Communication

Regioselective and Stereospecific Copper-Catalyzed Aminoboration of Styrenes with Bis(pinacolato)diboron and O-Benzoyl-N,N-dialkylhydroxylamines

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Regioselective and Stereospecific Copper-Catalyzed Aminoboration of Styrenes with Bis(pinacolato)diboron and *O*-Benzoyl-*N,N*-dialkylhydroxylamines

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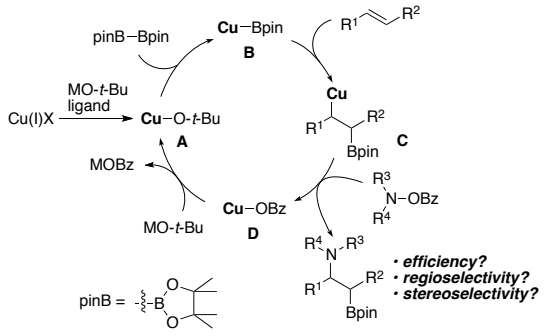
Supporting Information Placeholder

Abstract: A copper-catalyzed regioselective and stereospecific aminoboration of styrenes with bis(pinacolato)diboron and *O*-benzoyl-*N,N*-dialkylhydroxylamines has been developed to deliver the corresponding β-aminoalkylboranes in good yields. The copper catalysis enables introduction of both amine and boron moieties to C–C double bonds simultaneously in a *syn* fashion. Moreover, the use of chiral biphosphine ligand, (*S,S*)-Me-Duphos, can provide a catalytic enantioselective route to optically active β-aminoalkylboranes.

Organoborons constitute an important class of compounds in organic synthesis owing to their high utilities for carbon–carbon and carbon–heteroatom bond forming reactions. Now they are ubiquitously found in the synthesis of complex natural products, biologically active compounds, and functional materials.[1] Among numerous approaches to organoboron compounds, transition-metal-catalyzed addition reactions of boron functionalities to C–C multiple bonds have recently received significant attention. In particular, catalytic difunctionalization are strongly appealing because they enable introduction of both boron and other functional groups to organic molecules in one synthetic operation and provide a facile access to complex, densely functionalized organoboron compounds. To date, B–B,[2] B–Si,[3] B–Ge,[4] B–Sn,[5] B–S,[6] and B–C[7] single bonds are added across alkenes, alkynes, and dienes in the presence of a catalytic amount of metal complexes. In such a reaction, the special organoboron reagents are prepared in advance, and their boron-element single bonds are often activated through the oxidative addition to the low-valent metal center. A good alternative is the transmetalative approach, in which boron and carbon functionalities are incorporated from two different components.[8] Despite the above advances in this field, there is no successful report of catalytic, simultaneous addition of boron and nitrogen groups into C–C unsaturated molecules (aminoboration). Given the ubiquity of amino groups in natural products and pharmaceutical targets,[9] the expected product can be a highly useful building block in synthetic chemistry, and thus the development of a new catalytic system directed toward the aminoboration is strongly desired. Herein, we report a copper-catalyzed aminoboration of styrenes with bis(pinacolato)diboron and *O*-benzoyl-*N,N*-dialkylhydroxylamines. The reaction proceeds very smoothly even at room temperature with high regioselectivity and stereospecificity. Moreover, the preliminary catalytic enantioselective variant is achieved by using an appropriate chiral biphosphine ligand.

Our scenario for the catalytic aminoboration of alkenes is illustrated in Scheme 1. The working hypothesis is prompted by recent developments of copper-catalyzed hydroboration chemistry with bis(pinacolato)diboron[10] and current studies on umpolung, electrophilic aminations by our group[11] and others.[12] An initial ligand exchange of a Cu(I) complex and MO-*t*-Bu (**A**)[13] followed by σ-bond metathesis with bis(pinacolato)diboron generates a borylcopper species **B**.[14] Subsequent insertion of the alkene into Cu–B bond of **B** furnishes a borylated alkylcopper intermediate **C**.[15] An umpolung, electrophilc amination with the *O*-benzoylhydroxylamine then occurs to form the desired aminoboration product and a CuOBz complex **D**.[12j] Final ligand exchange with MO-*t*-Bu regenerates the starting CuO-*t*-Bu complex **A** to complete the catalytic cycle.[11c,12j,16] If the reaction of the borylcopper **B** with the alkene proceeded selectively even in the presence of the *O*-benzoylhydroxylamine, the chemoselective aminoboration could be realized.[17] An additional conceivable problem is a control of regio- and stereochemistry. In particular, the stereochemical course of the C–N forming process somewhat remains elusive,[18] while the alkenes are known to insert into the borylcopper Cu–B in a *syn* fashion.[15]

