Pd and B in 1,4-Additions

Conjugate Addition of Aryl Boronic Acids to Enones Catalyzed by Cationic Palladium(II)–Phosphane Complexes

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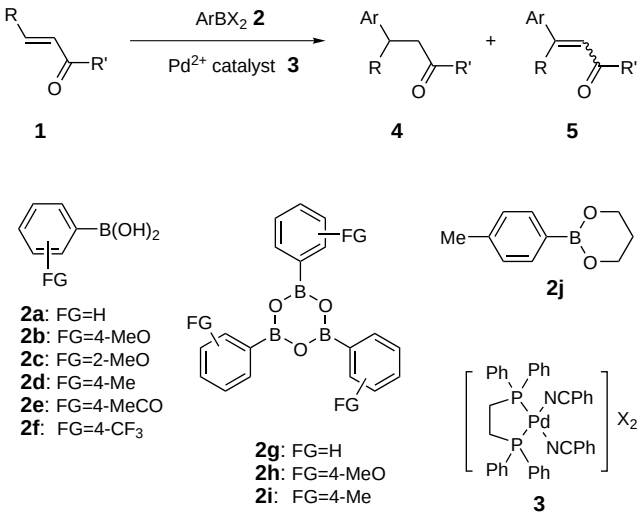
Rhodium(I) complexes are excellent catalysts for the 1,4-addition of aryl or 1-alkenyl boron,[1] silicon,[2] and tin[3] compounds to α,β-unsaturated carbonyl compounds. Various addition reactions analogous to copper-catalyzed reactions of lithium and magnesium reagents have been carried out that involve a catalytic cycle starting from transmetalation to yield an aryl or 1-alkenyl rhodium(I) intermediate. In contrast to the formation of O-bound enolates in the insertion of enones into a C–Rh bond,[4] a palladium catalyst yields C-bound enolates, resulting in β-hydride elimination.[5] Thus, the reaction of enones with RPdX, generated in situ by transmetalation of PdX_2 with an organometallic reagent or by the oxidative addition of RX to a palladium(0) complex, affords Heck coupling products with precipitation of palladium black. However, there are some reports that palladium(II) complexes catalyze 1,4-addition to enones. Products of a simple Michael-type reaction often predominate over the insertion–elimination products of the Heck reaction.[6] Cacchi et al. demonstrated the palladium(II)-catalyzed 1,4-addition of ArHgCl or $SnAr_4$ to enones in acidic water in the presence of Bu_4NCl.[7] In connection with our interest in metal-catalyzed reactions of organoboron compounds,[8] we report herein the 1,4-addition of aryl boronic acids and boroxines **2** to α,β-unsaturated carbonyl compounds **1**, catalyzed by cationic palladium(II) complexes (Scheme 1). $[Pd(dppe)(PhCN)_2]X_2$ **3**[9] (dppe = 1,2-bis(diphenylphophanyl)ethane) was found to be an excellent catalyst for the reaction at room temperature. The catalysts were designed on the basis of the findings of Espinet and co-workers that cationic palladium enolates are much more susceptible to hydrolytic C–Pd-bond cleavage than are neutral species.[10] Their high Lewis acidity and the very smooth insertion of a C–C or C–N double bond into a C–Pd bond are also great advantages of cationic palladium(II) catalysts[11], which have been demonstrated in the palladium-catalyzed Diels–Alder reaction,[12] Mannich reaction,[13] Wacker process,[14] and polymerization of alkenes.[15]



Scheme 1. Palladium(II)-catalyzed 1,4-addition of aryl boron compounds to α,β-unsaturated carbonyl compounds.

