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Copper(I)-Catalyzed Carbon–Halogen Bond-Selective Boryl Substitution of Alkyl Halides Bearing Terminal Alkene Moieties

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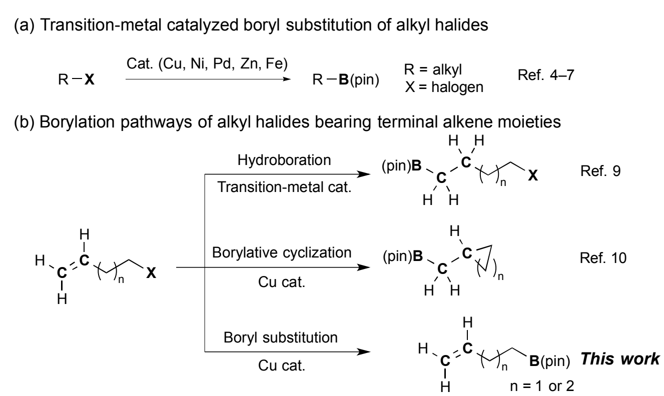
The selective boryl substitution of alkyl halides bearing terminal C=C double bonds has been achieved using a copper(I)/ tricyclohexylphosphine or copper(I)/*o*-diphenylphosphinophenol catalyst. This reaction represents a useful complementary approach to conventional procedures for the hydroboration of C=C double bonds or the borylative cyclization of alkyl halides bearing terminal alkenes.

Alkylboronate esters are recognized as useful intermediates in organic synthesis because of their versatility and synthetic utility.[1] Significant research efforts have been devoted to the development of the efficient methods for the synthesis of alkylboron compounds. In this context, the transition metal-catalyzed boryl substitution reactions of alkyl halides have emerged as facile and efficient procedures for the preparation of alkylboronate compounds. Furthermore, these reactions generally exhibit high functional group compatibility compared with conventional organolithium/boron electrophile reactions. Marder et al. were the first group to report the use of a CuCl/PPh_3/base catalyst system for the boryl substitution of alkyl halides.[2] Almost immediately after this publication, our own group reported the development of a CuCl/Xantphos/base catalyst system that showed similar high levels of activity towards the boryl substitution reactions of alkyl halides.[3] Following on from these early publications, several other methods have been reported for the boryl substitution of alkyl halides using a variety of different transition metal catalysts (e.g., Ni, Pd, Zn and Fe) (Scheme 1a).[4–8]

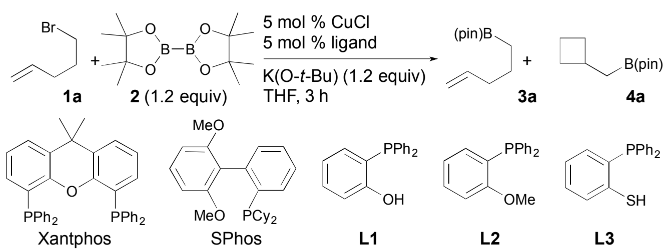
Alkyl halides bearing a terminal alkene moieties can be converted to a variety of borylation products through three different reaction pathways, including the hydroboration of the terminal C=C double bond,[9] borylative cyclization[10] and boryl substitution of the C–X bond (Scheme 1b). Conventional hydroboration reactions allow for the selective reaction of an organoborane compound with a C=C double bond to give the corresponding alkylboron compounds containing a carbon–halogen bond.[9] We recently reported successive papers describing the *exo*-borylative cyclization reaction of alkyl halides bearing terminal alkene moieties using a CuCl/Xantphos/base catalyst system.[10,11] Despite the success of these researches, the development of a complementally copper- or transition metal-catalyzed reaction for the selective boryl substitution of alkyl halides bearing terminal alkene moieties has been limited.[10,12] In this paper, we have developed a new method for the carbon–halogen bond-selective boryl substitution of alkyl bromides bearing terminal alkene moieties by successful switching the product selectivity through the careful tuning of the catalyst and the ligand. Experimental mechanistic study has also been conducted to develop a thorough understanding of this novel transformation.



