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Palladium-Catalyzed Addition of Arylboronic Acids to Aldehydes

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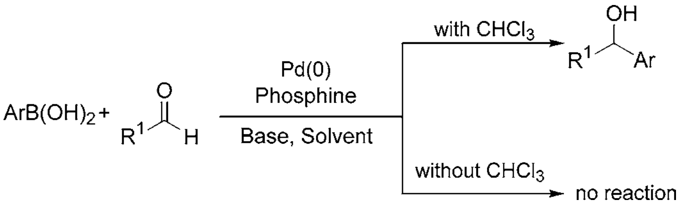
ABSTRACT



Arylboronic acids react with aldehydes in the presence of a base and a catalytic amount of a palladium(0) complex with chloroform, affording the corresponding secondary alcohols in good yields. General palladium complexes have no catalytic activity without chloroform. Chloroform is essential for this reaction, and palladium complex that was prepared from $Pd(PPh_3)_4$ with $CHCl_3$ showed good catalytic acitivty as well.

The transmetalation between organo-main group metal reagents and transition metal compounds is an important step for the generation of active organometallic species in metal-mediated organic synthesis.[1] In general, organoboron reagents are nontoxic and practically useful for carbon−carbon bond formations with various electrophiles in the presence of a transition metal.[2] Recently, rhodium-catalyzed carbon−carbon coupling reactions with organoboron reagents have been remarkably developed. Miyaura et al. found that rhodium(I) complexes catalyze 1,2-addition to aldehydes[3] and *N*-arylsulfonyl aldimines,[4] as well as 1,4-addition to α,*β*-unsaturated carbonyl compounds with aryl- and 1-alkenylboron compounds.[5] Palladium-catalyzed addition reaction of arylborons was also reported by Uemura, who demonstrated that palladium(0)-$SbCl_3$ catalyzes the conjugate addition to α,*β*-unsaturated carbonyl compounds.[6] A cationic palladium(II) complex is also usable as an active catalyst for the 1,4-addition reaction.[7] However, unlike the rhodium catalyst, the palladium complex catalyst provides a rare activity for the 1,2-addition of arylborons to carbon−heteroatom double bonds. The phosphapalladacyclic complex described by Cole-Hamilton and co-workers catalyzes the 1,2-addition of phenylboronic acid to 4-chlorobenzaldehyde.[8] Herein, we report 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 (Scheme 1).

Palladium-catalyzed addition of phenylboronic acid to 4-cyanobenzaldehyde was examined,[9] and the results are summarized in Table 1, which shows the effects of palladium precursors together with phosphine ligands. $Pd_2(dba)_3{\cdot}CHCl_3$ as a palladium(0) precursor catalyzed the 1,2-addition reaction in the presence of triphenylphosphine. However, the

Scheme 1

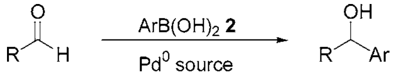


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Table 1. Effect of Pd Source and Phosphine on the Palladium-Catalyzed Reaction of Phenylboronic Acid to 4-Cyanobenzaldehyde

entry	Pd source	ligand [mol %]	yield [%][b]
1	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3 (5)	95 (94)[c]
2	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3 (10)	84
3	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3 (11)	43
4	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3 (15)	2
5	$Pd_2(dba)_3{\cdot}CHCl_3$	dppe (5)	0 (0)[d]
6	$Pd_2(dba)_3{\cdot}CHCl_3$	dppp (5)	0 (42)[d]
7	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb (5)	52
8	$Pd_2(dba)_3{\cdot}CHCl_3$	dppf (5)	75
9	$Pd_2(dba)_3{\cdot}CHCl_3$	(*R*)-binap (5)	89[e]
10	$Pd_2(dba)_3$	PPh_3 (5)	0
11	$Pd(dba)_2$	PPh_3 (5)	0
12	$[PdCl(\pi\text{-}C_3H_5)]_2$	PPh_3 (5)	0
13	$Pd(OAc)_2$	PPh_3 (5)	0
14	$Pd(OAc)_2$	PPh_3 (10)	0
15	$Pd(OAc)_2$	PPh_3 (15)	0
16	$Pd(acac)_2$	PPh_3 (10)	0
17[f]	$Pd(acac)_2$	PPh_3 (5)	0
18	$PdCl_2(CH_3CN)_2$	PPh_3 (5)	0
19	$Pd(PPh_3)_4$	none	0