Table 1 shows the effects of the catalyst, the type of boron compound, and the presence of a base in the addition of phenylboronic acid (**2a**), *p*-tolylboronic acid (**2d**), the boroxine **2i**, and the boronic ester **2j** to 2-cyclohexenone. Neutral palladium complexes such as $[PdCl_2(dppe)]$ were not effective

Table 1: Pd^{2+}-catalyzed reaction of 2-cyclohexenone with aryl boron compounds **2**.[a]

Entry	Catalyst	2	Additive (equiv)[b]	Yield [%][c]	4/5
1	$[PdCl_2(dppe)]$	**a**[d]	K_2CO_3 (1)	0	
2	**3** ($X=ClO_4$)$_2$	**a**[d]	K_2CO_3 (1)	52	90:10
3	**3** ($X=OTf$)$_2$	**a**[d]	K_2CO_3 (1)	43	96:4
4	**3** ($X=BF_4$)$_2$	**a**[d]	K_2CO_3 (1)	48	89:11
5	**3** ($X=PF_6$)$_2$	**a**[d]	K_2CO_3 (1)	59	96:4
6	**3** ($X=SbF_6$)$_2$	**a**[d]	K_2CO_3 (1)	63	95:5
7	**3** ($X=SbF_6$)$_2$	**a**[d]	none	63	>99:1
8	**3** ($X=SbF_6$)$_2$	**d**[e]	none	77	>99:1
9	**3** ($X=SbF_6$)$_2$	**d**[e]	H_2O (33)	95	>99:1
10	**3** ($X=SbF_6$)$_2$	**i**	none	43	>99:1
11	**3** ($X=SbF_6$)$_2$	**i**	H_2O (1.5)	91	>99:1
12	**3** ($X=SbF_6$)$_2$	**i**	H_2O (3)	95	>99:1
13	**3** ($X=SbF_6$)$_2$	**i**	H_2O (10)	89	>99:1
14	**3** ($X=SbF_6$)$_2$	**j**	none	54	>99:1
15	**3** ($X=SbF_6$)$_2$	**j**	H_2O (1)	40	>99:1

[a] All reactions were carried out in THF (6 mL) at 20°C for 23 h in the presence of 2-cyclohexenone (1 mmol), a phenyl- or *p*-tolylboron compound (1.5 mmol), a palladium(II) catalyst (5 mol%), and base or H_2O (if used). [b] Equivalents with respect to the boron compound. [c] Yields of isolated products based on 2-cyclohexenone starting material. [d] **2a**/**2g** = 68:32. [e] **2d**/**2i** = 87:13.

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(Table 1, entry 1), but cationic palladium–dppe complexes of ClO_4^-, OTf^-, BF_4^-, PF_6^-, and SbF_6^- catalyzed the reaction at room temperature (Table 1, entries 1–6). Although variation of the counteranion had no significant effect, the catalyst efficiency was greatly dependent on the phosphane ligand. Of the catalysts tested, the dppe complex was found to be the best choice, as the use of dppp (1,3-bis(diphenylphosphanyl)-propane), (*S*)-binap ((*S*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) and PPh_3 complexes resulted in no reaction. The cationic benzonitrile complexes are bench-stable catalysts that required no activation. The presence of benzonitrile was critical: The use of a nitrile-free catalyst generated in situ from $[PdCl_2(dppe)]$ and $AgSbF_6$ resulted in 45% yield, and the use of electron-poor benzonitrile complexes such as $[Pd(dppe)(4\text{-}CF_3C_6H_4CN)_2](SbF_6)_2$ led to less than 1% yield. Although K_2CO_3 was used to accelerate the reaction[8] and the yields were indeed highly dependent on the bases employed ($K_2CO_3 > KHCO_3 > Et_3N$), the use of a base always resulted in the formation of a Heck product (4–11%), whereas Heck products were negligible in the absence of a base (Table 1, entry 7). The reaction proceeded smoothly in less polar solvents, such as THF, dioxane, and cyclohexane, but was very slow in donating solvents such as *N,N*-dimethylformamide (DMF) and MeCN.

The reaction requires the presence of water, as does the analogous rhodium-catalyzed reaction.[1] The reactions with *p*-tolylboronic acid (**2d**, boronic acid/boroxine = 87:13) and tris(*p*-tolyl)boroxine (**2i**) resulted in 77% and 43% yields, respectively, in the absence of water (Table 1, entries 8 and 10). Both yields improved to 95% upon the addition of water to the boronic acid or boroxine, which are in equilibrium in an aqueous solution (Table 1, entries 9 and 12).[16] On the other hand, all attempts at using boronic esters were unsuccessful. The reactions of all five- and six-membered boronic esters tested occurred in low yields in either the presence or the absence of water (for example, Table 1, entries 14 and 15).