Scheme 1 Copper(I)-catalyzed selective borylation of alkyl halides bearing terminal alkene moieties.

The reaction of alkyl bromide bearing terminal alkene moieties **1a** with bis(pinacolato)diboron (**2**) was selected as a model reaction to optimize the conditions for the selective copper(I)-catalyzed boryl substitution of alkyl halides bearing terminal alkene moieties, and we began by screening a series of different ligands (Table 1). The initial optimization reactions were performed in the presence of CuCl and a series of different ligands (5 mol %) with 1.2 equivalents each of **2** and K(O-*t*-Bu), which was used as a base, in THF over a period of 3 h. As previously reported, substrate **1a** gave the four-membered cyclic product **4a** in high yield with perfect cyclic selectivity when Xantphos was used as the ligand (86%, **3a**/**4a** = <1:99; Table 1, entry 1).[10] The use of dppp and dppbz as ligands was also investigated (Table 1, entries 2 and 3). Dppp showed no selectivity (**3a**/**4a** = 58:42, entry 2), whereas dppbz afforded the substitution product **3a** with good selectivity (**3a**/**4a** = 93:7, entry 3). The use of monophosphine ligands led to high levels of substitution selectivity (entries 4–12). PPh_3, $P(C_6F_5)_3$ and SPhos also gave the substitution product **3a** in moderate yield (Table 1, entries 4–6).[13] It is noteworthy that P(*t*-Bu)$_3$ showed higher reactivity than the triarylphosphines (Table 1, entry 7). Furthermore, the use of PCy_3 as a ligand afforded an even better yield of the desired product **3a** than P(*t*-Bu)$_3$ (Table 1, entry 8). The *o*-diphenylphosphinophenol ligand **L1** also gave product **3a** in high yield with excellent selectivity (Table 1, entry 9). When this boryl substitution reaction was conducted at 30 ºC, protonation products were detected as side products. Finally, we found that the low reaction temperature can suppress the side reaction, with the desired product **3a** being given in its highest yield (Table 1, entries 10 and 11). The reactivity of **L2** bearing an anisole group was lower than that of **L1** (Table 1, entry 12). The use the *o*-diphenylphosphinothiophenol ligand **L3** resulted in very low reactivity, with the desired product being given in only 1% yield (Table 1, entry 13). Taken together, these results indicated that PCy_3 and **L1** were both suitable ligands for the selective copper(I)-catalyzed boryl substitution of alkyl halides bearing terminal alkene moieties.

Table 1 Copper(I)-catalyzed boryl substitution and borylative cyclization of alkyl bromide bearing terminal alkene moieties **1a**[a]

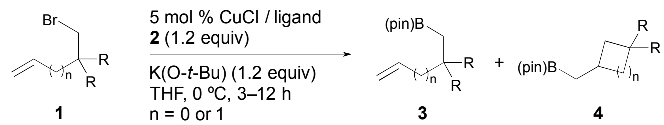


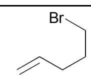
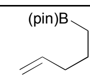
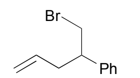
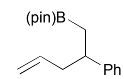
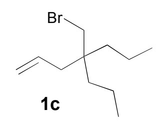
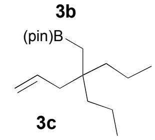
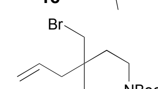
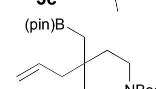
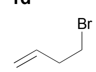
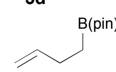
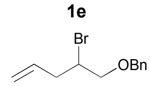
entry	ligand	temp. (ºC)	yield of **3a** (%)[b]	yield of **4a** (%)[b]	**3a**/**4a**[b]
1	Xantphos	30	<1	86	<1:99
2	dppp	30	34	25	58:42
3	dppbz	30	55	4	93:7
4	PPh_3	30	56	<1	99:1
5	$P(C_6F_5)_3$	30	53	1	98:2
6	SPhos	30	54	<1	>99:1
7	P(*t*-Bu)$_3$	30	62	<1	>99:1
8	PCy_3	30	74	<1	>99:1
9	**L1**	30	67	2	98:2
10	PCy_3	0	88	<1	>99:1
11	**L1**	0	80	<1	>99:1
12	**L2**	0	45 (62)[c]	<1	>99:1
13	**L3**	0	1	<1	-

