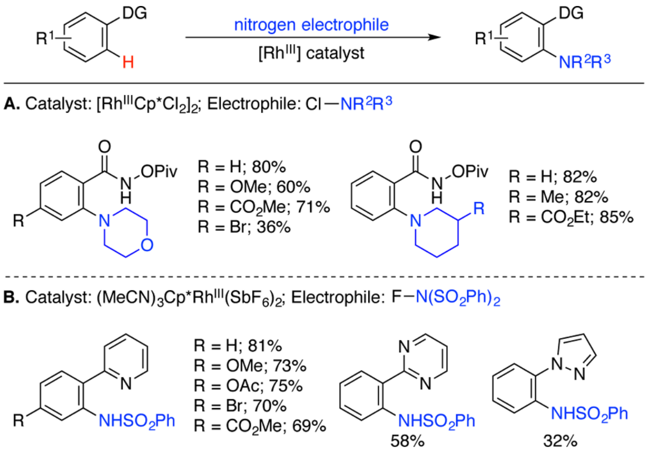


[a] Ratio of mono-/diamination. [b] Ar = 3,5-$(CF_3)C_6H_3$.

could also participate in this *ortho*-directed reaction. Using *O*-trichlorobenzoylhydroxycarbamates, the formation of aryl and heteroaryl primary carbamates was also reported with pyridine or *O*-methylhydroxyamide as a directing group (Scheme 9B).[40] While Boc-carbamoyl electrophiles were most efficient, Fmoc and Cbz groups were also viable. Heteroarenes, including thiophene, furan, and pyrroles, were also demonstrated as substrates with *O*-methylhydroxyamide directing groups. Alkyl and electron-deficient aryl azides were also viable nitrogen electrophiles toward the formation of anilines and *N*,*N*-biarylanilines (Scheme 9C).[41] The reactions were effective for arene substrates bearing aryl ethers, nitro groups, and even indoles for a range of directing groups such as oximes, amides, and pyrimidines. Similarly, sulfonyl azides have been utilized to generate *N*-arylsulfonamides with pyridyl and diazo-directing groups (Scheme 9D).[42] Arene electronics had a moderate influence on reaction efficiency, with both electron-donating groups (e.g., methoxy) and electron-withdrawing substituents (e.g., chloride) resulting in slightly lower yields. Substitution on the 2-pyridyl directing group was tolerated, including a potentially sensitive ketone group. Finally, with diazoanilines as a directing group, different arylsulfonyl azides were employed as electrophiles, allowing the introduction of nitrobenzene- or even heteroaryl thiophenesulfonamides. It is worth noting that similarly electron-deficient carbamoyl azides were also recently employed in rhodium-catalyzed C−H amidation of arenes and some heteroarenes.[43] Pyridyl and oxazoline directing groups permitted installation of Boc-protected anilines from C−H bonds in a single step.

Rhodium-catalyzed *ortho*-directed amination of arenes has also been reported using dialkyl-*N*-chloramine electrophiles (Scheme 10A).[44] With *O*-pivaloyl-protected hydroxamic acids as the directing group, this system gives monoamination at the *ortho*-position with high chemo- and regioselectivity at room temperature. Electronics significantly influenced reaction efficiency, with electron-donating aryl ethers and electron-withdrawing esters giving slightly lower yields. Surprisingly, aryl bromides were poorly tolerated under these conditions. The reaction favors cyclic amine substrates, such as morpholine, *N*-Boc-piperazine, and piperidines, including 3-methyl and 3-ethylcarboxylatopiperidines.

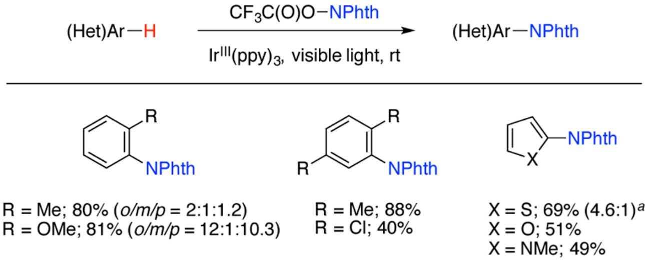
Scheme 10. Rhodium(III)-Catalyzed Arene *Ortho*-Amination Using *N*-Haloamines



Even the *N*-fluoride bond of *N*-fluorobenzenesulfonamide (NFSI) has been described as an electrophilic nitrogen precursor in the rhodium-catalyzed arene *ortho*-sulfonamidation (Scheme 10B).[45] Note that this reaction installs a *secondary* benzenesulfonamide. Moderate to good yields were obtained on various arenes with pyridine, pyrimidine or pyrazole serving as a directing groups, albeit with reduced efficiency in the latter cases.