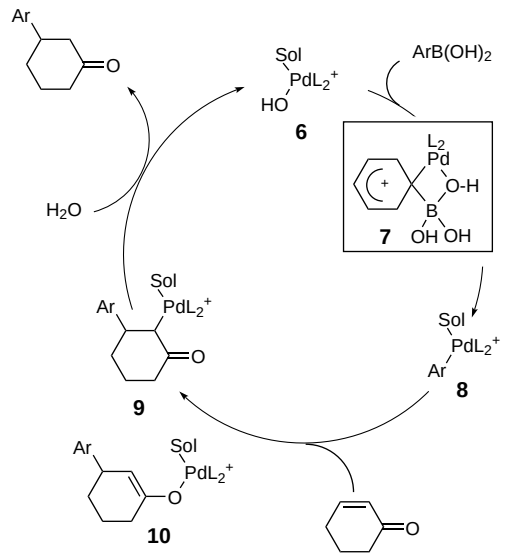
Results of the 1,4-addition of aryl boronic acids and boroxines to representative α,β-unsaturated carbonyl compounds at room temperature are summarized in Table 2. The reaction of 2-cyclopentenone with phenylboronic acid (**2a**, boronic acid/boroxine = 68:32) occurred in 63% yield in the absence of water, in 78% yield when water was added to the boronic acid, and in 91% yield when a mixture of the corresponding boroxine **2g** and water was used (Table 2, entries 1–3). These reactions selectively provided 1,4-addition products, whereas a Heck product was selectively formed in the presence of K_2CO_3 (Table 2, entry 4). Although various boronic acids gave the best yields in the presence of water in reactions with 2-cyclohexenone or 2-cycloheptenone (Table 2, entries 5–8 and 11), the presence of water was not critical for reactions with *p*-acetyl and *p*-trifluoromethylphenylboronic acid (Table 2, entries 9 and 10). An NMR spectroscopic study indicated that these two compounds were pure boronic acid with no accompanying boroxine. The protocol was easily extended to acyclic α,β-unsaturated ketones and aldehydes with a primary alkyl, secondary alkyl, or phenyl substituent on the β carbon atom (Table 2, entries 12–21). In most reactions 5 mol% of the catalyst was used. However, the loading could be decreased to less than 1 mol%: An almost quantitative yield was found in a reaction in which only 0.5 mol% of the catalyst was used (Table 2, entry 13). In contrast to the rhodium-catalyzed reaction, which gave a mixture of 1,4- and 1,2-addition products from enals,[17] the palladium catalysts selectively yielded 1,4-addition products (Table 2, entries 20 and 21). On the other hand, the addition of boronic acids to α,β-unsaturated esters was very slow, and Heck-coupling products predominated (Table 2, entry 22). No reaction was observed for the addition to *N*-benzylcrotonamide.

Table 2: 1,4-Addition of aryl boronic acids and boroxines.[a]

Entry	1	2	Product	Yield [%][b]
1	2-cyclopentenone	**a**	**4a**	63
2	2-cyclopentenone	**a**/H_2O[c]	**4a**	78
3	2-cyclopentenone	**g**/H_2O[d]	**4a**	91
4[e]	2-cyclopentenone	**a**	**5a**[f]	48
5	2-cyclohexenone	**a**/H_2O[c]	**4b**	87
6	2-cyclohexenone	**b**/H_2O[c]	**4c**	80
7	2-cyclohexenone	**c**/H_2O[c]	**4d**	95
8	2-cyclohexenone	**d**/H_2O[c]	**4e**	95
9	2-cyclohexenone	**e**	**4g**	96
10	2-cyclohexenone	**f**	**4h**	94
11	2-cycloheptenone	**a**/H_2O[c]	**4i**	87
12	(*E*)-$C_5H_{11}CH{=}CHCOCH_3$	**a**	**4j**	92
13[g]	(*E*)-$C_5H_{11}CH{=}CHCOCH_3$	**a**	**4j**	97
14	(*E*)-*i*-$C_3H_7CH{=}CHCOCH_3$	**a**/H_2O[c]	**4k**	82
15	(*E*)-$PhCH{=}CHCOCH_3$	**a**/H_2O[c]	**4l**	83
18	(*E*)-$PhCH{=}CHCOPh$	**a**	**4m**	92
20	(*E*)-$CH_3CH{=}CHCHO$	**g**/H_2O[d]	**4n**	83
21	(*E*)-$C_3H_7CH{=}CHCHO$	**a**/H_2O[c]	**4o**[h]	76
22	$CH_2{=}CHCO_2Et$	**a**	**4p**	5[i]

