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Copper(I)-Catalyzed Borylative *exo*-Cyclization of Alkenyl Halides Containing Unactivated Double Bond

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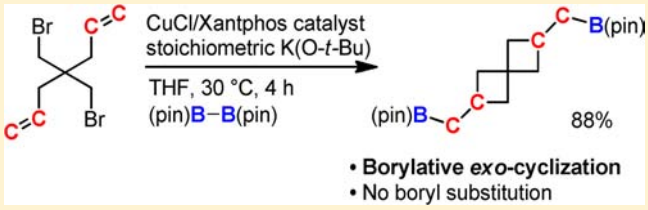
Supporting Information

ABSTRACT: A borylative *exo*-cyclization of alkenyl halides has been reported. The reaction includes the regioselective addition of a borylcopper(I) intermediate to unactivated terminal alkenes, followed by the intramolecular substitution of the resulting alkylcopper(I) moiety for the halide leaving groups. Experimental and theoretical investigations of the reaction mechanism have also been described. This reaction provides a new method for the synthesis of alkylboronates containing strained cycloalkyl structures from simple starting materials.

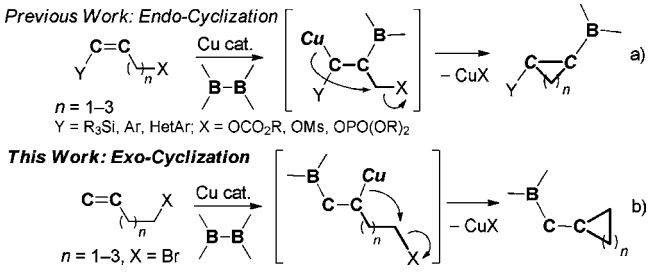


INTRODUCTION

Organoboron compounds are very important synthetic reagents, and their efficient preparation has attracted a considerable level of attention over the years.[1] The hydroboration of alkenes is an established method for alkylborane synthesis. When the hydroboration of a carbon−carbon double bond occurs with concomitant C−C bond formation, this can be highly beneficial for the efficient construction of alkylboronates. Furthermore, the products of these reactions invariably possess more complex structures than those that could be obtained via conventional hydroboration chemistries or other classical methods involving carbon nucleophiles. Despite these potential benefits, reactions based on this concept of 1,2-carboboration have been scarcely reported in the literature.[2−6]

We previously reported copper(I)-catalyzed borylative cyclizations as an example of a borylation process involving a C−C bond formation (Scheme 1a).[7−9] These reactions included the regioselective addition of the borylcopper(I) to alkene, which was facilitated by an electronic directing group (Y). The subsequent intramolecular substitution afforded a variety of different cycloalkylboronates as the *endo*-cyclization products. Herein, we report a new borylative cyclization reaction involving the unprecedented regioselective addition of a borylcopper(I) intermediate to an unactivated terminal double bond, followed by intramolecular cyclization to produce the *exo*-cyclization product (Scheme 1b).[9,10] The resulting products have interesting carbocyclic structure with a borylmethyl moiety. Derivatizations of the product using the boryl group, such as oxidation, homologation, and Suzuki−Miyaura coupling, were conducted to demonstrate the synthetic utility of this reaction. Experimental and theoretical investigations of the reaction mechanism have also been described.