Rhodium-catalyzed C−H amination reactions using N−X bonds provide direct access to a broad range of aminoarene products, yet commonly require the presence of an effective directing group on the arenes. Conversely, iridium-catalyzed C−H aminations are characterized by their generality to a broad scope of arenes. For example, a wide range of simple arenes and heteroarenes underwent iridium-catalyzed radical imidation using *O*-trifluoroacetylhydroxyphthalimide as an aminyl radical precursor (Scheme 11).[46] Under mild photocatalytic conditions with visible light, direct amination of various arenes was obtained in moderate to good yields. Electronics of the arenes influenced the efficiency and the regioselective outcome of this transformation. Simple toluene gave a mild preference toward the *ortho*- and *para*-positions, and more electron-rich anisole resulted in improved regioselectivity. Heteroarenes, such as thiophene, furan, and pyrrole, were also amenable to these conditions, affording 2-amidated products as major isomers. So far, this photocatalytic radical amination is limited to *O*-trifluoroacetylhydroxyphthalimide electrophiles; thus, the construction of more diverse aminoarenes remains a challenge for light-driven amination reactions.

Scheme 11. Iridium-Catalyzed Arene Amidation via Photoactivation of *O*-Trifluoroacetylhydroxyphthalimide

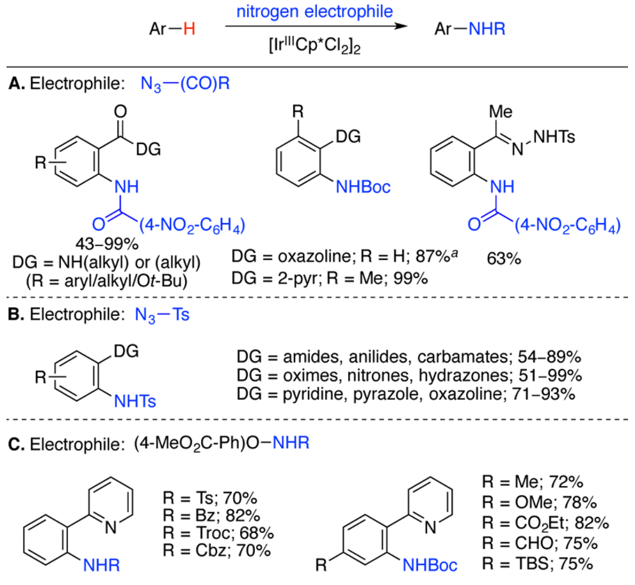


[a]Ratio of 2-and 3-amidation products. ppy = 2-phenylpyridinate.

Iridium-catalyzed arene *ortho*-amidation has also been achieved using azido- and hydroxylamine-derived electrophiles with a range of simple directing groups such as ketones, amides, anilides, carbamates, nitrones, pyridine, hydrazones, heteroaryls, and oxazolines (Scheme 12). For example, the low thermal barrier for iridium-catalyzed C−H activation allows for the use of carbamoyl azides and even relatively unstable acyl azides (Scheme 12A).[47] Tosyl azide was also used for the formation of aryl sulfonamide products (Scheme 12B).[48] Alternatively, the use of *O*-arylhydroxylamine electrophiles provided direct access to sulfonamides, amides, and carbamates with pyridine directing groups (Scheme 12C).[49] This reaction tolerated both electron-rich and electron-deficient arenes, with sensitive functionalities such as silyl and formyl groups untouched. Complemented by directing group generality and broad arene scope, iridium-catalyzed amination reactions will lead to even greater utility upon its expansion to a more diverse scope of nitrogen electrophiles, especially electron-rich amine precursors.

