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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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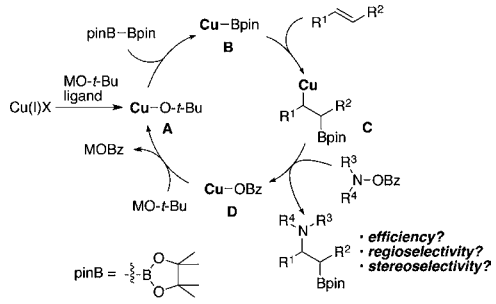
Supporting Information

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

Organoborons constitute an important class of compounds in organic synthesis because of their high utilities for C−C and C−heteroatom bond formation, and they are ubiquitous 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 is strongly appealing because it enables the introduction of both boron and other functional groups to organic molecules in one synthetic operation and provides facile access to complex, densely functionalized organoboron compounds. To date, B−E single bonds (E = B,[2] Si,[3] Ge,[4] Sn,[5] S,[6] and C[7]) can be added across alkenes, alkynes, and dienes in the presence of catalytic amounts of metal complexes. In such reactions, the special organoboron reagents are prepared in advance, and their B−E single bonds are often activated through oxidative addition to the low-valent metal center. A good alternative is transmetalation, in which the B and C functionalities are incorporated from two different components.[8] Despite the above advances in this field, there is no report of successful simultaneous catalytic addition of B and N groups to C−C unsaturated molecules (aminoboration). In view of the ubiquity of amino groups in natural products and pharmaceuticals,[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 aminoboration is strongly desired. Here we report a Cu-catalyzed aminoboration of styrenes with bis(pinacolato)diboron (pinB−Bpin) and *O*-benzoyl-*N*,*N*-dialkylhydroxylamines. The reaction proceeds very smoothly even at room temperature (rt) with high regio- and stereoselectivity. Moreover, a preliminary catalytic enantioselective variant was achieved by using an appropriate chiral biphosphine ligand.

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

Scheme 1. Working Hypothesis



In accordance with our hypothesis, we began our optimization studies with *trans*-β-methylstyrene [(*E*)-**1a**] and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2a**) as model substrates, as styrene derivatives tend to react with borylcopper species regioselectively, thus obviating regioselectivity issues.[10,15] After extensive screening of various Cu salts, ligands, bases, and solvents, we were pleased to find that a combination of CuCl/dppbz [dppbz =1,2-bis(diphenylphosphino)benzene] and LiO-*t*-Bu catalyzed

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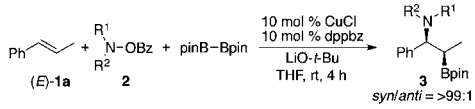
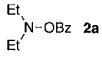
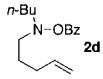
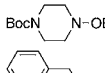
the desired transformation in tetrahydrofuran (THF) even at rt (Table 1, entry 1).[19] To our delight, the product **3aa** was obtained in good yield as a single regio- and diastereomer (syn/anti ≥ 99:1).[20] Under the optimized conditions, we performed the catalytic aminoboration of (*E*)-**1a** with 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 isolated yields of 83 and 73%, respectively (entries 2 and 3); additional derivatization of **3ab** and **3ac** could be facile after removal of the benzyl groups.[21] Hydroxylamine **2d** bearing 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 efficiently introduced into (*E*)-**1a** (entries 5 and 6). Moreover, morpholine, Boc-protected piperazine, and bicyclic tetrahydroisoquinoline could also be used (entries 7–9). Notably, in the latter two cases, NaO-*t*-Bu gave better results 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 the steric and electronic nature of **2**, the aminoboration proceeded with excellent regio- and diastereoselectivity: the amine and boron groups were selectively installed at the benzylic and homobenzylic positions, respectively, and the only syn stereoisomer was detected.

Table 1. Cu-Catalyzed Aminoboration of (*E*)-1a[a]

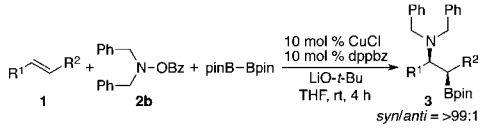


entry	2	3, yield (%)[b]
1	 **2a**	**3aa**, 81 (66)
2	 **2b**	**3ab**, 86 (83, 85[c])
3	 **2c**	**3ac**, 86 (73)
4	 **2d**	**3ad**, 91 (86)
5	 **2e**	**3ae**, 74
6	 **2f**	**3af**, 95
7	 **2g**	**3ag**, 44 (43)
8[d]	 **2h**	**3ah**, (58)
9[d]	 **2i**	**3ai**, (64)
10[e]	**2a**	**3ab'**, 30

[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 rt for 4 h under N_2. [b]^{1}H NMR yields using 1-methylnaphthalene as an internal standard. Isolated yields are given in parentheses. The lower isolated yields are due to partial decomposition during chromatographic purification.[27] [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 neoB–Bneo instead of pinB–Bpin.

