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Ligand-Controlled Regiodivergent Cu-Catalyzed Aminoboration of Unactivated Terminal Alkenes

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Supporting Information

ABSTRACT: A ligand-controlled regiodivergent Cu-catalyzed aminoboration of unactivated terminal alkenes with diboron reagents and hydroxylamines has been developed. The xantphos-ligated CuCl complex guides the boron and amino groups to the terminal and internal positions, respectively. On the other hand, the opposite regioisomers are selectively obtained under the N-heterocyclic carbene-based IPrCuBr catalysis. The two Cu catalysts can readily transform simple and abundant terminal alkenes into highly valuable β-borylalkylamines regiodivergently.

Terminal olefins are simple and abundant bulk commodities, and now more than 1600 compounds are commercially available from various suppliers. The derivatization of such feedstock materials is thus of great importance in organic synthesis. Particularly, the catalytic aminative difunctionalization is highly attractive from the synthetic point of view because the both positions of the alkene π bond are simultaneously functionalized in one synthetic operation, and relatively simple starting materials can be readily transformed into the highly functionalized alkylamines of high value in medicinal and material chemistry.[1] Although many synthetic chemists have developed numerous catalytic systems including the Os-catalyzed oxyamination[2] and Pd-,[3] Cu-,[4] and Fe-based[5] processes, the application to electronically unbiased, unactivated terminal alkenes in a fully intermolecular manner is still challenging. Additionally, when the two different functional groups are introduced (unsymmetrical difunctionalization), the regiochemical issue frequently occurs. While extensive screening of reaction conditions and/or elegant ligand evaluations sometimes gives one regioisomer successfully, another regioisomer is generally difficult to obtain.[6] Given the ready accessibility and robust nature of simple terminal alkenes, further development of their catalytic aminative difunctionalization with high regiocontrol is great appealing. Herein, we report a ligand-controlled, regiodivergent Cu-catalyzed aminoboration of unactivated terminal alkenes with diboron reagents and hydroxylamines: By the proper choice of ancillary ligands, both regioisomeric β-borylalkylamines are obtained with high regioselectivity from a single terminal alkene. The present Cu catalysts can provide an unprecedented regiodivergent approach to borylated alkylamines of high synthetic utility. Related regiodivergency is observed in the Cu-catalyzed hydroboration of terminal alkynes[7] and silacarboxylation of terminal allenes,[8] but the use of simple terminal alkenes still remains underdeveloped.

Recently, we focused on an umpolung, electrophilic amination strategy[9,10] and succeeded in the development of the Cu-catalyzed aminoboration of styrenes and strained alkenes.[11] In the course of continuous studies on the umpolung-enabled aminoboration, we performed the reaction of a simple terminal alkene, 1-octene (**1a**), with bis(pinacolato)diboron (pinB−Bpin)[12] and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**). Under the previous optimized conditions (a CuCl/dppbz catalyst and a LiO-*t*-Bu base in THF),[11a] however, a 31:69 regioisomeric mixture of **3aa-Bpin** and **4aa-Bpin** was formed in 31% combined yield (Table 1, entry 1). Similar low to moderate regioselectivity was observed with some representative bidentate and monodentate phosphine ligands (entries 2−6). On the other hand, the xantphos ligand showed unique high regioselectivity, forming **3aa-Bpin** and **4aa-Bpin** in a ratio of 88:12 (entry 7). Additionally notable is the effect of counter cations of the *tert*-butoxide bases: the regioselectivity increased in order of K > Na > Li (entries 7−9), while KO-*t*-Bu largely dropped the yield because of the competitive transesterification with benzoyl moiety in **2a**. Finally, with the isolated Cu(xantphos)Cl and NaO-*t*-Bu as the precatalyst and alkoxide base, respectively, we obtained terminally borylated **3aa-Bpin** in 76% yield with high regioselectivity (**3aa-Bpin**/**4aa-Bpin** = 93:7; entry 10). Although the exact reason is not clear, the premade Cu(xantphos)Cl forms a CuO-*t*-Bu/bisphosphine 1:1 complex more cleanly, which can be active species in the catalytic cycle (vide infra).

