Arylboration of Alkenes by Cooperative Palladium/Copper Catalysis

Kazuhiko Semba* and Yoshiaki Nakao*
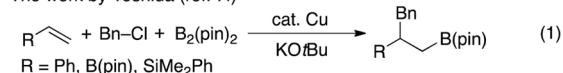
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan
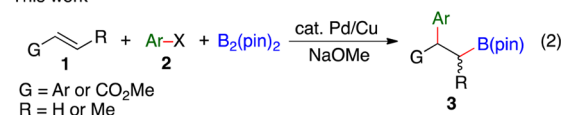
S *Supporting Information*

ABSTRACT: Arylboration of vinylarenes and methyl crotonate with aryl halides and bis(pinacolato)diboron by cooperative Pd/Cu catalysis has been developed, giving 2-boryl-1,1-diarylethanes and an α-aryl-β-boryl ester in a regioselective manner. The reaction is compatible with a variety of functionalities and amenable to be scaled-up to a gram scale with no detriment to the yield. A short synthesis of the biologically active compound CDP840 was performed using the present reaction as a key step.

Alkylboranes are versatile synthetic intermediates in organic synthesis,[1] and some of them possess interesting biological activity.[2] They are prepared conventionally by hydroboration of alkenes[3] and by substitution reactions of boron electrophiles with alkyllithium or Grignard reagents.[4] In recent years, transition-metal-catalyzed borylation reactions have been shown to be a powerful synthetic method for the preparation of alkylboranes in terms of functional group compatibility and unique reactivity.[5] Carboboration[6] of alkenes can be an effective method to prepare highly functionalized alkylboranes starting from readily available substrates.[7] Whereas *intramolecular* carboboration of alkenes using Pd or Cu catalysts has been studied extensively,[7a−e] *intermolecular* carboboration of alkenes has rarely been achieved and is limited to Cu-catalyzed benzylboration with highly electrophilic benzyl chloride and bis(pinacolato)diboron ($B_2(pin)_2$) (eq 1)[7f] and the uncatalyzed allylboration of highly reactive

The work by Yoshida (ref. 7f)

$$R\diagdown + Bn\text{-}Cl + B_2(pin)_2 \xrightarrow[\text{KO}t\text{Bu}]{\text{cat. Cu}} R\diagdown\overset{Bn}{\diagup}B(pin) \quad (1)$$

R = Ph, B(pin), SiMe₂Ph

This work

$$G\diagdown\diagup R + Ar\text{-}X + B_2(pin)_2 \xrightarrow[\text{NaOMe}]{\text{cat. Pd/Cu}} G\overset{Ar}{\underset{R}{\diagup}}B(pin) \quad (2)$$

1   **2**   **3**

G = Ar or CO₂Me
R = H or Me

1-methylcyclopropene with triallylborane.[7g] Here we report the first example of an intermolecular arylboration of various vinylarenes and methyl crotonate **1** with aryl halides **2** and $B_2(pin)_2$ by cooperative Pd/Cu catalysis,[8] giving 2-boryl-1,1-diarylethanes and an α-aryl-β-boryl ester **3** in a regioselective manner (eq 2). The present transformation affords potentially useful building blocks to access 1,1-diarylalkanes, which are widely found in bioactive compounds and medicines such as Detrol,[9] Zoloft,[10] and Condylox[11] (Figure 1).

Our working hypothesis to realize the arylboration of alkenes is shown in Scheme 1. The first step involves the catalytic generation of β-borylalkylcopper **4** via the reaction of an alkene
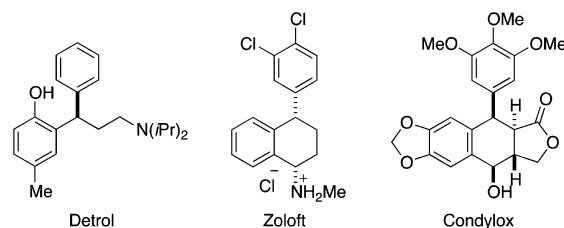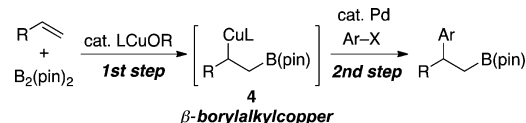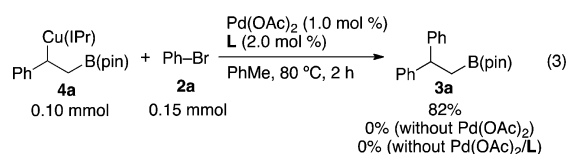