We next investigated the scope of alkene substrates using **2b** as the electrophilic nitrogen source (Table 2). *trans*-*β*-Methylstyrenes bearing an electron-donating or electron-withdrawing group underwent the aminoboration without any difficulties (entries 1 and 2). Terminal styrenes also reacted with the diboron and **2b** regioselectively, with B attached at the terminal position and N at the benzylic position. Electronically and sterically diverse substituents were tolerated under the 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 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 was also aminoborated with good regioselectivity (88:12) using 4,5-bis(diphenylphosphino)-9,9′-dimethylxanthene (Xantphos) as the ligand under otherwise identical conditions (entry 10). The catalysis accommodated steric hindrance at the allylic positions, as **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 H atom were introduced at the *β* and *α* positions, respectively (data not shown); the origin of the H atom was not clear at this stage.

Table 2. Cu-Catalyzed Aminoboration: Alkene Scope[a]



entry	R^1, R^2 (**1**)	**3**, yield (%)[b]
1	R^1 = 4-MeOC$_6$H$_4$, R^2 = Me (**1b**)	**3bb**, 81 (69)
2[c]	R^1 = 4-CF$_3$C$_6$H$_4$, R^2 = Me (**1c**)	**3cb**, 81 (76)[d]
3	R^1 = Ph, R^2 = H (**1d**)	**3db**, 91 (74)
4	R^1 = 4-MeOC$_6$H$_4$, R^2 =H (**1e**)	**3eb**, 78 (76)
5	R^1 = 4-CF$_3$C$_6$H$_4$, R^2 = H (**1f**)	**3fb**, 77 (73)
6	R^1 = 2-BrC$_6$H$_4$, 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$_2$OMe (**1i**)	**3ia**, 64 (48)
9	**1i**	**3ib**, 43 (42)
10[f]	R^1 = *n*-C$_6$H$_{13}$, R^2 = H (**1j**)	**3jb**, 71 (71)[g]
11[h]	R^1 = 3-ClC$_6$H$_4$, R^2 = *i*-Pr (**1k**)	**3kb**, (79)
12[f]	R^1 = *c*-C$_6$H$_{11}$, R^2 = H (**1l**)	**3 lb**, (67)[i]

[a]See Table 1, footnote *a*. [b]See Table 1, footnote *b*. [c]With a 96:4 *E*/*Z* mixture. [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 *E*/*Z* mixture. [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 the anti stereoisomer, probably resulting from contamination with the *Z* isomer of the starting styrene **1c**.[24] This suggested the potential for stereospecificity in the present catalysis. To check this possibility, we implemented aminoboration of *cis*-*β*-methylstyrene [(*Z*)-**1a**] (Scheme 2). Pleasingly, the reaction occurred stereospecifically to form *anti*-**3ab** exclusively,[20] but the efficiency was relatively low.[25] A cyclic *Z* alkene, indene (**1m**), was also transformed stereospecifically into the *cis*-1,2-aminoborane **3me**. These stereochemical outcomes

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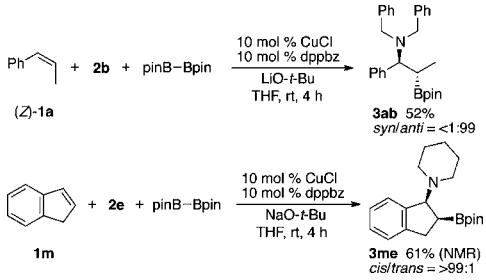
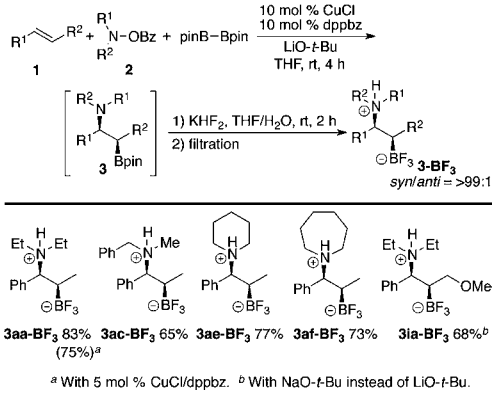
Scheme 2. Catalytic Aminoboration of (*Z*)-Styrenes



confirmed the syn addition mode of the present aminoboration.[26] In view of the syn addition of the Cu–B bond across the alkene (Scheme 1, **B** → **C**), C–N bond formation occurs with retention of configuration (Scheme 1, **C** → **D**).

In the above studies, some aminoborated products were unstable under column chromatographic purification, so the obtained isolated yields were lower than the ^{1}H NMR yields of the crude materials. Moreover, contamination with 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 to KHF_2 in THF/H_2O, the corresponding borate salts **3-BF$_3$** were obtained in generally higher yields through simple filtration.[27] Analogous to Molander's original work,[28] all of the **3-BF$_3$** salts were obtained as internal ammonium salts rather than potassium salts (Scheme 3). It

Scheme 3. Direct Conversion into Internal Borate Salts



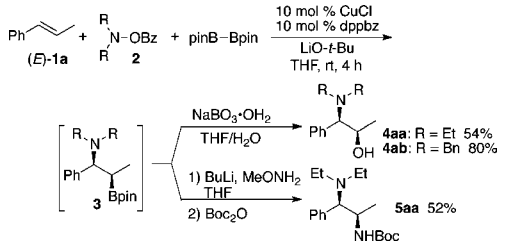
[a] With 5 mol % CuCl/dppbz. [b] With NaO-*t*-Bu instead of LiO-*t*-Bu.

should be noted that the trifluoroborates were isolated with high purity, as judged by ^{1}H NMR analysis. The analytically pure salts were quite stable and could be stored under ambient conditions at least for 3 months. Additionally, with the modified procedure, an acceptable isolated yield of **3aa-BF$_3$** was observed even in the presence of 5 mol % CuCl/dppbz.

