Copper-Catalyzed Electrophilic Amination of *gem*-Diborylalkanes with Hydroxylamines Providing α-Aminoboronic Acid Derivatives

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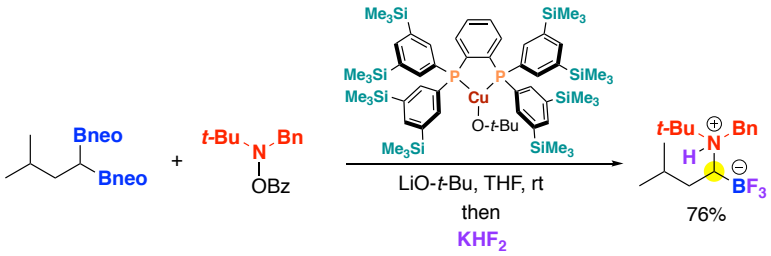
Supporting Information Placeholder



ABSTRACT: A copper-catalyzed electrophilic amination of *gem*-diborylalkanes with hydroxylamines has been developed. The key to its success is the use of the Me_3Si-modified 1,2-bis(diphenylphosphino)benzene ligand. Additionally, the reactivity of neopentylglycol derivatives compared to that of commonly used pinacol-derived ones is found to be higher, particularly in the case of relatively sterically congested substrates. The copper catalysis presented here enables the first successful catalytic carbon–heteroatom bond forming reaction of *gem*-diborylalkanes to form the corresponding α-aminoboronic acid derivatives, which are of great interest in medicinal and pharmaceutical chemistry.

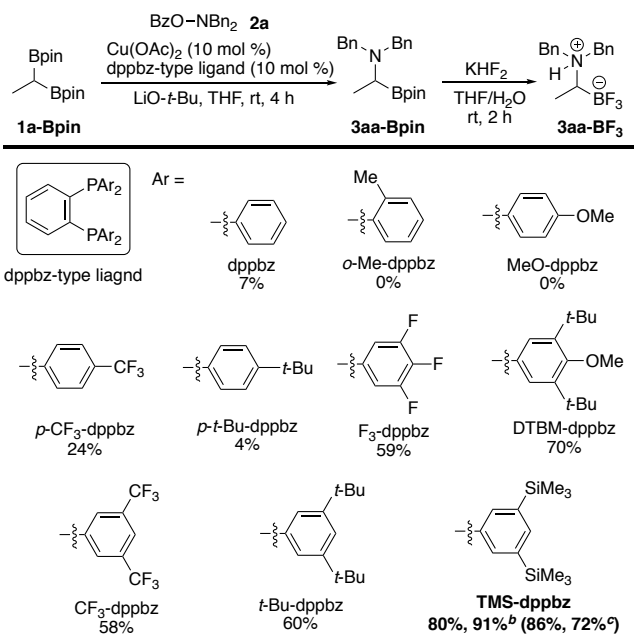
Organoboron compounds are indispensable synthetic intermediates in modern organic synthesis because the carbon–boron bond can be readily and selectively transformed into various carbon–carbon and carbon–heteroatom bonds under the appropriate conditions.[1] Additionally, organoboron compounds themselves are found to show unique biological activity.[2] Accordingly, the preparation of densely functionalized organoboron compounds is one of the important research subjects in synthetic communities. In this context, *gem*-diborylalkanes[3] have recently received a significant amount of attention. Since the pioneering work by Endo and Shibata,[4] versatile catalytic and noncatalytic functionalization of *gem*-diborylalkanes has been widely developed by the research groups of Morken,[5] Meek,[6] and others.[7] However, almost all reported procedures focused on carbon–carbon bond-forming reactions; there has been no report of successful carbon–heteroatom bond formation with *gem*-diborylalkanes, except for the selective oxidation of unsymmetrical *gem*-diborylalkanes recently developed by Sharma.[8] Thus, their synthetic potential remains underdeveloped.