In sharp contrast, a series of N-heterocyclic carbene (NHC) ligands preferably gave the opposite regioisomer **4aa-Bpin** (entries 11−13). Especially, IPr resulted in the highest regioselectivity (**3aa-Bpin**/**4aa-Bpin** = 4:96), albeit with a poor yield (entry 12). Extensive screening of bases and solvents did not improve the reaction efficiency. However, to our delight, the replacement of pinB−Bpin with a mixed diboron reagent, pinB−Bdan, which was originally developed by Suginome,[13] increased the yield to 51%, with the maintenance of the unique regioselectivity (**3aa-Bdan**/**4aa-Bdan** = 3:97; entry 14). Although additional ligand modifications gave negative impacts on both yield and regioselectivity (entries 15−18), we pleasingly found IPrCuBr to be a better catalyst precursor for the synthetically useful yield of the internally borylated **4aa-Bdan** (entry 20). A better leaving ability of Br can accelerate the initial salt metathesis to form the starting IPrCuO-*t*-Bu complex more smoothly (vide infra). Without any Cu salts, no aminoborated

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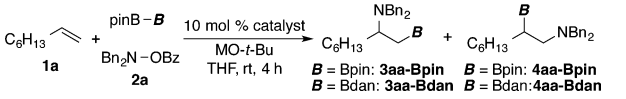
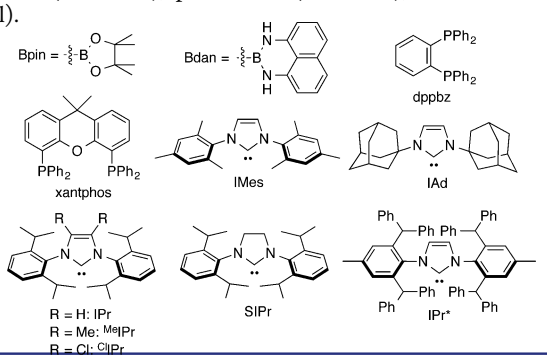
Table 1. Optimization Studies for Cu-Catalyzed Aminoboration of 1-Octene (1a)[a]



entry	catalyst	pinB−**B**	MO-*t*-Bu	% yield, **3**:**4**[b]
1	CuCl/dppbz	pinB−Bpin	LiO-*t*-Bu	31, 31:69
2	CuCl/dppe	pinB−Bpin	LiO-*t*-Bu	32, 25:75
3	CuCl/dppp	pinB−Bpin	LiO-*t*-Bu	14, 53:47
4	CuCl/dppf	pinB−Bpin	LiO-*t*-Bu	19, 53:47
5	CuCl/2PPh_3	pinB−Bpin	LiO-*t*-Bu	7, 33:64
6	CuCl/2PCy_3	pinB−Bpin	LiO-*t*-Bu	2, 28:72
7	CuCl/xantphos	pinB−Bpin	LiO-*t*-Bu	71, 88:12
8	CuCl/xantphos	pinB−Bpin	NaO-*t*-Bu	43, 93:7
9	CuCl/xantphos	pinB−Bpin	KO-*t*-Bu	25, 97:3
10[c]	**Cu(xantphos)Cl**	**pinB−Bpin**	**NaO-*t*-Bu**	**(76), 93:7**
11	CuCl/IMes	pinB−Bpin	LiO-*t*-Bu	25, 26:74
12	CuCl/IPr	pinB−Bpin	LiO-*t*-Bu	24, 4:96
13	CuCl/IAd•HBF_4	pinB−Bpin	LiO-*t*-Bu	50, 17:83
14	IPrCuCl	pinB−Bdan	LiO-*t*-Bu	51, 3:97
15	SIPrCuCl	pinB−Bdan	LiO-*t*-Bu	43, ~10:90
16	^{Me}IPrCuCl	pinB−Bdan	LiO-*t*-Bu	22, ~10:90
17	^{Cl}IPrCuCl	pinB−Bdan	LiO-*t*-Bu	5, ~10:90
18	IPr*CuCl	pinB−Bdan	LiO-*t*-Bu	21, ~10:90
19[d]	IPrCuCl	pinB−Bdan	LiO-*t*-Bu	59, 4:96
20[d]	**IPrCuBr**	**pinB−Bdan**	**LiO-*t*-Bu**	**(79), 4:96**