Scheme 1. Copper(I)-Catalyzed Boryl Cyclization



RESULTS AND DISCUSSION

In all of the previous reports concerning the copper(I)-catalyzed borylation of carbon−carbon double bonds, electronically activated substrates have been used (i.e., substrates with a low LUMO level capable of effectively interacting with the borylcopper(I) HOMO).[7,8,11,12] For our previous cyclization reactions, a silyl or an aryl group (Y) was required to promote the reaction and provide a high level of regioselectivity (Scheme 1a).[7] There have been no reports for the reaction between the borylcopper(I) intermediate and unactivated alkenes such as 1-hexene.[11,13] To design a new carboboration process, we initially checked this preconceived reactivity profile (Table 1). Pleasingly, the reaction between 1-hexene (**1a**) with bis(pinacolato)diboron (**2**) in the presence of a Cu(O-*t*-Bu)/Xantphos catalyst system with MeOH as a proton source proceeded smoothly to afford the hydroboration product **3a** in excellent yield with good regioselectivity (**3a**, 81%; **3a′**, 7%) (Table 1, entry 1). The same reaction proceeded well with the more readily available CuCl/Xantphos/K(O-*t*-Bu) catalytic system (entry 2).

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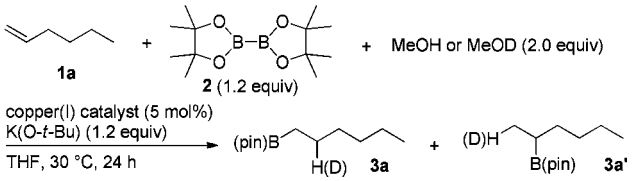
Table 1. Copper(I)-Catalyzed Hydroboration of an Unactivated Alkene[a]



entry	copper(I) catalyst	3a (%)[b]	3a′ (%)[b]
1[c]	Cu(O-*t*-Bu)/Xantphos	81	7
2	CuCl/Xantphos/K(O-*t*-Bu)	91	7
3[d]	CuCl/Xantphos/K(O-*t*-Bu)	92 (>95% D)	6
4	CuCl/PPh_3/(K(O-*t*-Bu)	14	3
5[e]	CuCl/IPr·HCl/K(O-*t*-Bu)	1	7
6[e]	CuCl/IMes·HCl/K(O-*t*-Bu)	12	16
7[f]	CuCl/Xantphos/K(O-*t*-Bu)	trace	0

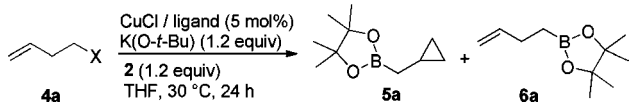
[a]Conditions: **1** (0.5 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), K(O-*t*-Bu)/THF (0.6 M, 1.0 mL), **2** (0.6 mmol), MeOH (1.0 mmol). [b]Yield was determined by GC analysis of the crude mixture with an internal standard. [c]Cu(O-*t*-Bu) (0.025 mmol) was used. [d]MeOD (1.0 mmol) was used. [e]IPr·HCl: 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride. IMes·HCl: 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride. [f]2-Hexene was used instead of 1-hexene.

The use of MeOD instead of MeOH gave the 2-deuterated product that corresponded to the trapping product of the alkylcopper(I) intermediate (entry 3). In contrast, the use of PPh_3 or *N*-heterocyclic carbenes (NHC) in the same reaction instead of Xantphos gave poor results without detection of *β*-hydride elimination products (entries 4−6). Interestingly, the investigation of a reaction using the internal alkene, 2-hexene, resulted only in failure even when the Xantphos ligand was used (entry 7).

With a new procedure in hand for the regioselective addition of borylcopper(I) to terminal double bonds, we proceeded to investigate the *exo*-cyclization process (Table 2). The desired product **5a** was exclusively produced from **4a** in excellent yield (entries 1 and 2) when chloride or bromide was used as the leaving group and the ligand was Xantphos. Although alkyl halides lacking a terminal double bond are good substrates for the copper(I)-catalyzed boryl substitution reaction, in this reaction, none of the simple boryl substitution product was detected.[9] Alkenyl iodide and tosylate were converted into an isomeric mixture of **5a** and **6a** (entries 3 and 4). We next investigated the ligand effect (entries 5−13). In the absence of a ligand, the reaction did not proceed to completion (entry 5). In the presence of the monophosphine ligands, the reactions tended to produce the boryl substitution product **6a** rather than the cyclization product **5a** (entries 6−9). When the reaction was conducted in the presence of rigid diphosphine ligands (Xantphos, dppf), they showed a preference for the cyclization reaction (entries 1−4, 13). Use of a stoichiometric amount of Cu(O-*t*-Bu) instead of CuCl/K(O-*t*-Bu) resulted in almost no reaction (entry 14), indicating that K(O-*t*-Bu) is needed for the cyclization step.