[a] The reaction was carried out with 4-cyanobenzaldehyde (1.0 mmol), phenylboronic acid (2.0 equiv), Cs_2CO_3 (1.0 equiv), and Pd source (5 mol %) in 2.0 mL of toluene at 60°C for 24 h. [b] Yields were relative to an internal standard by ^1H NMR spectroscopy. [c] Yield of product isolated by silica gel column chromatography, based on 4-cyanobenzaldehyde. [d] The reactions were carried out at 80 °C. [e] Corresponding alcohol was racemate. [f] $Cu(BF_4)_2{\cdot}6H_2O$ (20 mol %) was added.

yields of the 1,2-addition products decreased with the increase of the amount of triphenylphosphine (Table 1, entries 1−4). Bidentate phosphines with small bite angles such as dppe, dppp, and dppb showed lower performance as a ligand (Table 1, entries 5−7). However, bidentate phosphines with large bite angles were effective for the 1,2-addition reaction (Table 1, entries 8 and 9). Noteworthy is that no other palladium(II) complexes nor palladium(0) complex precursors favor the 1,2-addition reaction (Table 1, entries 10−19).

From the results in Table 1, we reasoned that chloroform was important. Thus, we tested the additive effect of chloroform on the palladium-catalyzed addition (Table 2). In the presence of a catalytic amount of chloroform, various palladium complexes showed a similar effect as $Pd_2(dba)_3{\cdot}CHCl_3$ (Table 2, entries 2−7). The reaction proceeded smoothly, although half the amount of PPh_3 was used for Pd when $Pd_2(dba)_3{\cdot}CHCl_3$ was used as palladium source (Table 2, entry 1). It was not effective though CH_2Cl_2 and CCl_4 had been used instead of $CHCl_3$.

Table 2. Additive Effect of Chloroform on the Palladium-Catalyzed Reaction of Phenylboronic Acid to 4-Cyanobenzaldehyde

entry	Pd source	ligand [mol %]	yield [%][b]
1	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3 (2.5)	86
2	$Pd_2(dba)_3$	PPh_3 (5)	95
3	$Pd(dba)_2$	PPh_3 (5)	97
4	$[PdCl(\pi\text{-}C_3H_5)]_2$	PPh_3 (5)	92
5	$Pd(OAc)_2$	PPh_3 (10)	98
6	$Pd(acac)_2$	PPh_3 (10)	82
7	$PdCl_2(CH_3CN)_2$	PPh_3 (5)	92

[a] The reaction was carried out with 4-cyanobenzaldehyde (1.0 mmol), phenylboronic acid (2.0 mmol), Cs_2CO_3 (1.0 mmol), Pd source (5 mol %), and chloroform (0.01 mL) in 2.0 mL of toluene at 60 °C for 24 h. [b] Determined by ^1H NMR spectroscopy using internal standard method.

Results of the reaction of aldehydes with aryl boronic acids are summarized in Table 3. Electronic effects both in the aldehydes and in the arylboronic acids showed a remarkable influence on the reaction; electron-withdrawing aldehydes and arylboronic acids with a donating group reacted easily (Table 3, entries 1−3, 10−12). On the other hand, electron-rich aldehydes gave biarylmethanols in lower yields (Table 3, entries 6 and 8), although addition to ortho-substituted electron-rich aldehydes such as 2-anisaldehyde and 2-tolaldehyde proceeded smoothly (Table 3, entries 7 and 9). Electron-deficient arylboronic acids reacted slowly with electron−neutral aromatic aldehydes such as 2-naphthaldehyde (Table 3, entries 13−15), but the reaction was facilitated with electron-withdrawing aldehydes such as 4-cyanobenzaldehyde (Table 3, entries 16 and 17).

Table 3. 1,2-Addition of Arylboronic Acids to Aldehydes

entry	$ArB(OH)_2$	aldehyde	yield (%)[b]
1	$PhB(OH)_2$	$4\text{-}CF_3C_6H_4CHO$	99
2	$PhB(OH)_2$	$4\text{-}MeOCOC_6H_4CHO$	88
3	$PhB(OH)_2$	$4\text{-}FC_6H_4CHO$	84
4	$PhB(OH)_2$	PhCHO	73
5	$PhB(OH)_2$	2-naphthaldehyde	70
6	$PhB(OH)_2$	$4\text{-}MeC_6H_4CHO$	58
7	$PhB(OH)_2$	$2\text{-}MeC_6H_4CHO$	70
8	$PhB(OH)_2$	$4\text{-}MeOC_6H_4CHO$	56
9	$PhB(OH)_2$	$2\text{-}MeOC_6H_4CHO$	75
10	$4\text{-}MeOC_6H_4B(OH)_2$	2-naphthaldehyde	86
11	$2\text{-}MeOC_6H_4B(OH)_2$	2-naphthaldehyde	87
12	$4\text{-}MeC_6H_4B(OH)_2$	2-naphthaldehyde	84
13	$4\text{-}FC_6H_4B(OH)_2$	2-naphthaldehyde	52
14	$2\text{-}FC_6H_4B(OH)_2$	2-naphthaldehyde	<1
15	$4\text{-}NCC_6H_4B(OH)_2$	2-naphthaldehyde	<1
16	$4\text{-}FC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	71
17	$2\text{-}FC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	75

