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Palladium-catalyzed direct coupling reaction of propargylic alcohols with arylboronic acids

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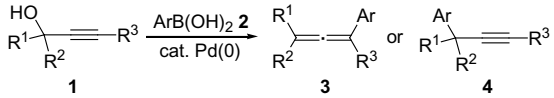
Abstract—The direct coupling of propargylic alcohols with arylboronic acids has been achieved using palladium catalyst. Various propargylic alcohols and arylboronic acids can be coupled to afford the corresponding allenic and propargylic arenes, which are selectively produced depending on the substituent on the propargylic alcohol, respectively.

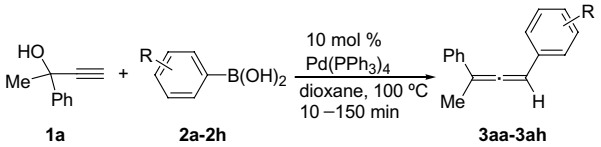
Organoboronic acids are widely used reagents in organic synthesis, and a variety of reactions using organoboronic acids are developed to form a carbon–carbon bond.[1] Palladium-catalyzed coupling of organoboronic acids with allylic,[2] propargylic,[3] and allenic[4] compounds are one of the useful reactions to produce substituted unsaturated compounds, in which halides, esters and carbonates were normally required as a leaving group. The use of the hydroxyl group that itself in the coupling reactions is highly beneficial from the viewpoint of atom economy although it is generally regarded that a hydroxyl group has poor reactivity as a leaving group. Recently, coupling reactions of allylic and allenic alcohols with boronic acids by transition metal catalyst have been reported, and it has been made clear that the hydroxyl group is effectively activated under the simple and mild reaction conditions to afford the various coupled products.[5,6] However, to the best of our knowledge, the direct coupling of propargylic alcohols with organo-boronic acids has not been reported. We communicate here our preliminary results of this type of coupling reaction (Eq. 1).



(1)

Our initial attempts were started by using 2-phenyl-3-butyn-2-ol (**1a**) and 2-methylphenylboronic acid (**2a**) (Table 1). When **1a** is treated with **2a** in the presence of 10 mol% $Pd(PPh_3)_4$ in dioxane at 100 °C, the reaction is completed within 30 min to afford a coupled allenic arene **3aa** in 99% yield (entry 1 in Table 1).[7,8] The reaction can be performed in the presence of 2 mol% palladium catalyst (entry 2). A series of substituted arylboronic acids **2b–h** were then subjected to the reaction (entries 3–9). The corresponding products **3ab–ad**

Table 1. Palladium-catalyzed coupling of propargylic alcohol **1a** with arylboronic acids **2a–h**



Entry	$ArB(OH)_2$	Product	Yield (%)
1	R = 2-methyl (**2a**)	**3aa**	99
2[a]	**2a**	**3aa**	90
3	R = 4-methyl (**2b**)	**3ab**	77
4	R = 2-methoxy (**2c**)	**3ac**	84
5	R = 4-methoxy (**2d**)	**3ad**	65
6	R = H (**2e**)	**3ae**	77
7	1-Naphthaleneboronic acid (**2f**)	**3af**	99
8	R = 4-acetyl (**2g**)	**3ag**	54
9	R = 3-nitro (**2h**)	**3ah**	51

[a] 2 mol% of $Pd(PPh_3)_4$ was used.

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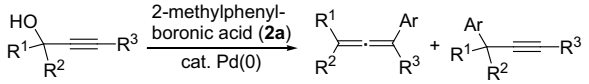
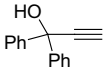
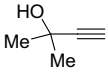
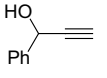
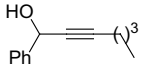
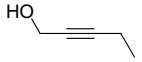
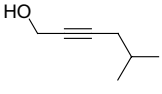
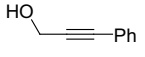
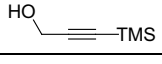
are obtained in good yields by the reactions with other methyl- and methoxy-substituted phenylboronic acids **2b–d** (entries 3–5). Phenyl- and 1-naphthaleneboronic acids (**2e** and **2f**) also give good results (entries 6 and 7). Arylboronic acids **2g** and **2h** having an electron-withdrawing group tolerate the reaction to produce the corresponding products **3ag** and **3ah** in moderate yields, respectively (entries 8 and 9).