Recently, our group reported the copper-[9] and rhodium-catalyzed[10] electrophilic (umpolung) amination[11] of aryl- and alkenylboronic acid derivatives with hydroxylamines[12] to form the corresponding anilines and enamines, respectively.[13] Because of our continuing interest in this chemistry, we envisioned application of *gem*-diborylalkane as the organoboron coupling partner. Here, we report a copper-catalyzed electrophilic amination of *gem*-diborylalkanes with *O*-benzoylhydroxylamines. The copper catalyst combined with the Me_3Si-modified 1,2-bis(diphenylphosphino)benzene-type ligand uniquely promotes the reaction. Additionally, we find a higher reactivity of *gem*-diborylalkanes derived from the neopentylglycolborane than from commonly used pinacolborane-derived ones. The products obtained are α-aminoboronic acid derivatives, which are of great interest in medicinal and pharmaceutical chemistry.[2,14]

On the basis of the reported copper-catalyzed reactions of *gem*-diborylalkanes,[6a,7] we selected pinacolborane-derived 1,1-diborylethane **1a-Bpin** and *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**2a**) as the model substrates and began optimization studies (Scheme 1). In an early experiment, treatment of **1a-Bpin** (0.25 mmol) with **2a** (1.5 equiv) in the presence of 10 mol % $Cu(OAc)_2$/1,2-bis(diphenylphosphino)benzene (dppbz) catalyst and LiO-*t*-Bu base at room temperature afforded the desired α-aminoboronate **3aa-Bpin**. Although the ^1H NMR yield was just 7%, this intriguing result prompted us to further evaluate related dppbz-based bisphosphine ligands. Whereas introduction of substituents at the *ortho* and *para* positions on the benzene ring resulted in no or just slight improvement (*o*-Me-dppbz, MeO-dppbz, *p*-CF_3-dppbz, or *p*-*t*-Bu-dppbz), several *meta*-substituted ligands greatly increased the reaction efficiency (F_3-dppbz, DTBM-dppbz,

CF_3-dppbz, *t*-Bu-dppbz, and TMS-dppbz). In particular, Me_3Si-modified TMS-dppbz furnished the targeted **3aa-Bpin** in 80% ^{1}H NMR yield.[15] Additional fine-tuning revealed that the reaction proceeded more smoothly with a 5 mol % catalyst loading to deliver **3aa-Bpin** in 91% yield. The pinacol-derived **3aa-Bpin** was unstable for silica gel column purification but, upon treatment with KHF_2, readily converted into the corresponding internal ammonium borate salt **3aa-BF$_3$**, which was successfully isolated in 86% yield by simple recrystallization.[16] Moreover, the reaction could be easily conducted on a 1.0 mmol scale, giving **3aa-BF$_3$** in 72% yield. Additional observations should be noted. Other representative monodentate and bidentate phosphine ligands such as PPh_3, binap, xantphos, and dppf showed much poorer performance; no formation of product was confirmed in the absence of any copper salts (see the Supporting Information for more detailed optimization studies).

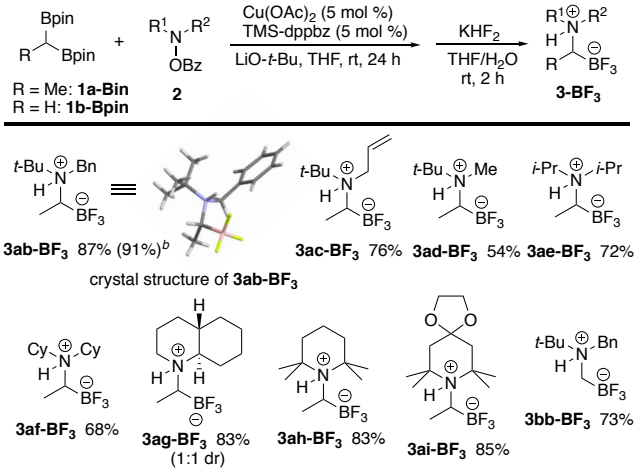
Scheme 1. Effects of dppbz-Type Ligands in Copper-Catalyzed Electrophilic Amination of Pinacolborane-Derived Diborylalkane 1a-Bpin with *O*-Benzoyl-*N,N*-dibenzylhydroxylamine (2a)[a]



[a] Reaction conditions for amination: **1a-Bpin** (0.25 mmol), **2a** (0.38 mmol), $Cu(OAc)_2$ (0.025 mmol), ligand (0.025 mmol), LiO-*t*-Bu (0.75 mmol), THF (1.5 mL), rt, 4 h, N_2. Reaction conditions for conversion into borate: KHF_2 (2.5 mmol), THF/H_2O (1.5 mL/0.5 mL), rt, 2 h. ^{1}H NMR yields of **3aa-Bpin** are shown. Isolated yields as the borate form **3aa-BF$_3$** are indicated in parentheses. [b] With $Cu(OAc)_2$ (0.013 mmol) and TMS-dppbz (0.013 mmol) for 8 h. [c] On a 1.0 mmol scale.