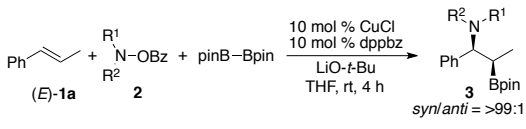
Scheme 1. Working Hypothesis



In accordance with the above assumption, we began our optimization studies with *trans*-β-methylstyrene ((*E*)-**1a**) and *O*-benzoyl-*N,N*-diethylhydroxylamine (**2a**) as model substrates, because styrene derivatives tend to react with the borylcopper species regioselectively and thus regioselective issues can be obviated.[10,15] After the extensive screening of various copper salts, ligands, bases, and solvents, we were pleased to find that a combination of CuCl/dppbz (dppbz = 1,2-bis(diphenylphosphino)benzene) catalyst and LiO-*t*-Bu catalyzed the desired transformation in THF even at room temperature (Table 1, entry 1).[19] To our delight, the product **3aa** was obtained in a good yield as the single regioisomer and diastereomer (*syn*/*anti* = >99:1).[20] Under the optimized conditions, we performed the catalytic aminoboration of (*E*)-**1a** with a variety of *O*-benzoyl-*N,N*-dialkylhydroxylamines **2**. Benzyl-substituted amines **2b** and **2c** underwent the reaction very smoothly to afford the corresponding aminoborated products **3ab** and **3ac** in 83% and 73% isolated yields, respectively; additional derivatization of which could be easily operative after the appropriate deprotection

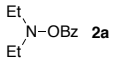
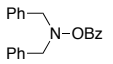
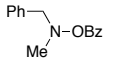
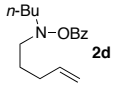
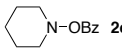
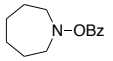
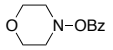
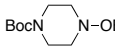
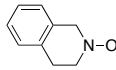
of benzyl groups[21] (entries 2 and 3). The *O*-benzoylhydroxylamine **2d** that bears a 1-pentenyl substituent furnished the usual product **3ad** exclusively (entry 4), excluding the possibility of an aminyl radical pathway.[22] Not only acyclic but also cyclic amines also participated in the reaction. The six-membered piperidine and seven-membered azepane were introduced to (*E*)-**1a** efficiently (entries 5 and 6). Moreover, morpholine, Boc-protected piperazine, and bicyclic tetrahydroisoquinoline are also available for use (entries 7–9). Notably, in latter two cases, NaO-*t*-Bu gave a better result than LiO-*t*-Bu (entries 8 and 9). In addition, the reaction could be carried out on a 4-fold larger scale, indicating the good reliability and reproducibility of the process (entry 2). On the other hand, bis(neopentylglycolato)diboron (neoB–Bneo) instead of pinB–Bpin gave a lower yield of the aminoborated product (entry 10). Regardless of steric and electronic nature of *O*-benzoyl-*N*,*N*-dialkylhydroxylamines, the aminoboration proceeded with excellent regioselectivity and diastereoselectivity: the amine and boron groups are selectively installed to the benzylic and homobenzylic positions, respectively, and the only *syn*-stereoisomer was detected in all entries.