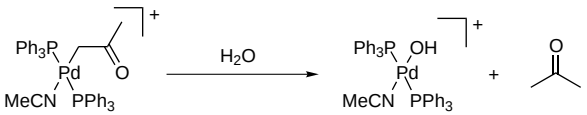
[a] All reactions were carried out at 20°C for 23 h in the presence of 2-cyclohexenone (1 mmol), an aryl boron compound (1.5 mmol), and $[Pd(dppe)(PhCN)_2](SbF_6)_2$ (5 mol%) in THF (6 mL), unless otherwise noted. The ratios of boronic acid/boroxine were: **2a**: 68:32, **2b**: 68:32, **2c**: 100:0, **2d**: 87:13, **2e**: 100:0, and **2f**: 100:0. [b] Yields of isolated products, after purification by chromatography. [c] The reaction was conducted in THF/H_2O (10:1, 6 mL). [d] An aryl boroxine (0.5 mmol) and water (3 mmol) were used in place of the boronic acid. [e] K_2CO_3 (1.2 mmol) was used. [f] 3-Phenyl-2-cyclopentene was formed selectively. [g] Catalyst used: 0.5 mol%. [h] 1,3-Diphenyl-1-hexanone (1.6%) was also obtained. [i] Ethyl cinnamate (31%) was also isolated.

A proposed catalytic cycle involving transmetalation, insertion, and hydrolytic C–Pd-bond cleavage is shown in Scheme 2. Organoboronic acids are inert to neutral palladium(II) halides, but they easily undergo transmetalation with cationic platinum(II) and palladium(II) complexes.[8,18] Although the mechanism has not yet been fully elucidated, the high reactivity of the cationic species suggests that a transmetalation occurs through a Wheland intermediate **7** to produce a cationic aryl palladium(II) species **8**.[19] Because of the difficulty in preventing double transmetalation to **6**, which results in the formation of a homocoupling product (Ar–Ar) and palladium black, palladium(II) complexes have rarely been used in reactions that occur through such a catalytic cycle, which starts with a transmetalation. However, the high turnover number of the catalyst observed in entry 13 of Table 2 indicates that the next insertion step is sufficiently fast to prevent a second transmetalation to **8**. Insertion of a C–C double bond into a C–Pd bond proceeds for electron-deficient alkenes, and this process can be further accelerated



Scheme 2. Proposed catalytic cycle. Sol = solvent molecule.

when cationic palladium complexes are used, as has been demonstrated in the Heck reaction.[5] Nucleophilic addition may occur with delivery of an aryl nucleophile to the β carbon atom of an enone to yield a C- or O-bound palladium enolate (**9** or **10**). As was demonstrated by Espinet and co-workers (Scheme 3),[10] the C-bound enolate **9** is the sole species that undergoes hydrolytic bond cleavage upon treatment with water. It is not yet known whether this process involves direct C–Pd-bond cleavage or the transformation of **9** into **10** before protonolysis (Scheme 2).



11 **12**

Scheme 3. Protonolysis of C-bound palladium enolates (Espinet).

In conclusion, the efficiency of cationic palladium(II) catalysts was demonstrated in the 1,4-addition of aryl boronic acids to α,β-unsaturated carbonyl compounds. Because of the simple experimental procedure and the neutral conditions of this reaction, extension to an asymmetric version is under investigation in our laboratories.

