

Palladium(II)-catalyzed addition of arylboronic acid to nitriles

Baowei Zhao and Xiyan Lu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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Abstract—The addition of arylboronic acid to nitriles catalyzed by palladium(II) species in the presence of bipyridine as the ligand was developed. The use of bipyridine is crucial for changing the properties of arylpalladium species from more electrophilic to more nucleophilic making the reaction possible.

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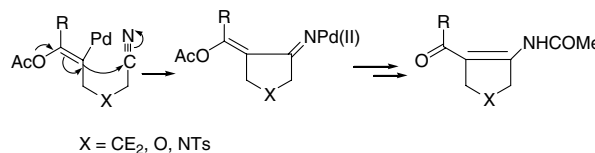
Insertion of carbon–carbon multiple bonds into carbon–transition-metal bonds, as a facile method of carbon–carbon bond formation, is a very important elementary reaction in organotransition-metal chemistry.¹ However, in contrast to the tremendous amount of reports about the insertion of carbon–carbon multiple bonds into carbon–transition-metal bonds, direct insertion of carbon–heteroatom multiple bonds, such as carbonyl, imino, and cyano groups, without using stoichiometric organometallic reagents received scant attentions.¹ In general, the organometallic compounds of late transition metals are less nucleophilic than other organometallics. While the arylpalladium species are commonly used as electrophiles in the carbon–carbon coupling reactions and in the reaction with alcohols and amines,¹ only few reports of the use of the arylpalladium species as nucleophiles to react with the polar electrophilic multiple bonds were reported.²

In general, nitriles are stable to organopalladium species. Thus, acetonitrile can be used as the solvent in the palladium-catalyzed reactions. PdCl₂(RCN)₂ (R = Me, Ph) are widely used as Pd catalysts. Recently, Larock's group reported a series of papers dealing with the addition of arylpalladium species to the cyano group using Pd(0) to initiate the reaction in the presence of DMF.^{3a–e} They also used the Pd(II) species as the catalyst in the presence of DMSO.^{3f} Larock's explanation

for the effect of DMSO involves the facile coordination between DMSO and Pd, which may either stabilize any Pd(II) reaction intermediate or facilitate the reoxidation of Pd(0) to Pd(II) (presumably by air) should the Pd(II) ever be reduced to Pd(0).^{3f}

Our group has recently reported the Pd(II)-catalyzed intramolecular addition of vinylpalladium species to the carbonyl and cyano groups in the presence of bipyridine (bpy) as the ligand.⁴ In this reaction, the vinylpalladium intermediate was formed from the acetoxy-palladation of the alkyne. The formed vinylpalladium species will be relatively nucleophilic due to the presence of the acetoxy group in the olefinic bond, making the addition of vinylpalladium species to the carbonyl and nitrile group possible (Scheme 1).⁴

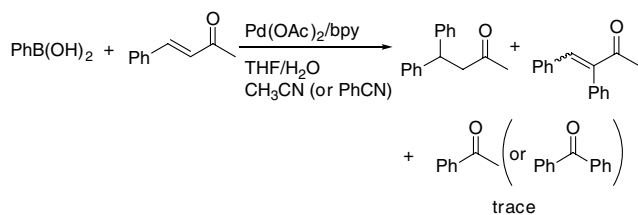
In our study of the Pd(II)-catalyzed conjugate addition of phenylboronic acid to α,β -unsaturated carbonyl compounds,⁵ trace amount of acetophenone or benzophenone was obtained when acetonitrile or phenylnitrile was used as the solvent (Scheme 2). It was suggested that these carbonyl compounds were formed from the addition of phenylboronic acids to nitrile compounds.



Scheme 1. The addition of 2-acetoxyvinylpalladium species to the nitrile group.

Keywords: Palladium; Nitrile; Bipyridine; Nucleophilic addition; Ligand.

* Corresponding author. Tel.: +86 21 54925158; fax: +86 21 64166128; e-mail: xylu@mail.sioc.ac.cn



Scheme 2. Reaction of phenylboronic acid and α,β -unsaturated carbonyl compounds under Pd(II) catalysis.

