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Palladium-catalyzed addition of arylboronic acids to isocyanates

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ABSTRACT

The addition of arylboronic acids to isocyanates catalyzed by palladium acetate in the presence of triphenylphosphine as the ligand is described.

Arylboronic acids are extremely useful organometallic reagents because they are non-toxic and stable compounds.[1] There are several methods available for the synthesis of complex arylboronic acids and large numbers are commercially available. Organoboronic acids and boronates are widely used in reactions catalyzed by transition metals such as palladium,[2] rhodium[3] and copper.[4] They are useful practically for carbon–carbon and carbon–heteroatom bond formation. Copper-catalyzed arylboronic acid coupling reactions with amines, sulfoximines, phenols and alkyl thiols enable carbon–heteroatom bond formation.

In 1997, Miyaura reported the conjugate addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones, which was shown to proceed under catalysis by a rhodium complex.[5] Miyaura also reported rhodium-catalyzed additions of arylboronic acids to aldehydes and imines.[6] Recently, rhodium-catalyzed addition of aryl- and alkenylboronic acids to isocyanates[7] and enantioselective additions of arylboronic acids to aliphatic imines,[8] *N*-Boc imines[9] and *N*-*tert*-butanesulfinyl imino esters[10] have been reported. Palladium-catalyzed addition reactions of arylborons were reported by Uemura, who demonstrated that palladium catalyzes the conjugate addition to α,β-unsaturated carbonyl compounds.[11] Now, palladium-catalyzed addition of arylboronic acids to carbon–carbon double and triple bonds and insertion of carbon–carbon multiple bonds into carbon–palladium bonds, as a facile method for carbon–carbon bond formation, are very important reactions in organopalladium chemistry.[2,12] However, in contrast to the numerous reports on the insertion of carbon–carbon multiple bonds into carbon–palladium bonds, direct insertion of carbon–heteroatom multiple bonds without using stoichiometric organopalladium reagents has received scant attention. Palladium complex catalysts show rare activity for the 1,2-addition of arylborons to carbon–heteroatom double bonds and only a few reports of the use of arylpalladium species as nucleophiles for reaction with polar electrophilic multiple bonds are available.[13] To the best of our knowledge, there are no reports concerning the addition of arylboronic acids to isocyanates catalyzed by palladium. Herein, we report the palladium-catalyzed addition of arylboronic acids to isocyanates under very mild reaction conditions.

We examined the reaction of phenylboronic acid and phenylisocyanate in different solvents such as CH_2Cl_2, DMF, toluene, dioxane and acetonitrile, in the presence of 5 mol % of $Pd(OAc)_2$. However, only a trace of the desired benzamide was obtained. To our delight, using THF as the solvent under an inert atmosphere increased the yield greatly. Other palladium catalysts, such as $PdCl_2$ and $Pd(dba)_2$, led to lower yields. It has been reported that the use of 2,2′-bipyridine (bpy) as a ligand is crucial in the addition of arylboronic acids to nitriles,[13c] however, no reaction was observed between arylboronic acids and isocyanates in the presence of bpy as ligand. The results are summarized in Table 1. Also, in the presence of the oxidant benzoquinone (BQ),[14] only a trace of the de-

Table 1
Optimization of the reaction conditions for the addition of $PhB(OH)_2$ to phenylisocyanate (1:1)

$$\mathrm{ArB(OH)_2} + \mathrm{RNCO} \xrightarrow[\text{THF, rt, Ar, 40 h}]{\mathrm{Pd(OAc)_2/PPh_3}} \underset{\mathbf{1}}{\mathrm{RNHCOAr}} + \underset{\mathbf{2}}{\mathrm{Ar{-}Ar}}$$

Entry	Catalyst (mol %)	Ligand	Solvent	**1** (%)
1	$Pd(OAc)_2$ (5)	PPh_3	THF[a]	64
2	$Pd(OAc)_2$ (5)	PPh_3	DMF[a]	Trace
3	$Pd(OAc)_2$ (5)	PPh_3	CH_2Cl_2[a]	Trace
4	$Pd(OAc)_2$ (5)	PPh_3	Toluene[a]	Trace
5	$Pd(OAc)_2$ (5)	PPh_3	Dioxane[a]	Trace
6	$Pd(OAc)_2$ (5)	PPh_3	MeCN[a]	Trace
7	$Pd(OAc)_2$ (10)	bpy	THF[a]	<5
8	$Pd(OAc)_2$ (5)	dppe	THF[b]	<5
9	$Pd(OAc)_2$ (5)	dpbp	THF[b]	<5
10	$PdCl_2$ (10)	PPh_3	THF[a]	21
11	$Pd(dba)_2$ (10)	PPh_3	THF[a]	18
12	$Pd(dba)_2$ (10)	bpy	THF[a]	<5

[a] Ratio of Ligand:Pd = 4:1.
[b] Ratio of Ligand:Pd = 2:1.

