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Copper-Mediated Diamination of Arylboronic Acids for the Synthesis of 2-Aryl Benzimidazoles Using Trimethylsilyl Azide as the Amino Sources with Aldehydes

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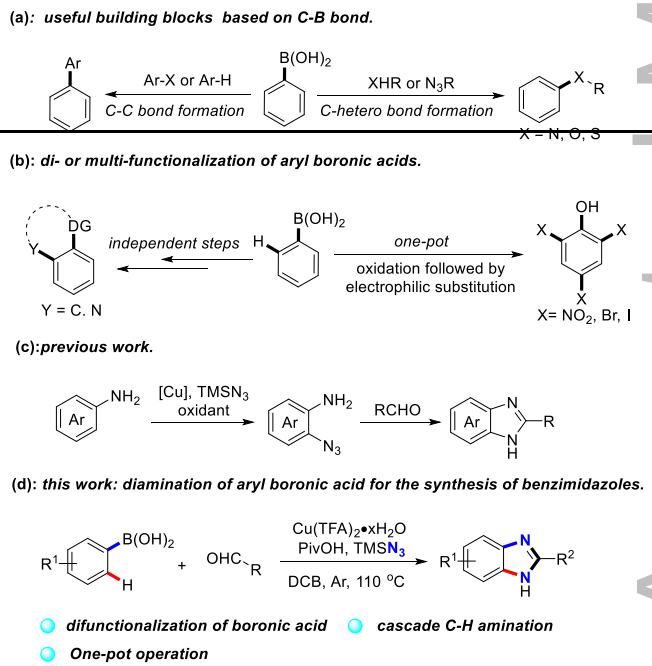
Abstract. A direct and versatile copper-mediated three-component reaction of arylboronic acids, trimethylsilyl azide and aldehydes for the synthesis of benzimidazoles is reported. The reaction is well tolerated by a wide range of substituted aromatic aldehydes and aromatic boronic acids to produce the corresponding benzimidazoles in moderate to high yields. Mechanism investigations demonstrated that copper-promoted Chan-Evans-Lam coupling, C-H amination, and oxidative cycloaddition are involved in the tandem processes.

Keywords: copper-mediated; three-component; benzimidazoles; Chan-Evans-Lam coupling; C-H amination

Organoboronic compounds are a class of useful building blocks that can be conveniently transformed into C-C, C-N, C-O and C-S bonds by employing Suzuki-Miyaura or Chan-Evans-Lam Couplings (Scheme 1, a),[1,2] and are widely applied to the synthesis of a variety of bioactive molecules.[3] Further extensions and modifications were also conducted to broaden the application of organoboronic compounds.[4,5] For instance, difunctionalization of arylboronic compounds has been reported by installation of directing groups to facilitate subsequent inter- or intramolecular C-C or C-N formation with multiple steps.[4] Organoboronic compounds could also be multifunctionalized by oxidization to phenols followed by electrophilic substitution in a one-pot procedure, but regioselectivity control is a major issue.[5] However, the direct one-pot difunctionalization of organoboronic compounds is rarely reported.

Recently, C-H amination/amidation using azides has been widely utilized as a new approach for the construction of heterocycles.[6] Driver et al reported that N-heterocycles were synthesized by intramolecular C-H amination/amidation of functionalized organoazides catalyzed by a Lewis acid.[7] Jiao and Li reported sequential C(sp^2)-H azidation/amination using organic or inorganic azides followed by intramolecular C-N or N-N bond formation to produce N-heterocycles (Scheme 1, c).[8a, b] Zhu also described the preparation of tri-substituted imidazoles and imidazo[1,5-a]pyridines via azidation of the alpha C(sp^3)-H bond of ketones and benzylic C(sp^3)-H amination, respectively.[9]



Scheme 1. Application of arylboronic acids.

