

Arylboration of Alkenes by Cooperative Palladium/Copper Catalysis

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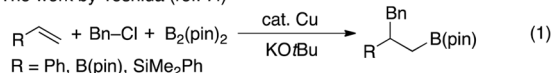
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S Supporting Information

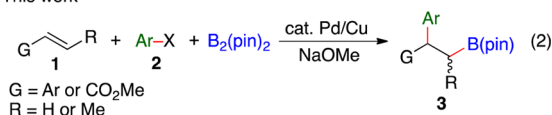
ABSTRACT: Arylboration of vinylarenes and methyl crotonate with aryl halides and bis(pinacolato)diboron by cooperative Pd/Cu catalysis has been developed, giving 2-boryl-1,1-diarylethanes and an α -aryl- β -boryl ester in a regioselective manner. The reaction is compatible with a variety of functionalities 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 alkenes³ 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 Carboboration⁶ 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 ($B_2(\text{pin})_2$) (eq 1)^{7f} and the uncatalyzed allylboration of highly reactive

The work by Yoshida (ref. 7f)



This work



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 $B_2(\text{pin})_2$ 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-diarylethanes, which are widely found in bioactive compounds and medicines such as Zolofit,⁹ and Condylox¹¹ (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

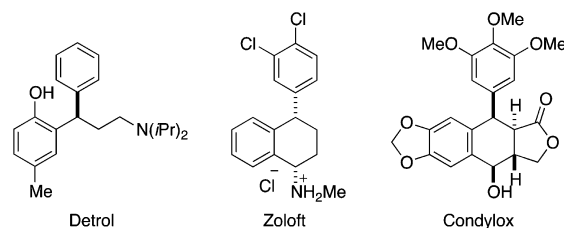
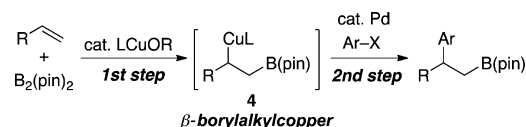
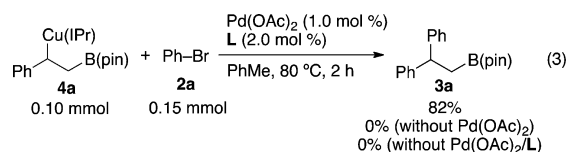


Figure 1. Medicines containing 1,1-diarylethane structures.

Scheme 1. Working Hypothesis for Alkene Arylboration



and $B_2(\text{pin})_2$ 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 -borylalkylcopper **4a**, which was prepared from styrene (**1a**), $B_2(\text{pin})_2$, 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



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 $B_2(\text{pin})_2$ 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**

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Table 1. Optimization of the Arylboration Reaction

Standard conditions: $\text{Pd}(\text{OAc})_2$ (1.0 mol %), L (2.0 mol %), $(\text{IPr})\text{CuCl}$ (5.0 mol %), NaOMe (0.15 mmol), $\text{B}_2(\text{pin})_2$ (0.15 mmol), PhMe , 80 °C, 2 h.

Ligand definitions:
 $\text{R}^1 = \text{R}^2 = \text{Me}$: L
 $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{H}$: S-phos
 $\text{R}^1 = \text{R}^2 = \text{iPr}$: X-phos
 $\text{X} = \text{H}$: IPr
 Cl : ClIPr
 Me : MeIPr
 $\text{R} = \text{Me}$: IMes
 $\text{C}(\text{H})\text{Ph}_2$: IPr^*

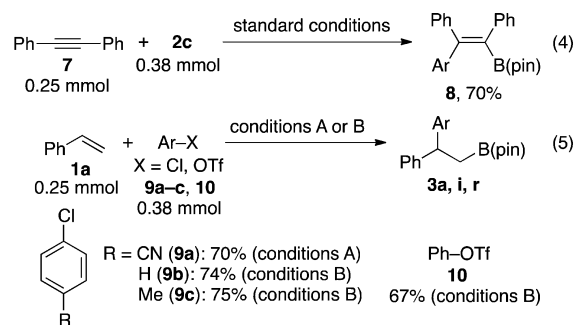
entry	variation from the standard conditions	yield of 3a + 3a' (%) ^{a,b}	yield of 5 (%) ^{a,b}	yield of 6 (%) ^{a,d}
1	none	>95 (>99:1)	5	8
2	PPh_3 instead of L	58 (98:2)	26	28
3	PCy_3 instead of L	87 (85:15)	7	11
4	PtBu_3 instead of L	21 (94:6)	29	8
5	S-phos instead of L	88 (>99:1)	10	10
6	X-phos instead 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	LiOtBu instead of NaOMe	>95 (>99:1)	0	9
14	Cs_2CO_3 instead of NaOMe	1	3	18
15	CsF instead of NaOMe	0	0	3
16	without $\text{Pd}(\text{OAc})_2/\text{L}$	0	22	0
17	without $(\text{IPr})\text{CuCl}$	0	0	36

^aDetermined by GC analysis with tridecane as an internal standard.^bBased on **1a**. ^cDetermined by GC analysis. ^dBased on **2a**.