We also tested the construction of cyclobutane frameworks through the borylative *exo*-cyclization (Scheme 2). 5-Bromopentene (**4b**) was successfully converted into the cyclobutylmethylboronate **5b** in good yield (88%) with excellent chemoselectivity (**6b**, <1%). In a manner similar to the cyclopropanation case, the cyclization/substitution selectivity could be switched when $P(C_6F_5)_3$ was used as the ligand (**5b**/**6b** = 12:88).

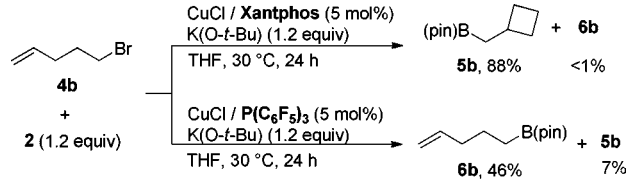
Table 2. Copper(I)-Catalyzed Borylative Cyclization and Substitution Reactions of Alkenyl Halides and Pseudo Halides 4a[a]



entry	X	ligand	5a (%)[b]	6a(%)[b]
1	Cl	Xantphos	99	<1
2	Br	Xantphos	99	<1
3	I	Xantphos	38	42
4	OTs	Xantphos	65	27
5	Br	none	15	7
6	Br	PPh_3	15	35
7	Br	$P(C_6F_5)_3$	6	45
8	Br	$P(OPh)_3$	6	32
9	Br	PBu_3	11	31
10	Br	dppe	32	33
11	Br	dppp	47	24
12	Br	dppb	9	47
13	Br	dppf	87	4
14[c]	Br	Xantphos	<1	4

[a]Conditions: **4a** (0.5 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), K(O-*t*-Bu)/THF (0.6 M, 1.0 mL), **2** (0.6 mmol). [b]Yield was determined by GC analysis of the crude mixture with an internal standard. [c]Cu(O-*t*-Bu) (0.5 mmol) was used instead of CuCl/K(O-*t*-Bu).

Scheme 2. Borylative Cyclization of 5-Bromopentene 4b



The synthesis of a variety of different cyclic compounds was then investigated (Table 3). The reactions of secondary alkenyl bromides (**4c** and **4d**) proceeded smoothly to give the corresponding cyclopropylmethyboronates (**5c**, 94% and **5d**, 92%, respectively; cyclization/substitution = >95:5) (entries 1 and 2). Unfortunately, however, the diastereoselectivity in these cases was poor (trans/cis = 1:1). This reaction can be applied to the construction of spirocyclic frameworks bearing the boryl group, which would otherwise be difficult to synthesize through a one-step procedure. Spiro[3.4]octan-2-methylboronate (**5e**) and spiro[3.5]nonan-2-methylboronate (**5f**) in particular were successfully obtained in high yields as singularly borylated products (90% and 92%, respectively) (entries 3 and 4). The application of a substrate containing a Boc-protected piperidine moiety (**4g**) gave the desired nitrogen-containing spirocyclic boronate (**5g**) in good yield (90%) with excellent chemoselectivity (**5g**/**6g** >95:5) (entry 5). Trisubstituted cyclobutanes (**5h** and **5i**) were formed in high yields (90% and 83%, respectively) from the corresponding alkenyl bromides (entries 6 and 7). The reactions of substrates containing aromatic rings (**4j** and **4k**) afforded the disubstituted cyclobutylmethylboronates (**5j** and **5k**) in excellent yields (entries 8 and 9). Pleasingly, the reaction of a dienyl halide (**4l**) proceeded smoothly to produce the desired bis-boryl products