Experimental Section

All cationic palladium(II) complexes were synthesized by reported procedures.[9]

General procedure: A flask charged with a palladium catalyst (0.05 mmol) and an aryl boronic acid (1.5 mmol) or boroxine (0.5 mmol) was flushed with argon. A solvent (6 mL), an enone (1.0 mmol), and water (if used, 0.054 mL for a boroxine and 0.6 mL for a boronic acid) were then added successively. The reaction mixture was stirred for 23 h at room temperature (20–25 °C), then the product was extracted with diethyl ether, washed with K_2CO_3 (0.5 M), and dried over $MgSO_4$. Chromatography on silica gel gave the analytically pure product.

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Keywords: boron · enones · Michael addition · palladium · synthetic methods

[1] a) T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052; b) S. Sakuma, M. Sakai, R. Itooka, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 5951; c) T. Hayashi, T. Senda, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **1999**, *121*, 11591; d) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579; e) M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229; for a review, see: f) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169.
[2] a) M. Murata, R. Shimazaki, M. Ishikura, S. Watanabe, Y. Masuda, *Synthesis* **2002**, 717; b) T. Koike, X. Du, A. Mori, K. Osakada, *Synlett* **2002**, 301; c) S. Oi, Y. Honma, Y. Inoue, *Org. Lett.* **2002**, *4*, 667.
[3] a) S. Oi, M. Moro, H. Ito, Y. Honma, S. Miyano, Y. Inoue, *Tetrahedron* **2002**, *58*, 91; b) T. Huang, Y. Meng, S. Venkatraman, D. Wang, C.-J. Li, *J. Am. Chem. Soc.* **2001**, *123*, 7451.
[4] G. A. Sough, R. G. Bergmann, C. H. Heathcock, *J. Am. Chem. Soc.* **1989**, *111*, 938.
[5] T. Jeffery in *Advances in Metal-Organic Chemistry, Vol. 5* (Ed.: L. S. Liebeskind), JAI, Greenwich, **1996**, p. 153.
[6] a) J. P. Konopelski, K. S. Chu, G. R. Negrete, *J. Org. Chem.* **1991**, *56*, 1355; b) A. Wada, H. Yasuda, S. Kanamoto, *Synthesis* **1988**, 771.
[7] S. Cacchi, D. Misiti, G. Palmieri, *Tetrahedron* **1981**, *37*, 2941.
[8] N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11.
[9] J. A. Davis, E. R. Hartley, S. G. Muray, *J. Chem. Soc. Dalton Trans.* **1980**, 2246.
[10] A. C. Albéniz, N. M. Catalina, P. Espinet, R. Redón, *Organometallics* **1999**, *18*, 5571.
[11] A. Yamamoto, *J. Organomet. Chem.* **1995**, *500*, 337.
[12] K. Mikami, K. Aikawa, Y. Yusa, *Org. Lett.* **2002**, *4*, 95.
[13] A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450.
[14] M. J. Gaunt, J. B. Spencer, *Org. Lett.* **2001**, *3*, 25.
[15] M. Brookhart, M. I. Wagner, *J. Am. Chem. Soc.* **1994**, *116*, 3641.
[16] Y. Tokunaga, H. Ueno, Y. Shimomura, T. Seno, *Heterocycles* **2002**, *57*, 787.
[17] M. Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450.
[18] a) K. Siegmann, P. S. Pregosin, L. M. Venanzi, *Organometallics* **1989**, *8*, 2659; b) S. Darses, T. Jeffery, J.-P. Genet, *Tetrahedron Lett.* **1996**, *37*, 3857; c) S.-K. Kang, H.-W. Lee, S.-B. Jang, P.-S. Ho, *J. Org. Chem.* **1996**, *61*, 4720.
[19] B. Crociani, F. D. Bianca, P. Uguagliati, L. Canovese, A. Berton, *J. Chem. Soc. Dalton Trans.* **1991**, 71.