[a]Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL). [b]Determined by GC analysis of the crude reaction mixture with an internal standard. [c]Reaction time of 9 h.

With the optimized conditions in hand, we proceeded to investigate the scope of the selective boryl substitution reaction using a variety of different alkyl halides bearing terminal alkene moieties (Table 2). We previously reported borylative cyclization reactions using Xantphos as a ligand to give the corresponding cyclization products **4a**–**f**.[10] The borylation reactions of **1a** and **1b** using PCy_3 or **L1** as a ligand proceeded with a high level of selectivity to afford the corresponding boryl substitution products **3a** and **3b** in good yields (**3a**: 68% and 60% **3**/**4** = >95:5; Table 2, entries 1 and 2, **3b**: 67% and 70%, **3**/**4** = >95:5; Table 2, entries 3 and 4). Notably, substrates **1c** and **1d** containing a quaternary carbon center adjacent to the carbon bonding bromine needed a 10 mol % loading of the catalyst and gave the corresponding products **3c** and **3d** in moderate yields with excellent selectivity (**3c**: 55%, **3**/**4** = >95:5; Table 2, entry 5, **3d**: 47%, **3**/**4** = >95:5; Table 2, entry 6). Furthermore, the reaction of homoallyl bromide (**1e**) with **2** using PCy_3 as a ligand gave homoallyl boronate **3e** in high yield and selectivity (**3e**: 73%, **3**/**4** = >95:5; Table 2, entry 7).[14] However, this catalyst system was not applicable to the secondary alkyl halide **1f**, where the reaction gave a complex mixture of products (Table 2, entry 8).

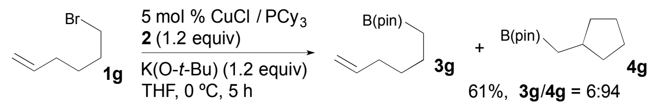
Table 2 Copper(I)-catalyzed borylation of alkyl bromides bearing terminal alkene moieties **1**[a]



entry	substrate	ligand	product	yield (%)[b]	**3**/**4**
1	 **1a**	PCy_3	 **3a**	68	>95:5
2		**L1**		60	>95:5
3	 **1b**	PCy_3	 **3b**	67	>95:5
4		**L1**		70	>95:5
5[c]	 **1c**	PCy_3	 **3c**	55	>95:5
6[c]	 **1d**	**L1**	 **3d**	47	>95:5
7	 **1e**	PCy_3	 **3e**	73	>95:5
8	 **1f**	PCy_3	-	complex mixture	

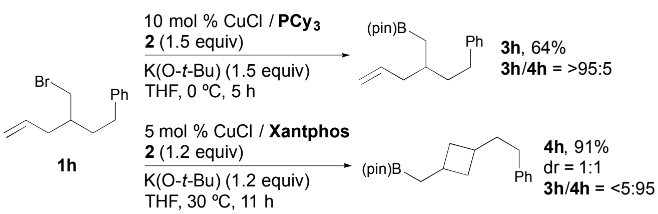
[a]Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1** (0.5 mmol), **2** (0.6 mmol), K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL) at 0 ºC. [b]Isolated yield. [c]10 mol % catalyst loading. The amount of K(O-*t*-Bu) and **2** added to each reaction was 0.75 mmol.