Ruthenium-catalyzed arene amination offers both the diverse scope of *N*-heteroatom electrophiles and the broad range of

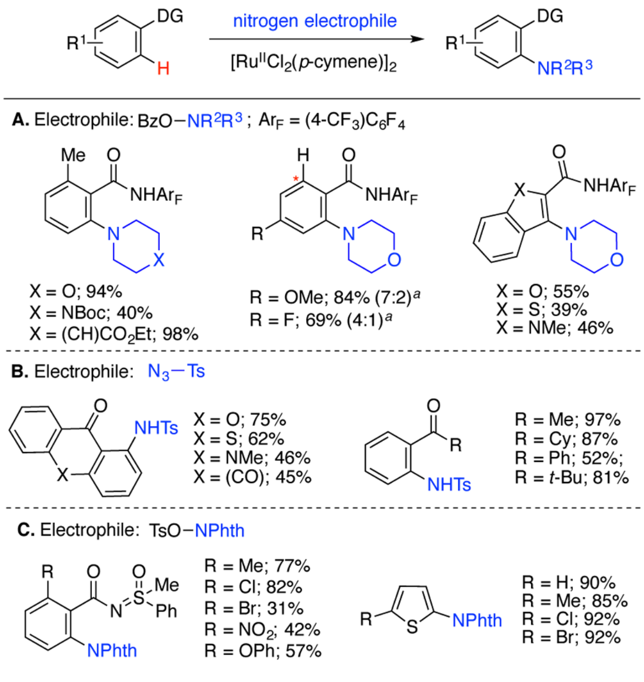
Scheme 12. Iridium-Catalyzed *Ortho*-Amidation of Arenes and Heteroarenes Using Azido- and Hydroxylamine-Derived Electrophiles



[a]Ratio of mono- and diamination (74:13).

directing groups, observed from rhodium and iridium, respectively. The Yu group has reported a ruthenium-catalyzed *ortho*-directed amination of benzamides using *O*-benzoylhydroxylamines (Scheme 13A).[50] In contrast to the palladium-catalyzed amination at elevated temperature,[35] this ruthenium-catalyzed variant proceeds at room temperature, enabled by a facile C−H metalation. Arene electronics also play an important role with electron-rich arenes to give better efficiency. The catalytic system was also effective on heteroarenes such as indole, benzofuran, and benzothiophene, yet less efficient. Chemoselectivity remains a challenge in this transformation, however, as 2,6-diaminated arenes were observed as minor products in most cases.

Scheme 13. Ruthenium-Catalyzed *Ortho*-Amination of Arenes and Heteroarenes



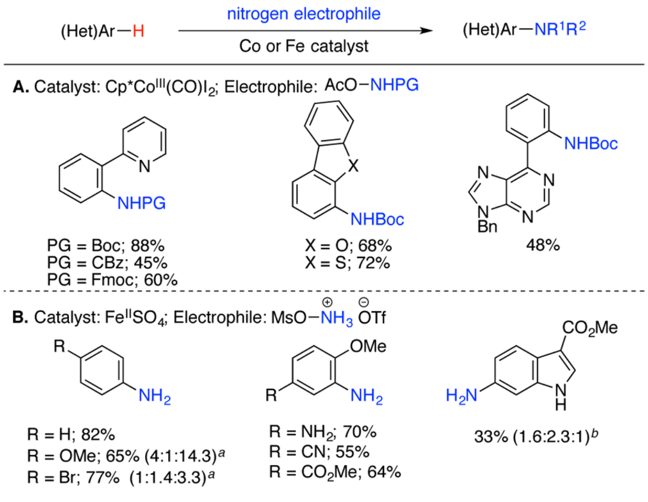
[a]Ratio of mono- and diamination.

Ruthenium-catalyzed sulfonamidation using sulfonyl azides also provided direct access to *ortho*-aminated aryl ketones (Scheme 13B).[51] Heteroatom substitutions on chromenes and xanthones were well tolerated, and the sensitive benzoquinone scaffold was also viable. Simple ketones can also serve as a directing group, with the best efficacy observed on electron-rich alkyl-phenones.

Using methylphenylsulfoximine as a readily deprotected directing group, ruthenium-catalyzed imidation using *O*-tosylhydroxyphthalimides was also achieved at elevated temperature on a variety of *ortho*-functionalized arene substrates (Scheme 13C).[52] Despite tolerating different functional groups, the reaction was less efficient in the presence of bromide, nitro, or even diaryl ether groups on the aryl ring. Conversely, the reaction was found to proceed in excellent yield with more electron-deficient thiophenes, even showing improved tolerance to aryl halides.

