Synthetic Methods

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Copper-Catalyzed Amination of Arylboronates with *N*,*N*-Dialkylhydroxylamines**

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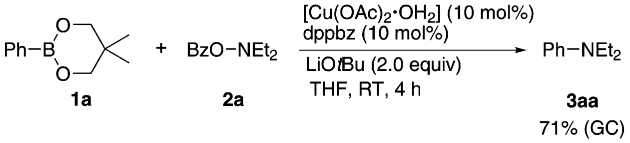
Metal-mediated aromatic C–N bond-forming reactions rank as one of the most useful and important transformations in organic synthesis because the resultant arylamine motifs are prevalent in many natural products and pharmaceutical targets.[1] Among them, the copper-promoted C–N bond formation of arylboronic acids with amines and amides (Chan–Lam coupling) is quite attractive owing to some benefits such as commercial availability, low toxicity, and tractability associated with copper salts and organoboron compounds.[2] Since the pioneering works in 1998,[3] a variety of reaction systems have been widely explored, and now catalytic variants are available. However, the coupling with dialkylamines is often inefficienct. In particular, the amination with secondary acyclic alkylamines still remains a challenge.[4] Herein, we report a copper-catalyzed amination of arylboronates with electrophilic aminating reagents, hydroxylamines. The catalysis allows the coupling of arylborons with various alkylamines, particularly secondary acyclic amines. In addition, by taking advantage of the high reactivity of an organocopper intermediate towards hydroxylamines in preference to aryl halides, the compatibility with aryl iodides as well as bromides is also achieved. Although related approaches are reported by Liebeskind and co-workers[5] and Lei and co-workers,[6] they are limited to amidation and imination.[7] Reported electrophilic amination reactions with hydroxylamines are restricted to highly reactive and moisture-sensitive organometallic reagents such as aryl Grignard reagents and arylzincs. The boron-based reagent is a more practical, easy-to-handle, and functional group tolerant alternative to the above organometallics.[8] Thus, the present strategy complements the precedented work and provides a new substrate class to the Chan–Lam-type coupling.

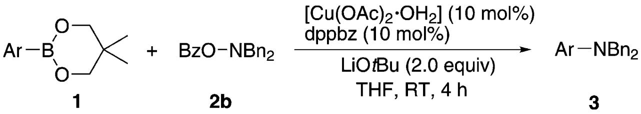
In a typical experiment, treatment of phenylboronic acid neopentylglycol ester (**1a**) with *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2a**) in the presence of 10 mol% [Cu($OAc)_2{\cdot}OH_2$]/dppbz (dppbz = 1,2-bis(diphenylphosphino)benzene) and 2.0 equivalents of LiO*t*Bu in THF at room temperature afforded *N*,*N*-diethylaniline (**3aa**) in 71% yield (GC; Scheme 1). Some observations concerning optimization studies are to be noted: other bases such as Cs_2CO_3, K_3PO_4, and $LiOH{\cdot}OH_2$ largely led to a reduced yield; anhydrous [$Cu(OAc)_2$] and CuOAc showed similarly high performances, so we employed [$Cu(OAc)_2{\cdot}OH_2$] for the subsequent experiments owing to its good tractability.[9]



Scheme 1. Optimized reaction conditions for copper-catalyzed amination of phenylboronic acid neopentylglycol ester (**1a**) with *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2a**).

Under the optimized reaction conditions (Scheme 1), we examined the scope of the boronates **1** with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2b**) (Table 1). In addition to the simple **1a** (entry 1), arylboronates bearing not only electron-donating groups (**1b**,**c**; entries 2 and 3) but also electron-withdrawing groups (**1d**–**f**; entries 4–6) underwent the amination smoothly. Particularly notable is the fact that aryl–halogen bonds including chloride, bromide, and iodide were tolerated under the reaction conditions (entries 4–6). The mildness of conditions accommodated methyl ester, phenyl