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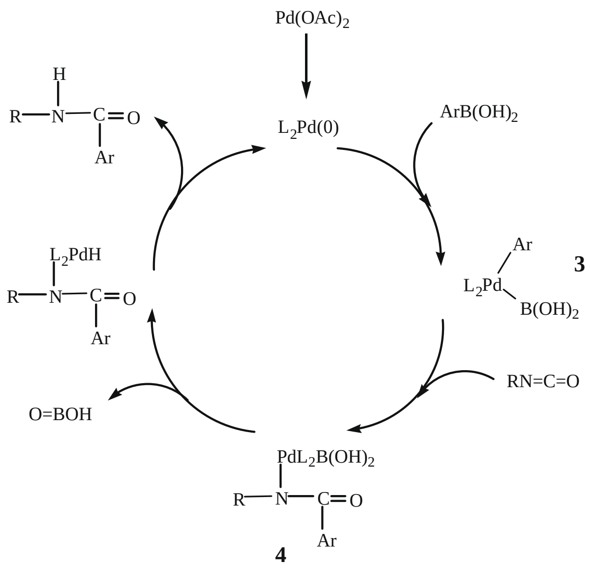
Table 2
Addition of various arylboronic acids to different isocyanates (1:1)

Ar	R	**1** (%)	2 (%)
Ph	Ph	64	27
3,4-$(MeO)_2C_6H_3$	Ph	49	3
4-*t*-BuC_6H_4	Ph	52	15
3-MeC_6H_4	Ph	60	12
4-BrC_6H_4	Ph	32	7
4-ClC_6H_4	Ph	32	6
1-Naphthyl	Ph	33	17
Ph	3-Cl,4-MeC_6H_4	56	11
3-MeC_6H_4	3-Cl,4-MeC_6H_4	40	10
1-Naphthyl	3-Cl,4-MeC_6H_4	43	16
4-BrC_6H_4	3-Cl,4-MeC_6H_4	37	19
4-*t*-BuC_6H_4	3-Cl,4-MeC_6H_4	56	30

Table 3
Influence of the amount of phenylboronic acid on the reaction (rt, 40 h)

$PhB(OH)_2$ (equiv)	Catalyst (mol %)	**1** (%)	**2** (%)
3.0	5	24	65
2.5	5	34	60
2.0	5	40	51
1.5	5	53	32
1.0	5	64	27



Scheme 1.

sired benzamide was obtained. Finally, for comparison, the reaction was carried out in the absence of $Pd(OAc)_2$ and no benzamide product could be detected. With the optimized conditions in hand, the addition of various arylboronic acids to different isocyanates was studied, and the results are shown in Table 2. The influence of the amount of the phenylboronic acid is shown in Table 3. A high yield of biphenyl **2** was obtained using 2.0 equiv of phenylboronic acid. Electronic effects in the arylboronic acids showed a remarkable influence on the reaction; electron-rich arylboronic acids reacted easily. On the other hand, arylboronic acids with electron-withdrawing groups gave benzamides in lower yields.

A possible mechanism for this palladium-catalyzed addition reaction of arylboronic acids to isocyanates is shown in Scheme 1. The catalytic cycle is presumably initiated by oxidative addition of the arylboronic acid to a Pd(0) complex which generates an arylpalladium(II) species **3**. Subsequent insertion of the isocyanate double bond into the σ-aryl-Pd–C bond produces intermediate **4**. It is reasonable to assume that boron departs in the form of a boric acid derivative such as metaboric acid[15] and affords intermediate **5**. Reductive elimination then regenerates the palladium(0) catalyst and the addition product.

In summary, we have developed a Pd-catalyzed addition of arylboronic acids to the C=N double bond of isocyanates in the presence of PPh_3 as a ligand to yield benzamides in moderate to good yields.

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