The borylation of 6-bromohex-1-ene (**1g**) using PCy_3 as a ligand under the standard conditions gave cyclopentylmethyl boronate **4g** as the major product (61%, **3g**/**4g** = 6:94 Scheme 2). This exceptional result can be explained by the contribution of a radical-mediated process during the boryl substitution reaction. The radical-mediated ring closure of a five-membered ring is well known to be a rapid reaction. For the reaction of **1g**, a rapid ring-forming pathway would exist as the dominant process over the alkyl halide borylation.[2,15]



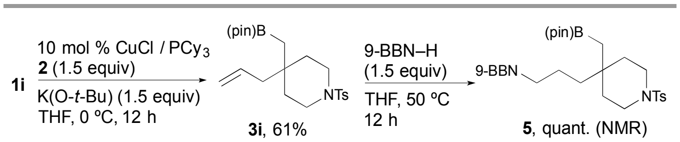
Scheme 2 Copper(I)-catalyzed borylation of 6-bromo-1-hexene (**1g**).

We then proceeded to investigate the ligand-controlled switching of the product in the borylation of **1h** (Scheme 3). When the borylation reaction of **1h** with **2** was conducted in the presence of PCy_3, the corresponding boryl substitution product **3h** was obtained in good yield with high selectivity (**3h**: 64%, **3h**/**4h** = >95:5). In contrast, the replacement of PCy_3 with Xantphos led to the borylative cyclization product in excellent yield with high product selectivity (**4h**: 91%, dr = 1:1, **3h**/**4h** = <5:95). These results therefore show that product selectivity could be perfectly controlled by changing the ligand.



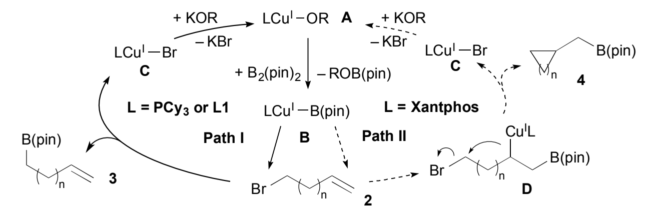
Scheme 3 Ligand-controlled selective borylation of **1h**.

To highlight the synthetic utility of this newly developed boryl substitution reaction, we investigated the functionalization of the terminal C=C double bond in the tosyl-protected piperidine substrate **1i** (Scheme 4). The boryl substitution product **3i** was synthesized using a $CuCl/PCy_3$ catalyst system. The subsequent hydroboration of **3i** gave the unsymmetrical diboration product **5**, which would be difficult to obtain from **1i** by any other borylation procedure.[16]



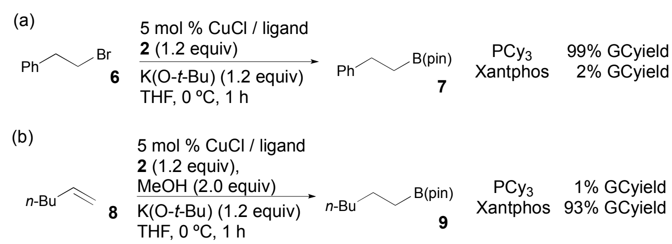
Scheme 4 Synthesis of unsymmetrical diboration product **5**.

The proposed reaction pathways for the production of the halogen selective borylation and borylative cyclization products are summarized in Scheme 5. The initial reaction of the copper catalyst precursor (**A**) with diboron would give the borylcopper(I) species (**B**). For the boryl substitution pathway (Path **I**), the borylcopper(I) species (**B**) would react with the C–Br bond of the substrate **2** to give the substitution product **3**. However, for the borylative cyclization pathway (Path **II**), the active borylcopper(I) species (**B**) would react with the C=C double bond of the alkyl halides bearing terminal alkene moieties to afford the alkylcopper(I) intermediate (**D**). This intermediate would then undergo an intramolecular cyclization reaction to give the cyclization product **4** and CuBr (**C**).[10] The key to the selectivity of this reaction lies in the reactivity preference of (**B**) for the C–Br or C=C double bond.