Table 1: Copper-catalyzed amination of various arylboronic acid neopentylglycol esters **1** with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2b**).[a]



Entry	**1** (Ar)	**3**, Yield [%][b]
1	**1a** (Ph)	**3ab**, 89
2	**1b** (4-MeC_6H_4)	**3bb**, 72
3	**1c** (4-$MeOC_6H_4$)	**3cb**, 68
4	**1d** (4-ClC_6H_4)	**3db**, 93
5	**1e** (4-BrC_6H_4)	**3eb**, 83
6	**1f** (4-IC_6H_4)	**3fb**, 53
7	**1g** (4-$MeOCOC_6H_4$)	**3gb**, 77
8	**1h** (4-$PhCOC_6H_4$)	**3hb**, 73
9	**1i** (4-$CHOC_6H_4$)	**3ib**, 81
10	**1j** (2,4,6-$Me_3C_6H_2$)	**3jb**, 64
11	**1k** (1-naphthyl)	**3kb**, 76
12	**1l** (2-thienyl)	**3lb**, 63
13	**1m** (3-thienyl)	**3mb**, 87

[a] Reaction conditions: [$Cu(OAc)_2{\cdot}OH_2$] (0.025 mmol), dppbz (0.025 mmol), LiO*t*Bu (0.50 mmol), **1** (0.25 mmol), **2b** (0.30 mmol), THF (1.5 mL), N_2, RT, 4 h. [b] Yield of the isolated product. Bn = benzyl.

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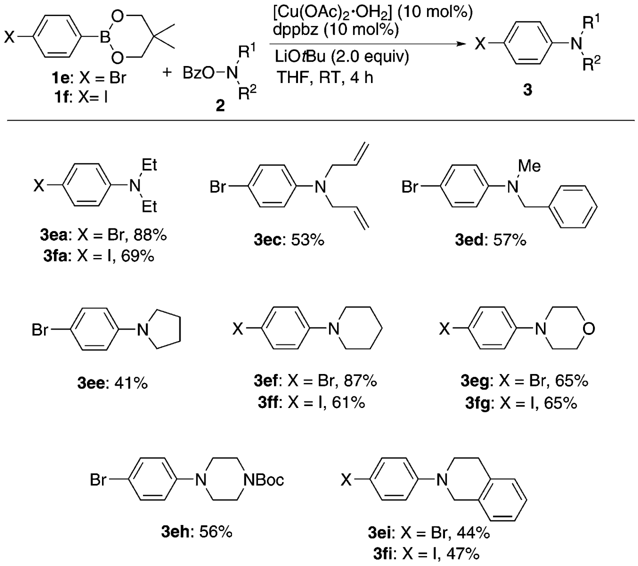
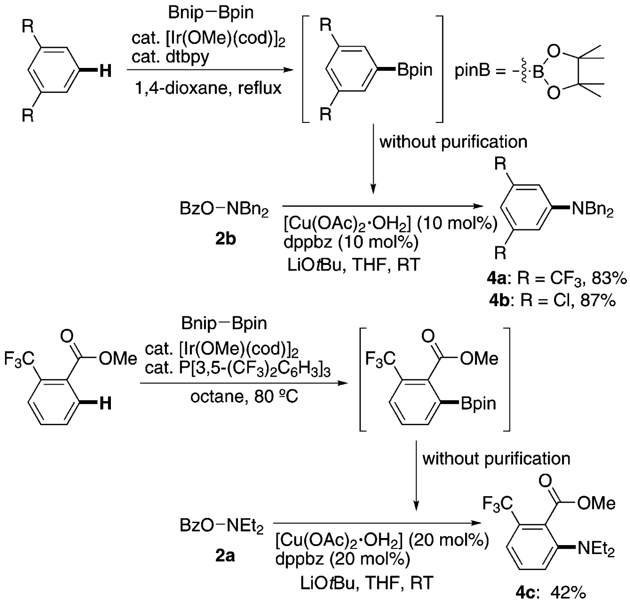
ketone, and aldehyde moieties (entries 7–9). The sterically demanding mesityl- and 1-naphthylboronates (**1j** and **1k**, respectively) also furnished the corresponding anilines **3jb** and **3kb** in synthetically useful yields (entries 10 and 11). Furthermore, the electrophilic amination protocol could be applied to the synthesis of heteroarylamines such as 2-thienyl- and 3-thienylamines (**3lb** and **3mb**, respectively; entries 12 and 13). Attempts to use alkylboronates such as butylboronic acid neopentylglycol ester remained unsuccessful.

