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Copper(I)-Catalyzed Boryl Substitution of Unactivated Alkyl Halides

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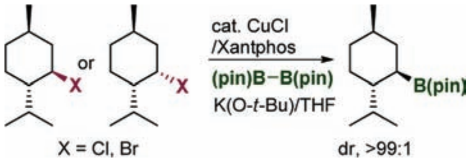
ABSTRACT



Borylation of alkyl halides with diboron proceeded in the presence of a copper(I)/Xantphos catalyst and a stoichiometric amount of K(O-*t*-Bu) base. The boryl substitution proceeded with normal and secondary alkyl chlorides, bromides, and iodides, but alkyl sulfonates did not react. Menthyl halides afforded the corresponding borylation product with excellent diastereoselectivity, whereas (*R*)-2-bromo-5-phenylpentane gave a racemic product. Reaction with cyclopropylmethyl bromide resulted in ring-opening products, suggesting the reaction involves a radical pathway.

Organoboron compounds are indispensable synthetic reagents in organic synthesis; much effort has therefore been devoted to the development of an efficient synthesis of organoborons.[1−8] Although many excellent procedures have been reported, boryl substitution of alkyl halides is still challenging. In conventional procedures for organoboron synthesis, alkyl halides are the starting materials for the organometallic nucleophiles, such as Grignard or organolithium reagents, which react with boron electrophiles. This procedure has significant limitations, especially in the presence of the functional groups often found in structurally complex molecules. Direct borylation of alkyl halides should be quite promising in this respect. Yamashita and Nozaki recently created a boryllithium

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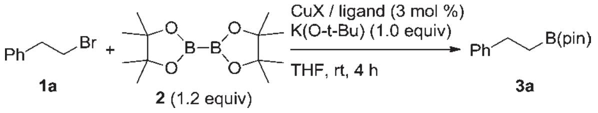
species by introducing significant steric hindrance around the boron atom.[3] Although this species has enough nucleophilicity to react with unactivated alkyl halides, this elaborate reaction is not suitable for many common organic syntheses. Miyaura and Marder also reported boryl substitutions of activated alkyl halides such as allyl and benzyl chlorides; however, there are no general borylation procedures for unactivated alkyl halides.[1,5a,5b,7] We report here the first practical method for boryl substitution that is applicable to a broad range of alkyl halides with various functional groups, offering a direct umpolung pathway for conventional reactions based on carbon nucleophiles generated from alkyl halides.

Recent advances in copper(I)-catalyzed reactions with diboron derivatives[4−8] enable introduction of boryl groups into various organic electrophiles such as α,β-unsaturated carbonyl compounds,[4a,5] allylic esters,[4b,c,f,g,6] aryl halides,[7] allyl and benzyl halides,[5a,b,7] and other substrates.[4d,h−k,8] We did not anticipate that unactivated alkyl halides could afford boron compounds by copper(I)-catalyzed borylation because we previously found that alkyl sulfonates, which are good substrates for nucleophilic substitutions, were resistant to direct boryl substitution.[4h,9]

In the course of our study, we accidentally found that an alkyl halide reacted with a diboron compound to produce the corresponding alkylboronate in the presence of a copper(I) catalyst, which is very similar to those we previously reported.[4b,h] As shown in Table 1, entry 1, the reaction between 2-phenylethyl bromide **1a** and bis(pinacolato)diboron **2** proceeded smoothly in the presence of a CuCl/Xantphos catalyst (3 mol %) and a stoichiometric amount of K(O-*t*-Bu) base (1.0 equiv). The reaction was complete within 4 h at room temperature and produced the corresponding boronate **3a** in high yield (94%) without any side-product detection (Table 1, entry 1). This catalysis requires a K(O-*t*-Bu) base, a copper(I) salt, and a ligand for the reaction to proceed (entries 2−4). Xantphos provided the best result among the phosphine ligands tested; the reactions with PPh_3, dppe, dppp, dppb, and dppf were slow and incomplete, resulting in moderate yields of the product, even after long reaction times (entries 5−9). Use of a copper(I)/NHC (NHC: *N*-heterocyclic carbene) catalyst gave a much slower initial reaction rate (entry 10). When a catalytic or stoichiometric amount of Cu(O-*t*-Bu) was used instead of a CuCl/K(O-*t*-Bu) combination, only trace amounts of the product were observed (entries 11 and 12). CuI, CuCN, and $Cu(OAc)_2$ can be used, but longer reaction times were required (entries 13−15).[10] A lower catalyst loading of 1 mol % also gave an excellent result (96%, 4 h, entry 16).

