Synthetic Methods

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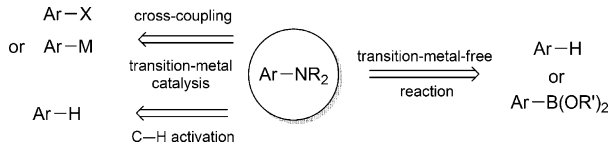
# Transition-Metal-Free Amination of Aryl boronic Acids and Their Derivatives

*Vincent Coeffard, Xavier Moreau, Christine Thomassigny, and Christine Greck**

amination · arenes · boronic acids · density functional calculations · synthetic methods

Aryl- and heteroarylamines are widespread in natural products, pharmaceuticals, materials, and are useful synthetic building blocks.[1] From a synthetic standpoint, the formation of $C_{aryl}$–N bonds has long been achieved by classical methods such as nucleophilic aromatic substitution, electrophilic nitration/reduction, or the copper-mediated arylation of amines, amides, or carbamates (Ullmann and Goldberg reactions). The past decades have witnessed spectacular advances in the realm of transition-metal chemistry and one of the thriving areas includes the selective and efficient construction of $C_{aryl}$–N bonds (Scheme 1).[2] The field is still

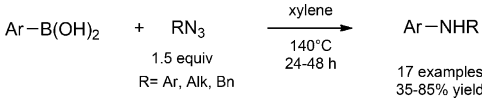



***Scheme 1.*** Methods for $C_{aryl}$–N bond formation.

dominated by the use of palladium, copper, and nickel catalysts in well-established reactions such as Buchwald–Hartwig or Ullmann-type coupling between aryl halides and amines, or Chan–Lam reactions between organoboron derivatives and nitrogen-containing compounds.[3] Recent developments in the metal-catalyzed electrophilic amination of various organometallic reagents (e.g., Mg, Zn, B) and direct C–H amination of aromatic and heteroaromatic rings have expanded the arsenal of catalytic methods to create $C_{aryl}$–N bonds.[4] In spite of the high efficiency of these methods, the issues often encountered with the use of transition metals (e.g., air and moisture sensitivity, cost of the catalytic system, metal waste) have prompted research groups to develop new strategies devoid of metal catalysts.

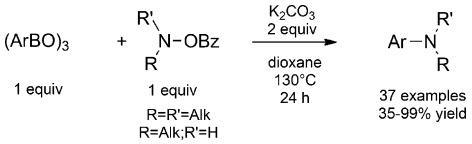
Besides hypervalent-iodide-mediated oxidative C–N bond formation,[5] transition-metal-free amination of aryl boronic acids or derivatives has recently appeared as an attractive strategy because of the ready accessibility, low toxicity, high stability, and applicability in a wide array of transformations of organoboron compounds.[6] In this Highlight, the recent advances in this field are discussed.

In 2011 the group of Yu reported a metal-free C–N bond formation between aryl boronic acids and organic azides,[7] which are valuable intermediates in organic synthesis in spite of their potential explosive properties.[8] Harsh reaction conditions (140 °C, xylene, 24–48 h) are required to ensure the formation of N-substituted anilines in moderate to good yields (Scheme 2). The best results are obtained with benzyl azide, thus leading to N-benzyl-protected anilines. However, heteroaryl boronic acids fail to react under these reaction conditions.




***Scheme 2.*** Coupling reaction between aryl boronic acids and organic azides.

In 2012, Wang et al. described the electrophilic amination of readily available arylboroxines with *O*-benzoylhydroxylamines in the presence of $K_2CO_3$ at 130 °C (Scheme 3).[9] This transformation is a useful method to access a wide array of diversely functionalized secondary and tertiary aromatic amines. Arylboroxines containing functional groups such as amide, ester, nitrile, bromo, and chloro groups are well tolerated, however, amination of heteroarylboroxines is not described.



