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

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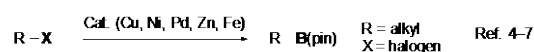
The selective boryl substitution of alkyl halides bearing terminal C=C double bonds has been achieved using a copper(I)/tricyclohexylphosphine or copper(I)/*o*-diphenylphosphinophenol catalyst. This reaction represents a useful complementary approach to conventional procedures for the hydroboration of 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/PPh₃/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}

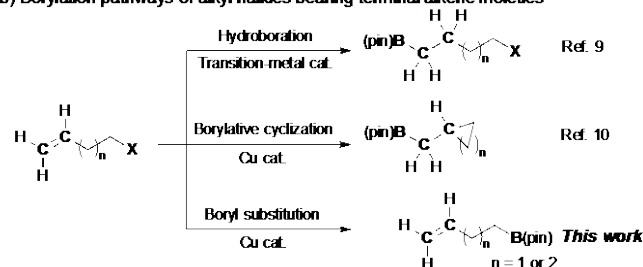
Alkyl halides bearing a terminal alkene moieties can be converted to a variety of borylation products through three different reaction pathways, including the hydroboration of the terminal C=C double bond,⁹ borylative cyclization¹⁰ and boryl substitution of the C–X bond (Scheme 1b). Conventional hydroboration 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.

(a) Transition-metal catalyzed boryl substitution of alkyl halides



(b) Borylation pathways of alkyl halides bearing terminal alkene moieties



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). PPh₃, P(C₆F₅)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 PCy₃ 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 °C, 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 of 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 PCy₃ 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. (°C)	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 ₆ F ₅) ₃	30	53	1	98:2
6	SPhos	30	54	<1	>99:1
7	P(<i>t</i> -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	-

^aConditions: 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). ^bDetermined by GC analysis of the crude reaction mixture with an internal standard. ^cReaction time of 9 h.

With the optimized conditions in hand, we proceeded to investigate the scope of the selective boryl substitution reaction

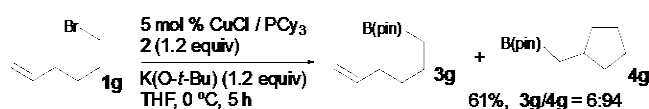
using a variety of different alkyl halides bearing terminal alkene moieties (Table 2). We previously reported borylative cyclization reactions using Xantphos as a ligand to give the corresponding cyclization products **4a–f**.¹⁰ The borylation reactions of **1a** and **1b** using PCy₃ or **L1** as a 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 PCy₃ 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 **1a**

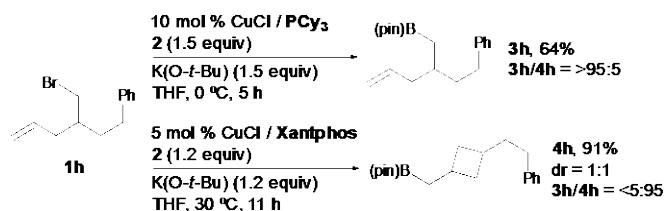
entry	substrate	ligand	product	yield (%) ^b	3/4
1	1a	PCy ₃	3a	68	>95:5
2	1a	L1	3a	60	>95:5
3	1b	PCy ₃	3b	67	>95:5
4	1b	L1	3b	70	>95:5
5 ^c	1c	PCy ₃	3c	55	>95:5
6 ^c	1d	L1	3d	47	>95:5
7	1e	PCy ₃	3e	73	>95:5
8	1f	PCy ₃	-	complex mixture	

^aConditions: 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 °C. ^bIsolated yield. ^c10 mol % catalyst loading. The amount of K(*O-t*-Bu) and **2** added to each reaction was 0.75 mmol.

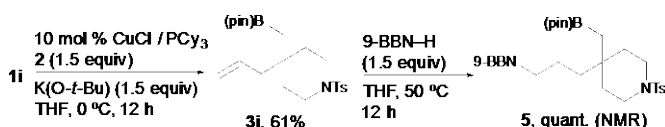
The borylation of 6-bromohex-1-ene (**1g**) using PCy₃ as a ligand under the standard conditions gave cyclopentylmethyl boronate **4g** as the major product (61%, **3g/4g** = 6:94 Scheme 2). This exceptional result can be explained by the contribution of a radical-mediated process during the boryl substitution 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 PCy₃, 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 PCy₃ 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**.

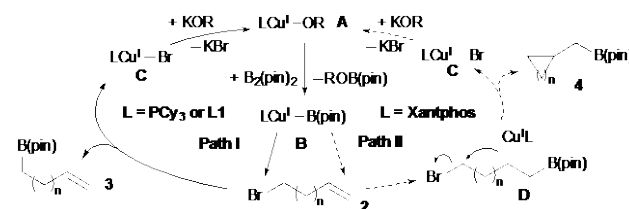
To highlight the synthetic utility of this newly developed boryl substitution reaction, we investigated the functionalization of the terminal C=C double bond in the tosyl-protected piperidine substrate **1i** (Scheme 4). The boryl substitution product **3i** was synthesized using a CuCl/PCy₃ catalyst 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**.

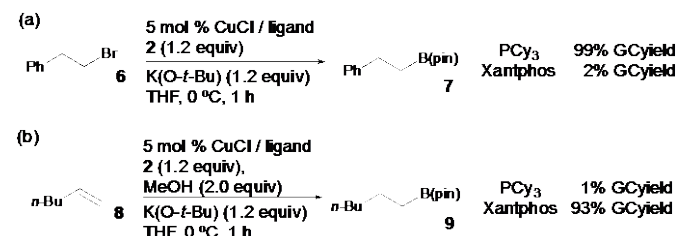
The proposed reaction pathways for the production of the halogen selective borylation and borylative cyclization products are summarized in Scheme 5. The initial reaction of the copper catalyst precursor (**A**) with diboron would give the borylcopper(I) species (**B**). For the boryl substitution pathway (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.

Comparison experiments involving the two different catalyst systems (i.e., CuCl/PCy₃ and CuCl/Xantphos) clearly demonstrated their contrasting chemoselectivities (Scheme 6). The boryl substitution reaction of **6** with the CuCl/PCy₃ 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/PCy₃ system (1%, 1 h) (Scheme 6b).



Scheme 5 Proposed mechanism.

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 ¹³C NMR spectra. See DOI: 10.1039/c000000x/

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- $$\begin{array}{c}
 \text{Br} \\
 | \\
 \text{CH}_2 = \text{CH} - (\text{CH}_2)_8 - \text{Br} \quad \xrightarrow[\text{THF, 24 h}]{\begin{array}{l} 5 \text{ mol } \% \text{ CuCl/P(C}_6\text{F}_5)_3 \\ \text{K(O-}t\text{-Bu) (1.2 equiv)} \\ \text{2a (1.2 equiv)} \end{array}} \quad \text{(pin)B} \quad + \quad \text{B(pin)} \quad + \quad \text{B(pin)} \\
 \text{1a} \qquad \qquad \qquad \text{3a, 46\%} \qquad \text{4a, 1\%} \qquad \text{10a, 7\%}
 \end{array}$$
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