# Amination of Aryl Boronic Acids with Alkylnitrites: A Convenient **Complement to Cu-Promoted Reductive Amination**

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**S** Supporting Information

**ABSTRACT:** Copper-catalyzed amination of aryl boronic acids with alkylnitrites leading to symmetrical diarylamines with a practical 50–80% yield was elaborated. Two  $C(sp^2)$ –N bonds are formed in the one-pot process under mild conditions. This new approach to diarylamines is a complement to the Cu-assisted reductive amination of aryl boronic acids avoiding preliminary synthesis of nitrosoarenes. The possible reaction scheme based on quantum chemical calculations was suggested, clarifying key intermediates.

mong metal-mediated C(sp<sup>2</sup>)-N bond formation pro-A cesses, copper-promoted N-arylation with aryl boronic acids is one of the most practical.<sup>1</sup> Boronic derivatives are sufficiently reactive; nevertheless, they can tolerate a wide range of functional groups. Mild and ecofriendly reaction conditions and high reaction yield make the N-arylation with aryl boronic acids a strongly required approach to aryl amines. Aromatic amines can be found in 37% of drug candidates,<sup>2</sup> they are applied in material science, biology, etc.,<sup>3</sup> making their availability a topical problem.

Cu-promoted oxidative amination of aryl boronic acids with arylamines (the Chan-Lam coupling) was suggested in the pioneering works<sup>4-6</sup>. Later, a wide range of the N-H-containing substrates (amines,<sup>7,8</sup> imides,<sup>9</sup> ureas,<sup>10</sup> carbamates,<sup>10</sup> and sulfonamides<sup>4</sup>) was involved in stoichiometric Cu-mediated C-N bond formation. Further improvements obtained by a correct choice of a copper source, base, or additives allowed broadening the scope of substrates:<sup>11-14</sup> it was shown that even simple and abundant inorganic reactants such as aqueous ammonia,<sup>15</sup> hydroxylamine hydrochloride,<sup>16</sup> and sodium azide<sup>17</sup> can be used as a nitrogen source for the C-N bond formation.

Oxidative amination of aryl boronic acids was later complemented with copper-promoted reductive amination in which arylnitroso compounds were applied instead of arylamines.<sup>18</sup> Both oxidative and reductive approaches led to diarylamines, though the latter is preferable for synthesis of bulky amines.<sup>19</sup> Later, complementary protocols for Cucatalyzed N-imination<sup>20</sup> and N-amidation<sup>21</sup> of arylboronic acids using O-acyl ketoximes and O-acetyl hydroxamic acids as reactants have been developed. These examples, along with the aforementioned Cu-mediated amination of aryl boronic acids using nitroso arenes, indicate a possibility for the N-O bond cleavage in Cu-catalyzed amination of arylboronic acids under



## Scheme 1

Cu-assisted N-O bond cleavage:



Figure 1. Ar<sub>2</sub>NH yield in the presence of additives (iAmONO/4tBuC<sub>6</sub>H<sub>4</sub>B(OH)<sub>2</sub> (1:2), DMF, 70 °C, 3 h).

nonbasic and nonoxidizing conditions (Scheme 1) often required in multistep syntheses. This testifies that application of aryl boronic acids for the C(aryl)--N formation has not yet exhausted its full synthetic potential. The search for new

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Figure 2. GC monitoring of  $Ar_2NH$  during the reaction course (iAmONO, 4-<sup>t</sup>BuC<sub>6</sub>H<sub>4</sub>B(OH)<sub>2</sub> (1:2), DMF, 70 °C, 3 h).



<sup>*a*</sup>Reaction procedure: a degassed solution of  $ArB(OH)_2$  (0.4 mmol) and i-AmONO (0.2 mmol) in 7.5 mL of anhydrous DMF (EtOH) was added to a mixture of CuI (0.2 or 0.02 mmol) and Et<sub>3</sub>N (0.2 or 0.04 mmol) in 7.5 mL of degassed DMF (EtOH) preheated to 70 °C using oil bath. The solution was stirred under argon at 70 °C for 3 h and poured into 50 mL of 5% aqueous ammonia. Ar<sub>2</sub>NH was extracted with ether and purified by column chromatography on silica gel (eluent: hexane/EtOAc). <sup>*b*</sup>The yields are given both for the stoichiometric (blue) and catalytic (red) protocols.

reactants active in this process is important for understanding the reaction mechanism (which is still underinvestigated) as well as for providing new synthetic strategies.

Recently, three-component coupling of arylboronic acid, tert-butyl nitrite, and alkyl bromide leading to the  $C(sp^3)-N$ bond construction has been reported;<sup>22</sup> the N–O bond cleavage in <sup>t</sup>BuONO was suggested as one of the key steps. The yields of alkylanilines are high, but the method suffers from the undesired formation of the nitroarene. To overcome the problem, treatment with SmI<sub>2</sub> and an excess of ArB(OH)<sub>2</sub> is required.

