Palladium Catalyzed Conjugate 1,4-Addition of Organoboronic Acids to α,β-Unsaturated Ketones

Tetsuya Yamamoto, Michiko Iizuka, Tetsuo Ohta,* and Yoshihiko Ito
Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto 610-0394

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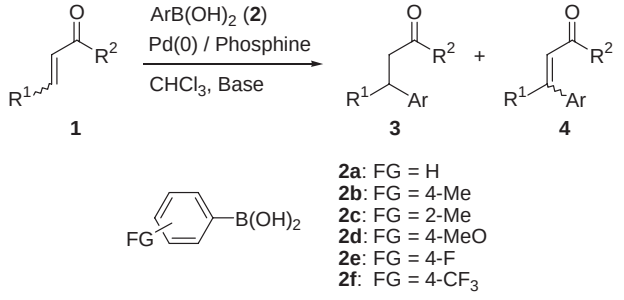
1,4-Addition of arylboronic acids to α,β-unsaturated ketones was smoothly catalyzed by palladium(0) phosphine complexes with chloroform in the presence of base. It is remarked that the palladium(0) complexes have no catalytic activity in the absence of chloroform. The reaction proceeded without β-hydride elimination.

The transition metal-catalyzed 1,4-conjugate addition reaction of organometallic reagents to α,β-unsaturated ketones is widely used for carbon–carbon bond formation giving β-substituted functionalized compounds.[1] Particularly, in various organo-main group metal compounds, organoboron compounds are non-toxic and effective for carbon–carbon bond forming reactions with various electrophiles in the presence of a transition metal.[2] Recently, rhodium-catalyzed carbon–carbon coupling reactions with organoboron reagents have remarkably been developed. Miyaura et al. found that rhodium(I) complexes catalyze 1,4-addition to α,β-unsaturated carbonyl with aryl- and 1-alkenylboron compounds.[3] Although, there are a few reports that the palladium-catalyzed addition reaction of arylboron reagents. Uemura and co-workers demonstrated the palladium(0) and $SbCl_3$-catalyzed conjugate addition of arylboron reagents to α,β-unsaturated carbonyl compounds.[4] Recently, Miyaura et al. reported the cationic palladium(II)-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated enones.[5] Very recently, we found that palladium(0) complexes coordinated by phosphine ligands catalytically induced 1,2-addition of arylboronic acids to aldehydes in the presence of base and a catalytic amount of chloroform.[6] Herein, we report the 1,4-addition of arylboronic acids to α,β-unsaturated ketones, catalyzed by palladium(0) phosphine complexes in the presence of a base and a catalytic amount of chloroform (Scheme 1).

Palladium-catalyzed addition of phenylboronic acid to 2-cyclohexenone was examined at 60 °C, and the results are summarized in Table 1. Palladium(0) complex precursors and neutral palladium(II) complex, such as $Pd(OAc)_2$, $Pd(dba)_2$ and $PdCl_2(CH_3CN)_2$, had no catalytic activity in the absence of chloroform



Scheme 1.

Table 1. Addition of $PhB(OH)_2$ to 2-cyclohexenone[a]

Entry	Catalyst/Phosphine (mol %)	Yield/%[b]	**3**/**4**[b]
1	$Pd(OAc)_2$ (5)/PPh_3 (5)	0	—
2	$Pd(dba)_2$ (5)/PPh_3 (5)	0	—
3	$PdCl_2(CH_3CN)_2$ (5)/PPh_3 (5)	0	—
4	$Pd_2(dba)_3 \cdot CHCl_3$ (3)/PPh_3 (6)	>99	>100:1
5[c]	$Pd(OAc)_2$ (5)/PPh_3 (10)	>99	>100:1
6[d]	$Pd_2(dba)_3 \cdot CHCl_3$ (3)/PPh_3 (6)	>99	>100:1
7	$Pd_2(dba)_3 \cdot CHCl_3$ (3)/PPh_3 (12)	43[e]	>100:1

[a]Reactions were carried out at 60 °C for 24 h in the presence of 2-cyclohexenone (1.0 mmol), phenylboronic acid (2.0 mmol), palladium complex, phosphine, and Cs_2CO_3 (1.0 mmol) in toluene (2 mL). [b]Determined by ^1H NMR spectroscopy. [c]$CHCl_3$ (0.01 mL) was added. [d]A catalytic amount of Cs_2CO_3 (0.2 mmol) was used. [e]Yield of product isolated by silica gel column chromatography, and based on 2-cyclohexenone.

(Table 1, Entries 1–3). On the other hand, phosphine–palladium(0) complexes catalyzed 1,4-addition in the presence of a catalytic amount of chloroform (Table 1, Entries 4–7). The reaction proceeded smoothly even using a catalytic amount of Cs_2CO_3 (Table 1, Entry 6). Other bases were also usable for this reaction but the yields slightly decreased (K_3PO_4 99%, K_2CO_3 70%, Na_2CO_3 77%, and KOH 72%). The yields of the 1,4-addition products decreased with the increase of triphenylphosphine (Table 1, Entries 4 and 7), and bidentate phosphines, such as dppe, dppp, dppb, and dppf, were less effective. In every reaction, formation of a considerable amount of biphenyl was observed. Addition of water slightly accelerated the reaction.