The use of more abundant transition metals as catalysts for aryl C−H amination is a topic of growing interest in the community. An example of cobalt-catalyzed *ortho*-directed C−H amidation has been reported with heteroarene directing groups using *O*-acetylhydroxycarbamate electrophiles (Scheme 14A).[53] Installation of *N*-carbamoyl-protected anilines at the 2′-position of 2-phenylpyridine proceeded in moderate to good yield. The reactions with a dibenzofuryl, dibenzothiophenyl, or purinyl directing group were efficient. Based on the available preliminary mechanistic studies, a cobalt−nitrene intermediate has been hypothesized in analogy to the reactivity with palladium.[37] Notable in this transformation is its application of inexpensive cobalt as a catalyst in aryl C−H functionalization. Similarly, iron is an economical alternative to precious-metal catalysts for aryl amination. Successful intermolecular, nondirected, C−H amination by iron(II) catalysis with N−O bond electrophiles has been reported for the installation of primary anilines from simple arenes and heteroarenes (Scheme

Scheme 14. Cobalt- and Iron-Catalyzed Electrophilic Amination of Arenes*



*Major isomer shown. [a]Ratio of *ortho*-, *meta*-, and *para*-amination products. [b]Ratio of 5-, 6-, and 7-aminoindole products.

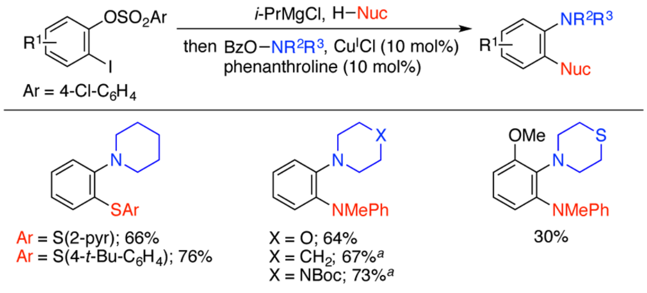
14B).[54] Using the triflate salt of *O*-mesylhydroxylamine, simple iron(II) sulfate catalyzed amination of electron-rich and electron-deficient arenes in good to moderate yields. Anisoles bearing *para*-substitution demonstrated excellent selectivity for *ortho*-amination, and functional groups such as bromides, amines, nitriles, and esters were well tolerated. Heteroarenes, such as indoles, could similarly undergo amination; however, lower regioselectivity was observed. Further development of abundant transition-metal catalysts, such as cobalt and iron, will provide valuable alternatives to precious-metal catalysis for efficient and selective aryl amination.

■ TRANSITION-METAL-CATALYZED ARENE AMINO DIFUNCTIONALIZATION USING NITROGEN–HETEROATOM BONDS

Amino difunctionalization of arenes has also been achieved by transition-metal-catalyzed reactions using *N*-heteroatom bonds via benzyne chemistry and norbornene-mediated C–H activation. Both strategies utilize N–O bonds as nitrogen electrophiles to quench *ortho*-functionalized organometallics generated in situ, allowing incorporation of the amine moiety. In contrast to the previously discussed N–X bond insertions, these methods utilize a diverse scope of exogenous nucleophilic partners to provide modular access to complex aminoarene products.

In 2008, Snowden reported an example of aryne carboamination that proceeded via the insertion of allylic cuprates followed by the subsequent amination of an arylcopper intermediate using *O*-benzoylhydroxypiperidine.[55] In 2015, Greaney reported a catalytic method using CuCl to achieve a modular synthesis of *ortho*-heteroatom-functionalized aminoarenes (Scheme 15).[56] In the presence of *i*-PrMgCl, aryne intermediates formed in situ were readily captured by magnesiated heteroatom nucleophiles, followed by CuCl-catalyzed amination. The efficiency of this transformation was influenced by the type of nucleophile, amine precursor, and aryne substrate. The regioselectivity was consistent with previously described nucleophilic addition to arynes, as seen in the reaction of 3-methoxyaryne. Nonetheless, this three-component coupling enabled a highly modular approach to *ortho*-functionalized aminoarenes, providing a valuable platform to rapidly access complex arene skeletons.