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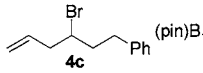
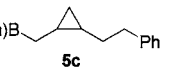
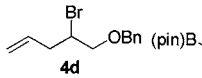
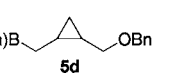
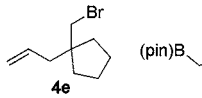
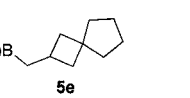
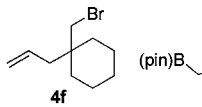
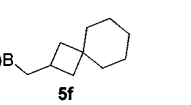
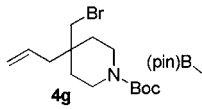
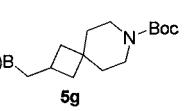
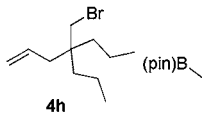
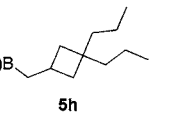
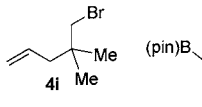
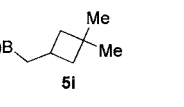
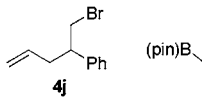
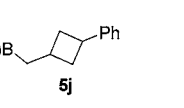
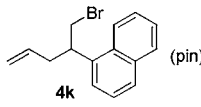
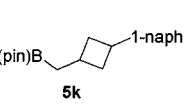
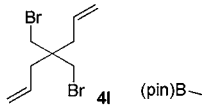
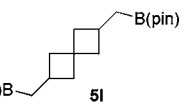
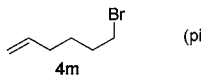
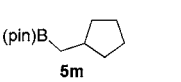
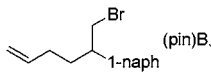
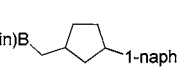
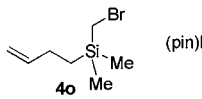
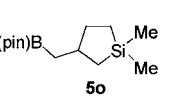
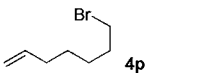
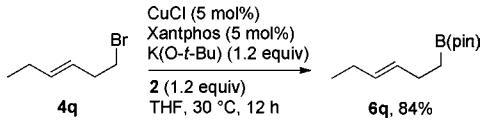
Table 3. Copper(I)-Catalyzed Borylative Cyclization of Unactivated Alkenyl Halides[a]

entry	substrate	product	time (h)	5/6 selectivity	yield[b] (%)
1	 **4c**	 **5c**	1.5	>95:5	94(1:1)
2	 **4d**	 **5d**	1	>95:5	92(1:1)
3	 **4e**	 **5e**	4	>95:5	90
4	 **4f**	 **5f**	4	>95:5	92
5	 **4g**	 **5g**	4	>95:5	90
6	 **4h**	 **5h**	3	>95:5	90
7	 **4i**	 **5i**	4	>95:5	83
8	 **4j**	 **5j**	4	>95:5	91(1.3:1)
9	 **4k**	 **5k**	4	>95:5	95(1.4:1)
10[c]	 **4l**	 **5l**	4	>95:5	88
11	 **4m**	 **5m**	24	>99:1	86
12	 **4n**	 **5n**	6	>95:5	87(1.1:1)
13[d]	 **4o**	 **5o**	4	>99:1	74
14[e]	 **4p**		20	–	4

[a]Conditions: **4** (0.5 mmol), CuCl (0.025 mmol), Xantphos (0.025 mmol), K(O-*t*-Bu)/THF (0.6 M, 1.0 mL), **2** (0.6 mmol), 30 °C. [b]Isolated yield. Values in parentheses are the stereoselectivity determined by GC analysis. [c]Conditions: **4l** (0.5 mmol), CuCl (0.1 mmol), Xantphos (0.1 mmol), K(O-*t*-Bu)/THF (0.73 M, 1.5 mL), **2** (1.1 mmol), 30 °C. [d]The *endo*-cyclization product (7%) was detected. [e]The reaction resulted in a complex mixture.