Figure 1. Medicines containing 1,1-diarylalkane structures.

Scheme 1. Working Hypothesis for Alkene Arylboration

and $B_2(pin)_2$ by Cu catalysis.[12] Subsequently, cross-coupling of **4** with aryl halides in the presence of a Pd catalyst gives the arylboration products.[13] Highly reactive benzyl chloride can react directly with **4** to achieve the benzylboration (eq 1).[7f] However, it may be challenging to further expand the scope due to the low reactivity of **4** toward the oxidative addition of other electrophiles such as aryl halides. In our scenario, the aryl electrophiles could be used as viable coupling partners by using Pd catalysts bearing electron-rich phosphine ligands, which readily undergo oxidative addition of aryl bromides and even aryl chlorides.[14] To test the working hypothesis, the cross-coupling reaction of β-borylalkyl-copper **4a**, which was prepared from styrene (**1a**), $B_2(pin)_2$, and (IPr)Cu(OtBu),[12] with phenyl bromide (**2a**) was performed in the presence of 1.0 mol % Pd(OAc)₂ and 2.0 mol % dicyclohexyl(2-mesitylphenyl)phosphine (**L**; for the structure of **L**, see Table 1) (eq 3). Gratifyingly, the desired coupling product

$$\underset{\substack{\textbf{4a}\\ \text{0.10 mmol}}}{Ph\diagup B(pin)} + \underset{\substack{\textbf{2a}\\ \text{0.15 mmol}}}{Ph\text{-}Br} \xrightarrow[\text{PhMe, 80 °C, 2 h}]{\substack{\text{Pd(OAc)}_2 \text{ (1.0 mol \%)}\\ \textbf{L} \text{ (2.0 mol \%)}}} \underset{\substack{\textbf{3a}\\ 82\%\\ \text{0\% (without Pd(OAc)}_2)\\ \text{0\% (without Pd(OAc)}_2/\textbf{L})}}{Ph\overset{Ph}{\diagup}B(pin)} \quad (3)$$

3a was obtained in 82% yield. In contrast, no trace amount of **3a** was observed in the absence of Pd(OAc)₂ or Pd(OAc)₂/**L**.[15]

To achieve a cooperative catalytic reaction, we optimized the reaction conditions employing **1a**, **2a**, and $B_2(pin)_2$ as model substrates (Table 1). After a variety of reaction parameters were screened, the arylboration of **1a** gave **3a** regioselectively in high yield using the standard conditions: Pd(OAc)₂ (1.0 mol %), **L**

Table 1. Optimization of the Arylboration Reaction

entry	variation from the standard conditions	yield of 3a + 3a' (%)[a,b] (3a/3a')[c]	yield of 5 (%)[a,b]	yield of 6 (%)[a,d]
1	none	>95 (>99:1)	5	8
2	PPh₃ instead of L	58 (98:2)	26	28
3	PCy₃ instead of L	87 (85:15)	7	11
4	P*t*Bu₃ instead of L	21 (94:6)	29	8
5	S-phos instead of L	88 (>99:1)	10	10
6	X-phos instead of L	91 (>99:1)	7	3
7	dppe instead of L	20 (90:10)	29	15
8	dppp instead of L	45 (96:4)	28	19
9	ᶜˡIPr instead of IPr	67 (>99:1)	3	11
10	ᴹᵉIPr instead of IPr	95 (>99:1)	4	9
11	IMes instead of IPr	71 (94:6)	8	30
12	LiOMe instead of NaOMe	0	0	8
13	LiO*t*Bu instead of NaOMe	>95 (>99:1)	0	9
14	Cs₂CO₃ instead of NaOMe	1	3	18
15	CsF instead of NaOMe	0	0	3
16	without Pd(OAc)₂/L	0	22	0
17	without (IPr)CuCl	0	0	36

[a]Determined by GC analysis with tridecane as an internal standard. [b]Based on 1a. [c]Determined by GC analysis. [d]Based on 2a.

