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Transition-Metal-Free Electrophilic Amination of Arylboroxines

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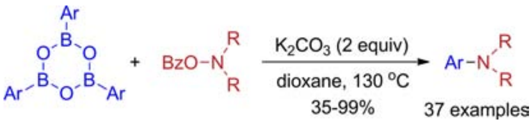
ABSTRACT



A transition-metal-free strategy to construct C(sp^2)−N bonds using arylboroxines and *O*-benzoyl hydroxylamines as coupling partners has been developed. This transformation provides a useful method to access various aromatic amines.

Aromatic amines exist widely in various natural products, useful pharmaceuticals, and important synthetic building blocks. Therefore, synthetic methodologies toward formation of C(sp^2)−N bonds have attracted considerable attention and various cross-coupling reactions have been developed (Scheme 1).[1] Among these methods, the Cu- or Pd-catalyzed cross-coupling reaction of electrophilic aryl halides with nucleophilic primary or secondary amines has been well established (Scheme 1, path **A**).[2−4] In 1998, the groups of Chan, Lam, and Evans independently developed Cu-mediated oxidative coupling reactions between nucleophilic arylboronic acids or esters with amines.[5] Subsequently, the catalytic variant of this transformation has been developed.[6] This reaction, named Chan−Lam coupling, provides a complementary method for the formation of aniline derivatives (Scheme 1, path **B**).

Recently, the transition-metal-catalyzed electrophilic amination of organometallic reagents with $R_1R_2N^+$ synthons has received attention as an Umpolung strategy of the previously established reactions (Scheme 1, path **C**).[7] In 2004, Johnson et al. reported their pioneering research on Cu-catalyzed amination of organozinc reagents with *N*,*N*-dialkyl-*O*-acyl hydroxylamine derivatives.[7a] Subsequently, Barker and Jarvo developed an analogous Ni-catalyzed reaction with organozinc reagents and *N*,*N*-dialkyl-*N*-chloramines.[7e] In addition to the amination of organometallic reagents, the $R_1R_2N^+$ synthons have

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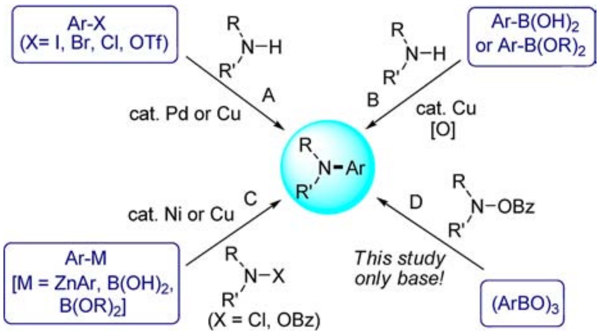
also been used as an effective nitrogen source for direct aromatic and heteroaromatic C–H amination *via* a similar catalytic process.[8]

Scheme 1. C(sp^2)–N Bond Formation

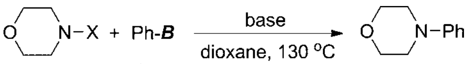


Organoboron compounds are generally more stable and less toxic over other organometallic reagents. It is thus highly desirable to develop a C(sp^2)–N bond forming reaction based on organoboron reagents. In 2008, Lei et al. reported a Cu-catalyzed amination of phenylboronic acid derivatives with *N*-chloro-*N*-arylacetamide.[7g] Very recently, groups of Miura and Lalic independently disclosed Cu-catalyzed cross-coupling reactions of arylboronates with *N*,*N*-dialkyl-*O*-acylhydroxylamine derivatives.[7h,i] This significant progress have made it possible to prepare bromo- and iodo-substituted dialkyl anilines directly.[9]

However, the above-described methods, although very powerful, all require transition metals such as palladium, nickel, and copper and in many cases the corresponding ligands as catalysts, which make these methods expensive and environmentally less friendly. Recently, great progress has been made in the development of transition-metal-free transformations to form C–C[10] and C–X (X = O, N, B)[11–13] bonds. In 2011, the groups of Antonchick,[12a] Chang,[12b] and DeBoef[12c] independently realized transition-metal-free C–N bond formation between ordinary arenes and amides or sulfonamides using $PhI(OAc)_2$ as an oxidant. At the same time, Nachtsheim's group achieved a similar transformation between benzoxazoles and amines using iodide as the catalyst under oxidative conditions.[12d]

As a continuation of our own interest in transition-metal-free transformations,[10c,13a,13c] we conceived that the reactions between electrophilic $R_1R_2N^+$ synthons and nucleophilic organoboron compounds might not require transition metal catalysts. Herein we report a novel and convenient strategy to construct C(sp^2)–N bonds by using arylboroxines and *O*-benzoyl hydroxylamines as coupling partners in the presence of only base (K_2CO_3) (Scheme 1, path **D**).