Scheme 5 Proposed mechanism.

Comparison experiments involving the two different catalyst systems (i.e., $CuCl/PCy_3$ and CuCl/Xantphos) clearly demonstrated their contrasting chemoselectivities (Scheme 6). The boryl substitution reaction of **6** with the $CuCl/PCy_3$ catalyst system at 0 °C afforded product **7** in quantitative yield (99%, 1 h), whereas the use of the CuCl/Xantphos catalyst system under the same conditions resulted in almost no reaction (2%, 1 h) (Scheme 6a). To evaluate the reactivity preference of the terminal alkene functionality, the monoborylation reaction of alkene **8** was carried out using both catalyst systems in the presence of MeOH as a proton source.[17] The reactivity of the CuCl/Xantphos system (93%, 1 h) was much higher than that of the $CuCl/PCy_3$ system (1%, 1 h) (Scheme 6b).



Scheme 6 Comparison experiments: (a) Copper(I)-catalyzed boryl substitution of alkyl halide **6**. (b) Copper(I)-catalyzed monoborylation of terminal alkene **8**.

In summary, we have successfully developed a new method for the carbon–halogen bond-selective copper(I)-catalyzed borylation of alkyl halides bearing terminal alkene moieties. The catalyst system for this reaction could be tuned to achieve a complete switch in the selectivity from the borylative cyclization reaction to a halogen selective boryl substitution. This reaction represents a complementary procedure to previously reported borylation pathways from alkyl halides bearing terminal alkene moieties. Furthermore, mechanistic studies have provided deeper insights into the ligand effects of this copper(I)-catalyzed borylation reaction. A detailed investigation of the mechanism of this boryl substitution reaction is currently in progress.

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Notes and references

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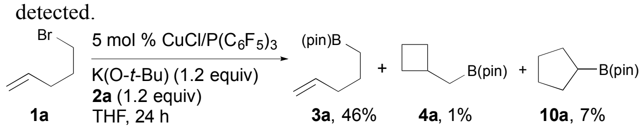
† Electronic Supplementary Information (ESI) available: Experimental procedure, compound characterization, DFT studies, ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c000000x/