(2.0 mol %), (IPr)CuCl (5.0 mol %), and NaOMe (0.15 mmol) in toluene at 80 °C for 2 h (entry 1). Notably, the formation of the expected byproducts 5 and 6, which could be derived from Cu-catalyzed hydroboration[16] of 1a and Pd- or Cu-catalyzed borylation[17] of 2a, respectively, were suppressed under the standard conditions. The effects of the phosphine ligands on Pd are summarized in entries 2–8. When PPh₃ or P*t*Bu₃ was employed, the yield of 3a was low and large amounts of byproducts 5 and 6 were observed (entries 2 and 4). In the case of PCy₃, the regioselectivity was modest (entry 3). Dicyclohexylbiarylphosphines such as S-phos and X-phos gave good results in terms of the observed activity and selectivity (entries 5 and 6). Bidentate phosphine ligands were not effective for this reaction (entries 7 and 8). Other N-heterocyclic carbene (NHC) ligands on Cu were also investigated (entries 9–11). Although less electron-donating ᶜˡIPr resulted in moderate activity, the use of more electron-donating ᴹᵉIPr showed higher productivity (entries 9 and 10). With sterically less demanding IMes, poorer yield and regioselectivity were observed, with the formation of a large amount of 6 (entry 11). The effect of various bases on the reaction was also tested (entries 12–15). LiO*t*Bu was also effective in promoting the reaction (entry 13), whereas other bases such as LiOMe, Cs₂CO₃, and CsF did not afford the desired product (entries 12, 14, and 15). In the absence of Pd(OAc)₂/L, 3a was not formed, as was the case with the use of a stoichiometric amount of 4a (eq 3), and only 5 was obtained in 22% yield (entry 16). In addition, when the reaction was performed without (IPr)CuCl, a large amount of 6 was observed without the

formation of 3a (entry 17). These results clearly indicate the cooperative action of the Pd and Cu catalysts in the arylboration of styrene. When the arylboration of 1a was performed in the presence of a catalytic (5.0 mol %) or stoichiometric (0.25 mmol) amount of TEMPO under the standard conditions, 3a was obtained in 94% or 45% yield, respectively. These results show that the present reaction does not proceed through a radical mechanism mediated by alkoxide bases.[18]