We next investigated the scope of hydroxylamines **2** with 1,1-diborylethane **1a-Bpin** (Scheme 2). Although slight modifications of reaction stoichiometry were essential (**1a-Bpin,** 2.0 equiv; hydroxylamine **2**, limiting reagent), several acyclic amines participated in the reaction. The *N*-*tert*-butyl-, *N*-isopropyl-, and *N*-cyclohexylamines were successfully coupled with **1a-Bpin** to form the corresponding α-aminoborates **3ab-BF$_3$**–**3af-BF$_3$** in good isolated yields. Also in these cases, the products could be readily purified by simple recrystallization. Cyclic amines were also tolerated under these conditions, giving the piperidine derivatives **3ag-BF$_3$**–**3ai-BF$_3$** in 83–85% yields. The structure of *N*-*tert*-butyl-*N*-benzylamine **3ab-BF$_3$** was unambiguously confirmed by X-ray analysis (CCDC 1912150). Again, **3ab-BF$_3$** could also be synthesized on a 1.0 mmol scale without any decrease in the isolated yield, thus indicating the good reliability and reproducibility of this process. Additionally, the nonsubstituted *gem*-diborylalkane **1b-Bpin** was also the viable substrate to afford **3bb-BF$_3$** in 73% yield. On the other hand, attempts to apply less sterically hindering amines such as *O*-benzoyl-*N,N*-diethylamine remained unsuccessful.

Scheme 2. Copper-Catalyzed Electrophilic Amination of 1a-Bpin and 1b-Bpin with Various Hydroxylamines 2[a]

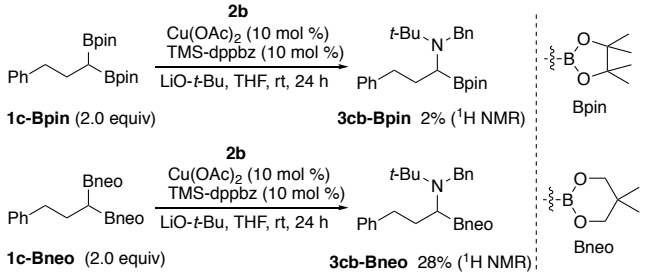


[a] Reaction conditions for amination: **1a-Bpin** (0.50 mmol), **2** (0.25 mmol), $Cu(OAc)_2$ (0.013 mmol), TMS-dppbz (0.013 mmol), LiO-*t*-Bu (0.75 mmol), THF (1.5 mL), rt, 24 h, N_2. Reaction conditions for conversion into borate: KHF_2 (2.5 mmol), THF/H_2O (1.5 mL/0.5 mL), rt, 2 h. Isolated yields as the borate form **3-BF$_3$** are shown. [b] On a 1.0 mmol scale.

