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Palladium(0)-catalyzed direct cross-coupling reaction of allyl alcohols with aryl- and vinyl-boronic acids†

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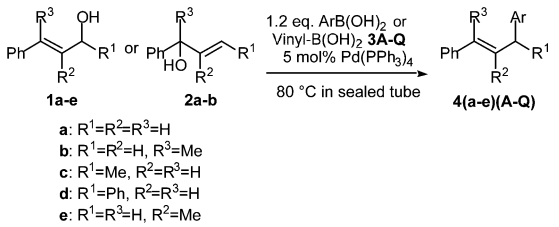
Allyl alcohols can be directly used for the palladium-catalyzed allylation of aryl- and vinyl-boronic acids without the aid of a base.

Palladium-catalyzed cross-coupling reaction with organometallics containing B, Mg, Zn, Sn, *etc*. has been a powerful tool for carbon–carbon bond formation in organic synthesis.[1] Among the organometallics, organoboronic reagents have been widely used because they are generally non-toxic, commercially available, stable and compatible with various functional groups.[2] Compared to the significant development of their Pd-catalyzed coupling reaction with aryl- and vinyl-halides or -sulfonates,[2] coupling reactions with allyl derivatives including halides,[3] carboxylates[4] and phenyl ethers[5] have received only scattered attention. These allyl derivatives are usually prepared from the corresponding allyl alcohols and their coupling reaction commonly requires stoichiometric amounts of a base except for allyl phenyl ethers.[5] The direct use of allyl alcohols for the cross-coupling reaction would omit the preparation steps of allyl derivatives and make the overall process of the coupling reaction atom economical.[6] However, allyl alcohols themselves are rarely used because hydroxide is a poor leaving group. Rh-[7] and Ni-catalysed[8] coupling of allyl alcohols with arylboronic acids have been reported, but their allylating reagents are only limited to cinnamyl alcohols and 2-cyclohexen-1-ol, respectively. We describe here the first palladium(0)-catalyzed cross-coupling reaction of a wider range of allyl alcohols with aryl- and vinyl-boronic acids in the absence of a base.

First, cinnamyl alcohol **1a** was examined as an allylating reagent for phenylboronic acid in the presence of 5 mol% tetrakis-(triphenylphosphine)palladium [$Pd(PPh_3)_4$] [9] (Scheme 1, Table 1, entries 1–4). To our surprise, the cross-coupling reaction readily proceeded upon heating at 80 °C in a sealed tube without any additive.[10] At lower temperature, bis(cinnamyl)ether was formed as a by-product and no reaction was observed in the absence of the palladium catalyst (data not shown). Although dichloromethane was found to be the most effective solvent, toluene, 1,4-dioxane and THF could be employed as alternatives (entries 1–4). Arylboronic acids with electron-donating (Table 1, entries 5–9) or -withdrawing groups (entries 10–16) could also be coupled with **1a** in satisfactory yields. Generally, the former boronic acids required a shorter reaction time and gave higher yields than the latter. In contrast to the Rh-catalyzed reaction,[7] steric factors did not affect the yield. *Ortho*-, *meta*- and *para*-tolylboronic acids reacted equally (entries 7–9). The highest yield was obtained in the coupling with 1-naphthylboronic acid **3N** (entry 17), whereas the lowest yield was obtained in the reaction with heteroarylboronic acid **3O** (entry 18) Allylation of *trans*- and *cis*-vinylboronic acid **3P** and **3Q** could be achieved in moderate yield and stereospecificity with respect to the boronic reagents (entries 19, 20).



Scheme 1 Coupling of cinnamyl alcohols **1a**–**e** and their isomers **2a**,**b** with organoboronic acids **3A**–**Q**.

Next, isomeric cinnamyl alcohols **2a**,**b** and substituted cinnamyl alcohols **1b**–**e** were examined as the allylating reagents for phenylboronic acid. α-Vinylbenzyl alcohol **2a**, a regioisomer of **1a**, gave the same product **4aA** in comparable yield (Table 1, entries 21 *vs.* 4). Although tertiary alcohol **2b** had a high reactivity, its parent cinnamyl alcohol **1b** decreased the reaction rate and product yield (entries 22, 23). Larger substituents at C-1 also resulted in slower reaction and lower yields (entries 24, 25). Introduction of a methyl group at the C-2 position in cinnamyl alcohol hindered the reaction (entry 26).