This reaction was then evaluated for various alkyl halides, as summarized in Table 2. Unactivated primary and secondary alkyl halides were converted to the corresponding alkylboronates in good yield (entries 1−6). The effects of the leaving group were investigated with cyclohexyl substrates (entries 2−5). Reaction of cyclohexyl bromide **1d** gave the borylation product **3c** in the highest yield, with a short reaction time (91%, 5 h), among cyclohexyl chloride **1c** and iodide **1e** (72%, 18 h; 79%, 48 h, respectively). In contrast, cyclohexyl mesylate **1f** did not react (entry 5). This lack of reactivity is consistent with our previous studies of related mesylate substrates.[4h] The reactions of tertiary alkyl halides **1h** and **1i** were quite sluggish (entries 7 and 8). An activated alkyl halide, benzyl bromide **1j**, also gave the desired product in moderate yield, accompanied by a small amount of a homocoupling side product (1,2-diphenylethane, 9%).[7] This reaction proceeded in the presence of various functional groups; acetal (**1k**), ester (**1l**), silyl ether (**1m**), and sulfonate (**1n**) were compatible under these reaction conditions (entries 9−14). Alkylboronates bearing a β-alkoxy group were not accessible by Grignard or organolithium methods because the corresponding organometallic compounds with a β-alkoxy group could not be easily prepared owing to facile β-alkoxy elimination. This method enables direct conversion of alkyl halide **1o** to **3o** (entry 14). Reactions of 1,1- and 1,3-dibromo compounds proceeded smoothly to

Table 1. Studies of Reaction Conditions for Copper(I)-Catalyzed Boryl Substitution of Alkyl Halide **1a**[a]



entry	CuX	ligand	base	yield (%)[b]
1	CuCl	Xantphos	K(O-*t*-Bu)	94
2	CuCl	Xantphos	none	0
3	none	Xantphos	K(O-*t*-Bu)	0
4	CuCl	none	K(O-*t*-Bu)	2
5	CuCl	PPh_3	K(O-*t*-Bu)	69 (66, 8 h)
6	CuCl	dppe	K(O-*t*-Bu)	73 (70, 8 h)
7	CuCl	dppp	K(O-*t*-Bu)	79 (83, 8 h)
8	CuCl	dppb	K(O-*t*-Bu)	65 (70, 8 h)
9	CuCl	dppf	K(O-*t*-Bu)	74 (74, 8 h)
10[c]	CuClIPr		K(O-*t*-Bu)	13 (78, 24 h)
11	Cu(O-*t*-Bu) /10 mol %	Xantphos /10 mol %	none	3
12	Cu(O-*t*-Bu) /100 mol %	Xantphos /10 mol %	none	2
13	CuI	Xantphos	K(O-*t*-Bu)	70 (100, 24 h)
14	CuCN	Xantphos	K(O-*t*-Bu)	47 (88, 24 h)
15	$Cu(OAc)_2$	Xantphos	K(O-*t*-Bu)	88 (86, 24 h)
16	CuCl /1 mol %	Xantphos /1 mol %	K(O-*t*-Bu)	96

[a] Conditions: **1a** (0.5 mmol), CuX (0.015 mmol), ligand (0.015 mmol), K(O-*t*-Bu)/THF (1.0 M, 0.5 mL), **2** (0.6 mmol). [b] Yield was determined by GC analysis of crude mixture with an internal standard. [c] CuClIPr: chloro[1,3-bis(2,6-diisopropylphenyl)-imidazole-2-ylidene] copper(I).

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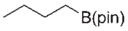
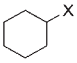
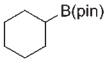
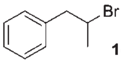
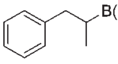
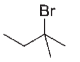
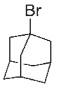
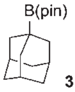
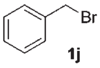
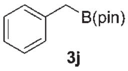
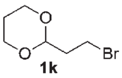
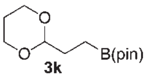
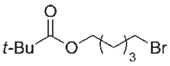
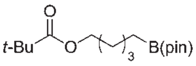
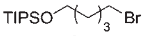
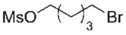
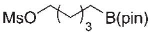
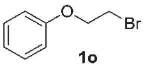
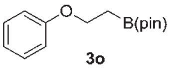
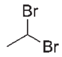
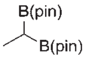
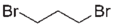
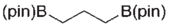
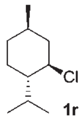
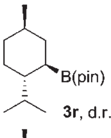
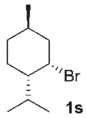
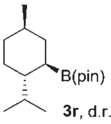
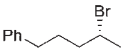
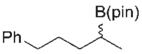
(9) We reported that a 4-silyl-3-butenyl methanesulfonate gave a cyclobutylboronate product under copper(I)-catalyzed conditions in the presence of diboron, in which no simple substitution product was detected.