(**5l**) bearing spiro[3.3]framework via double borylative cyclization (entry 10). The five-membered ring products (**5m** and **5n**) were also successfully synthesized with a high degree of chemoselectivity (>95:5) (entries 11 and 12). A silicon-containing product **5o** was obtained in good yield (entry 13) with a minor amount of the *endo*-cyclization product (7%). Notably, with the exception of entry 13, the *endo*-cyclization products originating from the regioisomeric insertion were not detected in the reactions shown in Table 3. Unfortunately, this reaction could not be successfully applied to the formation of six-membered rings (entry 14). As shown in Scheme 3, reaction

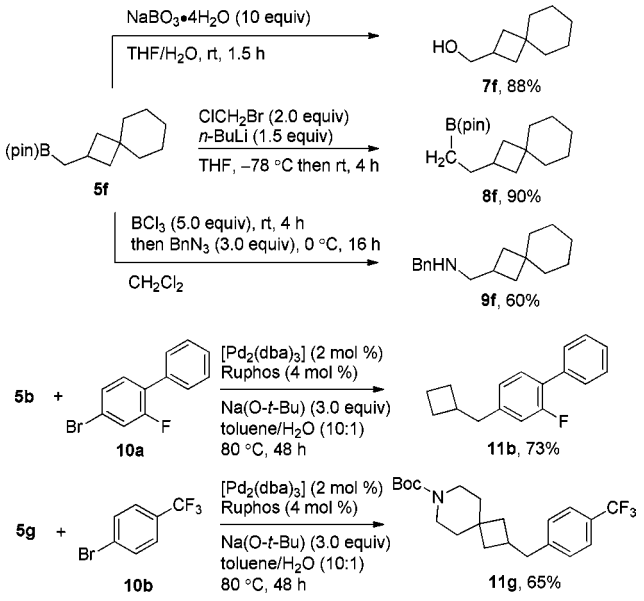
Scheme 3. Copper(I)-Catalyzed Reaction of Alkenyl Bromide 4q



of an alkenyl bromide **4q** with an internal double bond afforded the simple boryl substitution product **6q** in 84% yield exclusively. The cyclization product could not be detected.[14]

The borylative cyclization products are a useful synthetic block for preparation of carbocyclic compounds. The cyclization product **5f** was subjected to $NaBO_3$ oxidation, homologation with a halomethyl lithium reagent, or amination with benzyl azide (Scheme 4).[15−17] These reactions afforded

Scheme 4. Derivatizations of Borylative Cyclization Products



the corresponding alcohol **7f** (88%, isolated yield), alkyl boronate **8f** (90%), and benzylamine **9f** (60%), respectively. Suzuki−Miyaura cross-coupling reaction of borylative cyclization products (**5b** and **5g**) with aryl halides (**10a** and **10b**) also proceeded in the presence of Pd/Ruphos catalyst system to produce arylated products in reasonable yields (**11b** and **11g**, 73% and 65%, respectively).[9a,18]

To further demonstrate the synthetic utility of this reaction, we synthesized a biologically active compound, a histamine H3 receptor ligand **12** (IC_{50}: 6.56 nM), containing a piperidine sulfonamide structure (Scheme 5).[19] We first checked the

