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Palladium-catalyzed Carboboration: Borylative Coupling of Alkynes with Alkenes through Activation of Boron–Chlorine Bonds

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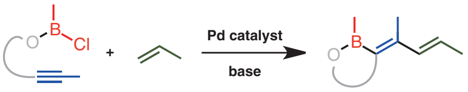
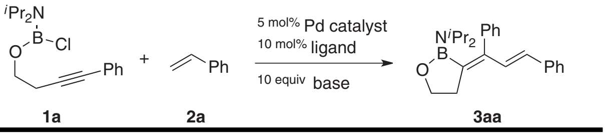
Alkynes tethered to a chloro(diisopropylamino)boryl group undergo palladium-catalyzed borylative coupling with styrenes and acrylates, giving substituted cyclic 1,3-dienylboronic acid derivatives in a stereoselective fashion.



Scheme 1. Borylative coupling of alkyne and alkene.

Table 1. Palladium-catalyzed cyclizative carboboration of **1a** with styrene (**2a**)[a]



Entry	Pd complex	Ligand	Base	Solvent	T/°C	%yield[b]
1	[Pd(allyl)Cp]	PPh_3	Et_3N	Toluene	110	39
2	[Pd(allyl)Cp]	PPh_3	Et_3N	Dioxane	110	67
3	[Pd(allyl)Cp]	PPh_3	Et_3N	NMP	110	67
4	[Pd(allyl)Cp]	PPh_3	Et_3N	DMSO	110	0
5	[Pd(allyl)Cp]	PPh_3	Et_3N	CH_3CN	110	69
6	[Pd(allyl)Cp]	PPh_3	Et_3N	CH_3CN	80	72
7	[Pd(allyl)Cp]	PPh_3	K_3PO_4	CH_3CN	80	71
8	[Pd(allyl)Cp]	PPh_3	Cs_2CO_3	CH_3CN	80	0
9	[Pd(allyl)Cp]	—	Et_3N	CH_3CN	80	5
10	[Pd(allyl)Cp]	PMe_3	Et_3N	CH_3CN	80	0
11	[Pd(allyl)Cp]	PCy_3	Et_3N	CH_3CN	80	15
12	[Pd(allyl)Cp]	PPh_2Cy	Et_3N	CH_3CN	80	74
13	[Pd(allyl)Cp]	DPPE	Et_3N	CH_3CN	80	0
14	$Pd(OAc)_2$	PPh_3	Et_3N	CH_3CN	80	59
15	$[Pd(dba)_2]$	PPh_3	Et_3N	CH_3CN	80	47
16	$[PdCl_2(PPh_3)_2]$	—	Et_3N	CH_3CN	80	67
17	[PdCl(allyl)]	PPh_3	Et_3N	CH_3CN	80	72

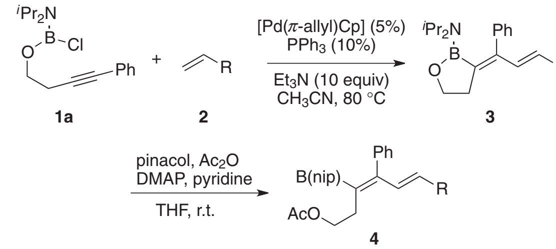
[a]A mixture of chloroborane **1a** (0.20 mmol), styrene (0.30 mmol), [Pd(allyl)Cp] (0.010 mmol), ligand (0.020 mmol), and base (2.0 mmol) was heated under a nitrogen atmosphere.[16]
[b]NMR yield.

Much effort has been devoted to the development of catalytic borylations, because of the increasing demands for organoboron derivatives in organic synthesis and drug discovery.[1] In addition to the simple substitutive borylation reactions such as C–H borylation[2] and C–X borylation,[3] borylative C–element bond formations,[4] in which boron and additional functional groups are concomitantly introduced across carbon–carbon multiple bonds, attract increasing attention. Catalytic hydroboration,[5] diboration,[6] and silaboration[7] have been extensively studied to establish efficient methods for the synthesis of highly functionalized organoboronic acids.

Among such catalytic boron–element addition reactions, carboboration is highly attractive in that C–C bonds are concomitantly formed along with B–C bonds.[8–10] Our initial effort on carboboration has focused on the B–C addition reactions, in which the B–C bond in cyanoborane or alkynylborane is activated and adds to a carbon–carbon multiple bond.[11,12] More recently, we have been involved in the development of transmetalative carboboration, in which activation of the B–Cl bond by palladium or nickel catalyst is crucially involved as the key elementary step.[13,14] In this particular carboboration, the organic groups are transferred from organozirconium as well as organotin reagents. Although the transmetalative carboboration was synthetically useful, the requirement of stoichiometric amounts of organometallic reagents detracts from its synthetic merit. It may be more attractive if the organic groups are derived from more easily accessible feedstock. Herein, we report new palladium-catalyzed carboboration with use of alkene as the source of organic group (Scheme 1). The reaction involves a mechanism well related to the Mizoroki–Heck reaction,[15] which involves insertion of alkenes into a C–Pd bond of organopalladium intermediates.