Inspired by the C-H amination involving azides, we envisioned that tandem Chan-Evan-Lam coupling/C-H amination using trimethylsilyl azide ($TMSN_3$) could be a new strategy to achieve difunctionalization of arylboronic acid and produce benzimidazoles which exist in many natural products and synthetic

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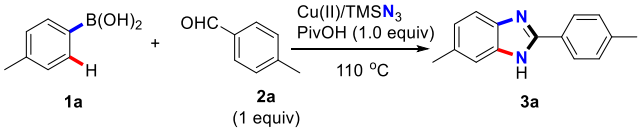
molecules with broad biological activities (Scheme 1, c).[10-12]

The investigation was initiated by reacting p-tolylboronic acid **1a** with *p*-tolualdehyde **2a** in the presence of $TMSN_3$ under conditions reported previously.[9] We were delighted to find that 2-aryl benzimidazole derivative **3a** could be isolated with 17% yield (entry 1, Table 1). Control experiments suggested that the copper salt was essential to this three-component reaction and that PivOH also played an important role in the transformation (entries 2 and 3).

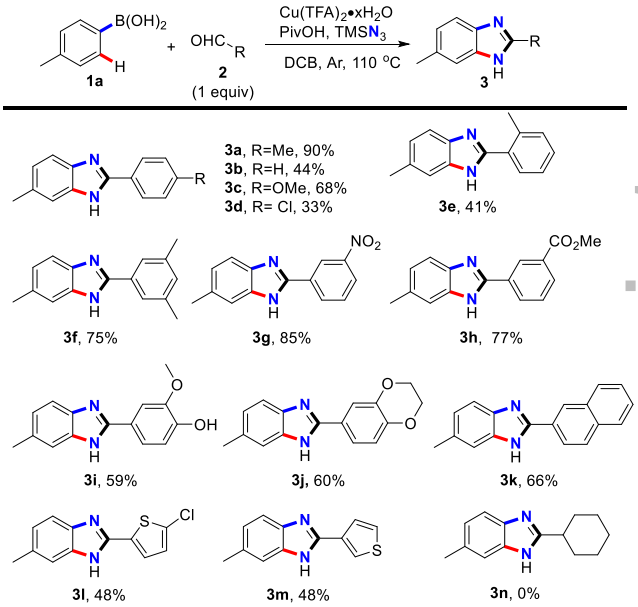
Table 1. Optimization of Reaction Conditions.[a]



entry	Copper (equiv)	Solvent (mL)	yield (%)
1	$Cu(TFA)_2{\cdot}xH_2O$ (1.0)	DCB (2)	17
2	-	DCB (2)	n.d.
3[b]	$Cu(TFA)_2{\cdot}xH_2O$ (1.0)	DCB (2)	11
4	$Cu(OAc)_2$ (1.0)	DCB (2)	<5
5	$CuCl_2$ (1.0)	DCB (2)	<5
6	$Cu(TFA)_2{\cdot}xH_2O$ (1.0)	toluene (2)	trace
7	$Cu(TFA)_2{\cdot}xH_2O$ (1.0)	DMF (2)	trace
8	$Cu(TFA)_2{\cdot}xH_2O$ (1.0)	DCE (2)	trace
9[c]	$Cu(TFA)_2{\cdot}xH_2O$ (0.2)	DCB (2)	<5
10d	$Cu(TFA)_2{\cdot}xH_2O$ (1.0)	DCB (2)	40
11[d,]	$Cu(TFA)_2{\cdot}xH_2O$ (1.0)	DCB (0.5)	55
12[d,e]	$Cu(TFA)_2{\cdot}xH_2O$ (1.0)	DCB (0.5)	80
13[d,e]	**$Cu(TFA)_2{\cdot}xH_2O$ (1.2)**	**DCB (0.5)**	**90**

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 equiv, 0.2 mmol), copper salt, PivOH (0.2 mmol), $TMSN_3$ (3.0 equiv), solvent, stirred at 110 °C under Ar for 18 h. [b] Withour PivOH. [C] Under O_2 atmosphere, [d] **1a** (2.0 equiv, 0.4 mmol), **2a** (0.2 mmol). [e] Addition of $TMSN_3$ (3.0 equiv) at the beginning of the reaction, and additional **1a** (1.0 equiv) + $TMSN_3$ (2.0 equiv) in DCB (0.2 mL) was added after 6 h. DCB = *o*-dichlorobenzene, PivOH = pivalic acid, TFA = trifluoroacetate.

