Palladium-Catalyzed Addition

The Palladium-Catalyzed Addition of Organoboronic Acids to Alkynes**

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Palladium-catalyzed cross-coupling of organoboronic acids with organic halides or their equivalents has long been the subject of intensive work in the area of transition-metal chemistry.[1] The Suzuki reaction is now one of the most

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Table 1: Pd-catalyzed hydroalkylation of alkynes **1** with organoboronic acids **2**.[a]

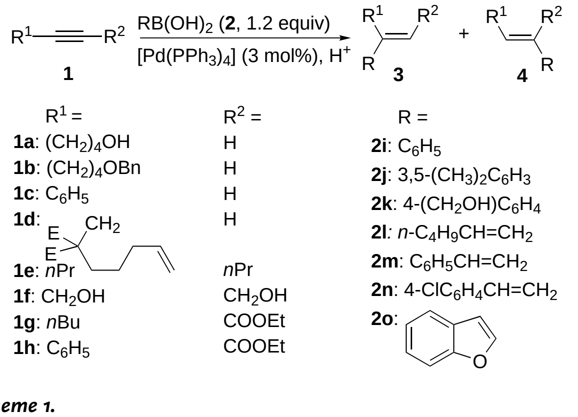
Entry	Alkyne	RB(OH)$_2$	T [°C]	t [h]	Products	Yield [%]
1	**1a**	**2i**	80	10	**3ai**	93
2	**1a**	**2j**	70	4	**3aj**	96
3	**1a**	**2k**	70	5	**3ak**	65
4	**1a**	**2l**	40	12	**3al**	88
5	**1a**	**2m**	60	6	**3am**	83
6	**1a**	**2n**	70	12	**3an**	83
7	**1a**	**2o**	70	12	**3ao**	92
8	**1b**	**2i**	60	2	**3bi**	90
9	**1b**	**2l**	60	3	**3bl**	88
10	**1c**	**2i**	80	12	**3ci**	91
11	**1c**	**2l**	80	12	**3cl**	75
12	**1d**	**2i**	50	15	**3di**	85
13	**1d**	**2l**	60	5	**3dl**	78
14	**1e**	**2i**	60	48	**3ei**	99
15	**1e**	**2l**	80	24	**3el**	89
16	**1f**	**2i**	80	6	**3fi**	94
17	**1f**	**2l**	80	4	**3fl**	72
18	**1g**	**2i**	80	8	**3gi, 4gi**	80 (4:1)[b]
19	**1g**	**2l**	80	8	**3gl, 4gl**	85 (3:1)[b]
20	**1h**	**2i**	80	4	**3hi, 4hi**	84 (4:1)[b]
21	**1h**	**2l**	80	4	**3hl, 4hl**	78 (1:1)[b]

[a] The reaction was carried out with **1** and organoboronic acid **2** (1.2 equiv) in 1.0 mL of 1,4-dioxane in the presence of 3 mol% of [Pd(PPh$_3$)$_4$] and acetic acid (0.10–0.15 equiv). [b] The combined yields and isomeric ratios were determined by ^{1}H NMR spectral analysis.

general reactions used to synthesize stereodefined biaryls,[2] alkadienes,[3] and trienes.[4] Since a variety of organoboron compounds have now become readily available, much attention has been devoted to develop a new aspect of organoboron chemistry.

Miyaura and co-workers reported the rhodium-catalyzed 1,4-conjugated addition of organoboronic acids to α,β-unsaturated ketones through a sequence of boron–rhodium transmetalation reactions.[5] The use of the chiral binap–rhodium (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) catalyst enabled asymmetric additions of organoboronic acids to aldehydes,[6] *N*-sulfonyl imines,[7] α,β-unsaturated enones,[8] and α,β-unsaturated esters to be achieved.[9] The rhodium-catalyzed additions of aryl boronic acids to unactivated alkenes and alkynes were also accomplished.[10] The well-accepted catalytic cycle for the hydroarylation of unactivated alkynes involves the addition of aryl–rhodium intermediates (Ar-Rh-L), formed by oxidative addition of the rhodium catalyst to the ArB(OH)$_2$ species, to the π bond of the substrate.[11] Similar hydroarylations have also been attained by nickel-catalyzed additions of aryl magnesium or aryl zinc reagents to alkynes or by titanium-catalyzed hydrozincations of alkynes.[12] Here we report the first example of palladium-catalyzed hydroarylations of alkynes with organoboronic acids and a mechanistic interpretation based on a isotope-labeling study.

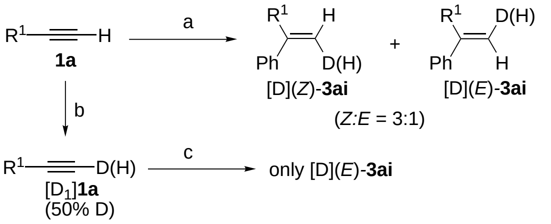
The palladium-catalyzed additions of a series of organoboronic acids (**2i**–**2o**) to various alkynes (**1a**–**1h**) were examined (Scheme 1, Table 1). The reaction of 5-hexyn-1-ol (**1a**) with phenylboronic acid (**2i**) was first examined in a variety of solvents (such as 1,4-dioxane, THF, and toluene) in the presence of a catalytic amount of formic or acetic acid. The optimal yield of 5-phenyl-5-hexen-1-ol (**3ai**) was obtained (entry 1) when a mixture of **1a, 2i** (1.2 equiv), acetic acid (0.10–0.15 equiv), and [Pd(PPh$_3$)$_4$] (3 mol% relative to **1a**) in 1,4-dioxane was heated at 80 °C for 10 h. The reaction took place very slowly (several days), even in the absence of an acid additive.