Table 1. Electrophilic Amination with Boron Compounds[a]



1a-c **2a-c** **3a**

entry	**1**, X	**2**, Ph–B (equiv)	base	yield (%)[b]
1	**1a**, OBz	**2a**, PhBin (3)[c]	K_2CO_3	none
2	**1a**, OBz	**2b**, $PhB(OH)_2$ (2)	K_2CO_3	42
3	**1b**, OAc	**2b**, $PhB(OH)_2$ (2)	K_2CO_3	18
4	**1c**, Cl	**2b**, $PhB(OH)_2$ (2)	K_2CO_3	trace[d]
5	**1a**, OBz	**2b**, $PhB(OH)_2$ (2)	Cs_2CO_3	30
6	**1a**, OBz	**2b**, $PhB(OH)_2$ (2)	K_3PO_4	26
7	**1a**, OBz	**2b**, $PhB(OH)_2$ (2)	none	21
8	**1a**, OBz	**2c**, $(PhBO)_3$ (1)	K_2CO_3	71
9[e]	**1a**, OBz	**2c**, $(PhBO)_3$ (1)	K_2CO_3	91

[a] Reaction conditions if not otherwise noted: **1** (0.6 mmol) and **2** in dioxane (3 mL) were heated for 8 h. [b] Yields of isolated product. [c] Bin: pinacolato. [d] Detected by GC-MS. [e] The solution of **1a** (0.6 mmol) in dioxane (1 mL) was added to the solution containing **2c** and K_2CO_3 in dioxane (2 mL) *via* syringe pump for 20 h, and then the reaction was carried out for an additional 4 h at the same temperature.

We started our investigation by using $R_1R_2N^+$ synthons **1a–c** to react with organoboron compounds **2** (Table 1). The reaction of *O*-benzoyl hydroxylamine **1a** with pinacol boronate **2a** failed to generate the expected product **3a** (Table 1, entry 1), while with $PhB(OH)_2$ **2b** the reaction did afford the 4-phenylmorpholine **3a**, albeit in low yield (Table 1, entry 2). The reaction with morpholino acetate **1b** and 4-chloromorpholine **1c** led to a reduced yield due to

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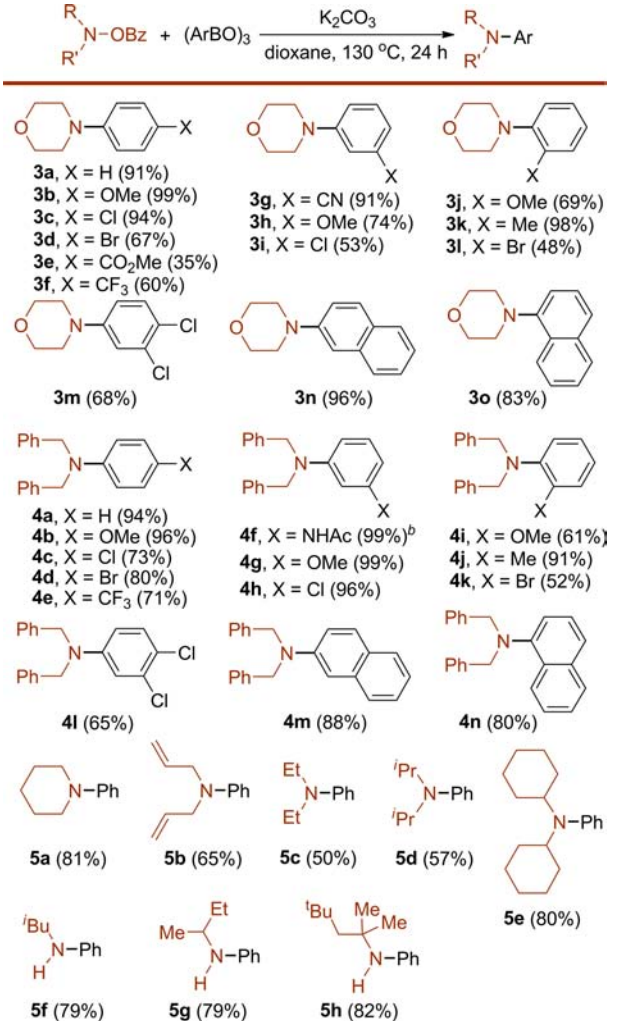
their high reactivity and instability under the reaction conditions (Table 1, entries 3, 4). The base shows marginal effect on the reaction. Cs_2CO_3 and K_3PO_4 led to diminished yields (Table 1, entries 5, 6), while, in the absence of base, **3a** can also be obtained in 21% yield (Table 1, entry 7). To our delight, the reaction of **1a** with phenylboroxine **2c** gave **3a** in 71% yield (Table 1, entry 8). The reaction can be further improved by adding **1a** with syringe pump over 20 h. Under the optimized reaction conditions (with K_2CO_3 as base in dioxane at 130 °C), the reaction of **1a** and **2c** afforded **3a** in 91% isolated yield (Table 1, entry 9).