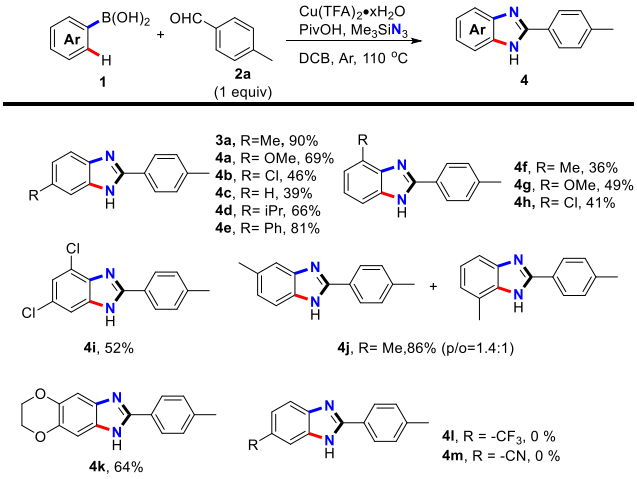
Investigation of the copper species showed that utilization of other copper salts such as $Cu(OAc)_2$, and $CuCl_2$, caused significantly decreased yields (entries 4-5). In addition, DCB (*o*-dichlorobenzene) was an optimal solvent compared to all of the organic solvents investigated, including toluene, DMF, and DCE (entries 6-8). Notably, when the reaction was conducted in air or O_2 with a catalytic amount of $Cu(TFA)_2{\cdot}xH_2O$ (0.2 equiv), only trace amounts of desired product **3a** were obtained (entry 9). The results also showed that *p*-tolylboronic acid **1a** could be consumed easily to cause a low yield of the product. The yield of **3a** could be improved to 40% when the amount of **1a** was double (entry 10). Additionally, the results further showed that a higher concentration of the reactants favored the transformation, and a yield of 55% was obtained when less solvent was utilized (0.5 mL, entry 11). Encouragingly, the addition of $TMSN_3$ (3+2 equiv) and boronic acid (2+1 equiv) in two portions significantly improved the yield to 80% (entry 12). The transformation yield was improved to 90% when 1.2 equiv of $Cu(TFA)_2{\cdot}xH_2O$ was applied (entry 13).



Scheme 2. Scope of Aldehydes. Reaction conditions: **1a** (0.4 mmol), **2** (1.0 equiv, 0.2 mmol), $Cu(TFA)_2xH_2O$ (1.2 equiv), PivOH (1.0 equiv), $TMSN_3$ (3.0 equiv), DCB (0.5 mL), stirred at 110 °C under Ar. After 6 h, a mixture of **1a** (1.0 equiv)+$TMSN_3$ (2.0 equiv) in DCB (0.2 mL) was further added, and the reaction time was prolonged to 18 h in total; Isolated yields shown.