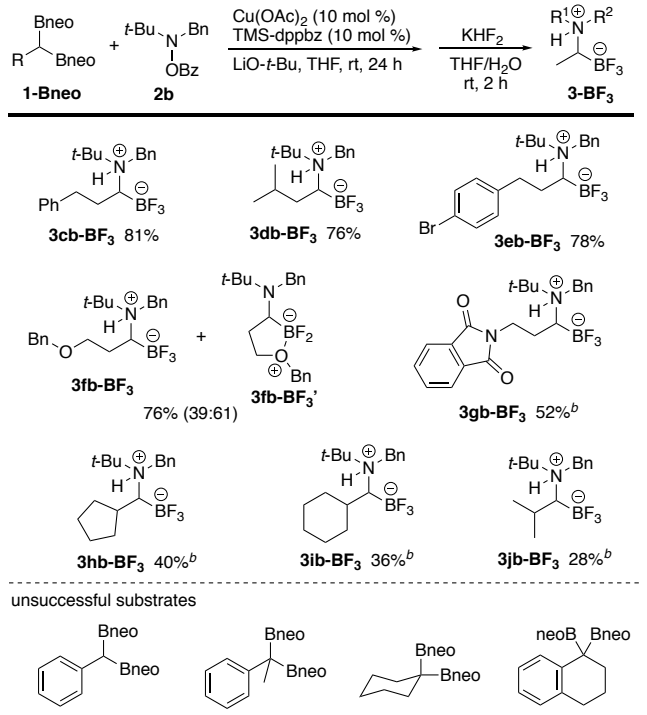
We then performed the reaction of the phenethyl-substituted **1c-Bpin** with **2b** to further examine the scope of *gem*-diborylalkane (Scheme 3). However, the targeted **3cb-Bpin** was detected in only 2% ^{1}H NMR yield under the standard reaction conditions. A similar lower reactivity of substituted *gem*-diborylalkanes other than **1a-Bpin** and **1b-Bpin** under copper catalysis was reported in the literature.[6a,7a-7e] Actually, we performed additional optimization studies on the copper catalyst, but no improvements were observed. Thus, we turned our attention to more sterically accessible neopentylglycolborane derivative **1c-Bneo**. Gratifyingly, the desired **3cb-Bneo** was formed in 28% ^{1}H NMR yield. Prompted by the preliminary but intriguing result, we further investigated the reaction stoichiometry. Finally, with 3.0 equiv of **1c-Bneo**, the ^{1}H NMR yield of **3cb-Bneo** increased to 90%, and the corresponding borate **3cb-BF$_3$** was successfully isolated in 81% yield (Scheme 4). With the Bneo-modified protocol, some *gem*-diborylalkanes **1-Bneo** could be coupled with **2b**. The isobutyl-substituted substrate was also smoothly aminated to form the desired α-aminoborate **3db-BF$_3$** in 76% yield; its

structure is observed in the proteasome inhibitors, Bortezomib and Ixazomib.[17] Functional groups such as Ar-Br, benzyl ether, and phthalimide were compatible with identical conditions (**3eb-BF$_3$**–**3gb-BF$_3$**). Notably, in the case of ether **3fb-BF$_3$**, the intramolecularly *O*-coordinated borane **3fb-BF$_3$'** was mainly formed. Additionally, more sterically hindered and thus challenging cyclopentyl-, cyclohexyl-, and isopropyl-substituted *gem*-diborylalkanes also participated in the reaction, giving borates **3hb-BF$_3$**, **3ib-BF$_3$**, and **3jb-BF$_3$**, respectively. Although the yields were still moderate, the observed positive effects of the Bneo group in the *gem*-diborylalkanes under copper catalysis are unprecedented and thus deserve significant attention. On the other hand, the benzyl-substituted and disubstituted *gem*-diborylalkanes did not give any detectable amount of targeted products under identical conditions.

Scheme 3. Effects of the Boryl Group in the Copper-Catalyzed Electrophilic Amination of Phenethyl-Substituted *gem*-Diborylmethanes 1c (Bpin vs Bneo)



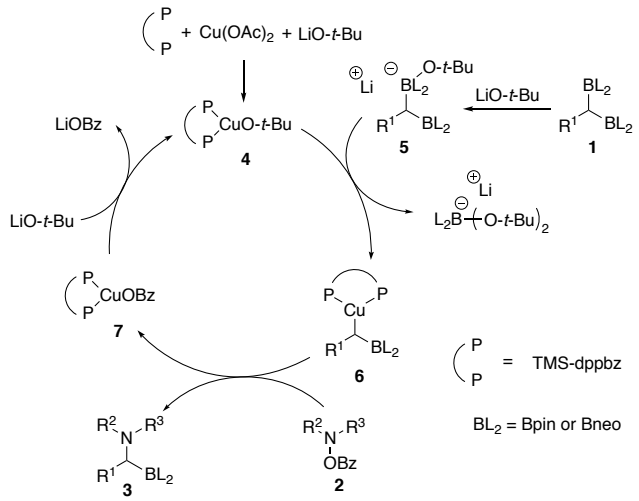
Scheme 4. Copper-Catalyzed Electrophilic Amination of Various *gem*-Diborylalkanes 1-Bneo with Hydroxylamines 2b[a]