Herein, we report an extensive study of alkylnitrites as aminating agents for the  $C(sp^2)$ -N bond formation. AlkONO contain two oxygen atoms to be used for coordination to the oxophilic boron atom. Consequently, Cu-assisted oxidative addition to the N-O bond followed by transmetalation and reductive elimination can provide two Ar-N bonds leading to *one-pot* formation of diarylamines. This approach has not been probed yet.

To test the idea, isoamylnitrite and 4-<sup>t</sup>BuC<sub>6</sub>H<sub>4</sub>B(OH)<sub>2</sub> were chosen. Initially, the process was carried out using reaction conditions previously described for the C–N coupling of aryl boronic acids with nitroso compounds:<sup>18</sup> isoamyl nitrite, a stoichiometric amount of CuCl, and 2 molar equiv of 4-<sup>t</sup>BuC<sub>6</sub>H<sub>4</sub>B(OH)<sub>2</sub> were stirred in DMF at 60 °C for 3 h under argon. Indeed, the targeted bis(*tert*-butylphenyl)amine was isolated from the reaction mixture in reasonable 40% yield indicating applicability of alkylnitrites as aminating agents.

Several parameters were varied (the type of alkylnitrite and copper salt, additives, the reaction time and temperature) to achieve practical yield of diarylamines. *t*-BuONO gave a lower yield of the targeted amine (26%); thus, isoamylnitrite was used in all subsequent experiments. Stirring the reaction mixture without CuCl gave no targeted amine. Among copper(I) halides, CuI gave better results (Figure 1). However, application of  $CuI_2^-$  gave no diarylamine. If a Lewis acid (ZnCl<sub>2</sub>) is taken instead of CuI, the reaction does not occur.

Further investigations showed that addition of 1 equiv of triethylamine offered a better yield of the targeted diarylamine (71%). To understand the role of  $Et_3N$  (a base, a ligand or something else), various amines and bases were tested (Figure 1). Application of the bidentate TMEDA ligand decreased the yield of the amine (53%), as well as the stronger bases, DBU (22%) and MeONa (36%). Thus, the role of the amine is adjusting the electronic properties of the copper center to suite the catalytic cycle requirements.

The reaction is sensitive to the temperature regime: 60-70 °C provides better yields of Ar<sub>2</sub>NH; a slight decrease in temperature (50 °C) as well as an increase (80 °C) diminishes the yield to 40% and 60%, respectively. Such nonlinear dependence is typical for competitive processes with different temperature coefficients. The kinetic measurements showed that ca. 70% yield is achieved in less than 1 h; further stirring of the reaction mixture gives no increase (Figure 2).

Keeping in mind that both Cu(I) and Cu(II) salts are efficient in N-imination of boronic acids with O-acyl ketoximes (also including the N–O bond cleavage<sup>20</sup>), we tried to replace Cu(I) with Cu(II) salt. Application of Cu(BF<sub>4</sub>)<sub>2</sub> gave a lower but still sufficient yield of the diarylamine (60% vs 70% for CuI). However, the process is slower and exhibits an induction period (Figure 2). Thus, the requisite Cu(I) catalyst should be either added to the reaction system or generated in situ through reduction of a Cu(II) precatalyst.

Scheme 3. General Reaction Scheme (Energies are in kcal/mol)





The yields of diarylamines which are ca.70% indicate that the reaction is hampered by a significant impact of byproducts formation. According to the GCMS analysis, these are phenol (2-10%) and ArH (4-10%), typically for Cu-mediated amination of arylboronic acids.<sup>11,23</sup>

The most informative was detection of  $Ar_2N-N=O$  (the product of  $Ar_2NH$  nitrosation) in the reaction mixture; this

Figure 4. GC monitoring of <sup>t-Bu</sup>PhH in the reaction probes.

Scheme 4. Ar<sub>2</sub>NH Recycling



Scheme 5. Catalytic Cycle



sheds light on the reaction mechanism (see below). The control experiments showed that the reaction of Ph<sub>2</sub>NH with *i*-AmONO in DMF in argon at 70 °C slowly gives Ph<sub>2</sub>N-N=O and is fastened with CuI (Figure 2), indicating that Cucontaining intermediate rather than i-AmONO is the nitrosating agent. This explains the decrease in the yield of diarylamines if an excess of i-AmONO is used. However, the addition of ArB(OH)<sub>2</sub> (2 equiv) to Ph<sub>2</sub>N-N=O in DMF in the presence of CuI restores diarylamines (Ph2NH and Ar<sub>2</sub>NH). That means that  $Ar_2N-N=O$  can also aminate arylboronic acid but less efficiently than i-AmONO (Figure 2). Thus, an interplay of three aforementioned processes (targeted amination of  $ArB(OH)_2$  with i-AmONO; nitrosation of the Ar<sub>2</sub>NH with Cu intermediate and the reaction of Ar<sub>2</sub>N-N=O with  $ArB(OH)_2$  yielding  $Ar_2NH$  determines the reaction outcome.