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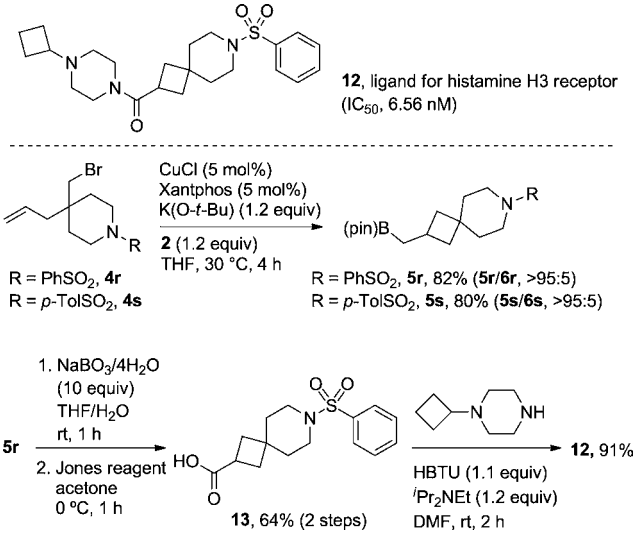
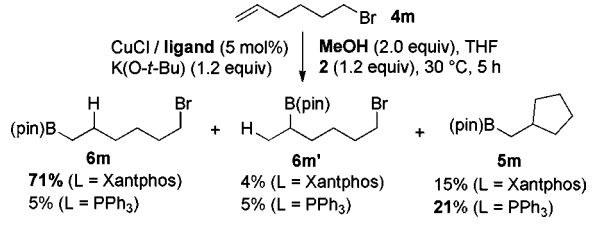
Scheme 5. Synthesis of Spirocyclobutyl Piperidine Structure through Borylative Cyclization



tolerance of sulfonamide functionality in this reaction; sulfonamides **4r** and **4s** gave the desired spirocyclic boronates (**5r** and **5s**) in good yields with excellent chemoselectivity (cyclization/substitution, >95:5). The boronate ester group in the borylative cyclization product **5r** was functionalized through $NaBO_3$ oxidation and Jones oxidation to afford carboxylic acid **13**, which was then coupled with 1-cyclobutylpiperazine to afford the histamine H3 receptor ligand **12**.

Liu, Steel, and Marder et al. reported the cyclization of **4m** to **5m** in their mechanistic studies of the boryl substitution reactions with a copper(I)/PPh_3 catalyst system.[9a,10] The cyclization suggested the possibility of a radical process, in which the borylcopper(I) species initially attacked the C−Br bond and then underwent a radical-mediated cyclization. However, the radical scavenger experiment did not support this idea. Our copper(I)/Xantphos catalyst system also gave the same product (Table 3, entry 11), although the reaction should proceed via the addition of borylcopper(I) to the alkene followed by an intramolecular substitution. The difference in the mechanisms between the two processes was evidenced by the protonation experiments (Scheme 6). When Xantphos was

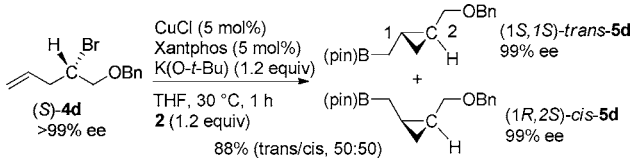
Scheme 6. Reactions of 4m in the Presence of Proton Source



used as the ligand, the protonated compounds (**6m** and **6m′**) were isolated as the major products. In contrast, the reaction with PPh_3 predominantly gave the cyclization product (**5m**) even in the presence of MeOH. We suppose that the reaction with PPh_3 proceeds through a radical-related mechanism. The product switch for **4a** and **4b** (Table 2 and Scheme 2) also corresponds well with the difference highlighted for the above mechanisms. The alkylcopper(I)-mediated substitution can afford cyclization of three- and four-membered rings; however, radical-mediated cyclization of both three- and four-membered rings is highly unfavorable.[20]

The borylative *exo*-cyclization of chiral substrates was also investigated to observe the stereochemistry of the leaving group (Scheme 7). Optically active (*S*)-**4d** was subjected to the **2**/