[a] The reaction was carried out with aldehyde (1.0 mmol), arylboronic acid (2.0 mmol), Cs_2CO_3 (1.0 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 mmol), and PPh_3 (0.05 mmol) in 2.0 mL of toluene at 80 °C for 24 h. [b] Yield of product isolated by silica gel column chromatography, based on aldehyde.

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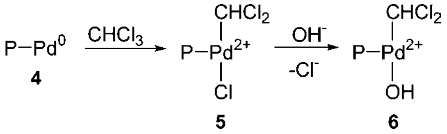
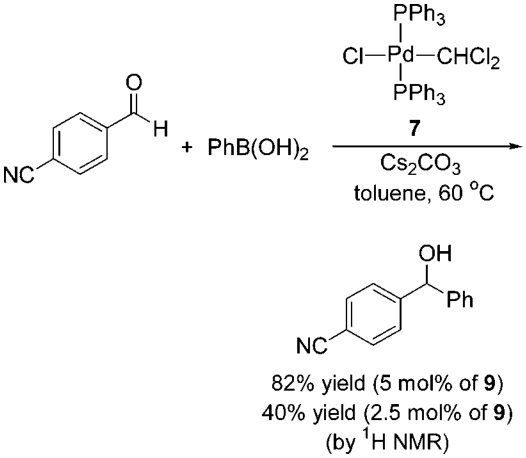
(9) **General Procedure.** Pd complex (0.025 or 0.05 mmol, 5 mol %) and phosphine (0.05 mmol, 5 mol %), arylboronic acid (2.0 mmol), aldehyde (1.0 mmol), and Cs_2CO_3 (1.0 mmol) were dissolved in toluene (2 mL) and chloroform (0.01 mL). After the mixture was stirred at 80 °C for 24 h, then the product was extracted with CH_2Cl_2. The analytically pure alcohol was obtained by chromatography on silica gel.

We propose the possible catalytic cycle of this reaction. At first, phosphine and dichloromethyl-coordinating palladium(II) intermediate **5** is generated by oxidative addition of chloroform to phosphine-coordinated palladium(0) complex **4**, and dichloromethylpalladium(II) intermediate **5** produces a hydroxyl palladium(II) species **6** by counteranion exchange (Scheme 2). Then, transmetalation between arylboronic acid and the hydroxyl palladium(II) species **6** occurs to generate an arylpalladium(II) intermediate, and the insertion of the aldehyde into the carbon–palladium bond affords the palladium alkoxide. The palladium alkoxide complex is hydrolyzed to give the corresponding alcohol, and the hydroxyl palladium(II) species **6** is reproduced. Herrmann et al. reported chloro(dichloromethyl)-palladium(II) coordinated with two triphenylphosphines **7** that was prepared from $Pd(PPh_3)_4$ with $CHCl_3$.[10] We used the complex **7** as a catalyst for the addition of phenylboronic acid to 4-cyanobenzaldehyde at 60 °C (Scheme 3). As a result, the palladium complex **7** was similarly effective for the combination of $Pd_2(dba)_3 \cdot CHCl_3$ with 2 equiv of PPh_3 (Table 1, entry 2). There are still some possibilities for catalytic intermediates, because multinuclear palladium complexes were formed by the reaction of $Pd_2(dba)_3$, polyhalomethane, and phosphine.[11] We tried other polyhalomethanes as an additive. Bromoform ($CHBr_3$), bromodichloromethane ($CHBrCl_2$), and tetrachloromethane (CCl_4) proved much less effective for this reaction (11%, 14%, 7% yields, respectively). Further mechanistic study and application of this catalytic system are now underway.

Scheme 2. Possible Intermediates



Scheme 3



In conclusion, arylboronic acids react with aldehydes in the presence of base and a catalytic amount of a palladium(0) complex with chloroform, affording the corresponding secondary alcohols in good yield. General palladium complexes have no catalytic activity without chloroform but become active by addition of a catalytic amount of chloroform to the reaction mixture.

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Supporting Information Available: Spectra and detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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