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Synthetic Methods

Palladium(0)-Catalyzed Cross-Coupling of 1,1-Diboronates with Vinyl Bromides and 1,1-Dibromoalkenes**

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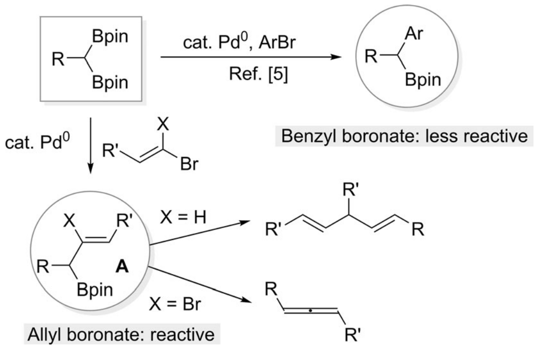
Abstract: *Palladium-catalyzed cross-coupling reactions of 1,1-diboronates with vinyl bromides and dibromoalkenes were found to afford 1,4-dienes and allenes, respectively. These reactions utilize the high reactivities of both 1,1-diboronates and allylboron intermediates generated in the initial coupling.*

Organoboron compounds have found wide applications in carbon–carbon bond formations, in particular as nucleophiles in palladium-catalyzed cross-coupling reactions (Suzuki–Miyaura coupling).[1] In contrast to aryl- or vinylboron compounds, which are the nucleophilic coupling partners typically employed in Suzuki–Miyaura coupling reactions, alkylboron compounds provide opportunities to construct carbon(sp^3)–carbon bonds in similar coupling reactions. However, these otherwise straightforward coupling reactions usually encounter difficulties, such as low reactivity and side reactions. For this reason, alkylboron compounds have not been appreciably explored in transition-metal-catalyzed coupling reactions.[1c,2]

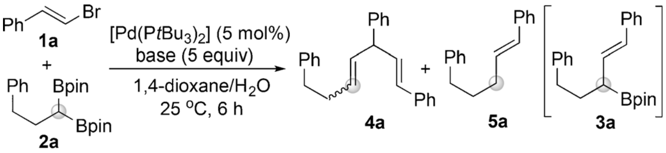
Recent studies on 1,1-diboron compounds have revealed some unique reactivity of these compounds in cross-coupling reactions.[3] It has been observed that in the case of 1,1-diboron alkanes, the palladium-catalyzed cross-coupling reactions with aryl,[3a,c] allyl,[3d] and benzyl[3d] bromides are highly efficient, thus affording monocoupling products, with one of the two boron groups remaining intact. The interesting observation is that the adjacent boron group facilitates the cross-coupling reaction of the other boron group. However, because of the low reactivity of the produced monoboron alkanes, further coupling under the same reaction system does not occur. To utilize the remaining boron group for carbon–carbon bond formation, a different reaction system has to be applied upon the completion of the first coupling reaction, and thus considerably limits the application of 1,1-diboron compounds in the construction of multiple carbon–carbon bonds.[3d]

In contrast to alkylboron compounds, allyboron compounds show high reactivity and have been explored in coupling reactions and other reactions.[4] We thus conceived that the allylboron compound **A**, generated through palladium-catalyzed coupling of 1,1-diboron alkanes with vinyl bromides, should undergo subsequent transformations in the same reaction system (Scheme 1). Herein we report the investigation based on this design. We have found that in the case of the reaction with vinyl bromides, 1,4-dienes are formed as the products, while in the reaction with 1,1-dibromoalkenes, allenes are obtained.



Scheme 1. Palladium(0)-catalyzed cross-coupling with 1,1-dibronates. pin = pinacol.

We initially investigated the vinyl bromide **1a** in the coupling reactions with the 1,1-diboronate **2a** using [Pd(PtBu$_3$)$_2$] as the catalyst and aqueous KOH (10 M) as the base (Scheme 2). As anticipated, the coupling reaction proceeded efficiently. However, the allyl boronate product **3a** could not be isolated. Instead, it further couples with vinyl bromide to



base = 10 M KOH; **4a**, 57%; **5a**, 34%
base = 4 M LiOH; **4a**, 79% (*E*/*Z* = 11:1); **5a**, 20%

Scheme 2. Reactions of 1,1-diboronates with vinyl bromide. Reaction conditions: **1a** (0.4 mmol), **2a** (0.3 mmol), [Pd(PtBu$_3$)$_2$] (5 mol%), base, 1,4-dioxane (2 mL). The products were isolated by silica gel chromatography. The *E*/*Z* ratio was determined by ^{1}H NMR analysis of the final product.