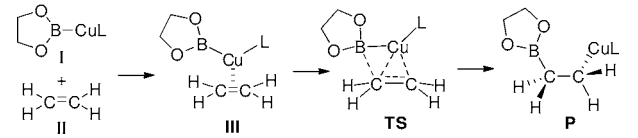
Scheme 7. Synthesis of Enantioenriched Disubstituted Cyclopropylmethylboronate



CuCl/K(O-*t*-Bu)/Xantphos borylation system. The reaction proceeded in a perfect stereoselective manner in terms of the substitution at the C2 position, in that the alkyl halide substitution showed inversion of stereochemistry, whereas no selectivity was observed around the C1 position, reflecting the lack of stereoselectivity during the initial borylcopper(I) addition to the double bond. This high level of stereoselectivity also excluded the possibility of a radical-related mechanism during the cyclization step.

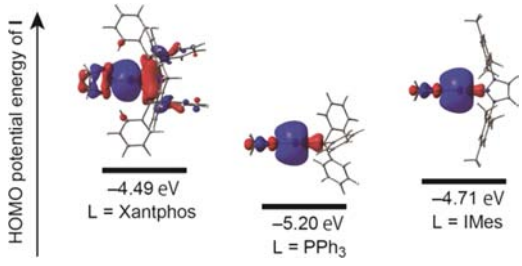
Preliminary density functional theory (DFT) calculations (B3PW91/cc-pVDZ) were used to explain the strong ligand influence observed in this reaction. The activation free energy for the addition of a model borylcopper(I)/Xantphos intermediate (**I**) to ethylene (**II**) was lower than those with the PPh_3 and NHC (IMes) complexes by 1.43 and 1.35 kcal/mol (Table 4). The HOMO level of **I** with Xantphos (−4.49 eV) was considerably higher than those of the PPh_3 (−5.20 eV) and NHC (−4.71 eV) complexes, indicating that the Xantphos complex had a stronger back-donation ability to alkenes, which is considered to be important for the addition of borylcopper(I) to alkenes.[12] To understand the ligand effect, distortion/interaction analysis was also performed.[21] When the structures

Table 4. DFT Calculations (B3PW91/cc-pVDZ) of Alkene Addition Step in Copper(I)-Catalyzed Borylation



	ΔG (298 K, 1.0 atm, gas phase),[a] kcal mol^{-1}			
L	I+II	III	TS	P
Xantphos	0	7.1 (−6.5)	17.6 (2.1)	−11.4 (−24.9)
PPh_3	0	3.5 (−10.4)	19.0 (3.6)	−16.2 (−30.5)
IMes	0	7.3 (−8.1)	18.9 (3.0)	−14.2 (−30.1)

[a]Electronic energies are shown in parentheses.



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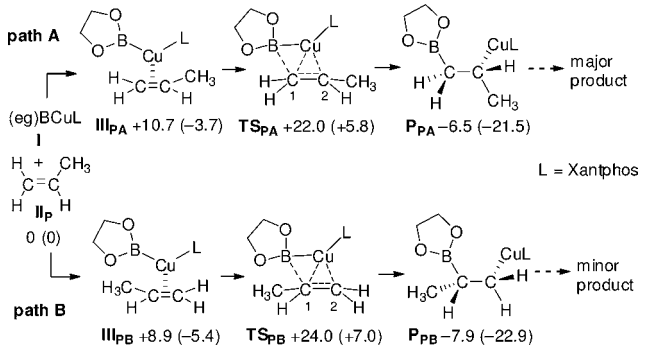
of the borylcopper(I) complexes (**I**) with PPh_3 and NHC were distorted to the structure in the transition states, the additional free energies were needed by 16.2 and 18.6 kcal/mol, respectively (Supporting Information). Contrary, the Xantphos complex only required 11.7 kcal/mol for the conformation change from **I** to **TS**, indicating the preactivation nature of the Xantphos complex (**I**) in the addition to alkenes.