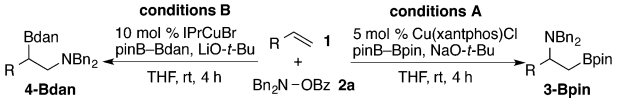
[a]A mixture of catalyst (0.025 mmol), **1a** (0.25 mmol), pinB−**B** (0.38 mmol), **2a** (0.38 mmol), and MO-*t*-Bu (0.75 mmol) in THF (1.5 mL) was stirred at rt for 4 h under N_2. [b]Combined yield of **3aa** and **4aa**, judged by ^{1}H NMR using 1-methylnaphthalene as an internal standard. Isolated yields are given in parentheses. The ratio of **3aa**:**4aa** is determined by ^{1}H NMR of the crude material. [c]With 0.013 mmol (5 mol %) of Cu(xantphos)Cl and 0.50 mmol of NaO-*t*-Bu. [d]With **2a** (1.0 mmol), pinB−Bdan (1.0 mmol), and LiO-*t*-Bu (1.0 mmol).

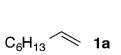
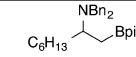
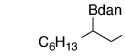
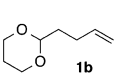
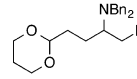
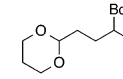
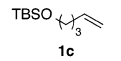
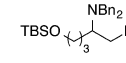
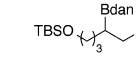
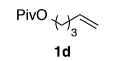
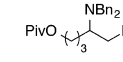
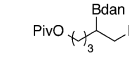
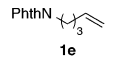
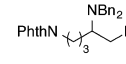
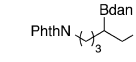
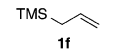
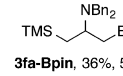
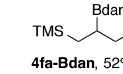
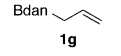
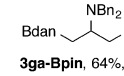
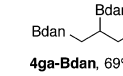
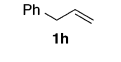
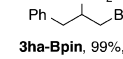
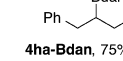
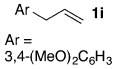
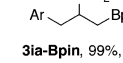
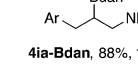
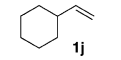
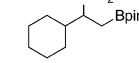
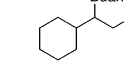
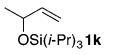
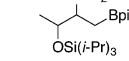
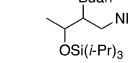


products were detected even in the presence of xantphos or IPr (data not shown).[14]

Under the optimal two conditions of entries 10 and 20 in Table 1 (conditions A and B, respectively), we performed the Cu-catalyzed regiodivergent aminoboration of an array of unactivated terminal alkenes **1** with **2a** (Table 2). Both conditions accommodated oxygen-based functional groups including acetal (**1b**), silyl ether (**1c**), and ester (**1d**), and the corresponding aminoborated products were obtained in good yields and high regiodivergency (95:5−96:4 for **3-Bpin** and 7:93−4:96 for **4-Bdan**) (entries 2−4). On the other hand, phthalimide-protected aminoalkene **1e** underwent the aminoboration smoothly and regioselectively under conditions A, whereas conditions B deprotected the imide protection to decompose the substrate (entry 5). The catalytic aminoboration