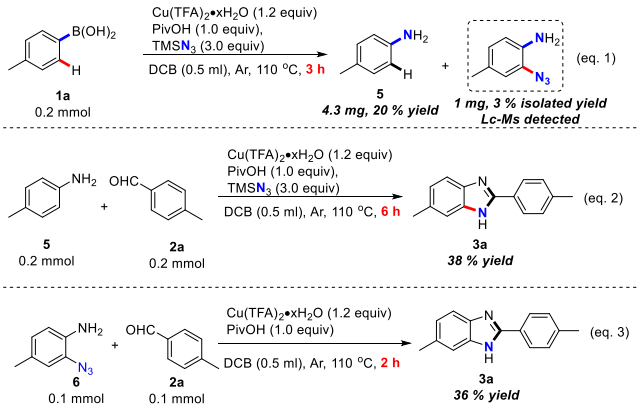
After identifying the optimal reaction conditions, we examined the scope of aldehydes applicable to this three-component reaction (Scheme 2). Benzaldehydes bearing electron-donating groups, e.g., 4-Me or 4-OMe, at the *para*-position proceeded smoothly with **1a** to give the corresponding products in 90% and 68% yields, respectively (**3a**, **3c**). Benzaldehydes bearing electron-withdrawing groups such as NO_2 and CO_2Me at the meta-position also performed well to afford the corresponding products in good yields (**3g**, **3h**). The above results demonstrated that the electronic density of the aromatic aldehydes had little impact on the product formation. Further investigation showed that *meta*-methyl and *ortho*-methyl substituted benzaldehydes resulted in decreased yields (**3f**, **3e**), suggesting that the reaction was sensitive to steric hindrance of the substituents at the *ortho*-position of aldehydes. Notably, natural isovanillin containing hydroxy group and oxidatively labile 2, 3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde were also tolerated in the reaction (**3i**, **3j**). We further tested other aromatic aldehydes such as 2-naphthaldehyde (**3k**) and heterocyclic aromatic aldehydes such as 5-chlorothiophene-2-carbaldehyde

(**3l**) and thiophene-3-carbaldehyde (**3m**). The results showed that they were also compatible in the reaction, leading to the corresponding products with 48-66% yields. Unfortunately, aliphatic aldehydes failed to deliver the corresponding products in this reaction.



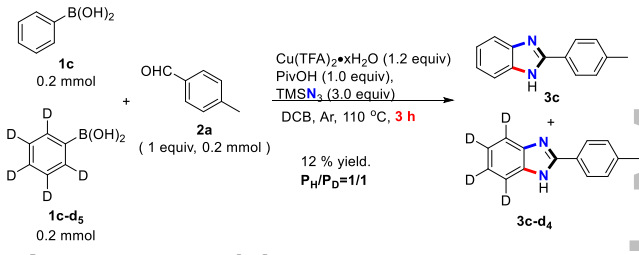
Scheme 3. Scope of Arylboronic Acids. Reaction conditions: **1a** (0.4 mmol), **2** (1.0 equiv, 0.2 mmol), $Cu(TFA)_2xH_2O$ (1.2 equiv), PivOH (1.0 equiv), $TMSN_3$ (3.0 equiv), DCB (0.5 mL), stirred at 110 °C under Ar. Addition the mixture of **1a** (1.0 equiv)+$TMSN_3$ (2.0 equiv) in DCB (0.2 mL) occurred after 6 h, and the reaction continued for a total of 18 h; Isolated yields are shown.

The reactions of *p*-tolualdehyde **2a** with diverse substituted arylboronic acids were also investigated (Scheme 3). Phenylboronic acid bearing *para*-Me, *i*-Pr, Ph, OMe or Cl reacted smoothly with **2a** to furnish the corresponding benzimidazoles in 39-90% yields (**3a**, **4a-e**). The steric hindrance of substituents at the *ortho*-position of the phenylboronic acid slightly decreased the yields (**4f-i**). In addition, 3-tolylboronic acid delivered a mixture of products with a total yield of 86% (*para*/*ortho* ratio = 1.4:1) (**4j**). Unfortunately, the phenylboronic acids with an electron-withdrawing substituted group only furnished trace amounts of products (**4l**, **4m**), while that an electron-donating group proceeded well with a 64% yield (**4k**).

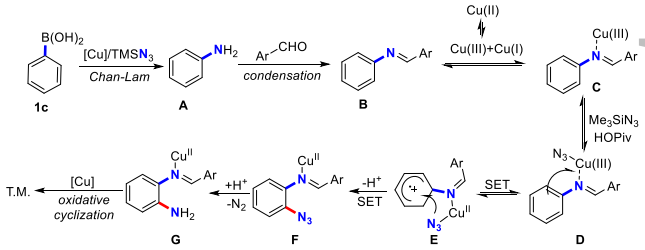


Scheme 4. Probable Intermediate Verification.