1 D. G. Hall, *Boronic Acids*: *Preparation and Applications in Organic Synthesis, Medicine and Materials*, Wiley-VCH, Weinheim, 2nd edn, 2011, vol. 1 and 2.
2 C. T. Yang, Z. Q. Zhang, H. Tajuddin, C. C. Wu, J. Liang, J. H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder and L. Liu, *Angew. Chem. Int. Ed.*, 2012, **51**, 528–532.
3 H. Ito and K. Kubota, *Org. Lett*., 2012, **14**, 890–893.
4 A. S. Dudnik and G. C. Fu, *J. Am. Chem. Soc.*, 2012, **134**, 10693–10697.
5 (*a*) J. Yi, J. H. Liu, J. Liang, J. J. Dai, C. T. Yang, Y. Fu and L. Liu, *Adv. Synth. Catal*., 2012, **354**, 1685–1691. (*b*) A. Joshi-Pangu, X. Ma, M. Diane, S. Iqbal, R. J. Kribs, R. Huang, C. Y. Wang and M. R. Biscoe, *J. Org. Chem.*, 2012, **77**, 6629–6633.
6 S. K. Bose, K. Fucke, L. Liu, P. G. Steel and T. B. Marder, *Angew. Chem. Int. Ed.*, 2014, **53**, 1799–1803.
7 (*a*) T. C. Atack, R. M. Lecker and S. P. Cook, *J. Am. Chem. Soc.*, 2014, **136**, 9521–9523. (*b*) R. B. Bedford, P. B. Brenner, E. Carter, T. Gallagher, D. M. Murphy and D. R. Pye, *Organometallics*, 2014, **33**, 5940–5943.
8 Transition-metal (Pd, Ni, Cu, Zn) catalyzed borylations of aryl halides have been reported. For Pd-catalyzed reactions see: (*a*) T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508–7510. For Cu-catalyzed reactions see: (*b*) C. Kleeberg, L. Dang, Z. Lin and T. B. Marder, *Angew. Chem. Int. Ed.*, 2009, **48**, 5350–5354. For Ni-catalyzed reactions see: (*c*) T. Yamamoto, T. Morita, J. Takagi and T. Yamakawa, *Org. Lett.*, 2011, **13**, 5766–5769. For Zn-catalyzed reactions see: (*d*) Y. Nagashima, R. Takita, K. Yoshida, K. Hirano and M. Uchiyama, *J. Am. Chem. Soc.*, 2014, **135**, 18730–18733.
9 Y. Yamamoto, R. Fujikawa, T. Umemoto and N. Miyaura, *Tetrahedron*, 2004, **60**, 10695–10700.
10 K. Kubota, E. Yamamoto and H. Ito, *J. Am. Chem. Soc*., 2013, **135**, 2635–2640.
11 For selected examples of the *endo*-selective copper(I)-catalyzed borylative cyclization of alkenes, see: (*a*) H. Ito, Y. Kosaka, K. Nonoyama, Y. Sasaki and M. Sawamura, *Angew. Chem. Int. Ed.*, 2008, **47**, 7424–7427. (*b*) H. Ito, T. Toyoda and M. Sawamura, *J. Am. Chem. Soc.*, 2010, **132**, 5990–5992.
12. Marder's group reported that copper(I)-catalyzed boryl substitution of 10-bromodec-1-ene. This substrate has different reactivity from those we investigated in this paper. The long distance between the alkene and C–Br moiety in this substrate hampers the borylative cyclization, see: ref. 2 and 10.
13 In our previous paper (ref. 10), we reported that **4a** was produced in 7% yield in the similar CuCl/P(C_6F_5)$_3$/K(O-*t*-Bu) catalyst system. After careful investigation in this study, we found that this 7% side products should be assigned as **10a** as shown in the following scheme. Under the optimized conditions for the boryl substitution (Table 1, entries 10 and 11), side products **4a** and **10a** were not detected.


14 Homoallylboronate **3e** were synthesized in 79% yield for three steps from **1e** through preparation of Grignard reagent. P. Sušnik and G. Hilt, *Organometallics,* 2014, **33**, 5907–5910.
15 Marder's group has been also reported the similar result that the borylation of **1g** gave cyclic product **4g**, see: ref. 2.
16 Alkyl-9-BBN is known to be very reactive organoboron compounds in the presence of copper(I) catalyst, see: H. Ohmiya, U. Yokobori, Y. Makida and M. Sawamura, *J. Am. Chem. Soc.*, 2010, **132**, 2895–2897. The reverse reaction sequence of **1i**, 9-BBN hydroboration first then copper(I)-catalyzed boryl substitution, resulted in complex mixture.
17 For selected examples of the copper(I)-catalyzed monoborylation of alkenes, see: (*a*) H. Ito, H. Yamanaka, J. Tateiwa and A. Hosomi, *Tetrahedron Lett.*, 2000, **41**, 6821–6825. (*b*) K. Takahashi, T. Ishiyama and N. Miyaura, *Chem. Lett*., 2000, **29**, 982–983. (*c*) S. Mun, J. E. Lee and J. Yun, *Org. Lett.*, 2006, **8**, 4887–4889. (*d*) Y. Sasaki, C. Zhong, M. Sawamura and H. Ito, *J. Am. Chem. Soc.*, 2010, **132**, 1226–1227. (*e*) A. Parra, L. Amenós, M. Guisán-Ceinos, A. López, J. L. G. Ruano and M. Tortosa, *J. Am. Chem. Soc.*, 2014, **136**, 15833–15836.
18 The DFT studies of the reaction between borylcopper(I) intermediate and alkene were reported in ref. 10 and Supplementary Information.