As with allyl alcohols, unsubstituted allyl alcohol **5a** and alkyl-substituted allyl alcohol **5b**–**g** were used for the allylation of 1-naphthylboronic acid (Scheme 2, Table 2). The reaction of 2-propenyl alcohol (**5a**) gave **6a** in good yield (Table 2, entry 1). The two regioisomers of crotyl alcohol (**5b** and **5c**) were converted into **6b**-*E*, **6b**-*Z* and **6c** with the same regio- and stereo-selectivity

Table 1 Coupling of cinnamyl alcohols and their isomers with organoboronic acids[a]

Entry	Cinnamyl alcohol	Boronic acid	Product	*t*/h	Isolated yield (%)
1	**1a**	Phenyl **3A**	**4aA**	3	61
2	**1a**	Phenyl **3A**	**4aA**	3	68
3	**1a**	Phenyl **3A**	**4aA**	3	69
4	**1a**	Phenyl **3A**	**4aA**	3	80
5	**1a**	*p*-Methoxyphenyl **3B**	**4aB**	4	78
6	**1a**	*p*-Methylthiophenyl **3C**	**4aC**	21	78
7	**1a**	*p*-Tolyl **3D**	**4aD**	6	76
8	**1a**	*o*-Tolyl **3E**	**4aE**	2	78
9	**1a**	*m*-Tolyl **3F**	**4aF**	5	75
10	**1a**	*p*-Chlorophenyl **3G**	**4aG**	15	69
11	**1a**	*p*-Fluorophenyl **3H**	**4aH**	11	58
12	**1a**	*p*-(Trifluoromethyl)phenyl **3I**	**4aT**	7	63
13	**1a**	*p*-Formylphenyl **3J**	**4aJ**	15	70
14	**1a**	*p*-Acetylphenyl **3K**	**4aK**	19	78
15	**1a**	*p*-Cyanophenyl **3L**	**4aL**	19	77
16	**1a**	*m*-Nitrophenyl **3M**	**4aM**	19	50
17	**1a**	1-Naphthyl **3N**	**4aN**	2	92
18	**1a**	3-Thiophene **3O**	**4aO**	6	28
19	**1a**	*trans*-β-Styryl **3P**	**4aP**	8	53
20	**1a**	*cis*-Propenyl **3Q**	**4aQ**	6	52
21	**2a**	Phenyl **3A**	**4aA**	4	71
22	**2b**	Phenyl **3A**	**4bA**	4	70 (*E*:*Z* 5:3)[b]
23	**1b**	Phenyl **3A**	**4bA**	33	52 (*E*:*Z* 3:2)[b]
24	**1c**	Phenyl **3A**	**4cA**	33	63
25	**1d**	Phenyl **3A**	**4dA**	24	36
26	**1e**	Phenyl **3A**	**4eA**	39	18 (*E*:*Z* 5:2)[b]

[a] The reaction was carried out in THF (entry 1), 1,4-dioxane (entry 2), toluene (entry 3) and dichloromethane (entries 4–26). [b] *E*:*Z* ratio was determined by ^{1}H-NMR.

† Electronic supplementary information (ESI) available: spectral data of compounds. See http://www.rsc.org/suppdata/cc/b4/b402256d/

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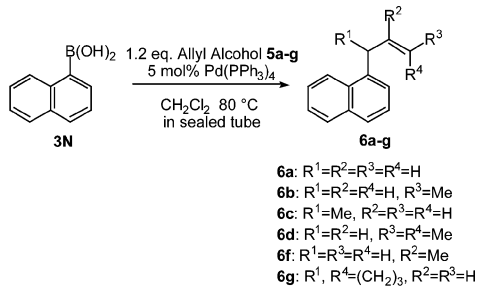


Scheme 2 Coupling of 1-naphthylboronic acid **3N** with aliphatic allyl alcohols **5a**–**g**.