An alkyne-tethered chloroborane **1a**, which was used in our previous cyclizative carboboration with organozirconium and -tin reagents,[13a,13b] was reacted with styrene under varied reaction conditions (Table 1). Use of [Pd(allyl)Cp] as a reliable precursor for the generation of Pd(0) species with triphenylphosphine as a ligand allowed us to obtain the desired carboboration product albeit in low yield at 110 °C in toluene in the presence of triethylamine (Entry 1). We observed marked solvent effect: dioxane, *N*-methylpyrrolidone (NMP), and acetonitrile afforded acceptable reaction yields (Entries 2, 3, and 5), whereas dimethyl sulfoxide (DMSO) failed to give product (Entry 4). The reaction proceeded even at 80 °C in acetonitrile in higher yield (Entry 6). We also examined effect of base on the reaction yields to find triethylamine and potassium phosphate were the bases of choice rather than cesium carbonate (Entries 7 and 8). The reaction hardly proceeded in the absence of phosphine ligand (Entry 9). Upon screening the phosphine ligands, we found that PPh_3 and PPh_2Cy gave good reaction yields (Entries 6 and 12), while trialkylphosphines and bidentate phosphines gave much inferior yields (Entries 10, 11, and 13). We finally looked into the effect of precursor palladium complexes. It turned out that, in addition to [Pd(allyl)Cp], we could use other palladium sources, although the reaction yields varied significantly (Entries 14–17). Note that the alkenylbora-

Table 2. Palladium-catalyzed cyclizative carboboration of **1a** with alkenes **2a**–**2h** followed by treatment with Ac_2O and pinacol[a]



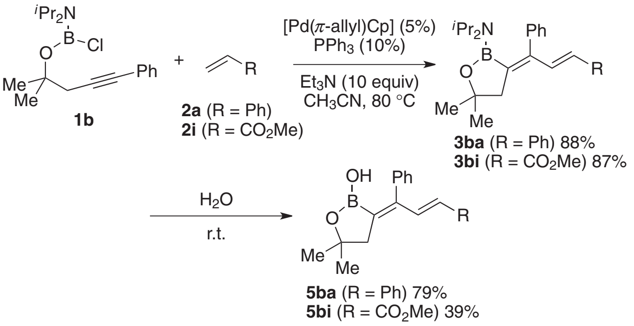
Entry	Alkene (R)	Time	%yield of 3[b]	%yield of 4[c]
1	**2a** (Ph)	32 h	72 (**3aa**)	70 (**4aa**)
2	**2b** (p-$MeOC_6H_4$)	24 h	68 (**3ab**)	62 (**4ab**)
3	**2c** (p-$EtO_2CC_6H_4$)	24 h	68 (**3ac**)	63 (**4ac**)
4	**2d** (p-ClC_6H_4)	24 h	67 (**3ad**)	61 (**4ad**)
5	**2e** (p-NCC_6H_4)	24 h	63 (**3ae**)	53 (**4ae**)
6	**2f** (1-naphthyl)	3 d	44 (**3af**)	37 (**4af**)
7	**2g** (2-pyridyl)	5 d	48 (**3ag**)	44 (**4ag**)
8	**2h** (n-C_6H_{13})[d]	2 d	26 (**3ah**)	20 (**4ah**)

[a] A mixture of chloroborane **1a** (0.20 mmol), alkene (0.30 mmol), [Pd(allyl)Cp] (0.010 mmol), PPh_3 (0.020 mmol), and Et_3N (2.0 mmol) was heated under a nitrogen atmosphere, unless otherwise noted.[16] [b] NMR yield. [c] Isolated yield. [d] 10 equiv.

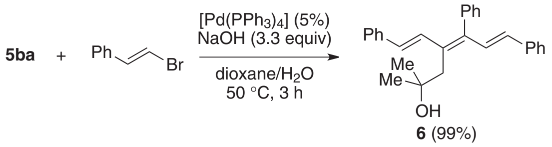
tion took place in a *trans*-addition fashion as observed in the palladium- and nickel-catalyzed cyclizative carboboration using organozirconium and organotin derivatives as transmetalation agents.[13a,13b] We confirmed the stereochemistry by a NOE measurement for the derivatized product **4aa**.