[a] Reaction conditions for amination: **1-Bneo** (0.45 mmol), **2b** (0.15 mmol), $Cu(OAc)_2$ (0.015 mmol), TMS-dppbz (0.015 mmol), LiO-*t*-Bu (0.60 mmol), THF (0.9 mL), rt, 24 h, N_2. Reaction conditions for conversion into borate: KHF_2 (3.0 mmol), THF/H_2O (1.5 mL/0.5 mL), rt, 2 h. Isolated yields as the borate form **3-BF$_3$** are shown. [b] At 30 °C.

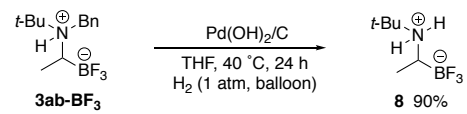
We attempted to propose that the mechanism of the reaction of *gem*-diborylalkane **1** with hydroxylamine **2** is as follows (Scheme 5). Initial reduction and salt metathesis of $Cu(OAc)_2$ with LiO-*t*-Bu and coordination with the TMS-dppbz ligand form the starting copper alkoxide species **4**. On the other hand, the organoborate **5** is generated in situ from the *gem*-diborylalkane **1** and LiO-*t*-Bu.[4-7] Transmetalation between **4** and **5** is followed by the electrophilic amination with the hydroxylamine **2** to afford the targeted α-aminoboronic acid derivative **3**. The ligand exchange of concurrently formed CuOBz **7** with LiO-*t*-Bu regenerates the copper alkoxide **4** to complete the catalytic cycle. The less congested neopentylglycol-derived **1-Bneo** can undergo the transmetalation step much more readily than the pinacol-derived **1-Bpin**. Additionally, the formation of reactive borate **5** is enhanced, which was confirmed by ^1H and ^{11}B NMR analysis (see the Supporting Information for details). Although the exact reason for the uniquely high performance of TMS-dppbz remains unclear (Scheme 1), an attractive London dispersion is likely involved to accelerate the otherwise challenging transmetalation.[18]

Scheme 5. Plausible Mechanism



Finally, we attempted the deprotection of the benzyl substituent from the α-aminoborate **3ab-BF$_3$** (Scheme 6). The hydrogenolysis proceeded under the standard $Pd(OH)_2$/C-catalyzed conditions without any detectable decomposition to deliver the corresponding secondary amine **8** in 90% yield; the free NH moiety can be a good synthetic handle for further manipulation of the α-aminoborate.

Scheme 6. Deprotection of 3ab-BF$_3$



In conclusion, we have developed a copper-catalyzed electrophilic amination of *gem*-diborylalkanes with the hydroxylamines. The reaction proceeds with high chemoselectivity under mild conditions, giving the α-aminoborates that have great potential in medicinal and pharmaceutical chemistry. The copper catalysis is the first example of a successful catalytic substitution reaction of *gem*-diborylalkanes with heteroatom coupling partners, to the best of our knowledge. Additionally, we have found the reactivity of neopentylglycol-derived diborylalkanes is higher than those of the more common pinacol-derived ones, which will find additional applications in further developments of *gem*-diborylalkanes in transition metal catalysis. Our laboratory is currently seeking to improve catalyst turnover, expand the substrate scope, and develop asymmetric catalysis.[19]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01640.

^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}, and ^{11}B NMR spectra, ORTEP drawing, and NMR studies (PDF)

Accession Codes

CCDC 1912150 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) We preliminarily screened some chiral ligands and found (*S,S*)-Xyl-BDPP to induce enantioselectivity, but the enantiomeric ratio (er) was just 75:25. See the Supporting Information for more details. Additionally, we also tried the Suzuki-Miyaura cross-coupling reaction of **3ab-BF$_3$** under conditions suitable for the α-amidotrifluoroborate, which were recently reported by Ohmura and Suginome: Ohmura, T.; Miwa, K.; Awano, T.; Suginome, M. *Chem–Asian J.* **2018**, *13*, 2414. However, only <10% product was detected.