Table 2. Cu-Catalyzed Regiodivergent Aminoboration of Various Unactivated Terminal Alkenes 1 with 2a[a]



entry	**1**	**3-Bpin**, yield, **3**:**4**[b]	**4-Bdan**, yield, **3**:**4**[b]
1	 **1a**	 **3aa-Bpin**, 76%, 93:7	 **4aa-Bdan**, 79%, 4:96
2	 **1b**	 **3ba-Bpin**, 83%, 95:5	 **4ba-Bdan**, 74%, 6:94
3	 **1c**	 **3ca-Bpin**, 78%, 96:4	 **4ca-Bdan**, 67%, 4:96
4	 **1d**	 **3da-Bpin**, 67%, 96:4	 **4da-Bdan**, 44%, 7:93
5	 **1e**	 **3ea-Bpin**, 83%, 96:4	 **4ea-Bdan**, 0%, –
6	 **1f**	 **3fa-Bpin**, 36%, 56:44[c]	 **4fa-Bdan**, 52%, 1:99
7	 **1g**	 **3ga-Bpin**, 64%, 95:5	 **4ga-Bdan**, 69%, 5:95
8	 **1h**	 **3ha-Bpin**, 99%, 99:1	 **4ha-Bdan**, 75%, 13:87
9	 **1i**	 **3ia-Bpin**, 99%, 99:1	 **4ia-Bdan**, 88%, 17:83
10	 **1j**	 **3ja-Bpin**, 90%, 98:2	 **4ja-Bdan**, 78%, 13:87
11	 **1k**	 **3ka-Bpin**, 0%, –	 **4ka-Bdan**, 59%, 1:99[d]

[a]Conditions A: Cu(xantphos)Cl (0.013 mmol), **1** (0.25 mmol), **2a** (0.38 mmol), pinB−Bpin (0.38 mmol), NaO-*t*-Bu (0.50 mmol), THF (1.5 mL), rt, 4 h, N_2. Conditions B: IPrCuBr (0.025 mmol), **1** (0.25 mmol), **2a** (1.0 mmol), pinB−Bdan (1.0 mmol), LiO-*t*-Bu (1.0 mmol), THF (1.5 mL), rt, 4 h, N_2. [b]Combined isolated yields are given. The ratio of **3**:**4** is determined by ^{1}H NMR. [c]Contaminated with pinacol-derived impurities (~10%). [d]83:17 dr. The relative stereochemistry is not determined.

of allylsilane **1f** and allylborane **1g** successfully afforded the functionality-rich C3 units (entries 6 and 7). Exceptionally, negligible regioselectivity toward **3fa-Bpin** was observed (**3fa-Bpin**/**4fa-Bpin** = 56:44; entry 6) probably because the hyperconjugation associated with the silicon atom (*β*-silicon effect)[15] are competitive to the steric factors induced by the xantphos (vide infra). More sterically hindered allylbenzenes **1h** and **1i** and vinylcyclohaxane (**1j**) gave better regioselectivity in the presence of the Cu(xantphos)Cl catalyst (**3-Bpin**/**4-Bpin** = 98:2−99:1; entries 8−10), while the IPrCuBr catalysis showed somewhat lower but still synthetically useful regioselectivity (**3-Bdan**/**4-Bdan** = 17:83−13:87; entries 8−10). The allyl alcohol derivative **1k** also could be converted to **4ka-Bdan** with nearly perfect regioselectivity under the IPrCuBr-promoted conditions

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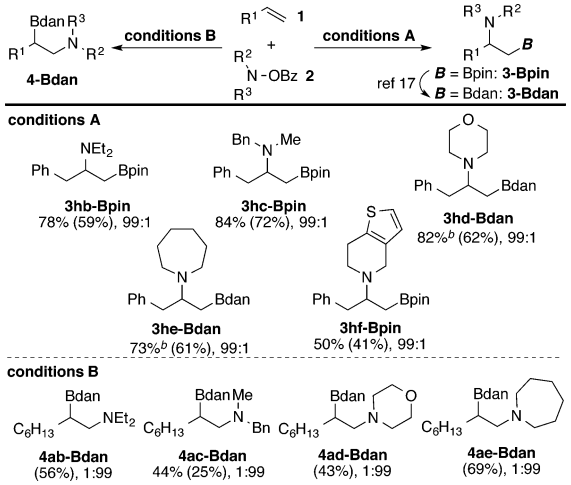
B, although the Cu(xantphos)Cl-based system A caused the competitive allylic substitution,[12] providing a complicated mixture (entry 11).[16]