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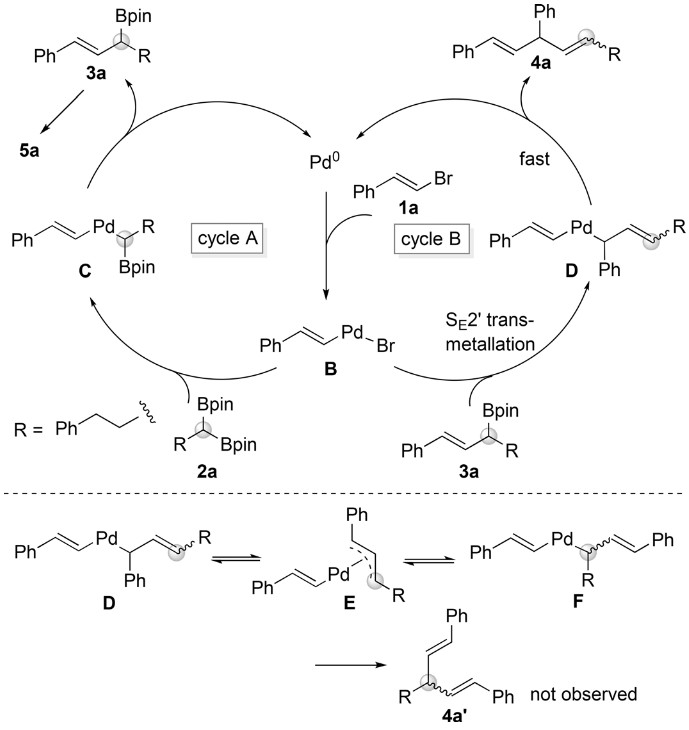


Scheme 3. Proposed reaction mechanism.

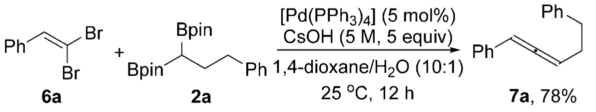
form the 1,4-diene **4a** as the main product, together with **5a** as the side product. The side-product **5a** is formed through protodeboronation of the allyl boronates intermediate **3a**. By switching the base from KOH to LiOH, the yield of **4a** could be slightly improved.[5]

A possible reaction mechanism has been proposed as shown in Scheme 3. First, oxidative addition of vinyl bromide to Pd^0 generates the intermediate **B**, which is followed by transmetallation with 1,1-diboronates to form the Pd^{II} species **C**. Reductive elimination from **C** gives **3a** (cycle A). As a result of the high reactivity of **3a**, it effectively competes with 1,1-diboronate substrate to form the Pd^{II} species **D**, which follows reductive elimination to give the linear 1,4-pentadiene product **4a** (cycle B). Because of the bulky ligand P*t*Bu$_3$, the isomerization of **D** to the intermediate **F** through the π-allylic Pd^{II} species **E** is slow, while the reductive elimination of **D** to form **4a** is fast. As a result, only the linear product **4a** is obtained and the branched **4a'** is not observed. This result is consistent with the γ-selectivity commonly observed for the palladium-catalyzed cross-coupling of allyboron compounds.[4d–h,j]

Since the synthetic methodology for 1,4-dienes is highly demanded in organic synthesis,[6] we subsequently studied the scope of this reaction. First, a series of vinyl bromides **1a–m** were subjected to the reaction with **2a** (Table 1). In most cases, the yields were moderate to good, however, the *E*/*Z* ratio varied depending on the structure of vinyl bromides. For the 1,1-diboronate, **2b** and **2c** were studied. In both cases, the *E*/*Z* selectivity is excellent (Table 1, entries 11 and 12). For the vinyl bromides, several substrates with R = H or alkyl groups were also studied, the reaction gave comparable results (Table 1, entries 13–15).