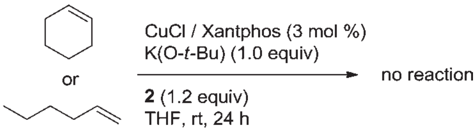
(10) Copper(II) salt was most probably reduced to copper(I) at the initial step of the catalysis. See also ref 6a.

Table 2. Copper(I)-Catalyzed Boryl Substitution of Alkyl Halides[a]

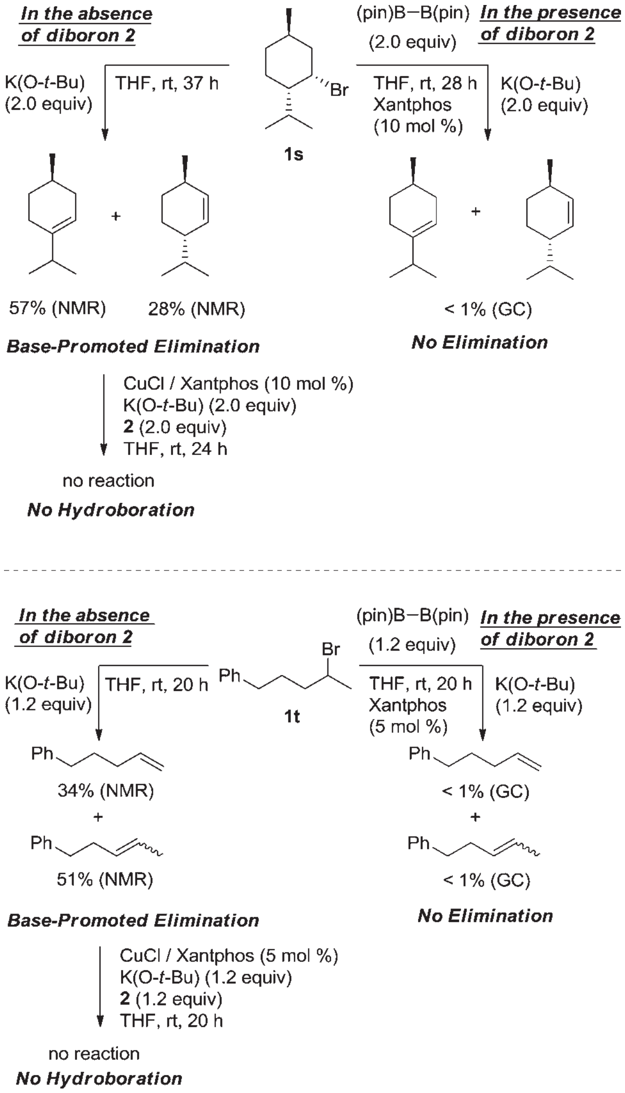
entry	substrate	product	time (h)	yield (%)[b]
1	 **1b**	 **3b**	4	85
				
2	**1c**, X = Cl	**3c**	18	72
3	**1d**, X = Br		5	91
4	**1e**, X = I		48	79
5	**1f**, X = OMs		18	0
6	 **1g**	 **3g**	5	90
7	 **1h**		44	0
8	 **1i**	 **3i**	48	17
9	 **1j**	 **3j**	5	51 (59)
10	 **1k**	 **3k**	5	86
11[c]	 **1l**	 **3l**	24	80
12[c]	 **1m**	 **3m**	24	82
13	 **1n**	 **3n**	6	80
14	 **1o**	 **3o**	6	51 (65)
15[d,e]	 **1p**	 **3p**	24	62
16[d,e]	 **1q**	 **3q**	30	68
17[f,e]	 **1r**	 **3r**, d.r. >99:1	31	85
18[f,e]	 **1s**	 **3r**, d.r. >99:1	30	81
19[c]	 (*R*)-**1t**, >99% ee	 (*rac*)-**3t**	24	93

[a] Conditions: **1** (0.5 mmol), CuCl (0.015 mmol), Xantphos (0.015 mmol), K(O-*t*-Bu)/THF (1.0 M, 0.5 mL), **2** (0.6 mmol), room temperature. [b] Isolated yield. Values in parentheses are the yields determined by ^{1}H NMR analysis of the crude mixture. [c] 5 mol % of catalyst and 1.2 equiv of K(O-*t*-Bu) were used. [d] Reaction was conducted at 40 °C with 15 mol % of catalyst and 2.2 equiv of **2**. [e] 2.0 equiv of K(O-*t*-Bu) was used. [f] 10 mol % of catalyst and 2.0 equiv of **2** were used.