With this inspiring result in hand, we optimized the reaction conditions. Phenylacetonitrile was chosen as the substrate. The results are shown in Table 1.

When we used the condition reported in conjugated addition,⁵ the addition product was obtained in 57% yield (Table 1, entry 1). The addition of bases such as alkoxy, hydroxy, and fluoride anions exerts a remarkable accelerating effect on the transmetalation step of phenylboronic acid and the palladium acetate.⁶ The yield increased to 71% (Table 1, entry 2) when 1 equiv of $\text{KF}\cdot 2\text{H}_2\text{O}$ (based on PhB(OH)_2) was added in the reaction. The best yield (85%) was obtained in the presence of 2 equiv of $\text{KF}\cdot 2\text{H}_2\text{O}$ at 80 °C (Table 1, entry 3). In the absence of HOAc, the results are not good (Table 1, entries 9–11). A similar result could be obtained if replacing THF by 1,4-dioxane (Table 1, entry 12). The following condition was chosen as the optimized condition. PhB(OH)_2 (1.5 mmol), RCN (0.5 mmol), Pd(OAc)_2 (0.025 mmol), bpy (0.1 mmol), and $\text{KF}\cdot 2\text{H}_2\text{O}$ (3 mmol) in the presence of HOAc (0.5 ml), THF (0.25 ml), and H_2O (0.15 ml) at 80 °C.

Different ligands were surveyed in the reaction. The results are summarized in Table 2.

The best result was obtained when 2,2'-bipyridine (bpy) was used as the ligand (Table 2, entry 2). In the absence of bpy, the reaction mixture became black immediately and only a small amount of the coupling product diphenyl was obtained (Table 2, entry 1). 2,2'-Bipyridines with electron-donating (OMe) or electron-withdrawing (NO_2) groups at 4,4'-positions gave lower yields than the nonsubstituted bipyridines (Table 2, entries 3 and 4). Phenanthroline gave a medium yield (Table 2, entry 5). Other ligands did not give good results. These results may imply that the ligand 2,2'-bipyridine plays an important role and is crucial for this reaction. It may stabilize the divalent palladium species and inhibit the coupling reaction of two phenylboronic acids to form the diphenyl.^{5,7} The success of the addition reaction of phenylboronic acid to nitriles may also imply that the presence of bpy makes the arylpalladium species from electrophilic to more nucleophilic.

The ratio of Pd(OAc)_2 to bpy was surveyed too (Table 3). The yields of ketone were decreased with the decrease of the amount of bpy. Too much of bpy made the rate of the reaction slower and decreased the yield.

Other phenylboron compounds were used for this reaction and arylboronic acid showed the best result (Table 4).

With the optimized condition in hand, the addition of arylboronic acids to different kinds of nitriles studied. The results are shown in Table 5.

From the table, it was shown that substituted benzophenones were obtained in from 31% to 70% yield. The aryl palladium species could also add to the alkylnitriles, but the yields were lower (Table 5, entries 10–13). It should be noted that the 4-nitrophenylnitrile gave higher yield

Table 1. Palladium(II)–bipyridine catalyzed addition of phenylboronic acid to phenylacetonitrile^a

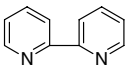
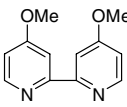
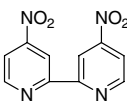
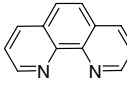

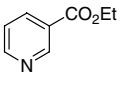
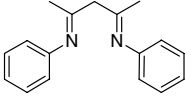
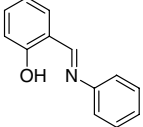