Next, the amination with an array of *O*-benzoylhydroxylamines was carried out. To further demonstrate the halogen compatibility of the process, the bromo- (**1e**) and iodo-substituted (**1 f**) compounds were selected as the arylboronate (Scheme 2). Acyclic amines bearing *N*,*N*-diethyl, *N*,*N*-diallyl, *N*-benzyl-*N*-methyl substituents were compatible under standard reaction conditions (**3ea**–**ed** and **3 fa**). In particular, **3ec** and **3ed** could enjoy additional structural elaboration after appropriate removal of the allyl and benzyl groups.[10] The reaction with cyclic systems was subsequently investigated. The six-membered piperidine and morpholine derivatives coupled with both **1e** and **1 f** effectively (**3ef**, **eg** and **3 ff**, **fg**), whereas the hydroxylpyrrolidine showed a somewhat lower reactivity (**3ee**). The piperazine rings bearing a Boc group, as well as the bicyclic tetrahydroisoquinoline derivative were also compatible (**3eh**, **ei** and **3 fi**).



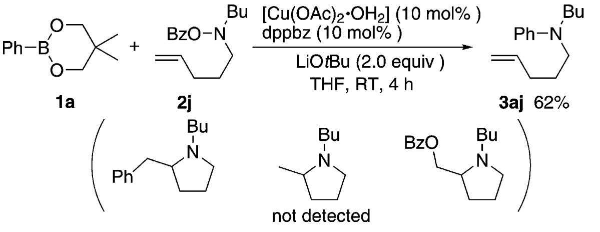
Scheme 2. Copper-catalyzed amination of arylboronates **1 e** and **1 f** with various hydroxylamines **2** performed using the reaction conditions from Table 1. Boc = *tert*-butoxycarbonyl.

Our copper-catalyzed electrophilic amination could be easily combined with the iridium-catalyzed direct C–H borylation of simple arenes (Scheme 3).[11] Namely, 1,3-bis(trifluoromethyl)benzene was directly borylated with pinB-Bpin using the $[Ir(OMe)(cod)]_2$/dtbpy (dtbpy = 4,4′-di(*tert*-butyl)-2,2′-bipyridine; cod = 1,5-cyclooctadiene) catalyst, and the resulting mixture was then transferred into a solution of *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2b**), copper catalyst, and LiO*t*Bu in THF without any purifications. The amination reaction proceeded very smoothly to furnish the corresponding aniline **4a** in 83 % yield based on **2b**. With the same protocol, *meta*-dichlorobenzene was also converted into **4b** with good efficiency. In addition, a $[Ir(OMe)(cod)]_2/P[3,5-(CF_3)_2C_6H_3]_3$-catalyzed *ortho* borylation[12] could be followed by the amination to furnish the corresponding 1,2,3-trisubstituted aniline **4c**. These examples demonstrate that the sequential Ir/Cu process could give a rapid and concise approach to anilines having electron-deficient substituents. Moreover, the introduction of the electrophilic amination reagent allows more sterically demanding pinacol boronates to be adopted directly in the C–N bond formation at a synthetically useful level. This is a significant advantage because the pinacol boronates tend to be less reactive than the parent boronic acids and their successful conversion is not trivial under the conventional Chan–Lam coupling conditions.[13]



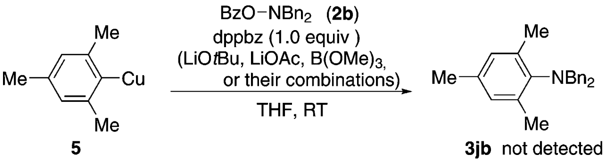
Scheme 3. Iridium-catalyzed C–H borylation/copper-catalyzed electrophilic amination sequence.