Scheme 2. Transition-Metal-Free Amination of Arylboroxine with *O*-benzoyl hydroxylamine[a]



[a] Reaction conditions if not otherwise noted: *O*-benzoylhydroxylamine (0.6 mmol), arylboroxine (0.6 mmol), K_2CO_3 (1.2 mmol), dioxane (3 mL), 24 h. The yields refer to isolated yields. [b] Under the reaction conditions, the benzyl groups were removed.

With the optimized reaction conditions in hand, the scope of this transformation was explored by using various arylboroxines and *O*-benzoyl hydroxylamines (Scheme 2). Treatment of morpholino benzoate with a series of arylboroxines furnished the corresponding products **3a**–**o** in moderate to good yields. The reaction is not significantly affected by the substituents on the aromatic ring of arylboroxines. Both electron-rich and -deficient aryl -substituted boroxines were effective, affording the corresponding products (**3b**, **j**, **k** and **3c**–**g**, **i**, **l**, **m**). Moreover, the sterically demanding *ortho*-substituted phenylboroxines can also give good results (**3j**–**k**). It is noteworthy that functional groups, such as alkoxyl, nitrile, ester, trifluoromethyl, chloro, and bromo groups, are all tolerated under the reaction conditions. The reaction also worked well with naphthylboroxines (**3n**, **o**).

Taking into account the convenience of the subsequent derivatization of the corresponding products, we employed *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine as another electrophilic nitrogen source for this reaction. Similarly, a series of arylboroxines with diverse substituents show their high reactivities in this transformation, affording the corresponding products in moderate to excellent yields (**4a**–**n**).

Finally, the scope of *O*-benzoyl hydroxylamines was investigated. The reaction was examined with a series of *O*-benzoyl hydroxylamines, which were treated with phenylboroxines under the optimized reaction conditions. The derivatives of either cyclic amines or dialkyl amines all undergo the amination reaction smoothly and provide the corresponding amination products in moderate to good yields. The reactions with those derived from sterically hindered amines, such as diisopropylamine and dicyclohexylamine, also afford good results (**5d**, **e**). This reaction can also be applied to *O*-benzoyl-*N*-alkylhydroxylamine (**5f**–**h**).

To gain further understanding of the reaction, we have carried out experiments that are focused on the transition-metal-free reaction mechanism. First, the effect of trace transition metals remained in the substrates can be roughly excluded based on the following observations: (1) arylboroxines prepared from the corresponding boronic acids that are from different sources afford the amination product with similar yields under the identical reaction conditions; (2) the reaction with the K_2CO_3 of either 98% or 99.995% purity affords the same results; (3) no transition metals are involved in the preparation of *O*-benzoyl hydroxylamines.[7c]

To substantiate the transition-metal-free conditions, the contents of the transition metals (including Cu, Ag, Au, Ni, Pd, Co, Fe, Rh, and Ru) in the reaction substrates are analyzed by ICP-MS (detection limit $= 10^{-9}$). The results are summarized in Table 2. For the K_2CO_3 (with 99.995% purity), all the transition metals mentioned above are not detected except Fe, which has a concentration of 25.5 ppm. In *O*-benzoyl hydroxylamine **1a**, Co, Ru, Ag, Au, and Fe is not detected, while Ni, Cu (less than 1 ppm), Pd, and Rh (less than 0.016 ppm) have been identified. In phenylboronic acid, which is the precursor of the corresponding phenylboroxine, Au is not detected; the Ru, Rh, and Ag contents are < 0.015 ppm; the Co, Ni, and Pd contents are < 1 ppm, and the Cu content is 1.045 ppm.