Entry	Solvent	Additive ^b $\text{KF}\cdot 2\text{H}_2\text{O}$ (equiv)	T (°C)	Yield ^c (%)
1	HOAc/THF/ H_2O (0.5 ml/0.25 ml/0.15 ml)	0	80	57
2	HOAc/THF/ H_2O (0.5 ml/0.25 ml/0.15 ml)	1	80	71
3	HOAc/THF/ H_2O (0.5 ml/0.25 ml/0.15 ml)	2	80	85
4	HOAc/THF/ H_2O (0.5 ml/0.25 ml/0.15 ml)	3	80	85
5	HOAc/THF/ H_2O (0.5 ml/0.25 ml/0.15 ml)	2	40	7
6	HOAc/THF/ H_2O (0.5 ml/0.25 ml/0.15 ml)	2	60	44
7	HOAc/THF/ H_2O (0.5 ml/0.25 ml/0.15 ml)	2	100	63
8	HOAc/THF (0.5 ml/0.25 ml)	2	80	80
9	THF/ H_2O (0.25 ml/0.15 ml)	2	80	58
10	THF (1.0 ml)	0	80	69
11	THF (1.0 ml)	2	80	Trace
12	HOAc/dioxane/ H_2O (0.5 ml/0.25 ml/0.15 ml)	2	80	83
13	HOAc/THF/ H_2O (0.1 ml/1.0 ml/0.15 ml)	2	80	49

^a Reaction conditions: PhB(OH)_2 (1.5 mmol), PhCH_2CN (0.5 mmol), Pd(OAc)_2 (0.025 mmol), bpy (0.10 mmol) in solvents at the indicated temperature.

^b The amount of $\text{KF}\cdot 2\text{H}_2\text{O}$ in equivalents based on that of PhB(OH)_2 .

^c Isolated yield.

Table 2. The ligand effect of the addition of phenylboronic acid to phenylacetonitrile catalyzed by Pd(II) species^a

Entry	Ligand	Yield ^b (%)
1	none	Pd black
2		85
3		68
4		46
5		56
6		4
7		6
8		Trace
9		Trace
10		No reaction

^a Reaction conditions: PhB(OH)₂ (1.5 mmol), PhCH₂CN (0.5 mmol), Pd(OAc)₂ (0.025 mmol), ligand (0.10 mmol), KF·2H₂O (3 mmol) in HOAc (0.5 ml), THF (0.25 ml), and H₂O (0.15 ml) at 80 °C for 2 days.

^b Isolated yield.

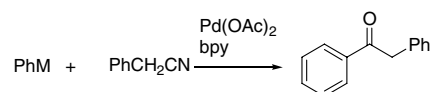
than other aryl nitriles (Table 5, entry 5). It should be noted here that the nitro group could tolerate the reaction conditions, while they are reactive in the presence of Grignard reagents or lithium reagents. 2-Aminophenyl nitrile which has active hydrogens can still react normally although the yield is not satisfactory (Table 5, entry 7).

Table 3. The effect of Pd(OAc)₂/bpy on the reaction^a

Entry	Pd(OAc) ₂ /bpy	Yield ^b
1	1/1	70
2	1/2	75
3	1/4	85
4	1/6	67

^a Reaction conditions: PhB(OH)₂ (1.5 mmol), PhCH₂CN (0.5 mmol), Pd(OAc)₂ (0.025 mmol), KF·2H₂O (3 mmol) and bpy in HOAc (0.5 ml), THF (0.25 ml), and H₂O (0.15 ml) at 80 °C for 2 days.

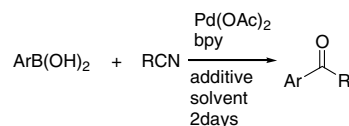
^b Isolated yield.

Table 4. The addition of phenylboron compounds to phenylacetonitrile^a

Entry	PhM (equiv based on PhCH ₂ CN)	Yield ^b (%)
1	PhB(OH) ₂ (3)	85
2	NaBPh ₄ (1)	Trace
3	(PhBO) ₃ (1)	72
4	PhBF ₃ K (3)	63

^a Reaction conditions: phenylboron compounds, PhCH₂CN (0.5 mmol), Pd(OAc)₂ (0.025 mmol), bpy (0.1 mmol), and KF·2H₂O (2 equiv based on the phenylboron compounds) in HOAc (0.5 ml), THF (0.25 ml), and H₂O (0.15 ml) at 80 °C for 2 days.

^b Isolated yield.