Using the optimized conditions (stoichiometric CuI, Et<sub>3</sub>N, 3 h, 70 °C), the scope of new methodology was examined; various arylboronic acids were tested. Both electron-rich and electron-deficient aryl boronic acids participate in the reaction, though the former gave much better yields (Scheme 2). The observed reactivity is in line with the previously reported data on Cu-mediated C–N bond formation using  $ArB(OH)_2$ .<sup>19</sup>

The approach is practical for synthesis of symmetrical *para*and *meta*-substituted arylamines; for *ortho*-substituted arylboronic acids, the yields are lower. Bulkiness of the aromatic moiety impedes transmetalation step<sup>19</sup> due to an increase in sterical repulsion in the tetracoordinated transition state (see below).

To reveal a possible reaction path, quantum-chemical calculations were performed using ab initio MP2/def2-SVP method with SMD solvation model.<sup>24,25</sup> Alkylnitrite addition to CuCl in DMF results in reversible formation of a new complex (Int-1 which can exist in two forms dependent on the type of bonding with the Cu center, Scheme 3). The following oxidative addition to the N–O bond yielding Int-2 is thermodynamically favorable and has low activation energy.

Addition of  $ArB(OH)_2$  to the solution of Int-2 immediately changes the color to deep green, yielding Int-3 in which the oxophilic boron atom is coordinated to the alkoxy group. The following thermodynamically favorable transmetalation step gives Int-4. Thus, alkyl nitrites as coupling reactants provide the "N-containing moiety" for the C–N bond formation and the internal "oxygenate" partner (OR) to pair with the B(OH)<sub>2</sub> fragment. A four-membered oxo-metal transmetalation pathway (see the SI) is consistent with the previously reported organoboron transmetalation in metal-catalyzed couplings.<sup>23,26,27</sup>

Further transformation of Cu(III) Int-4 is reductive elimination creating the C–N bond. Thus formed Int-5 reacts with the second equivalent of  $ArB(OH)_2$ . Thermodynamics and activation barriers for the rest steps have been already estimated in our previous paper<sup>19</sup> describing the Cu-mediated reductive amination of  $ArB(OH)_2$  with nitrosoarenes.

Voltammetric monitoring of the reaction course (Figure 3) visualizes fast transformations of the copper complexes under consecutive addition of the reactants: addition of i-AmONO to the solution of CuCl + Et<sub>3</sub>N shifts the CV response for 135 mV into anodic area due to Int-2 formation; further addition of ArB(OH)<sub>2</sub> to the greenish blue solution immediately changes the color and the CV response: a new peak at -1.03 V (more likely attributed to Int-5) appears and gradually increases while the peaks corresponding to Int-1 and Int-2 are gradually decreased.

As an additional support for the suggested reaction scheme, GC monitoring of <sup>t-Bu</sup>PhH amount formed after workup of the reaction probes with NH<sub>3</sub>·H<sub>2</sub>O was performed (Figure 4). <sup>t-Bu</sup>PhH is more likely formed in hydrolytic destruction of arylated copper intermediates which are formed and consumed with different rates. The fast decrease in the <sup>t-Bu</sup>PhH amount at the beginning of the process indicates fast consumption of the reactive arylated intermediate. Unfortunately, gradual accumulation of a certain amount of ArH byproduct which is typical for Cu-mediated arylation with aryl boronic acids<sup>23</sup> during the reaction course prevents monitoring of the other Cu–Ar intermediates.

Int-2 is worth special discussing. This four-coordinated halonitrosyl complex exhibits nitrosative reactivity<sup>28</sup> toward  $Ar_2NH$  and is responsible for  $Ar_2N-N=O$  byproduct formation. It is easily formed at room temperature and is accumulated in solution. The more is the concentration of the targeted amine, the more is the impact of its side nitrosation. However, the subsequent Cu-mediated reaction of  $Ar_2N-N=O$  with aryl boronic acid (Figure 2) is sufficiently fast to restore the targeted diarylamine (Scheme 4).

To render the reaction catalytic in copper, Cu(III) intermediate should be converted back to Cu(I), to finish one catalytic cycle and to start a new one. Thus, a reductant is necessary. Several reductants were tested without any success: ascorbic acid (as it has been used in the early Liebeskind publication<sup>18</sup>); Cu(0) dust; electric current (for the reaction performed in the electrochemical cell). Finally, a simple and elegant approach was found: the solvent can be used as a reductant. If the reaction is performed in EtOH, less than 10 mol % of CuI give 50–80% yield of the diaryl amine. The catalytic scheme is given in Scheme 5. All intermediates are the same as for the noncatalytic path, except the final step which restores Cu(I). Efficiency of the catalytic protocol was tested on various arylboronic acids (Scheme 2, the isolated yields are given).

To summarize, a new method for Cu-catalyzed amination of aryl boronic acids with alkylnitrites yielding diarylamines was elaborated. Mild conditions, cheap reactants, and ease of the workup procedure after the one-pot process determine the synthetic value of the method. New approach to diarylamines is a complement to the Cu-assisted reductive amination of aryl boronic acids, avoiding preliminary synthesis of nitrosoarenes.

# ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03961.

> Details of the kinetic and CV experiments, characterization of the new and previously known compounds, and results of the QC calculations (PDF)

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Notes

The authors declare no competing financial interest.

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