Table 1. Copper-Catalyzed Aminoboration of *trans-b*-Methylstyrene ((*E*)-1a) with Bis(pinacolato)diboron and Various *O*-Benzoylhydroxylamines 2[a]



(*E*)-**1a** **2** **3**

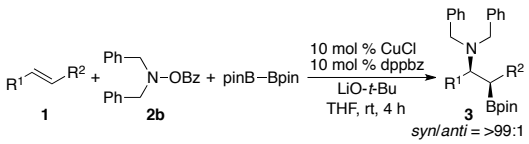
syn/*anti* = >99:1

entry	**2**	**3**, yield (%)[b]
1	 **2a**	**3aa**, 81 (66)
2	 **2b**	**3ab**, 86 (83, 85[c])
3	 **2c**	**3ac**, 86 (73)
4	 **2d**	**3ad**, 91 (86)
5	 **2e**	**3ae**, 74
6	 **2f**	**3af**, 95
7	 **2g**	**3ag**, 44 (43)
8[d]	 **2h**	**3ah**, (58)
9[d]	 **2i**	**3ai**, (64)
10[e]	**2a**	**3ab'**, 30

[a] A mixture of CuCl (0.025 mmol), dppbz (0.025 mmol), (*E*)-**1a** (0.25 mmol), **2** (0.38 mmol), pinB–Bpin (0.38 mmol), and LiO-*t*-Bu (0.75 mmol) in THF (1.5 mL) was stirred at room temperature for 4 h under N_2. [b] Yield estimated by ^{1}H NMR with 1-methylnaphthalene as an internal standard. Yield of isolated product in parenthesis. The lower isolated yield is due to the partial decomposition during chromatographic purification. See the Supporting Information for the detailed procedure. [c] On a 1.0 mmol scale. [d] With **2** (0.30 mmol), pinB–Bpin (0.30 mmol), and NaO-*t*-Bu (0.50 mmol). [e] With bis(neopentylglycolato)diboron (neoB–Bneo) instead of pinB–Bpin.

We next investigated the scope of alkene substrates with **2b** as an electrophilic nitrogen source (Table 2). *trans*-*β*-Methylstyrenes that bear electron-donating methoxy as well as electron-withdrawing groups underwent the aminoboration without any difficulties (entries 1 and 2). Terminal styrenes also reacted with the diboron and **2b** regioselectively, in which the boron was introduced to the terminal position while the nitrogen atom was attached to the benzylic position. Electronically and sterically diverse substituents were tolerated under reaction conditions (entries 4–6). Particularly notable is the compatibility with the aryl-Br bond (entry 6).[23] The fused naphthalene ring did not interfere with the reaction (entry 7). It is noteworthy that the cinnamyl alcohol derivative **1i** produced the corresponding densely functionalized alkylboranes **3ia** and **3ib** in synthetically useful yields (entries 8 and 9). Moreover, the simple aliphatic olefin, 1-octene, also could be aminoborated with good regioselectivity (88:12) with 4,5-bis(diphenylphosphino)-9,9'-dimethylxanthene (xantphos) as a ligand under otherwise identical conditions (entry 10). The catalysis accommodated the steric hinderance at the allylic positions; **1k** and **1l** also underwent the aminoboration without any difficulties (entries 11 and 12). On the other hand, (*E*)-ethyl crotonate and (*E*)-crotonitrile provided the corresponding hydroborated products, in which the boryl group and hydrogen atom were introduced to the β and α positions, respectively, but the origin of the hydrogen atom was not clear at this stage (data not shown).

Table 2. Copper-Catalyzed Aminoboration of Various Alkenes 1 with Bis(pinacolato)diboron and *O*-Benzoyl-*N*,*N*-dibenzylhydroxylamines (2b)[a]