DFT calculations revealed that the activation barrier difference is a key factor for this regioselectivity (Scheme 8).

Scheme 8. DFT Calculations (B3PW91/cc-pVDZ) for Two Diastereomeric Pathways[a]

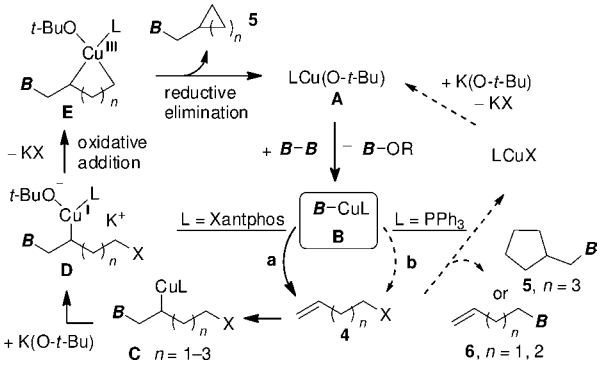


[a]Relative *G* value (kcal mol^{-1}) at 298 K, 1.0 atm, gas phase. Electronic energies are shown in parentheses.

In the proposed alkylcopper intermediate, the bulky Cu-(xantphos) moiety is placed at the sterically congested internal carbon. On the basis of the structure of the addition product, this seems to be unfavorable. DFT calculations with propene substrate for the two diastereomeric pathways were conducted. Path A can afford the major product for the addition of borylcopper(I), whereas path B corresponds to the formation of the minor product. The activation free energy for path A was lower than that of path B by 1.94 kcal/mol. Contrary, π-complex **III$_P$** and the alkylcopper product **P$_P$** were more stabilized in path B than in path A. In the transition state, the C1 carbon, which will bind to boron atom in the product, formed a transient five-coordinated geometry with highly congested environment. The substituent on the C1 atom thus causes destabilization of the transition state. This can explain the transition state in path A has the lower barrier as compared to that in path B.

We have proposesd a mechanism for the process, as shown in Scheme 9. The copper(I) alkoxide (**A**) formed via the reaction of the CuCl, ligand, and K(O-*t*-Bu) mixture initially reacts with diboron to form the borylcopper(I) intermediate (**B**). When Xantphos was used as the ligand, the borylcopper(I) intermediate possessed the ability to add to the C–C double bond of the substrate **4** (path **a**) to form the alkylcopper(I) species (**C**) with concomitant formation of an ate complex (**D**) by coordination of the alkoxide. Subsequent sequential oxidative addition and elimination of bromide with inversion of the stereochemistry gives the cyclic copper(III) intermediate (**E**), in a manner similar to that of the S_N2 reaction postulated for the alkyl substitution of alkyl halides with cuprates.[22] Subsequent reductive elimination of the copper moiety from the **E** produces the cyclization product **5**, as well as reproducing **A**. The cyclization of six-membered rings would not proceed according to this mechanism because the seven-membered ring intermediate (**E**, $n = 4$) appeared to be unstable (Table 3, entry 14). When a monophosphine were used as the ligand, the reactivity of the borylcopper(I) toward alkene addition would be less favorable (path **b**), with boryl substitution (n = 1,2) or radical cyclization proceeding (n = 3) instead.

Scheme 9. Proposed Mechanism for the Copper(I)-Catalyzed Borylative Cyclization



CONCLUSION

In summary, we have identified an unprecedented reactivity of borylcopper(I) toward unactivated terminal alkenes and developed a borylative *exo*-cyclization reaction, which allows for the one-step construction of alkylboronates with complex structures, such as spirocyclic frameworks, from simple starting materials. The undesired boryl substitution of the alkyl bromide moiety in the starting materials was suppressed by choosing an appropriate ligand (Xantphos), which enhanced the reactivity of the key borylcopper(I) intermediate toward addition to the carbon–carbon double bonds.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, and details of the DFT calculations. 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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