Under the optimized reaction conditions, reactions of **1a** with various styrenes and an aliphatic alkene were carried out (Table 2). Since the products were hydrolytically unstable, we converted the primary products **3** into **4** by treatment with acetic anhydride and pinacol in the presence of a catalytic amount of DMAP with pyridine.[11a,13a,13b] Thus obtained **4** was isolated by silica gel column chromatography. Styrenes bearing electron-donating and -withdrawing functional groups at the para positions successfully gave the corresponding products **4aa**–**4ae** (Entries 1–5). 1-Vinylnaphthalene (**2f**) and 2-vinylpyridine (**2g**) afforded the corresponding carboboration products sluggishly in moderate yields (Entries 6 and 7). 1-Octene gave **4ah** albeit in low yield (Entry 8). Note that terminal and alkyl-substituted alkynes did not give the corresponding products.

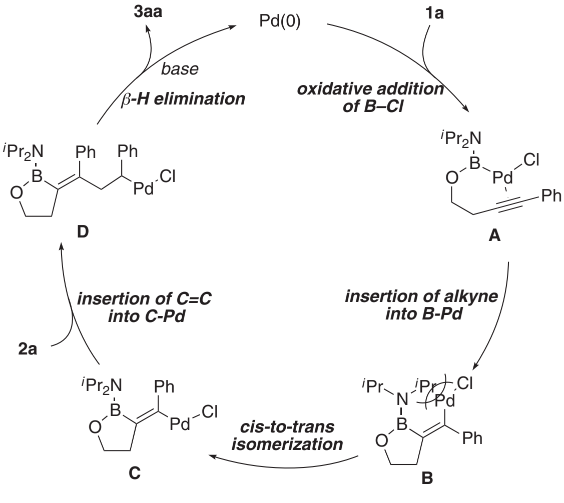
Use of the *tert*-alcohol-derived, alkyne-tethered chloroborane **1b** afforded the corresponding cyclization product in higher yields (Scheme 2). Reaction with styrene gave **3ba** in 88% yield. Moreover, use of **1b** allowed reaction with methyl acrylate (**2i**) in high yield, while **2i** afforded the corresponding product only in low yield (ca. 20%) in the reaction with **1a**. These products **3ba** and **3bi** obtained from *tert*-alcohol-derived **1b** were transformed into chromatographically stable **5** by hydrolysis. Attempted treatment with pinacol/Ac_2O failed to give the corresponding acetylated products like **4**. The half-ester-type dienylboronic acid derivative **5ba** was utilized in the Suzuki–Miyaura coupling with 2-bromostyrene, giving a conjugated triene product **6** in high yield (Scheme 3).[17]



Scheme 2. Palladium-catalyzed cyclizative carboboration of **1b** with styrene (**2a**) and methyl acrylate (**2i**) followed by hydrolysis.[16]



Scheme 3. Cross-coupling of **5ba** with *trans*-2-bromostyrene.[16]



Scheme 4. Possible mechanism of palladium-catalyzed cyclizative carboboration of **1a** with styrene (**2a**).

The mechanism of the cyclizative carboboration is assumed to be as shown in Scheme 4. In the initial step, oxidative addition of the B–Cl bond to palladium(0) phosphine species takes place, giving a borylpalladium intermediate **A**.[18] This B–Cl bond activation leads to the intramolecular insertion of carbon–carbon triple bond, giving alkenylpalladium intermediate **B**, in which the boron and palladium atoms are located in a *cis* fashion.[13b,18] A related alkenylpalladium intermediate was isolated in our previous work on the transmetalative, cyclizative carboboration.[13b] The intermediate **B** undergoes *cis*-to-*trans* isomerization to **C**, because of the large steric repulsion between the palladium moiety and the *N*-isopropyl group, which is inevitably located in the same plane as the five-membered ring due to the double bond nature of the B–N bond.[13a] The intermediate **C** may be more reactive than **B** toward styrene, which inserts into the carbon–palladium bond in a regioselective manner to give **D**. The catalytic cycle ends up with β-hydride elimination to form carboboration product **3aa** with regeneration of the palladium(0) species in the presence of base. These final steps are mechanistically similar to the Mizoroki–Heck reaction, where organopalladium intermediates undergo insertion into their carbon–palladium bonds and subsequent β-hydride elimination.[15]

In summary, we have demonstrated new catalytic carboboration in which the activation of B–Cl bond play a key role. Although the scope of the reaction is still limited, the study shows new possibilities of utilizing B–Cl bond activation in catalysis for the synthesis of organoboronic acid derivatives.

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