Scheme 1. Attempts of Copper(I)-Catalyzed Hydroboration of Alkenes with Diboron **2**



Scheme 2. Experiments for Exclusion of Elimination/Hydroboration Pathway of **1s** and **1t**



produce the corresponding bis-boryl products (entries 14 and 15). (1*R*,2*R*,4*R*)-Menthyl boronate **3r** was synthesized with excellent diastereoselectivity (>99:1) from both (1*S*,2*R*,5*R*)-menthyl chloride **1r** and (1*S*,2*S*,4*R*)-neomenthyl bromide **1s** (entries 16 and 17, 85% and 81%, respectively).

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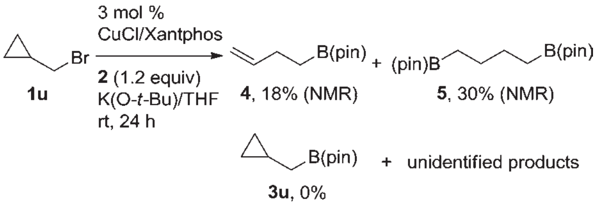
(11) For stereochemistry of alkylation with copper(I) reagents, see: (a) Whitesides, G. M.; Fischer, W. F.; San Filippo, J.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871. (b) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777. (c) Lipshutz, B.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696. (d) Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294. (e) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086.

The reaction of the optically active secondary alkyl halide (*R*)-**1t** afforded the racemic product **3t** (entry 19). These results indicate that the stereocenter originating from the chiral $C(sp^3)$−X bond undergoes rapid interconversion of configuration during the reaction. This may cause epimerization to a thermodynamically stable product (entries 17 and 18) and complete racemization (entry 19). This is quite different from the results of our previous studies on copper(I)-catalyzed substitution of acyclic allylic carbonates with diboron, where the *anti*-S_N2' reaction proceeded with high stereospecificity.[4b,11]

This reaction does not include a base-promoted elimination/alkene hydroboration pathway. The following experiments exclude this mechanism. (1) Alkenes did not undergo hydroboration under the reaction conditions presented in Tables 1 and 2 (Schemes 1 and 2). (2) Base-promoted elimination of alkyl halides proceeded quickly in the presence of *t*-BuOK; however, by addition of **2**, base-promoted elimination was completely inhibited (Scheme 2). Complexation of *t*-BuOK and Lewis acidic **2** would reduce the basicity of *t*-BuOK siginificantly. (3) Our boryl substitution of secondary alkyl halides was regiospecific (Table 2, entries 6, 17, 18, and 19). However, elimination products of secondary alkyl halides should give regioisomers in terms of the double bond (Scheme 2). It is difficult to assume product convergence in hydroboration of regioisomeric alkenes. In addition, the base-promoted elimination products from **1s** and **1t** did not undergo hydroboration under the conditions for our copper(I)-catalyzed boryl substitution of alkyl halides (Scheme 2).

To probe the reaction mechanism further, we also carried out the copper(I)-catalyzed borylation of cyclopropylmethyl bromide (**1u**), as illustrated in Scheme 3. 3-Butenylboronate **4** (18%) and bis-boryl product **5** (30%), which could be derived from **4** through further borylation of the terminal double bond, were found in the reaction mixture, but the simple boryl substitution product **3u** was not detected. The formation of the ring-opening products suggests that this reaction could include a radical pathway; this assumption is not inconsistent with the stereochemical outcomes observed in entries 17−19, Table 2.[12,13] However, further studies are needed for a full explanation of the reaction mechanism.

Scheme 3. Copper(I)/Xantphos-Catalyzed Borylation of Cyclopropylmethyl Bromide (**1u**)



In summary, we have developed a novel copper(I)-catalyzed reaction as the first practical procedure for boryl substitution of unactivated alkyl halides. This reaction offers a direct umpolung pathway for the conventional carbon nucleophile method and has high functional group compatibility and interesting stereochemical-controlling properties. We believe that this procedure will be a powerful synthetic method for a broad range of alkylboronates, including those that could not be synthesized by previous methods.

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Supporting Information Available. Details of experimental procedure, ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For radical pathways in reactions of lithium organocuprate with alkyl halides, see: (a) Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* **1982**, *23*, 5251. (b) Ashby, E. C.; Coleman, D. *J. Org. Chem.* **1987**, *52*, 4554.

(13) For rapid isomerization of a cyclopropyl radical to the butenyl radical, see: (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

(14) During submission process of this paper, a similar reaction with CuCl/PPh_3/base was published. Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528.