1 **2b** **3**

syn/*anti* = >99:1

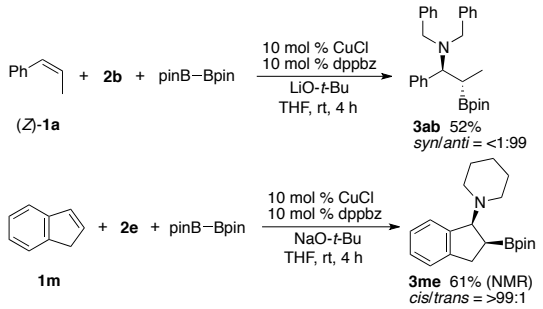
entry	R^1, R^2 **1**	**3**, yield (%)[b]
1	R^1 = 4-$MeOC_6H_4$, R^2 = Me (**1b**)	**3bb**, 81 (69)
2[c]	R^1 = 4-$CF_3C_6H_4$, R^2 = Me (**1c**)	**3cb**, 81 (76)[d]
3	R^1 = Ph, R^2 = H (**1d**)	**3db**, 91 (74)
4	R^1 = 4-$MeOC_6H_4$, R^2 =H (**1e**)	**3eb**, 78 (76)
5	R^1 = 4-$CF_3C_6H_4$, R^2 = H (**1f**)	**3fb**, 77 (73)
6	R^1 = 2-BrC_6H_4, R^2 = H (**1g**)	**3gb**, (66)
7	R^1 = 2-naphthyl, R^2 = H (**1h**)	**3hb**, (51)
8[e]	R^1 = Ph, R^2 = CH_2OMe (**1i**)	**3ia**, 64 (48)
9	**1i**	**3ib**, 43 (42)
10[f]	R^1 = *n*-C_6H_{13}, R^2 = H (**1j**)	**3jb**, 71 (71)[g]
11[h]	R^1 = 3-ClC_6H_4, R^2 = *i*-Pr (**1k**)	**3kb**, (79)
12[f]	R^1 = *c*-C_6H_{11}, R^2 = H (**1l**)	**3lb**, (67)[i]

[a,b] See the footnote of Table 1. [c] With a 96:4 mixture of *E*/*Z* isomer. [d] Isolated as a 96:4 mixture of *syn*- and *anti*-stereoisomers. [e] With **2a** instead of **2b**. [f] With xantphos instead of dppbz. [g] Isolated as an 88:12 regioisomeric mixture of **3jb** and **3jb'**. [h] With a 92:8 mixture of *E*/*Z* isomer. [i] Isolated as a 90:10 regioisomeric mixture of **3lb** and **3lb'**.

In entry 2 of Table 2, we observed a small but significant amount of *anti*-stereoisomer probably owing to the contamination of *Z*-isomer of the starting styrene **1c**.[24] The phenomenon suggests the potential of stereospecificity under the present catalysis. To check the possibility, we implemented aminoboration of *cis*-*β*-methylstyrene ((*Z*)-**1a**) (Scheme 2).

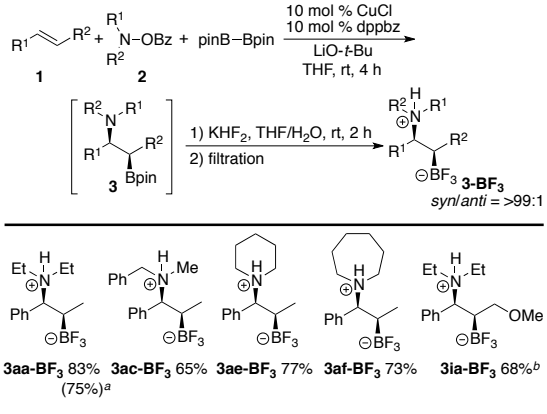
Pleasingly, the reaction occurred stereospecifically and *anti*-**3ab** was formed exclusively,[20] while the efficiency was relatively low.[25] The cyclic *Z*-alkene, indene (**1m**) was also transformed stereospecifically into the *cis*-1,2-aminoborane **3me**. The stereochemical outcomes again confirm the *syn*-addition mode of the present aminoboration.[26] Given the *syn* addition of the borylcopper Cu–B across alkenes (Scheme 1, B to C), the C–N bond formation occurs with retention of configuration (Scheme 1, C to D).

Scheme 2. Catalytic Aminoboration of Z-Styrenes



In the above studies, some aminoborated products were unstable for the column chromatographic purification, and the relatively lower isolated yields were obtained compared to those checked by ^{1}H NMR in the crude materials. Moreover, contamination of some impurities was inevitable in several cases. Thus, to modify the purification process, we attempted the direct conversion into trifluoroborate salts. Gratifyingly, upon exposure of the crude reaction mixture into KHF_2 in a THF/H_2O mixed solvent, the corresponding borate salts **3-BF$_3$** could be obtained generally in higher yields through simple filtration.[27] Analogous to Molander's original work,[28] all **3-BF$_3$** were obtained as not a potassium salt but an internal ammonium salt (Scheme 3). It should be noted that the trifluoroborates were isolated with high purity, judged by ^{1}H NMR. The analytically pure salts are quite stable and can be stored under ambient conditions at least for three months. Additionally, with the modified procedure, an acceptable isolated yield of **3aa-BF$_3$** was observed even in the presence of 5 mol % of CuCl/dppbz.