The reaction on a 0.25 mmol scale under the standard conditions gave 3a in 77% yield after purification by medium-pressure column chromatography on silica gel (Table 2, entry 1). The scope of substrates was surveyed employing various styrene derivatives (1a–e) and aryl bromides (2a–m) (Table 2). All of the reactions proceeded with excellent regioselectivity, and various functional groups such as amino, siloxy, acyl, alkoxycarbonyl, aminocarbonyl, cyano, chloro, fluoro, and trifluoromethyl groups were tolerated under the standard conditions. Neither electron-donating (entries 2–5) nor electron-withdrawing (entries 6–10) groups at the para position of 2a affected the yield, and the corresponding 1,1-diarylethylboronates were obtained in good to high yields. The procedure could be scaled up to a gram scale (entry 3). An ortho substituent was also compatible (entry 11). Heteroaromatic bromides 2l and 2m reacted efficiently, giving 3l and 3m in high yields (entries 12 and 13). Electron-rich and electron-deficient styrene derivatives (1b–d) gave the corresponding products in good yields (entries 14–16). 2-Vinylnaphthalene (1e) afforded the desired product 3p in 71% yield with (ᶜˡIPr)CuCl as the Cu catalyst (entry 17). In addition to vinylarenes, methyl crotonate (1f) also participated in the present arylboration to give β-boryl ester 3q in 66% yield as a mixture of diastereomers when (IPr*)CuCl was used (see Table 1 for the structure of IPr*) instead of (IPr)CuCl (entry 18), whereas aliphatic alkenes such as 1-octene and cyclohexene reacted sluggishly under the standard reaction conditions. The arylboration of diphenylacetylene (7) also proceeded efficiently under the standard conditions, affording alkenylboronate 8 in 70% yield (eq 4).
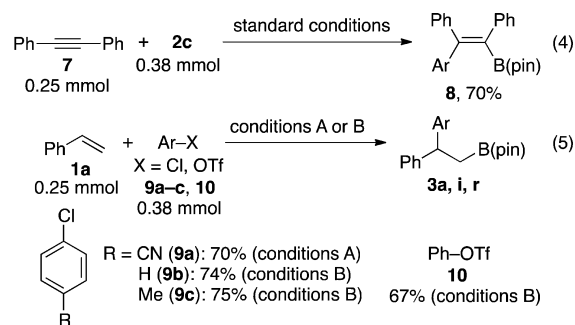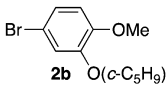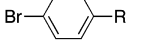

conditions A: Pd(OAc)₂ (2.0 mol %), L (4.0 mol %), (ᶜˡIPr)CuCl (5.0 mol %), NaOMe (0.38 mmol), 1a (0.25 mmol), B₂(pin)₂ (0.38 mmol), at 80 °C, for 6 h. conditions B: Pd(OAc)₂ (1.0 mol %), X-phos (2.0 mol %), (IPr)CuCl (5.0 mol %), LiO*t*Bu (0.38 mmol), 1a (0.25 mmol), 9 or 10 (0.38 mmol), B₂(pin)₂ (0.38 mmol), at 80 °C, for 4 h.

Next, we examined the arylboration of 1a with inexpensive and readily available aryl chlorides (9a–c) (eq 5). Activated aryl chloride 9a underwent the arylboration under conditions similar to the standard ones (conditions A). When X-phos and LiO*t*Bu instead of L and NaOMe (conditions B) were used, the products were obtained in good yields also from nonactivated aryl chlorides such as 9b and 9c as well as aryl triflate 10.

A plausible reaction mechanism is depicted in Scheme 2. The catalytic cycle consists of two individual cycles involving (A) Pd and (B) Cu catalysis. Cycle A is initiated by the oxidative addition

Table 2. Arylboration of 1 with 2 and B$_2$(pin)$_2$

entry	1	2	yield (%)[a]
1	**1a**	**2a**	77 (**3a**)
2	**1a**	**2b** (Br–aryl with OMe, O(c-C$_5$H$_9$))	92 (**3b**)
3[b]	**1a**	R = OMe (**2c**)	72 (**3c**)
4[c]	**1a**	NEt$_2$ (**2d**)	56 (**3d**)
5	**1a**	CH$_2$OTBS (**2e**)	86 (**3e**)
6[d]	**1a**	Ac (**2f**)	86 (**3f**)
7[e]	**1a**	CO$_2$Me (**2g**)	79 (**3g**)
8	**1a**	C(O)N(iPr)$_2$ (**2h**)	70 (**3h**)
9[f]	**1a**	CN (**2i**)	68 (**3i**)
10[g]	**1a**	Cl (**2j**)	73 (**3j**)
11	**1a**	**2k**	61 (**3k**)
12	**1a**	**2l**	76 (**3l**)
13	**1a**	**2m**	89 (**3m**)
14	R = 4-OMe (**1b**)	**2a**	60 (**3c**)
15	4-F (**1c**)	**2a**	70 (**3n**)
16	3-CF$_3$ (**1d**)	**2a**	68 (**3o**)
17[h]	**1e**	**2a**	71 (**3p**)
18[i]	**1f**	**2c**	66[j] (**3q**)