To further study the scope of the reaction, vinyl bromides with different structures were investigated (Scheme 4). When *cis*-1-bromo-1-propene (**1n**) was used, the 1,4-diene product **4p** with an *E* configuration was isolated in high yield. For the reactions with 1-substituted 1-bromoethylenes **1o** and **1p**, the corresponding products **4q** and **4r** were obtained. Interestingly, when 1-bromo-2-methylpropene (**1q**) was used as the substrate, the allyl boronate **3s** could be isolated in moderate yield, with only trace amount of the 1,4-diene product. This outcome is presumably attributed to the steric hindrance of two methyl substituents in **3s**, which suppress the subsequent transmetallation process.

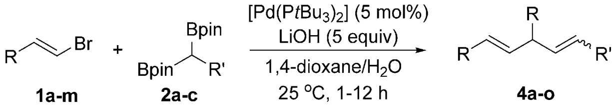
Next, we proceeded to study the palladium-catalyzed coupling reaction of the 1,1-dibromoalkene **6a** with **2a**. Through experiments on the reaction conditions,[5] it was concluded that under the reaction conditions shown in Equation (1), the allene product **7a** could be isolated in good yield.



(1)

Allenes are highly useful in organic chemistry and their synthetic methods are still rather limited.[7,8] Under the reaction conditions shown in Equation (1), the substrate scope was next investigated. First, various dibromoalkenes

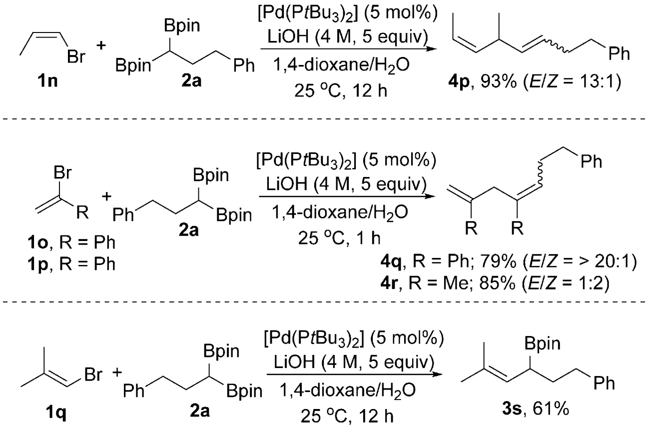
Table 1: Palladium(0)-catalyzed cross-coupling of vinyl bromides with 1,1-diboronates.[a]



2a, R' = PhCH$_2$CH$_2$; **2b**, R' = Cy; **2c**, R' = *i*Pr

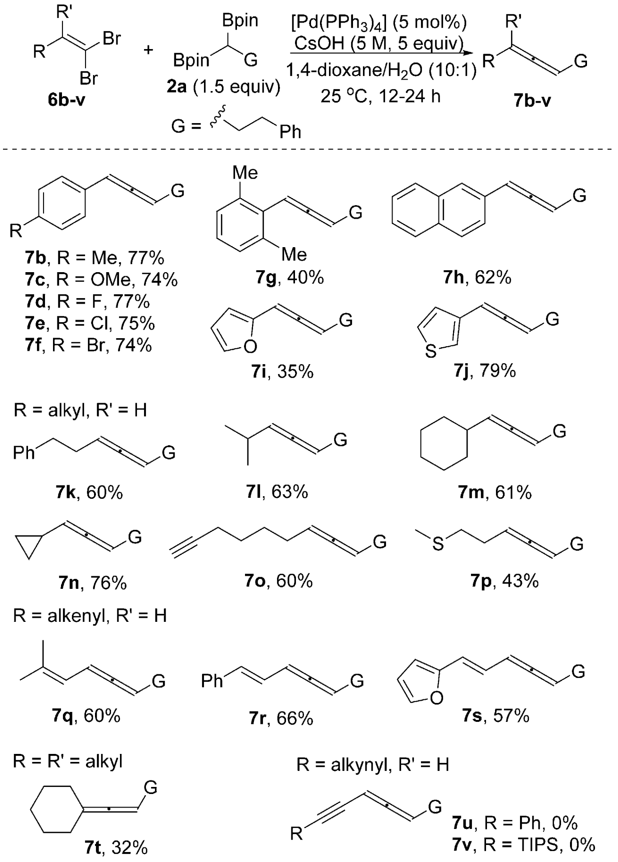
Entry	1	2	Yield [%][b]	*E*/*Z*
1	R = Ph, **1a**	**2a**	**4a**, 80	11:1
2	R = *o*-FC$_6$H$_4$, **1b**	**2a**	**4b**, 59	15:1
3	R = *p*-FC$_6$H$_4$, **1c**	**2a**	**4c**, 72	10:1
4	R = *p*-MeC$_6$H$_4$, **1d**	**2a**	**4d**, 74	8:1
5[b]	R = 3,4-(-OCH$_2$O-)C$_6$H$_3$, **1e**	**2a**	**4e**, 63	6:1
6[b]	R = *p*-MeOC$_6$H$_4$, **1f**	**2a**	**4f**, 58	2:1
7	R = *o*-MeC$_6$H$_4$, **1g**	**2a**	**4g**, 86	17:1
8	R = *o*-MeOC$_6$H$_4$, **1h**	**2a**	**4h**, 83	14:1
9	R = 1-naphthyl, **1i**	**2a**	**4i**, 67	19:1
10	R = 2-thienyl, **1j**	**2a**	**4j**, 45	14:1
11[b]	R = Ph, **1a**	**2b**	**4k**, 57	> 20:1
12[b]	R = Ph, **1a**	**2c**	**4l**, 45	> 20:1
13	R = H, **1k**	**2a**	**4m**, 74	4:1[c]
14	R = Me, **1l**	**2a**	**4n**, 94	2:1
15[d]	R = cyclohexyl, **1m**	**2a**	**4o**, 84	2:1[c]