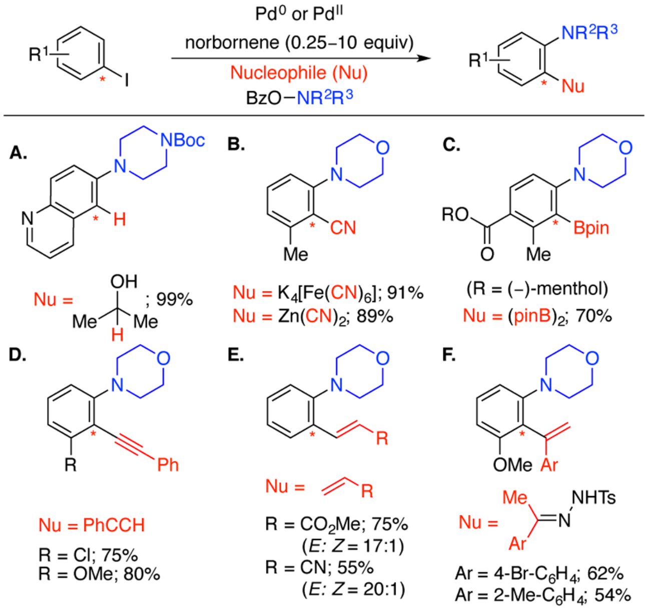
Scheme 15. *Ortho*-Aminofunctionalization of Arynes by Organometallic Nucleophilic Addition and Copper-Catalyzed Electrophilic Amination



^{a}Transmetalation with 0.5 equiv of ZnCl$_2$ prior to amination.

Using norbornene as a transient directing group has been a successful strategy for palladium-catalyzed tandem *ortho*-C–H and *ipso*-difunctionalization of aryl iodides (i.e., the Catellani reaction[57]). Recent applications of this strategy using *O*-benzoylhydroxylamines have offered a rapid approach to access various *ortho*-amino-functionalized arenes (Scheme 16). With *i*-PrOH as a hydride donor, the traceless *ortho*-amination of 5-iodoquinoline afforded 6-aminoquinoline product selectively (Scheme 16A).[58] The formation of aminobenzonitriles was reported with either iron- or zinc-derived cyanide donors (Scheme 16B).[59] Note that one of the positions *ortho* to the iodoarenes needed to be blocked in most examples in order to prevent diamination. At the same time, with sterically hindered aryl iodides being well tolerated, this strategy allows for the delivery of highly functionalized aminoarenes such as when (Bpin)$_2$ is used as a nucleophilic boron donor (Scheme 16C).[60] This reaction offers synthetically valuable arylboronate products and excellent functional group compatibility, presenting great potential for the construction of complex arenes. Carbon-derived nucleophiles have also been employed. With acetylenes as a nucleophile, carboamination of arenes was observed in good yields on different aryl iodide precursors (Scheme 16D).[61] Analogous Heck-type reactivity was also exploited to achieve alkenylamination of arenes; however, only highly activated alkenes were amenable (Scheme 16E).[62] For example, electron-deficient α,β-unsaturated esters and nitriles readily provided alkene products with good to excellent selectivity. The incorporation of more diverse olefins was achieved in the alkenylamination reaction with carbenes formed in situ from tosyl hydrazones (Scheme 16F).[63] The presence of various substitutions, such as aryl bromides, was tolerated, permitting access to a diverse scope of *o*-aminostyrenyl products.

Scheme 16. Palladium-Catalyzed Norbornene-Mediated Tandem C–H *Ortho*-Amination and *Ipso*-Functionalization of Aryl Iodides



■ SUMMARY

In conclusion, nitrogen–heteroatom bonds have been distinguished by their versatile reactivity and accessibility as a platform for developing novel amination strategies. This synopsis outlines recent methods and their elegant applications toward the synthesis of important aminoarene scaffolds. New development of N–X bond derived aryl amination strategies will continuously evolve to broaden their capacity and impact in the synthetic community. Further efforts are anticipated to advance these new amination methods in the late-stage amination of highly functionalized small molecules as well as in the direct amination of simple feedstock chemicals to generate significantly more valuable products.

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Qiu Wang started her independent career as an assistant professor of chemistry at Duke University in 2011. She received her Ph.D. at Emory University with Professor Albert Padwa (2005) and undertook postdoctoral training with Professor Andrew Myers at Harvard University (2005−2007) and Professor Stuart Schreiber at the Broad Institute of Harvard and MIT (2007−2011). Her current research interests focus on the synthesis and studies of biologically important nitrogen-containing molecules.

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