To investigate whether the catalysis involves an aminyl radical species (or its copper-coordinated form), we conducted the aminaion with **2j** containing a pendant olefinic moiety [Eq. (1)]. If the radical process was operative, some pyrrolidine-containing products would be formed through a 5-exo cyclization.[14] However, the usual coupling product **3aj** was obtained exclusively, thus excluding the radical pathway. Further mechanistic studies were carried out with the isolated MesCu complex **5**.[15] A stoichiometric reaction of **5** with **2b** in the presence of dppbz gave no detectable amount



(1)

of **3jb** [Eq. (2)]. Any additives such as LiO*t*Bu, LiOAc, B(OMe)$_3$, or combinations thereof did not form **3jb** at all. In contrast, upon treatment of **5** with **1e** as an additional aryl source, the corresponding anilines **3jb** and **3eb** were produced with a quantitative combined yield in a ratio of 39:61 [Eq. (3)]. Moreover, the mesitylcopper **5** catalyzed the amination of **1j** with **2b** very efficiently [Eq. (4)]. The phenomenon suggests that a monoarylcopper like **5** could be included in the catalytic cycle, but an active species responsible for the C–N bond formation can be a diarylcuprate rather than monoaryl species.



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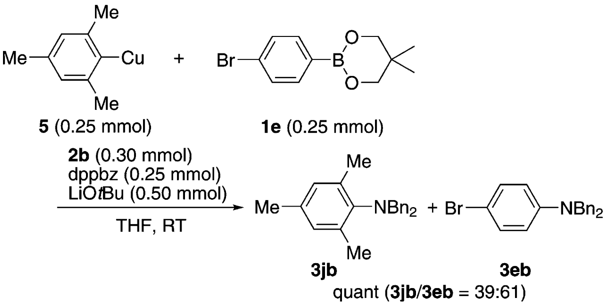

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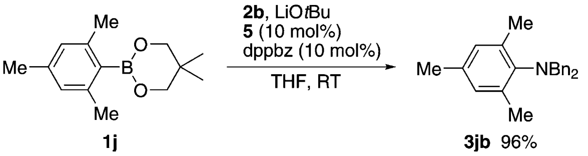
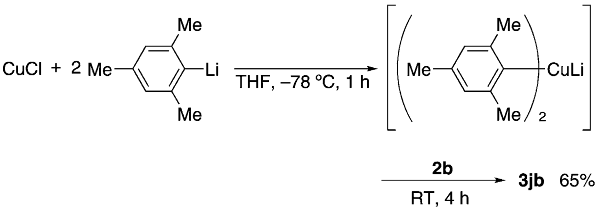


(4)

Based on the above considerations and literature information, we propose the mechanism for the amination as illustrated in Scheme 4. There is initial reduction of Cu^{II} into Cu^{I} and ligand exchange with LiO*t*Bu to generate the CuO*t*Bu species **6**. Subsequent transmetalation with the neopentylglycol boronate **1** furnishes the monoarylcopper **7**.[16] A second equivalent of boronate **1** then reacts with **7** with the aid of additional LiO*t*Bu to generate a more reactive ate-type diarylcuprate **8**.[17] The aniline product **3** would the result from the reaction of **8** with the hydroxylamine **2**, and the monoarylcopper **7** is regenerated to complete the catalytic cycle. The proposed diarylcuprate **8** can account for the result in Equation (3); a heterodiarylcuprate formed in situ transfers one of its aryl groups with moderate selectivity in favor of the formation of **3eb**, probably owing to steric factors. A stoichiometric reaction with Mes$_2$CuLi prepared from CuCl and 2.0 equivalents of MesLi also support the hypothesis [Eq. (5)]. The postulated reaction order of the copper complex (transmetalation then interaction with the electrophilic amination reagent) contrasts with the precedented works, in which an alternative is suggested.[5,6] The difference might arise from the lower electrophilicity of the hydroxylamines **2** than hydroxylamides or chloroamides.[18] Additionally notable is that under the current system the monoarylcopper species does not couple with the hydroxylamine **2**, whereas [(phen)CuC$_6$F$_5$] does couple very smoothly even without any additives in our previous work.[19] These results indicate that the reactivity of organocopper complexes toward electrophilic amination reagents depends highly upon the steric and electronic nature of both their anionic and neutral ancillary ligands, and thus provide some beneficial insights into the electrophilic, umpolung C–N bond-forming process by copper catalysts.