(2.0 mol %), $(\text{IPr})\text{CuCl}$ (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 hydroboration¹⁶ of **1a** and Pd- or Cu-catalyzed borylation¹⁷ of **2a**, respectively, were suppressed under the standard conditions. The effects of the phosphine ligands on Pd are summarized in entries 2–8. When PPh_3 or PtBu_3 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 PCy_3 , 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). LiOtBu was also effective in promoting the reaction (entry 13), whereas other bases such as LiOMe , Cs_2CO_3 , and CsF did not afford the desired product (entries 12, 14, and 15). In the absence of $\text{Pd}(\text{OAc})_2/\text{L}$, **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 $(\text{IPr})\text{CuCl}$, 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 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 $(\text{IPr}^*)\text{CuCl}$ was used (see Table 1 for the structure of IPr^*) instead of $(\text{IPr})\text{CuCl}$ (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: $\text{Pd}(\text{OAc})_2$ (2.0 mol %), L (4.0 mol %), ClIPr CuCl (5.0 mol %), NaOMe (0.38 mmol), **1a** (0.25 mmol), **9** (0.38 mmol), $\text{B}_2(\text{pin})_2$ (0.38 mmol), at 80 °C, for 6 h. conditions B: $\text{Pd}(\text{OAc})_2$ (1.0 mol %), X-phos (2.0 mol %), $(\text{IPr})\text{CuCl}$ (5.0 mol %), LiOtBu (0.38 mmol), **1a** (0.25 mmol), **9** or **10** (0.38 mmol), $\text{B}_2(\text{pin})_2$ (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 LiOtBu 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 $B_2(\text{pin})_2$

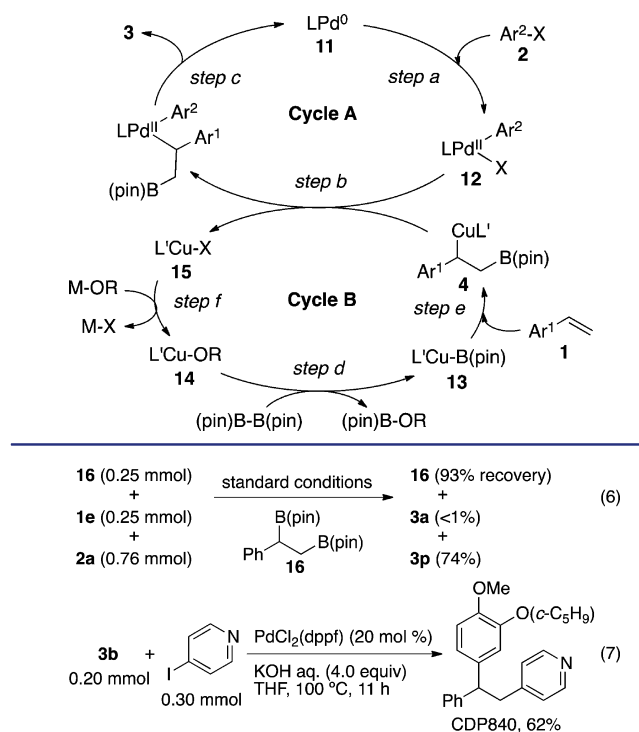
$ \begin{array}{c} \text{G}-\text{CH}=\text{CH}-\text{R} \quad \text{1} + \text{Ar}-\text{Br} \quad \text{2} \\ 0.25 \text{ mmol} \quad 0.38 \text{ mmol} \end{array} \xrightarrow[\text{PhMe, 80 }^\circ\text{C, 2 h}]{\text{Pd(OAc)}_2 (1.0 \text{ mol } \%), \text{L} (2.0 \text{ mol } \%), (\text{IPr})\text{CuCl} (5.0 \text{ mol } \%), \text{NaOMe} (0.38 \text{ mmol}), B_2(\text{pin})_2 (0.38 \text{ mmol})} \begin{array}{c} \text{Ar} \\ \\ \text{G}-\text{CH}-\text{CH}-\text{R} \\ \quad \\ \text{B}(\text{pin}) \quad \text{3} \end{array} $			
entry	1	2	yield (%) ^a
1	1a	2a	77 (3a)
2	1a	2b	92 (3b)
		2b	
		2b	
		2b	
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(<i>i</i> Pr) ₂ (2h)	70 (3h)
9 ^f	1a	CN (2i)	68 (3i)
10 ^g	1a	Cl (2j)	73 (3j)
11	1a	2k	61 (3k)
		2k	
12	1a	2l	76 (3l)
		2l	
13	1a	2m	89 (3m)
		2m	
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)
	1e		
18 ⁱ	MeO 1f	2c	66 ^j (3q)
	1f		

^aIsolated yields of **3**. ^bRun for 5 h using **1a** (7.5 mmol), **2c** (11 mmol), $B_2(\text{pin})_2$ (11 mmol), and NaOMe (11 mmol). ^cPd(OAc)₂ (2.0 mol %) and **L** (4.0 mol %) were used. ^dRun at 50 °C for 4 h using **1a** (0.38 mmol) and **2a** (0.25 mmol). ^eRun at 50 °C for 4 h using (^{Cl}IPr)CuCl (5.0 mol %). ^fRun at 50 °C for 4 h. ^gRun 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 $B_2(\text{pin})_2$ (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 diboration²⁰ 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 $B_2(\text{pin})_2$, **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-diarylethane and subsequent Cu-catalyzed hydroboration,¹⁶ but this is unlikely because the MH reaction typically gives the 1,2-diarylethane.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 PdCl₂(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 $B_2(\text{pin})_2$ 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

Supporting Information

Procedures, analytical data, and NMR spectra. 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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