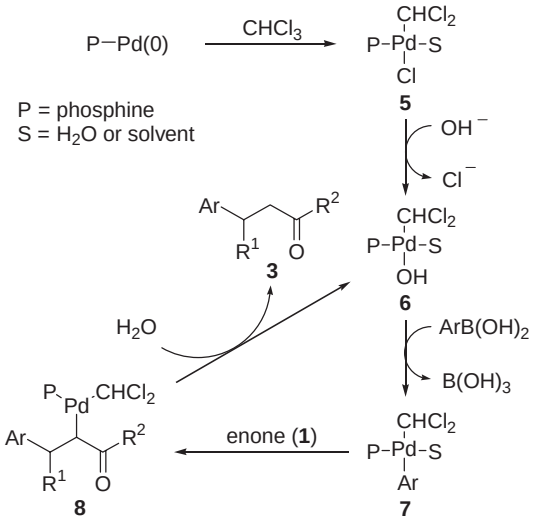
Results of the reaction of enones with arylboronic acids are summarized in Table 2.[7] The palladium-catalyzed addition of phenylboronic acid proceeded smoothly to several acyclic and cyclic enones (Table 2, Entries 1–8). Electron-rich arylboronic acids such as 4-tolylboronic acid and 4-methoxyphenylboronic acid reacted smoothly as well as phenylboronic acid (Table 2, Entries 9 and 11). On the other hand, ortho-substituted or electron-deficient arylboronic acids such as 2-tolylboronic acid, 4-fluorophenylboronic acid, and 4-trifluoromethylphenylboronic acid reacted slightly slow to 2-cyclohexenone (Table 2, Entries 10, 12, and 13). α,β-Unsaturated aldehyde and nitrile were also arylated to give the product in good yield ((*E*)-2-hexenal, 16 h >99% yield; (*E*)-2-pentenenitrile, 60 °C, H_2O (1.0 mmol) 79% yield). It is remarked that all reactions proceed without β-hydride elimination except the reaction of 2-pentenenitrile.[8]

We propose the catalytic cycle of this reaction in Scheme 2. At first, phosphine and dichloromethyl coordinating palladium(II) intermediate **5** was generated by oxidative addition of chloroform to phosphine coordinated palladium(0) complexes,[9] and dichloromethyl palladium(II) intermediate **5** is converted to a hydroxyl palladium(II) species **6** by ligand exchange. Then, the transmetalation between arylboronic acid and the hydroxyl

Table 2. Addition of $ArB(OH)_2$ to enones[a]

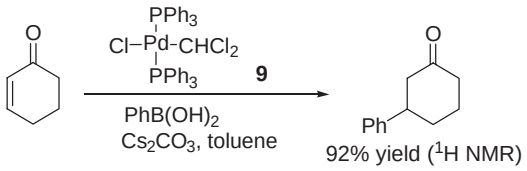
Entry	2	Enone	Yield/%[b]	3/4[c]
1	**2a**	PhCH=CHCOPh	99	>100:1
2	**2a**	PhCH=CHCOCH$_3$	89	>100:1
3	**2a**	*n*-C_3H_7CH=CHCOCH$_3$	92	>100:1
4	**2a**	CH_3CH=CHCOC_2H_5	91	>100:1
5	**2a**	*iso*-C_3H_7CH=CHCOCH$_3$	80	>100:1
6	**2a**	2-cyclopentenone	>99	>100:1
7	**2a**	2-cycloheptenone	>99	>100:1
8	**2a**	2-cyclohexenone	>99	>100:1
9	**2b**	2-cyclohexenone	>99	>100:1
10	**2c**	2-cyclohexenone	87	>100:1
11	**2d**	2-cyclohexenone	96	>100:1
12	**2e**	2-cyclohexenone	83	>100:1
13	**2f**	2-cyclohexenone	70	>100:1

[a]All Reactions were carried out at 80 °C for 24 h in the presence of enone (1.0 mmol), arylboronic acid (2.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Cs_2CO_3 (1.0 mmol), and $CHCl_3$ (0.01 mL) in toluene (2 mL). [b]Yield of product isolated by silica gel column chromatography, and based on enoes. [c]Determined by ^{1}H-NMR spectroscopy.



Scheme 2.

palladium(II) species **6** occurs to generate an arylpalladium(II) intermediate **7**, and the insertion of the enone into carbon–palladium bond affords a C-bound enolate **8**. The palladium enolate **8** was hydrolyzed to give the corresponding ketone and the hydroxyl palladium(II) species **6** was reproduced. Espinet et al. demonstrated that C-bound palladium enolate is very easy to suffer hydrolytic carbon–palladium bond cleavage.[10] A small amount of water might be present in our reaction system. Addition of H_2O to the reaction improved the ratio of addition product/Heck type product in case of 2-pentenenitrile (without H_2O, 52:7; with H_2O, 79:2). As Herrmann et al. reported the chloro(dichloromethyl)bis(triphenylphosphine)palladium(II) (**9**) that was prepared from $Pd(PPh_3)_4$ with $CHCl_3$,[9] we used the complex **9** as a catalyst for the addition of phenylboronic acid to 2-cyclohexenone at 80 °C (Scheme 3), and this acted as a catalyst as well.



Scheme 3.

In conclusion, aryl boronic acids react with α,β-unsaturated ketones in the presence of base and a catalytic amount of a palladium(0) complex with chloroform, affording the corresponding ketones in good yields. Newly, we investigate an asymmetric version of this reaction.

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7 General procedure (Table 2). $Pd(OAc)_2$ (0.05 mmol, 5 mol %) and PPh_3 (0.1 mmol, 10 mol %), arylboronic acid (2.0 mmol), aldehyde (1.0 mmol), and Cs_2CO_3 (1.0 mmol) were dissolved in toluene (2 mL) and chloroform (0.01 mL, 12 mol %). After the mixture was stirred at 80 °C for 24 h. The analytically pure ketone was obtained by chromatography on silica gel.

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