Scheme 1.

Both 3,5-dimethylphenylboronic acid (**2j**) and 4-(hydroxymethyl)phenylboronic acid (**2k**) added to the alkyne **1a** under the optimal conditions to give the hydroarylation products **3aj** and **3ak** in yields of 96 and 65%, respectively (entries 2 and 3). In addition, *trans*-1-hexenylboronic acid (**2l**), *trans*-2-phenylvinylboronic acid (**2m**), *trans*-2-(4-chlorophenyl)vinylboronic acid (**2n**), and 2-benzofuranylboronic acid (**2o**) added to the alkyne **1a** to give the corresponding dienes **3al, 3am, 3an**, and **3ao** in yields of 88, 83, 83, and 92%, respectively (entries 4–7). Next, the palladium-catalyzed addition of organoboronic acids to various terminal alkynes was tested. As expected, both aryl and alkenylboronic acids **2i** and **2l** added to the alkynes **1b–d** to give the corresponding products **3bi, 3bl, 3ci, 3cl, 3di**, and **3dl**, respectively, in excellent yields (entries 8–13). Two internal alkynes, 4-octyne (**1e**) and 2-butyne-1,4-diol (**1f**), also underwent hydroarylation with organoboronic acids (**2i** and **2l**) in excellent yields, although 4-octyne (**1e**) required a relatively long reaction time for completion (entries 14–17). Finally, the two alkynes **1g** and **1h** conjugated with electron-withdrawing groups were treated with boronic acids (**2i** and **2l**) under the same conditions. As expected, the reactions were very facile but gave a mixture of regioisomers of the addition products **3** and **4**.

To gain more insight into the mechanism of the present reaction the reaction of alkyne **1a** with phenylboronic acid was conducted using deuterated acetic acid (DOAc; Scheme 2). Only 40% of the deteurium-incorporated product

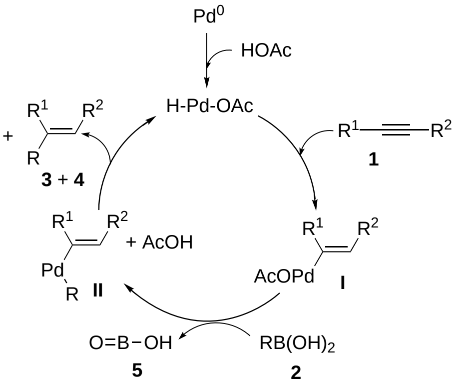


a) 3 mol% $[Pd(PPh_3)_4]$, 3 equiv DOAc, 1.2 equiv **2i**, 1,4-dioxane, 80 °C, 5 h.
b) 3 mol% $[Pd(PPh_3)_4]$, 3 equiv DOAc, 1,4-dioxane, 80 °C, 2 h.
c) 3 mol% $[Pd(PPh_3)_4]$, 3 mol% HOAc, 1.2 equiv **2i**, 1,4-dioxane, 80 °C, 5 h.

Scheme 2.

[D]**3ai** was isolated in a *Z*:*E* ratio of 3:1 as evident by ^{1}H NMR analysis when 3.0 equivalents of deuterated acetic acid were used. This result indicated that there was some stereochemical scrambling or deuterium exchange between the alkyne-H and AcOD prior to the addition of D-Pd-OAc to the triple bond.[13] In fact, the 50% deuterated alkyne $[D_1]$**1a** was obtained when alkyne **1a** was exposed to similar conditions in the absence of phenyboronic acid. When the reaction of the 50% deuterated alkyne $[D_1]$**1a** with **2i** was examined in the presence of a catalytic amount of acetic acid, $[D_1]$(*E*)-**3ai** was obtained exclusively without any loss of deuterium.[14]

A proposed mechanism based on the deuterium-labeling study is shown in Scheme 3. The *syn* addition of the H-Pd-OAc species into the triple bond would form the alkenylpalladium intermediate **I**. The reaction was complete even in the presence of a catalytic amount of the acid, which suggests that a proton source for the hydropalladation reaction could be the organoboronic acid. The organic group can transfer from the metal–boron species to the metal–palladium species to form the intermediates (**II**) containing two organic ligands in the coordination sphere of the palladium center, acetic acid, and a boric acid derivative such as metaboric acid. It has been well-documented that the high oxophilicity of the boron center and the electron richness of palladium(0) and platinum(0) complexes would induce transmetalation, whereby organic groups on the boron atom readily transfer to $Pd(OAc)_2$,[15] $[\eta^3\text{-}C_3H_5PdOAc]_2$,[16] $[\eta^3\text{-}C_3H_5Pd(acac)]$ (acacH = acetylacetone),[17] $[Pd(OR)L_2]$ (R = H, Me, Ac), and $[Pt(OR)(S)L_2]$ (R = H, Me; S = solvent) under neutral conditions. The reductive elimination of the intermediate **II** would form the desired products (**3** and **4**) and the eliminated Pd^0 species.



Scheme 3.

The presence of a mineral base has been generally believed to be fundamental for the success of the Suzuki-type cross-coupling. The present study shows importantly that the alkenylpalladium intermediates **I** could be smoothly cross-coupled with organoboronic acids even in acidic media. It is noteworthy that no base is involved in the catalytic cycle.

In conclusion, we have shown for the first time that palladium compounds can catalyze the addition of organoboronic acids to alkynes. The ready availability of alkynes and organoboronic acids combined with the excellent chemical yields and mild reaction conditions of this process suggest that the present reaction should find wide application in organic synthesis.

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terminal olefinic carbon atom was observed at $\delta = 111.89$ ppm (t, $J = 24$ Hz) in the NMR spectra.
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