We next tested various hydroxylamines **2** under both conditions A and B. Representative products **3** and **4** are illustrated in Scheme 1. Acyclic *N*,*N*-diethyl- and *N*-benzyl-*N*-

Scheme 1. Cu-Catalyzed Regiodivergent Aminoboration with Various Hydroxylamines 2[a]

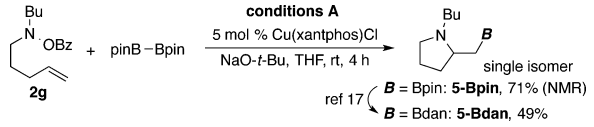


[a]Conditions A and B: see Table 2. ^{1}H NMR yields are given. Isolated yields are provided in parentheses Ratios of **3**:**4** are shown. [b]^{1}H NMR yields in the Bpin form.

methylamines could be employed (**3hb-Bpin**, **3hc-Bpin**, **4ab-Bdan**, and **4ac-Bdan**). The benzyl moiety in **3hc-Bpin** and **4ac-Bdan** as well as all products in Table 2 can be a useful synthetic handle for further manipulation after an appropriate deprotection.[17] The catalytic aminoboration was compatible with cyclic amines involving morpholine (**3hd-Bdan** and **4ad-Bdan**), azepane (**3he-Bdan** and **4ae-Bdan**), and thienopiperidine (**3hf-Bpin**). Also note that some aminoborated products were relatively unstable and difficult to handle in the Bpin form. In such cases, we converted the crude products into the more stable Bdan derivatives under the reported Fe-promoted conditions:[18] These products were readily isolated by chromatographic purification (**3hd-Bdan** and **3he-Bdan**). In all cases, the regioselectivity was uniformly high (99:1 for **3** under conditions A and 1:99 for **4** under conditions B).[19]

The Cu(xantphos)Cl-based system was also effective for the intramolecular version. While preliminary, one example is shown in Scheme 2. The hydroxylamine **2g** bearing the pendant olefinic

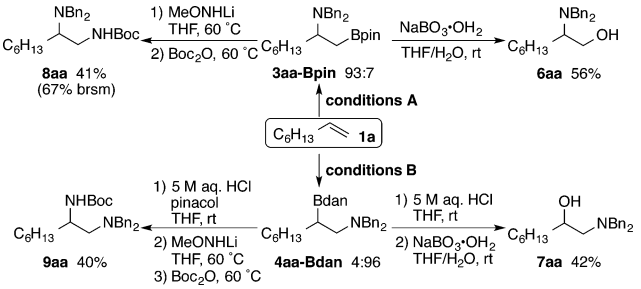
Scheme 2. Intramolecular Aminoboration



moiety coupled with pinB−Bpin under the identical conditions A to furnish the (borylmethyl)pyrrolidine **5-Bpin** as the single regioisomer in 71% ^{1}H NMR yield. Subsequent ligand exchange with 1,8-diaminonaphthalene was followed by column chromatography to provide **5-Bdan** in 49% isolated yield. Unfortunately, the IPrCuBr catalysis could not be applied to the reaction of **2g**.[20]

The derivatizations of the aminoborated products highlight the synthetic utility of the present regiodivergent Cu catalysis (Scheme 3). The single 1-octene (**1a**) was regiodivergently

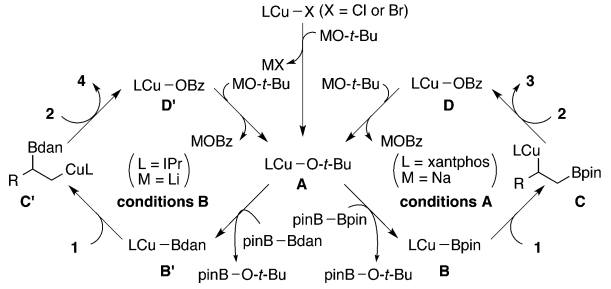
Scheme 3. Transformations of the Aminoborated Product



transformed into regioisomeric 1,2-aminoalcohols **6aa** and **7aa** through the catalytic aminoboration and subsequent oxidation with $NaBO_3$. The amination of the boron functionality with MeONHLi[10g] afforded the 1,2-diamines **8aa** and **9aa** with the orthogonal Bn and Boc protecting groups. These sequential manipulations can provide regiodivergent access to functionalized alkylamines from the readily available simple terminal alkene.