Results of reactions of various propargylic alcohols **1b–i** are summarized in Table 2. When the reactions of the substrates **1b** and **1c** possessing a diphenyl and dimethyl groups at the propargylic position are carried out with boronic acids **2a** and **2f**, the coupled allenic arenes **3ba** and **3cf** are obtained in 67% and 65% yield, respectively (entries 1 and 2). Substrates **1d** and **1e** having a secondary hydroxyl group is uneventfully reacted with **2a** to afford the product **3da** and **3ea** in 89% and 79% yield (entries 3 and 4). On the other hand, the different reactivity has been observed in case of primary propargylic alcohols **1f–i** (entries 5–8). When 2-pentyn-1-ol (**1f**) and 5-methyl-2-hexyn-1-ol (**1g**) are subjected to the reaction, the propargylic arenes **4fa** and **4ga** are obtained along with the corresponding allenic arenes **3fa** and **3ga**, respectively (entries 5 and 6). The propargylic arenes **4ha** and **4ia** are predominantly produced by the reaction of phenyl- and TMS-substituted **1h** and **1i** (entries 7 and 8). These results indicate that the site selectivity of the reaction is governed by the substituent on the propargylic alcohols.

Table 2. Reactions of various substituted propargylic alcohols **1b–i** with 2-methylphenylboronic acid **(2a)**[a,b]

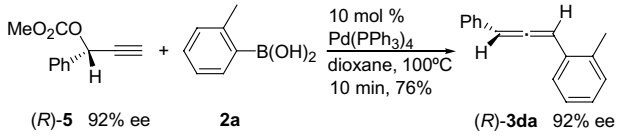


1b-1i **3ba-3ha** **4fa-4ia**

Entry	Substrate		Product	Yield (%) (**3**:**4**)
1		**1b**	**3ba**	67
2[c]		**1c**	**3cf**[d]	65
3		**1d**	**3da**	89
4		**1e**	**3ea**	79
5		**1f**	**3fa** + **4fa**	66 (1:1)
6		**1g**	**3ga** + **4ga**	92 (1:1.8)
7		**1h**	**3ha** + **4ha**	72 (1:13)
8		**1i**	**4ia**	76

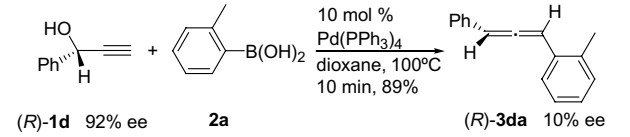
[a] Reactions were carried out in the presence of 10 mol% $Pd(PPh_3)_4$ in dioxane at 100 °C for 0.2–24 h.
[b] Ar = 2-methylphenyl except **3cf**.
[c] 1-Naphthaleneboronic acid **(2f)** was used as a boronic acid.
[d] Ar = 1-naphthyl.

We next investigated the reaction using a chiral propargylic alcohol. It is known that chiral allenes can be synthesized by the reaction of chiral propargylic compounds via stereoselective S_N2' attack of palladium catalyst.[9] Actually, the reaction of chiral propargylic carbonate (*R*)-**5** with **2a** in the presence of 10 mol% $Pd(PPh_3)_4$ yields the chiral allene (*R*)-**3da**[10] without any loss of enantiomeric purity (Eq. 2). On the other hand, the enantiomeric purity is dramatically decreased when chiral propargylic alcohol (*R*)-**1d** is examined under the same reaction conditions (Eq. 3). It is noteworthy that the significant difference in the reactivity has been observed depending on the leaving group.



(*R*)-**5** 92% ee **2a** (*R*)-**3da** 92% ee

(2)

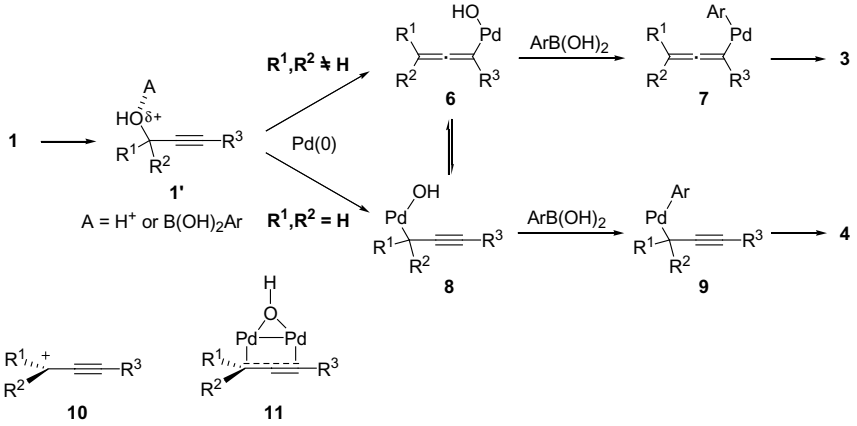


(*R*)-**1d** 92% ee **2a** (*R*)-**3da** 10% ee

(3)