[a]Isolated yields of **3**. [b]Run for 5 h using **1a** (7.5 mmol), **2c** (11 mmol), B$_2$(pin)$_2$ (11 mmol), and NaOMe (11 mmol). [c]Pd(OAc)$_2$ (2.0 mol %) and **L** (4.0 mol %) were used. [d]Run at 50 °C for 4 h using **1a** (0.38 mmol) and **2a** (0.25 mmol). [e]Run at 50 °C for 4 h using (^{Cl}IPr)CuCl (5.0 mol %). [f]Run at 50 °C for 4 h. [g]Run for 0.5 h. [h](^{Cl}IPr)CuCl (5.0 mol %) was used. [i](IPr*)CuCl (5.0 mol %), **1f** (0.38 mmol), and **2c** (0.25 mmol) were used. [j]**3q** was isolated as an 80:20 mixture of diastereomers.

of aryl halide **2** to LPd(0) **11** (step a in cycle A). On the basis of the results shown in eq 3, transmetalation between LPdAr(X) **12** and β-borylalkylcopper **4** (step b in cycle A), which is generated via addition of borylcopper **13** across **1** (step e in cycle B),[12] is followed by reductive elimination to give **3** and regenerate **11** (step c in cycle A). In cycle B, borylcopper **13** is produced by the reaction of copper alkoxide **14** with B$_2$(pin)$_2$ (step d in cycle B).[19] After transmetalation, LCu-X **15** reacts with the metal alkoxide base to regenerate **14** (step f in cycle B).

One could argue that the reaction proceeds through diboration of the vinylarene to give the 1-aryl-1,2-diborylethane followed by cross-coupling with the aryl halide. To check this possibility, the reaction of 1,2-diboryl-1-phenylethane **16** (prepared by NaOtBu-catalyzed diboration[20] of **1a**) with **2a** in the presence of **1e** was

Scheme 2. Plausible Reaction Mechanism

investigated (eq 6). Although **3p** was obtained in 74% yield via arylboration of **1e** with **2a** and B$_2$(pin)$_2$, **16** was not converted to styrene arylboration product **3a**. Another possible reaction pathway would involve an initial Pd-catalyzed Mizoroki–Heck (MH) reaction of the vinylarene to give the 1,1-diarylethene and subsequent Cu-catalyzed hydroboration,[16] but this is unlikely because the MH reaction typically gives the 1,2-diarylethene.[21] The facts that **4a** gives the arylboration product in good yield in the presence of Pd catalyst (eq 3) and that the reaction requires both Pd and Cu catalysts (Table 1), in addition to the above discussion, support the proposed cooperative Pd/Cu catalysis.

Finally, to demonstrate the synthetic utility of the alkylboronates obtained by the present method, we examined their use in the Suzuki–Miyaura cross-coupling reaction (eq 7). **3b** (Table 2, entry 2) was reacted with 4-iodopyridine in the presence of PdCl$_2$(dppf) (20 mol %) and KOH(aq) to give CDP840, a phosphodiesterase IV inhibitor, in 62% yield.[22]

In conclusion, we have developed an arylboration reaction of various vinylarenes and methyl crotonate with aryl halides and B$_2$(pin)$_2$ by cooperative Pd/Cu catalysis, giving 2-boryl-1,1-diarylethanes and an α-aryl-β-boryl ester in highly chemo- and regioselective manners. The synthetic utility of the alkylboron compounds obtained by the present method was also demonstrated by a short synthesis of the phosphodiesterase IV inhibitor CDP840. This novel cooperative catalytic system has great potential in the development of carboboration and other carbon–carbon bond-forming reactions.

■ ASSOCIATED CONTENT

⑤ Supporting Information
Procedures, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors
semba.kazuhiko.5n@kyoto-u.ac.jp
nakao.yoshiaki.8n@kyoto-u.ac.jp

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