[a] Reaction conditions: **1** (1.0 mmol), **2** (0.75 mmol), [Pd(P*t*Bu$_3$)$_2$] (5 mol%), LiOH (4 M, 625 μL), 1,4-dioxane (5 mL). Reactions were monitored by TLC analysis. Products were isolated by silica gel chromatography and the *E*/*Z* ratios were determined by ^{1}H NMR analysis. [b] The vinyl bromides were not completely consumed in these cases. [c] The ratio was estimated according to the ^{13}C NMR spectra. [d] Reaction conditions: **1** 0.6 mmol), **2** (0.45 mmol), [Pd(P*t*Bu$_3$)$_2$] (5 mol%), LiOH (4 M, 375 μL), 1,4-dioxane (3 mL).



Scheme 4. Reactions of 1,1-diboronates with various vinyl bromides.

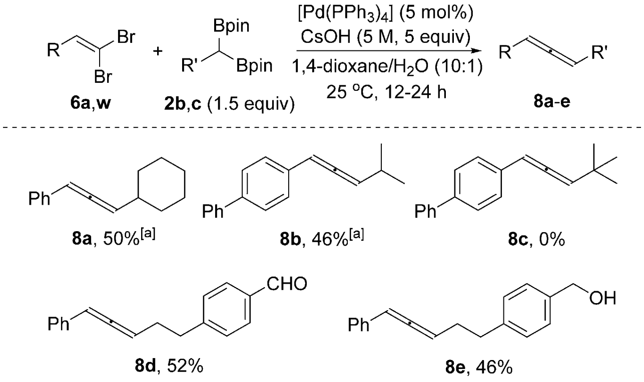
were examined (Scheme 5). When the R substituent in **6** was an aryl group, the reaction worked well with those bearing electron-donating groups (**7b,c**). However, for these bearing strong electron-withdrawing groups the reaction gave poor results, presumably because of direct HBr elimination under the basic conditions.[9] Halide substituents tolerated the reaction conditions (**7d–f**). The yield was moderate when the aromatic ring bears two *ortho*-methyl substituents (**7g**). Heteroarenes were also compatible in the reaction (**7i,j**).



Scheme 5. Substrate scope of 1,1-dibromoalkenes. Reaction conditions: **6** (0.5 mmol), **2a** (0.75 mmol), [Pd(PPh$_3$)$_4$] (0.025 mmol), CsOH (5 M, 500 μL), 1,4-dioxane (5 mL). Products were isolated by silica gel chromatography. TIPS = triisopropylsilyl.

When R is an alkyl group, the yields are moderate to good for various substrates (**7k–p**; Scheme 5). When R is an alkenyl group, the allene products are also obtained in moderate to good yields (**7q–s**). However, when R is alkynyl, no allene product can be observed as a result of the HBr elimination of the dibromoalkene substrates. In the case of the dibromoalkene **6t**, only low yield of the trisubstituted allene **7t** was obtained. In general, the reactivity is significantly diminished for the dibromoalkenes derived from ketones.