To demonstrate synthetic utility of the present aminoboration, transformations of the products were carried out (Scheme 4). Aminoboration followed by oxidation with $NaBO_3{\cdot}OH_2$ afforded the corresponding *syn*-1,2-aminoalcohols **4** in good overall yields. Moreover, stereoretentive amination of the C–B bond[12m] with MeONHLi formed *syn*-1,2-diamine **5aa** at a synthetically useful level. These sequential manipulations are a good alternative to the precedented Os-catalyzed oxyamination[29] and diamination[30] of styrenes.

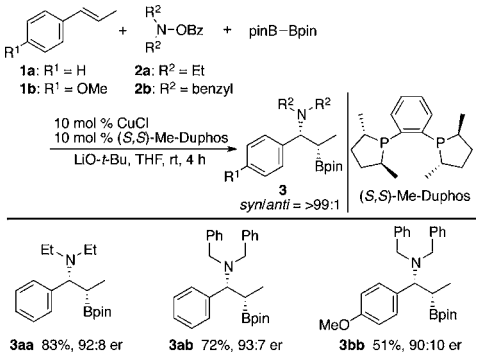
Finally, we applied the present protocol to catalytic enantioselective aminoboration by using an appropriate optically active ligand. Preliminary investigations using some representa-

Scheme 4. Transformations of the Aminoborated Products



tive chiral biphosphines identified a Duphos-type ligand to be a promising candidate (Scheme 5). Aminoboration of (*E*)-**1a** with

Scheme 5. Catalytic Enantioselective Aminoboration



2a in the presence of (*S*,*S*)-Me-Duphos afforded **3aa** in 83% yield with 92:8 er.[31] Similar enantiomer ratios were observed for other substrate combinations. Further efforts to increase the enantioselectivity and elucidate the stereochemical course are now in progress.

In conclusion, we have developed a Cu-catalyzed aminoboration of styrenes with bis(pinacolato)diboron and *O*-benzoyl-*N*,*N*-dialkylhydroxylamines. The key to its success is the introduction of the umpolung electrophilic amination chemistry. The catalytic reaction is very smooth even at room temperature and is regio- and stereospecific. Also, asymmetric catalysis was achieved using an appropriate chiral biphosphine ligand, although further improvements are essential. Efforts to elucidate the detailed reaction mechanism,[32] expand the substrate scope, and develop additional useful transformations of the aminoborated products are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and characterization data. 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 interest.

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(19) In the absence of CuCl, dppbz, or CuCl/dppbz, no aminoborated product was detected (see the SI for optimization details).

(20) The relative stereochemistry was confirmed after oxidation to the corresponding aminoalcohol (see the SI for details).

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(23) The conceivable Br migration reaction was not detected at all. See: Grigg, R. D.; Hoveln, R. V.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 16131.

(24) Although **1k** also contained the *Z* isomer, only the syn product was observed, probably because the *Z* isomer had much lower reactivity and could not participate in the reaction (see ref 25 for the effect of 1,3-allylic strain in the insertion step).

(25) Such a reactivity trend is consistent with reported literature and probably occurs because 1,3-allylic strain decreases the aryl−alkene conjugation, which lowers the alkene π^* orbital, resulting in more effective back-bonding. See ref 10a and: (a) Dang, Li.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824. (b) Deng, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443.

(26) Cyclohexene gave the corresponding *cis*-1,2-aminoborane stereospecifically, albeit in only 17% ^{1}H NMR yield.

(27) See the SI for the detailed procedure.

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(31) The enantiomeric ratio and absolute configuration were determined after oxidation to the corresponding aminoalcohol (see the SI for details).

(32) LiO-*t*-Bu also can accelerate some elementary steps by coordination to the Cu or B center. For a relevant discussion, see: (a) Lee, K.-s.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253. (b) Kleeberg, C.; Crawford, A. G.; Batsanov, A. S.; Hodgkinson, P.; Apperley, D. C.; Cheung, M. S.; Lin, Z.; Marder, T. B. *J. Org. Chem.* **2012**, *77*, 785. (c) Pubill-Ulldemolins, C.; Bonet, A.; Bo, C.; Gulyás, H.; Fernández, E. *Chem.—Eur. J.* **2012**, *18*, 1121. (d) Ito, H.; Miya, T.; Sawamura, M. *Tetrahedron* **2012**, *68*, 3423. (e) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277.

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