To gain insight into the mechanism of this diamination process, we tried to detect the probable intermediates in the reaction of *p*-tolylboronic acid without benzaldehydes under standard conditions. Encouragingly, *p*-toluidine **5** and 2-azidoaniline **6** were isolated although the yields were relatively low (eq. 1, Scheme 4). Additionally, intermediate **5** could be transformed to the final product with *p*-tolualdehyde in 38% yield, which demonstrated a higher yield than that with *p*-tolylboronic acid as the substrate under the same conditions (Table 1, entry 1) due to avoiding the yield loss caused by the Chan-Evans-Lam process during the reaction. In addition, intermediate **6** also delivered the benzimidazoles in 36% yield, suggesting that the aniline and 2-azidoaniline could be the key intermediates for this reaction (eq. 2, 3, Scheme 4). An intermolecular kinetic isotope labeling experiment was further performed to study the C-H azidation process. When the mixture of **1c** and **1c-d$_5$** was subjected to the reaction conditions, a 1:1 mixture of **3c** and **3c-d$_4$** was obtained in 3 h according to ^{1}H-NMR detection, although it showed a low yield due to the absence of an additional amount of $TMSN_3$ compared to the standard condition with shorter reaction time, which also proved that the C-H activation process might not be the rate-determining step in the reaction (Scheme 5).



Scheme 5. Isotope Labeling Experiment.



Scheme 6. Proposed Mechanism.

As a result, a plausible mechanism was proposed (Scheme 6). Phenylboronic acid **1c** initially underwent Chan-Evans-Lam coupling reaction with $TMSN_3$ to give aniline **A**. Intermediate imine **B** was then produced via condensation with aldehyde. Complex **C** could be consequently formed by chelation of the imine nitrogen with Cu(III) derived from the disproportionated reaction of Cu(II). Subsequently, the azido anion derived from HOPiv and $TMSN_3$ replaced the ligand of **C** to form intermediate **D**. A single electron transfer (SET) from the aryl ring to the metal center **D** yielded

intermediate **E** which was followed by the formation of **F** via transfer of the azido anion to the aryl ring with the release of protons through SET process.[8d] Copper-assisted transformation of azide into amine gave intermediate **G**.[13] Finally, oxidative cyclization by Cu(II) occurred to give the desired product.[14]

In summary, an efficient and novel method for the synthesis of benzimidazole starting from arylboronic acid and aldehydes using $TMSN_3$ as an amino source was developed. Two nitrogen atoms derived from $TMSN_3$ were formally inserted into the heterocyclic products by the formation of multiple C-N bonds. In this process, tandem Chan-Evans-Lam coupling and C-H amination of boronic acid followed by oxidative cyclo-condensation with aldehydes was proposed to be a possible mechanistic pathway.

Experimental Section

General procedure for the synthesis of 2-arylbenzimidazoles

Arylboronic acid (0.4 mmol) and $Cu(TFA)_2 \cdot xH_2O$ (0.24 mmol) were added to a Schlenk tube. Then, the tube was vacuumed and refilled with argon for 3 times. A solution of aldehyde (0.2 mmol), pivalic acid (0.2 mmol), $TMSN_3$ (0.6 mmol), and o-dichlorobenzene (0.5 mL) was added via a syringe. The reaction mixture was stirred at 110 °C, followed by the addition of a solution of $TMSN_3$ (0.4 mmol) and arylboronic acid (0.2 mmol) in 0.2 mL of *o*-dichlorobenzene via a syringe after 6 h. The reaction was stirred for another 12 h at this temperature. After cooling, saturated aqueous NaCl (10 mL), NH_4OH (1 mL) and EtOAc (10 mL) were added to the reaction mixture. The aqueous phase was further extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to provide the desired product.

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UPDATE

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