A plausible mechanism for the reaction is shown in Scheme 1. The propargylic alcohol **1** would be initially activated by a proton, which is derived from a boronic acid, or boronic acid itself as a Lewis acid[5b] to form the reactive species **1′**. Attack of palladium on **1′** would afford the allenylpalladium hydroxide **6** and the propargylpalladium hydroxide **8**. It is expected that there is an equilibrium between **6** and **8**,[11] and the ratio depends on the substituent on the substrate. When the substituent R^1 and R^2 is not hydrogen, the alteration of the equilibrium to allenylpalladium **6** would occur. The complex **6** is subjected to the transmetalation with arylboronic acid **2** to lead the intermediate **7**, and subsequent reductive elimination of palladium produces the allenic arene **3**. On the other hand, the propargylpalladium **8** would predominantly exist when the substituent R^1 and R^2 is hydrogen, and especially R^3 is large substituent, which results in the formation of the propargylic arene **4** via the intermediate **9**. Although the cause of the loss of the chirality in the reaction of chiral propargylic alcohol (*R*)-**1d** is not clear, it is assumed that the attack of palladium to **1′** proceeds in stepwise via the achiral propargylic cation intermediate **10**. As another possibility, racemization of allenylpalladium **6** could occur through the formation of the dinuclear complex **11**.[12]

In conclusion, we have developed a coupling reaction of propargylic alcohols with arylboronic acids by palladium catalyst. Various allenic and propargylic arenes



Scheme 1. Proposed reaction mechanism.

can be directly synthesized from the corresponding propargylic alcohols, and neither carbonates nor esters are required as a leaving group. Applications and mechanistic studies of this coupling reaction are now in progress.

References and notes

1. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11; (c) Suzuki, A.; Brown, H. C. In *Organic Syntheses Via Boranes*; Aldrich Chemical Company, Inc.: Milwaukee, 2003; Vol. 3.
2. (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972; (b) Moreno-Manas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396; (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384; (d) Bouyssi, D.; Gerusz, V.; Balme, G. *Eur. J. Org. Chem.* **2002**, 2445.
3. Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149.
4. Morita, T.; Furuuchi, T.; Miyaura, N. *Tetrahedron* **1994**, *50*, 7961.
5. (a) Kabalka, G. W.; Dong, G.; Venkataiah, B. *Org. Lett.* **2003**, *5*, 893; (b) Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* **2004**, 1200.
6. Yoshida, M.; Gotou, T.; Ihara, M. *Chem. Commun.* **2004**, 1124.
7. General procedure: To a stirred solution of 2-phenyl-3-butyn-2-ol (**1a**) (51.5 mg, 0.352 mmol) in 1,4-dioxane (3.52 mL) were added 2-methylphenylboronic acid (**2a**) (95.7 mg, 0.704 mmol) and $Pd(PPh)_4$ (40.7 mg, 0.035 mmol) at rt, and the stirring was continued for 30 min at 100 °C. Filtration of the reaction mixture using a small amount of silica gel and the residue upon workup was chromatographed on silica gel with hexane as eluent to give **3aa** (76.9 mg, 99%) as a colorless oil. $R_f = 0.68$ (10% AcOEt in hexane); IR (neat) 3020, 2947, 1933, 1599, 1493 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.08 (9H, m), 6.65 (1H, q, $J = 3.0$ Hz), 2.40 (3H, s), 2.21 (3H, d, $J = 3.0$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 207.6, 136.7, 135.4, 132.8, 130.8, 128.6, 128.6, 127.7, 127.1, 127.0, 126.3, 125.9, 125.9, 103.6, 94.2, 20.1, 17.0; MS m/z 220 (M^+); HRMS m/z calcd for $C_{17}H_{16}$ 220.1252 (M^+), found 220.1244.
8. It is known about the transition metal-catalyzed additions of organoboronic acids to alkynes (see below), but the corresponding adducts were not observed in our reactions. Pd: (a) Oh, C. H.; Jung, H. H.; Kim, K. S.; Kim, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 805; Rh: (b) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918; (c) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123; (d) Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762.
9. (a) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103; (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 367; (c) Dixneuf, P.; Guyot, T.; Ness, M. D.; Roberts, S. M. *Chem. Commun.* **1997**, 2083; (d) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, 1360.
10. Enantiomeric excesses of (*R*)-**3da** was determined by using chiral HPLC (CHIRALCEL OF), and the absolute configuration was tentatively assigned on the basis of the specific rotation of known (*R*)-1,3-diphenyl-1,2-propadiene.
11. (a) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687; (b) Ogoshi, S.; Kurosawa, H. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 14.
12. Ogoshi, S.; Nishida, T.; Shinagawa, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 7164, and see also Ref. 11b.