

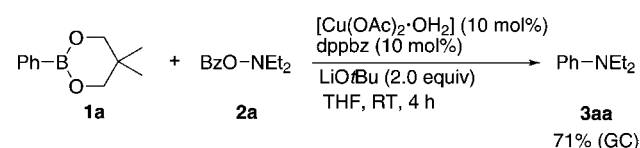
Copper-Catalyzed Amination of Arylboronates with *N,N*-Dialkylhydroxylamines**

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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 inefficient. 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·OH₂]/dppbz (dppbz = 1,2-bis(diphenylphosphino)-benzene) and 2.0 equivalents of LiOtBu 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 Cs₂CO₃, K₃PO₄, and LiOH·OH₂ largely led to a reduced yield; anhydrous [Cu(OAc)₂] and CuOAc showed similarly high performances, so we employed [Cu(OAc)₂·OH₂] 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 ₆ H ₄)	3bb , 72
3	1c (4-MeOC ₆ H ₄)	3cb , 68
4	1d (4-ClC ₆ H ₄)	3db , 93
5	1e (4-BrC ₆ H ₄)	3eb , 83
6	1f (4-IC ₆ H ₄)	3fb , 53
7	1g (4-MeOCOC ₆ H ₄)	3gb , 77
8	1h (4-PhCOC ₆ H ₄)	3hb , 73
9	1i (4-CHOC ₆ H ₄)	3ib , 81
10	1j (2,4,6-Me ₃ C ₆ H ₂)	3jb , 64
11	1k (1-naphthyl)	3kb , 76
12	1l (2-thienyl)	3lb , 63
13	1m (3-thienyl)	3mb , 87

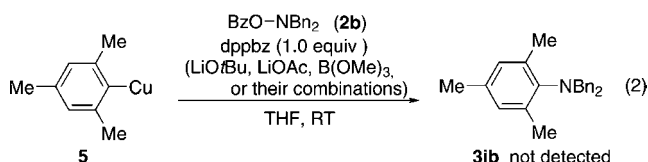
[a] Reaction conditions: [Cu(OAc)₂·OH₂] (0.025 mmol), dppbz (0.025 mmol), LiOtBu (0.50 mmol), **1** (0.25 mmol), **2b** (0.30 mmol), THF (1.5 mL), N₂, RT, 4 h. [b] Yield of the isolated product. Bn = benzyl.

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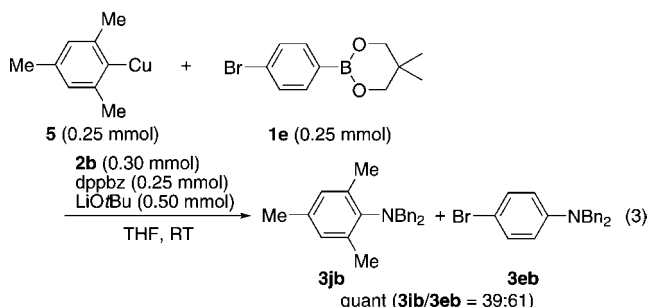
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of **3jb** [Eq. (2)]. Any additives such as LiOtBu, LiOAc,



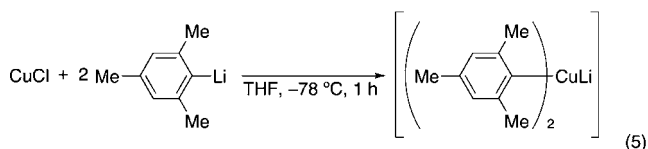
B(OMe)₃, or combinations thereof did not form **3jb** at all. In contrast, upon treatment of **5** with **1e** as an additional aryl source, the corresponding anilines **3jb** and **3eb** were produced with a quantitative combined yield in a ratio of 39:61 [Eq. (3)]. Moreover, the mesitylcopper **5** 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.

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 LiOtBu to generate the CuOtBu 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 LiOtBu to generate a more reactive ate-type diarylcuprate **8**.^[17] The aniline product **3** would be 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 Mes₂CuLi prepared from CuCl and 2.0 equivalents of MesLi also support the hypothesis [Eq. (5)]. The postulated reaction order of the copper

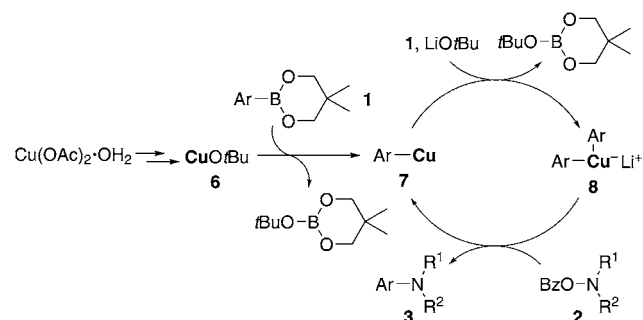


complex (transmetalation then interaction with the electrophilic amination reagent) contrasts with the precedented works, in which an alternative is suggested.^[5,6] The difference might arise from the lower electrophilicity of the hydroxylamines **2** than hydroxylamides or chloroamides.^[18] Additionally notable is that under the current system the monoarylcopper species does not couple with the hydroxylamine **2**, whereas [(phen)CuC₆F₅] 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.

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 complement 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·OH₂] (5.0 mg, 0.025 mmol), 1,2-bis(diphenylphosphino)benzene (dppbz, 11 mg, 0.025 mmol), and LiOtBu (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,



Scheme 4. Plausible reaction mechanism.

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 Et₂O, neutralized with 6 M NaOH aq. (40 mL), and then extracted four times with Et₂O. 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/Et₃N (40:1:0.25, v/v/v) as an eluent gave *N,N*-dibenzylaniline (**3ab**, 61 mg, 0.22 mmol) in 89 % yield.

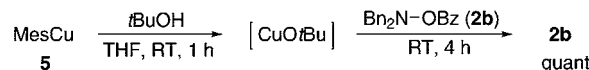
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