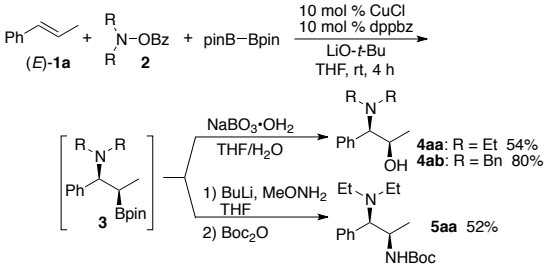
Scheme 3. Direct Conversion into Internal Borate Salts



[a] With 5 mol % of CuCl/dppbz. [b] With NaO-*t*-Bu instead of LiO-*t*-Bu.

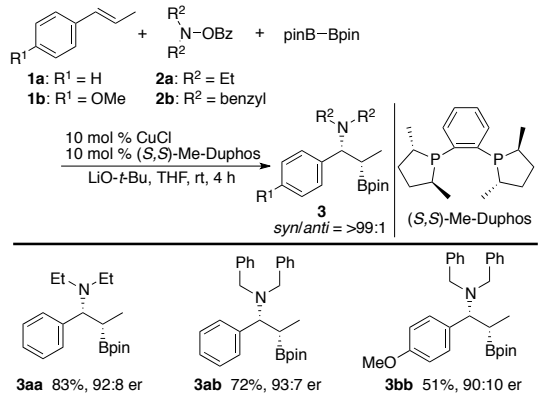
To demonstrate synthetic utilities of the present aminoboration, transformation of the products was carried out (Scheme 4). The catalytic aminoboration followed by oxidation with $NaBO_3$•OH_2 afforded the corresponding *syn*-1,2-aminoalcohols **4** in good overall yields. Moreover, the stereoretentive amination of the resultant C–B bond[12m] with MeONHLi also proceeded to form the *syn*-1,2-diamine **5aa** at the synthetically useful level. These sequential manipulations are a good alternative to the precedented osmium-catalyzed oxyamination[29] and diamination[30] of styrenes.

Scheme 4. Transformation of Aminoborated Products



Finally, we applied the present protocol to the catalytic enantioselective aminoboration by using an appropriate optically active ligand. Preliminary investigation into some representative chiral biphosphines identified a Duphos-type ligand to be a promising candidate (Scheme 5). The aminoboration of (*E*)-**1a** with **2a** in the presence of (*S*,*S*)-Me-Duphos afforded the corresponding aminoborane **3aa** in 83% yield with 92:8 er.[31] Similar enantiomer ratios were observed for other substrate combinations. Further efforts on increasing the enantioselectivity and elucidation of the stereochemical course are now in progress.

Scheme 5. Catalytic Enantioselective Aminoboration



In conclusion, we have developed a copper-catalyzed aminoboration of styreneswith bis(pinacolato)diboron and *O*-benzoyl-*N*,*N*-dialkylhydroxylamines. The key to success is the introduction of the umpolung, electrophilic amination chemistry. The catalytic reaction takes place very smoothly even at room temperature as well as regioselectively and stereospecifically. Moreover, the asymmetric catalysis is also achieved by using an appropriate chiral biphosphine ligand, while further improvements are essential. Current research seeks to elucidate the detailed reaction mechanism,[32] expand the substrate scope, and develop additional useful transformations of the aminoborated products.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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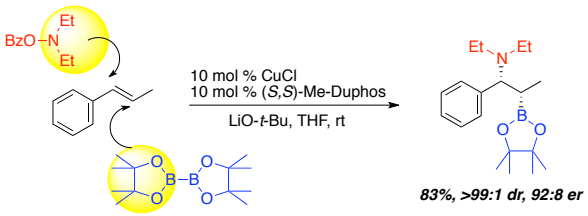
BzO
N
Et
Et
10 mol % CuCl
10 mol % (S,S)-Me-Duphos
LiO-t-Bu, THF, rt
Et
N
Et
B
O
O
O
B
O
O
83%, >99:1 dr, 92:8 er