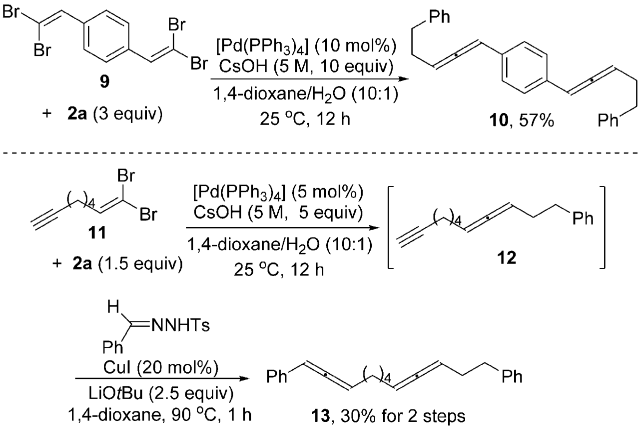
Next, we investigated the scope of diboronates (Scheme 6). It was observed that the reaction was affected by steric hindrance of the 1,1-diboronate substrates. For 1,1-diboronates **2b** and **2c**, high catalyst loading was needed to achieve moderate yields (**8a,b**). For the 1,1-diboronate bearing a bulky *t*Bu substrate, the coupling reaction did not work (**8c**). Notably, functional groups, such as formyl and hydroxy, could tolerate the reaction (**8d,e**).



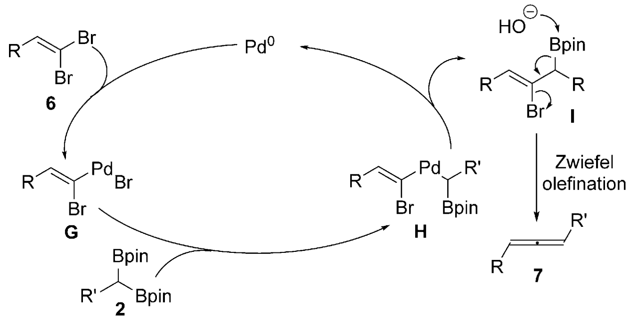
Scheme 6. Substrate scope of 1,1-diboronates. Reaction conditions: **6** (0.5 mmol), **2** (0.75 mmol), [Pd(PPh$_3$)$_4$] (0.025 mmol), CsOH (5 M, 500 μL), 1,4-dioxane (5 mL). Products were isolated by silica gel chromatography. [a] 10 mol% of [Pd(PPh$_3$)$_4$] (0.1 mmol) was used.

To further demonstrate the scope of the reaction, 1,4-bis(2,2-dibromovinyl)benzene (**9**) was applied as the substrate in the reaction with **2a**. The reaction afforded the symmetric diallene **10** in moderate yield. Moreover, with a 1,1-dibromoalkene bearing a terminal alkynyl group as the substrate, the palladium(0)-catalyzed coupling with **2a** can be followed by CuI-catalyzed allenation reaction with *N*-tosylhydrazones.[10] In this manner, the unsymmetric diallene **13** could be obtained (Scheme 7).

A possible reaction mechanism has been proposed as shown in Scheme 8. The allylboronate intermediate **I** is formed from **6** and **2** via the intermediates **G** and **H**. Under basic conditions, from intermediate **I** B-Br elimination (Zweifel olefination)[11] occurs to afford the allene product. Zweifel olefination is a useful method to construct C=C bonds by B-Br elimination. However, reactions involving allenic C=C bond formations have not been reported previously. An indirect evidence to support the mechanistic rationale is that



Scheme 7. Synthesis of symmetric and unsymmetric diallenes. Ts = 4-toluenesulfonyl.



Scheme 8. Proposed reaction mechanism.

β-bromoallylsilane has been reported to undergo similar elimination under basic conditions to give allene.[12]

In conclusion, the unique reactivity of allylboronates has been explored in the palladium(0)-catalyzed cross-coupling of 1,1-diboronates with vinyl bromides and 1,1-dibromoalkenes. 1,4-Dienes or allenes can be synthesized through this method. The high reactivity of the 1,1-diboronates and the intermediate allylboronates may open up new possibilities in this type of coupling reaction, including asymmetric catalysis. Research along these lines is ongoing in our laboratory.

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