On the basis of the literature information and our findings, we are tempted to assume the reaction mechanism as follows (Scheme 4). Initial salt metathesis of the Cu catalyst precursor,

Scheme 4. Plausible Mechanism



Cu(xantphos)Cl or IPrCuBr, with MO-*t*-Bu (M = Li or Na) generates the starting Cu alkoxide **A**. Subsequent σ-bond metathesis with pinB−Bpin or pinB−Bdan forms the borylcopper species LCu−Bpin (**B**) or LCu−Bdan (**B′**), respectively. Under conditions **B** (the left cycle), the exclusive Bdan group transfer to the Cu center occurs because the Lewis basic O-*t*-Bu ligand in **A** attacked at the more Lewis acidic Bpin group in pinB−Bdan.[11c,13b,c] The migratory insertion of the terminal alkene into the Cu−B bond (**B** → **C** or **B′** → **C′**) is followed by the stereoretentive electrophilic amination[10f,11a] with **2** to furnish the aminoborated product **3** or **4** and LCu−OBz species **D** or **D′**. The catalytic cycle is closed by the regeneration of **A** through the ligand exchange with MO-*t*-Bu.

The overall regioselectivity can be controlled in the insertion step (**B** → **C** or **B′** → **C′**). The xantphos-ligated borylcopper species **B** uniquely creates a transient five-coordinated geometry at the borylated carbon and destabilizes the transition state much more when the borylation occurs at the more crowded internal position.[12b] Thus, the Bpin group is selectively incorporated at the less hindered terminal carbon to form the intermediate **C**. The origin of the cation-dependent regioselectivity observed in Table 1 (entries 7−9) is not clear, but the alkoxide base can

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coordinate to the borylcopper **B** and affect the regioselectivtiy in the insertion step.[21] On the other hand, electronic and steric factors are generally competitive in the insertion of the simple terminal alkenes into NHC-supported borylcopper complexes: from the electronic point of view, the nucleophilic borylation at the more electrophilic internal carbon is preferable, whereas steric hindrances around the borylated carbon favors the borylation at the less congested terminal position.[22] However, the IPr-ligated Cu complex has uniquely large buried volume (% V_{bur})[23] and exceeds the steric disadvantage in the internal borylation: the more bulky IPrCu moiety is preferably located at the terminal position. Thus, the formation of the internally borylated **C′** is desirable in view of both electronic and steric reasons.[12c] Nevertheless, the decreased regioselectivity observed in entries 8−10 of Table 2 (**4ha-Bdan**−**4ja-Bdan**) cannot be explained at this stage. Further studies are essential for clarification of the detailed mechanism[24,25]

In conclusion, we have developed a Cu-catalyzed regiodivergent aminoboration of unactivated terminal alkenes. By the proper choice of ancillary ligands, both regioisomers are obtained with high regioselectivity from a single alkene. The Cu catalysis transforms the simple and readily accessible terminal alkenes regiodivergently into the functionalized alkylamines of great value. Further manipulations of the aminoborated products and application to the asymmetric catalysis are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02775.

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Notes

The authors declare no competing financial interest.

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(19) The reaction of allylbenzene (**1h**) with *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2b**) under conditions B gave the moderate regioselectivity (**3hb-Bdan**:**4hb-Bdan** = 22:78), which is similar to that of entry 8 in Table 2.

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(24) The regioselectivity is less dependent on the electrophiles: the control experiments with MeOH in place of the hydroxylamine **2** resulted in a similar regioselectivity (see the SI for details). However, we cannot completely exclude the possibility that the borylcupration is reversible and the subsequent C−N forming step controls the overall regiochemical outcome. Also see ref 7.

(25) In the intramolecular reaction (Scheme 2), an aminyl radical pathway cannot be discarded, while we confirmed the negligible effects of TEMPO and galvinoxyl (the SI).

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