Table 2 Coupling of 1-naphthylboronic acid with aliphatic allyl alcohols

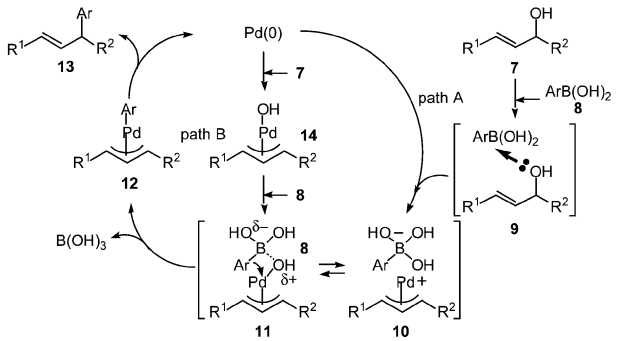
Entry	Allyl alcohol	Product	*t*/h	Isolated yield (%)
1	Allyl alcohol (**5a**)	**6a**	11	76
2	Crotyl alcohol (**5b**)	**6b** + **6c**	9	78 (**6b**-*E*:**6b**-*Z*:**6c** = 6:1:3)[a]
3	3-Buten-2-ol (**5c**)	**6b** + **6c**	9	81 (**6b**-*E*:**6b**-*Z*:**6c** = 6:1:3)[a]
4	Prenyl alcohol (**5d**)	**6d**	48	72
5	2-Methyl-3-buten-2-ol (**5e**)	**6d**	48	84
6	Methallyl alcohol (**5f**)	**6f**	39	37
7	2-Cyclohexen-1-ol (**5g**)	**6g**	24	23

[a] *E*:*Z* ratio was determined by ^{1}H-NMR.

(entries 2, 3). Similarly, the reaction of prenyl alcohol **5d** and its isomer **5e** gave the same product **6d** exclusively (entries 4, 5). The use of methallyl alcohol **5f** with a methyl group at C-2 like **1e** or cyclic allyl alcohol **5g** led to a lower yield (entries 6, 7).

Formation of the same products from allyl alcohols and their isomers may suggest the participation of π-allylpalladium intermediates in the reaction process. It is noteworthy that in spite of the heated reaction conditions, the formation of conjugated 1,3-dienes caused by Pd–H elimination from π-allylpalladium intermediates was not observed in the reactions of **1b**,**c**, **2b** and **5b**–**e**,**g**.[4c,11]

The plausible mechanism for the cross-coupling reaction is outlined in Scheme 3. Oxidative addition of allyl alcohol **7** activated by the coordination with arylboronic acid **8** to the Pd(0) species[12] leads to a cationic π-allylpalladium intermediate **10** with an arylborate counter anion (path A, through **9**). This intermediate exists in equilibrium with arylboronic acid **8** and (π-allylhydroxo)-palladium complex **11**, which would smoothly undergo transmetalation to give diorganopalladium complex **12**.[2,5,13] Reductive elimination of the coupling product **13** from **12** reproduces the palladium(0) complex. At this time, it is not possible to rule out a mechanism involving direct oxidative addition of allyl alcohol **7** to



Scheme 3 Possible catalytic cycle for the coupling reaction of allyl alcohols with arylboronic acids.

the palladium(0) complex to give **14** which has been approved in the Tsuji–Trost reaction[14] of 1,3-dicarbonyl compounds with allyl alcohols as allylating agents[15] (path B). However, no coupling products were obtained when cinnamyl alcohol **1a** was heated in THF with boronate complexes such as sodium tetraphenylborate and potassium phenyltrifluoroborate, which would not work as a Lewis acid.

The present study offers an extremely facile allylation procedure for aryl- and vinyl-boronic acids with a wide variey of functional groups. As for allyl alcohols, cinnamyl alcohols and their isomers, unsubstituted and alkyl-substituted allyl alcohols could be directly used. Neither preparation of allyl halides and esters nor addition of stoichiometric amounts of a base are required. Although the reaction required heating, it was not accompanied by the elimination of hydrogen from π-allylpalladium complexes to generate conjugated 1,3-diene. Further studies on the detailed mechanism of the cross-coupling reaction and application to deprotection of allyl ether, one of the most useful protecting groups in organic synthesis, are underway in our laboratory.

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10 Typical procedure: a mixture of substrate (0.30 mmol), organoboronic acid (0.36 mmol), $Pd(PPh_3)_4$ (0.015 mmol) and dry dichloromethane (1 mL) was heated at 80 °C in a sealed tube under argon atmosphere. After being stirred at the same temperature for the time described in Table 1 and 2, the reaction mixture was evaporated and purified by preparative thin layer chromatography to give the allylated product.

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