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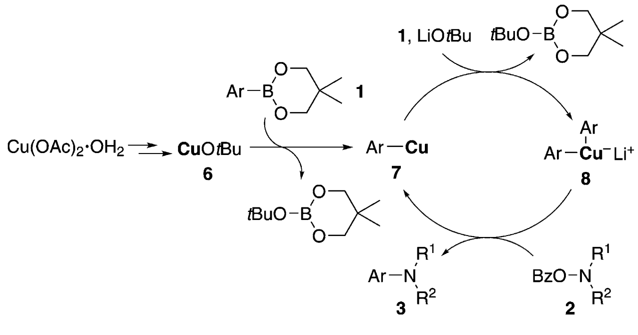

Scheme 4. Plausible reaction mechanism.

In conclusion, we have developed a copper-catalyzed amination of arylboronates with *O*-benzoylhydroxylamines bearing alkyl groups. The copper-based electrophilic, umpolung amination approach enables the use of secondary acyclic amines, which is a relatively difficult substrate class for the conventional Chan–Lam couplings. Moreover, the catalysis accommodates a diverse set of functional groups including chlorides, bromides, and iodides as well as aldehydes, ketones, and esters. The reaction system may complements previous work and provides a new substrate class for the Chan–Lam coupling. Investigations into the improvement of the catalytic turnover towards a more practical C–N coupling, a more detailed mechanism,[20] and additional developments of related electrophilic amination reactions are now in progress.

Experimental Section

Copper-catalyzed amination of phenylboronic acid neopentylglycol ester (**1a**) with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2b**) (Table 1, entry 1): [Cu(OAc)$_2$·OH$_2$] (5.0 mg, 0.025 mmol), 1,2-bis(diphenylphosphino)benzene (dppbz, 11 mg, 0.025 mmol), and LiO*t*Bu (40 mg, 0.50 mmol) were placed into a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. THF (0.50 mL) was then added to the flask, and the suspension was stirred for 15 min at ambient temperature. Finally, a solution of phenylboronic acid neopentylglycol ester (**1a**, 48 mg, 0.25 mmol), *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2b**, 95 mg, 0.30 mmol), and 1-methylnaphthalene (ca. 25 mg, internal standard) in THF (1.0 mL) was added dropwise. The solution was stirred at ambient temperature for additional 4 h. The resulting mixture was quenched with water. An aqueous solution of 4 M HCl (60 mL) was added to the mixture. The aqueous layer was washed four times with Et_2O, neutralized with 6 M NaOH aq. (40 mL), and then extracted four times with Et_2O. The combined organic layers was dried over sodium sulfate. Concentration in vacuo and subsequent purification by column chromatography on silica gel with *n*-hexane/ethyl acetate/Et_3N (40:1:0.25, v/v/v) as an eluent gave *N*,*N*-dibenzylaniline (**3ab**, 61 mg, 0.22 mmol) in 89% yield.

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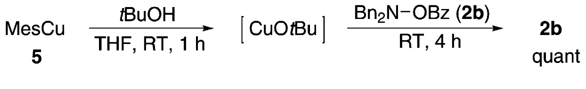

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