

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

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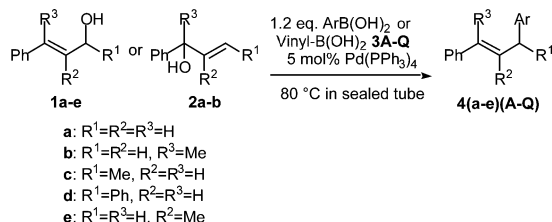
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Allyl alcohols can be directly used for the palladium-catalyzed allylation of aryl- and vinyl-boronic acids without the aid of a base.

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 carboxylates⁴ and phenyl ethers⁵ 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-catalysed⁸ 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(PPh₃)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



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

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

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).

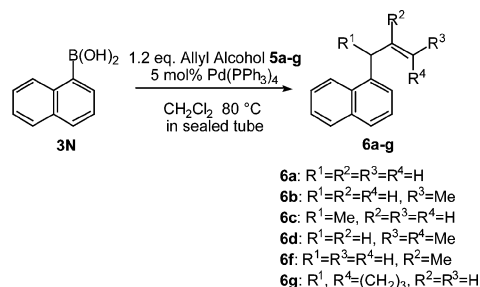
Next, isomeric cinnamyl alcohols **2a,b** and substituted cinnamyl alcohols **1b–e** were examined as the allylating reagents for phenylboronic acid. α -Vinylbenzyl alcohol **2a**, a regioisomer of **1a**, gave the same product **4aA** in comparable yield (Table 1, entries 21 vs. 4). Although tertiary 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	<i>p</i> -Methoxyphenyl 3B	4aB	4	78
6	1a	<i>p</i> -Methylthiophenyl 3C	4aC	21	78
7	1a	<i>p</i> -Tolyl 3D	4aD	6	76
8	1a	<i>o</i> -Tolyl 3E	4aE	2	78
9	1a	<i>m</i> -Tolyl 3F	4aF	5	75
10	1a	<i>p</i> -Chlorophenyl 3G	4aG	15	69
11	1a	<i>p</i> -Fluorophenyl 3H	4aH	11	58
12	1a	<i>p</i> -(Trifluoromethyl)phenyl 3I	4aI	7	63
13	1a	<i>p</i> -Formylphenyl 3J	4aJ	15	70
14	1a	<i>p</i> -Acetylphenyl 3K	4aK	19	78
15	1a	<i>p</i> -Cyanophenyl 3L	4aL	19	77
16	1a	<i>m</i> -Nitrophenyl 3M	4aM	19	50
17	1a	1-Naphthyl 3N	4aN	2	92
18	1a	3-Thiophene 3O	4aO	6	28
19	1a	<i>trans</i> - β -Styryl 3P	4aP	8	53
20	1a	<i>cis</i> -Propenyl 3Q	4aQ	6	52
21	2a	Phenyl 3A	4aA	4	71
22	2b	Phenyl 3A	4bA	4	70
					(<i>E</i> : <i>Z</i> 5:3) ^b
23	1b	Phenyl 3A	4bA	33	52
					(<i>E</i> : <i>Z</i> 3:2) ^b
24	1c	Phenyl 3A	4cA	33	63
25	1d	Phenyl 3A	4dA	24	36
26	1e	Phenyl 3A	4eA	39	18
					(<i>E</i> : <i>Z</i> 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 ¹H-NMR.



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

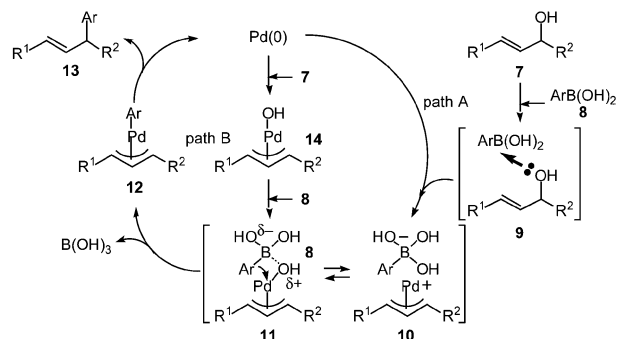
Entry	Allyl alcohol	Product	t/h	Isolated yield (%)
1	Allyl alcohol (5a)	6a	11	76
2	Crotyl alcohol (5b)	6b + 6c	9	78 (6b - E : 6b - Z : 6c = 6:1:3) ^a
3	3-Buten-2-ol (5c)	6b + 6c	9	81 (6b - E : 6b - Z : 6c = 6:1:3) ^a
4	Prenyl alcohol (5d)	6d	48	72
5	2-Methyl-3-buten-2-ol (5e)	6d	48	84
6	Methallyl alcohol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

^a E:Z ratio was determined by ¹H-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) species¹² 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 reaction¹⁴ of 1,3-dicarbonyl compounds with allyl alcohols as allylating agents¹⁵ (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 variety 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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- The Pd₂(dba)₃ (2.5 mol%)–PPh₃ (10 mol%) catalytic system could be used instead of Pd(PPh₃)₄.
- Typical procedure: a mixture of substrate (0.30 mmol), organoboronic acid (0.36 mmol), Pd(PPh₃)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.
- Uozumi *et al.*^{4c} reported that the Pd(PPh₃)₄-catalyzed coupling reaction of acetyl derivative of **1c** with phenylboronic acid **3A** in the presence of Na₂CO₃ gave **4cA** and 1-phenylbutadiene in 14 and 38% yield, respectively. Tsuji *et al.*, reported that no elimination was observed with allyl alcohol under the Pd(OAc)₂–PPh₃ catalytic system in the absence of a base: J. Tsuji, T. Yamakawa, M. Kaito and T. Mandai, *Tetrahedron Lett.*, 1978, **24**, 2075.
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