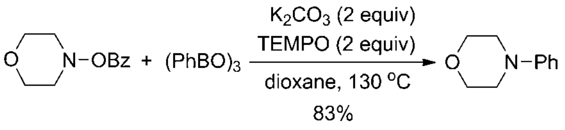
The transition-metal-free process is substantiated by the very low concentration level of transition metals in the reaction system. However, in view of the fact that several examples of coupling reactions catalyzed by trace copper or palladium have been documented,[14] the possibility

Table 2. ICP-MS Analysis of Trace Transition Metals in the Substrates[a]

metal	K_2CO_3 (99.995%)[b]	$(PhBO)_3$[c]	*O*-benzoyl hydroxylamine **1a**
Co	$<10^{-3}$	1.857×10^{-1}	$<10^{-3}$
Ni	$<10^{-3}$	7.349×10^{-1}	1.498×10^{-1}
Ru	$<10^{-3}$	4.687×10^{-3}	$<10^{-3}$
Rh	$<10^{-3}$	3.366×10^{-3}	4.044×10^{-3}
Pd	$<10^{-3}$	4.299×10^{-1}	1.576×10^{-2}
Ag	$<10^{-3}$	1.482×10^{-2}	$<10^{-3}$
Au	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$
Cu	$<10^{-3}$	1.045	6.929×10^{-2}
Fe	2.553×10^{-2}	216.7	$<10^{-3}$

[a] 1 unit = 1 μg/g (ppm); the detection limit = 10^{-9} (10^{-3} ppm). [b] K_2CO_3 (99.995% purity) was purchased from Aldrich. [c] The corresponding precursor $PhB(OH)_2$ was purchased from Alfa.

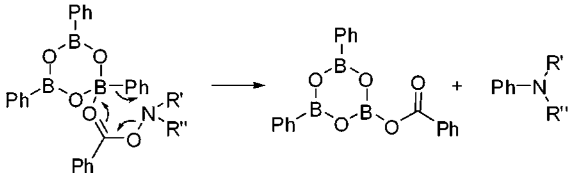
Scheme 3. Reaction in the Presence of TEMPO



cannot be completely ruled out that this amination is catalyzed by trace quantities of transition metals, such as copper. Moreover, it is noteworthy that the Fe content of the phenylboronic acid is up to 0.02%. We have found that the boronic acids from different sources all contain a similar concentration of Fe.[15] However, a possible Fe-catalyzed process may be excluded based on the following considerations: (1) to the best of our knowledge, a Fe-catalyzed aromatic amination with a boron reagent is not known in the literature; (2) 0.02% Fe would not display significant catalytic activity in cross-coupling reactions.[16]

To investigate whether the reaction involves a radical process, we conducted the amination with 4-vinylphenylboroxine. Under the standard reaction conditions, the expected amination product could be obtained in only a trace amount. A polymer, which is not soluble both in water and in organic solvents such as CH_2Cl_2, MeCN, dioxane, THF, and 1,2-dichlorobenzene, was identified as the major product. On the other hand, in the absence of *O*-benzoyl hydroxylamine, the 4-vinylphenylboroxine remained unchanged under the otherwise identical reaction conditions. These results imply that the *O*-benzoylhydroxylamines may initiate the radical polymerization. However, when TEMPO was added into the standard reaction (Scheme 3), the amination was almost unaffected. Moreover, neither the Ph-TEMPO nor morpholine-TEMPO adduct could be detected in the reaction. These observations seem not to be supportive of a radical process.

Scheme 4. Mechanistic Rationale



Electrophilic amination reactions of nonstabilized carbanions to form the C–N bond is a well-established process. A wide range of $R^1R^2N^+$ synthons, especially R^1R^2NCl, are employed for this transformation with highly active sp^2- or sp^3-hybridized carbon nucleophiles such as RLi or RMgX.[17] Therefore, we have proposed a direct substitution reaction mechanism to account for this transition-metal-free amination (Scheme 4). However, further experiments are needed to rigorously confirm the reaction mechanism.

In summary, we have developed an efficient amination reaction of arylboroxines with *O*-benzoyl hydroxylamines in the presence of K_2CO_3, affording the corresponding arylamines in moderate to good yields. *O*-Benzoylhydroxylamines can be prepared efficiently from amines and benzoyl peroxide under mild conditions,[7c] while arylboroxines are easily available from the corresponding arylboronic acids. Therefore, this operationally simple and cost-effective transition-metal-free amination reaction provides a useful method for the synthesis of aniline derivatives.

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Supporting Information Available. Experiment procedure, characterization data, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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