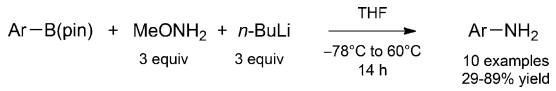

***Scheme 3.*** Electrophilic amination of arylboroxines. Bz = benzoyl.

Very recently, the groups of Morken[10] and Kürti[11] independently worked on transition-metal-free amination reactions for direct access to primary aromatic amines. Straightforward syntheses of such compounds generally employ ammonia as the simplest nitrogen-containing reagent

[*] Dr. V. Coeffard, Dr. X. Moreau, Dr. C. Thomassigny, Prof. C. Greck
Institut Lavoisier de Versailles, UMR CNRS 8180
Université de Versailles Saint-Quentin-en-Yvelines
45, Avenue des Etats-unis, 78035 Versailles Cedex (France)
E-mail: greck@chimie.uvsq.fr

but high pressure or temperature and transition-metal catalysts are usually required for these transformations.[12]

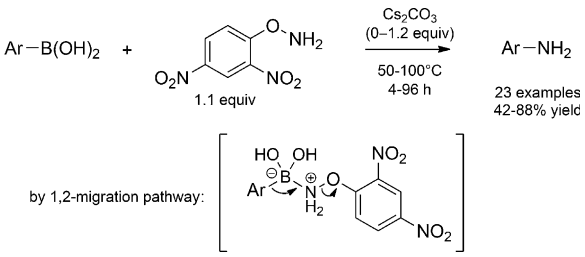
The group of Morken has described the direct amination of alkyl and aryl pinacol boronates which are known to be challenging substrates owing to their stability (Scheme 4).[10]




***Scheme 4.*** Direct amination of aryl pinacol boronates.

Given that amination of organoboron compounds generally proceeds through formation of a tetravalent "boronate" complex, the guiding philosophy of this research is that the reduced Lewis acidity of pinacol boronates requires the amination reagent to be extremely reactive. The authors identified the use of three equivalents of the nucleophilic lithiated methoxyamine[13] to be particularly effective for the amination of alkyl pinacol boronates without preactivation of the substrates (12 examples). When applied to a narrow set of aryl pinacol boronates, the reaction proved to be sensitive to the electronic properties of the aromatic ring. Electron-rich substrates gave the best results (71–89%) while heteroaryl pinacol boronates failed to react. Chiral boronates were subjected to the amination reaction and the corresponding compounds were obtained stereospecifically with retention of configuration at the carbon atom.

Kürti and co-workers have remarkably disclosed the first metal-free synthesis of primary aryl amines starting with aryl




***Scheme 5.*** Synthesis of primary amines starting with aryl boronic acids.

boronic acids and it constitutes a significant step forward to constructing $C_{aryl}$–N bonds (Scheme 5).[11] *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) was chosen as the aminating reagent in preference to different hydroxylamine or hydrazine derivatives, which proved to be unreactive. In addition, this reagent is commercially available or easily synthesized, by the two-step procedure reported by Legault and Charette,[14] and is stable at 0 °C for several months. By using only 1.1 equivalents of DPH and $Cs_2CO_3$ in some specific examples, a diverse array of primary aromatic amines were obtained in moderate to good yields by reaction in toluene; in some cases other solvents were more successful. In particular, halogen-substituted aryl boronic acids were well tolerated and afforded a variety of halogenated anilines which often cannot be obtained by transition-metal-catalyzed amination of boronic acids and aryl halides. Interestingly, one heterocyclic boronic acid derived from dibenzofuran gave the aminated product (66%), however, the method was not effective for substrates derived from pyrrole, indole, thiophene, or aryl ketones. The methodology can be readily scaled up to gram scale and was extended to boronic acid derivatives such as pinacol boronates and trifluoroborate.

Density functional theory (DFT) calculations were performed to shed light on the mechanism. The authors demonstrated that after the formation of a B–N dative bond, a concerted mechanism involving a 1,2-aryl migration pathway and concomitant cleavage of the N–OAr bond takes place (Scheme 5). The *ortho*-$NO_2$ group in DPH was shown to be important because it both stabilizes the developing leaving-group anion and participates in the hydrogen-bonding interaction with one of the N–H bonds, thus providing a low free-energy barrier to the 1,2-aryl migration step.

The transition-metal-free direct amination of aryl boronic acids and derivatives summarized in this Highlight represents a breakthrough in the area of heterofunctionalization of arenes, but further studies on the reaction conditions and substrate scope are needed for pushing back the frontiers of this reaction. Important challenges lie in the design of more atom-economical reagents and the application to the direct amination of heteroarenes and diversely functionalized architectures.

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