Table 5. The addition of arylboronic acids to nitriles^a

Entry	Ar-	R-	Product	Yield ^b (%)
1	Ph	Bn	1	85
2	Ph	PhOCH ₂	2	84
3	Ph	Ph	3	67
4	Ph	4-Me-C ₆ H ₄	4	60
5 ^c	Ph	4-NO ₂ -C ₆ H ₄	5	70
6	Ph	3-NO ₂ -C ₆ H ₄	6	63
7	Ph	2-NH ₂ -C ₆ H ₄	7	31
8	Ph	2,6-Di-F-C ₆ H ₃	8	31
9	Ph	2-Py	9	52
10	Ph	C ₂ H ₅	10	15
11	Ph	ⁿ C ₃ H ₇	11	31
12	Ph	ⁿ C ₅ H ₁₁	12	38
13	Ph	Cl(CH ₂) ₃	13	13
14	4-Me-C ₆ H ₄	Bn	14	65
15	β-Naphthyl	Bn	15	67
16	4-Cl-C ₆ H ₄	Bn	16	80
17	4-F-C ₆ H ₄	Bn	17	58

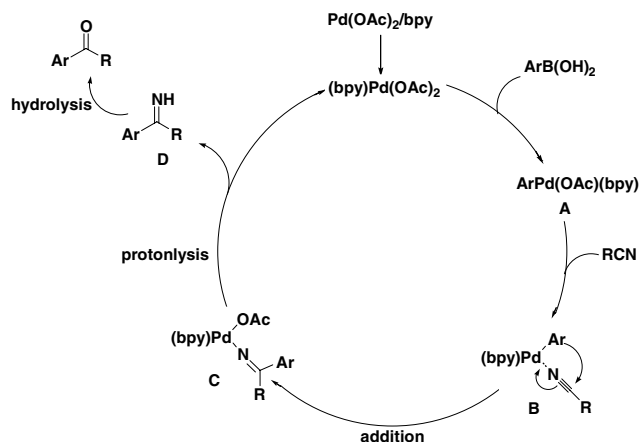
^a Reaction conditions:⁸ ArB(OH)₂ (1.5 mmol), RCN (0.5 mmol), Pd(OAc)₂ (0.025 mmol), bpy (0.1 mmol), KF·2H₂O (3 mmol) in HOAc (0.5 ml), THF (0.25 ml), and H₂O (0.15 ml) at 80 °C for 2 days.

^b Isolated yield.

^c The reaction was conducted for 7 days, but the yield did not change much (73%).

The possible mechanism for this palladium(II) catalyzed addition reaction of arylboronic acids and nitriles is proposed as Scheme 3.

First, transmetalation of arylboronic acids and palladium acetate generated arylpalladium species **A**, which was followed by the coordination of nitrile giving intermediate **B**. The ligand bpy made the arylpalladium species more nucleophilic resulting in the addition of the arylpalladium species to the C≡N bond to form intermediate **C**. The protonolysis of **C** gave **D** and regener-



Scheme 3. Possible mechanism for the Pd(II)-catalyzed addition of arylboronic acids to nitriles.

ated the palladium catalyst. Hydrolysis of **D** yielded the arylketones as the products.

In summary, we developed a Pd(II)-catalyzed addition of arylboronic acids to C≡N bond in the presence of 2,2'-bipyridine as a ligand to yield arylketones with moderate to excellent yield. The use of 2,2'-bipyridine, which may switch the arylpalladium species from more electrophilic to more nucleophilic, was crucial in this reaction. Further study about the role of 2,2'-bipyridines is underway in our laboratory.

Acknowledgements

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Supplementary data

Experimental procedure and characterization data for compounds **1–17** are provided. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.07.074](https://doi.org/10.1016/j.tetlet.2006.07.074).

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- Typical procedure for the addition of arylboronic acid to nitriles: To a Schlenk tube were added phenylboronic acid (183 mg, 1.5 mmol), phenylacetonitrile (58.5 mg, 0.5 mmol), KF·2H₂O (282 mg, 3.0 mmol), Pd(OAc)₂ (5.6 mg, 0.025 mol), bpy (15.6 mg, 0.10 mmol), HOAc (0.5 ml), THF (0.25 ml), and H₂O (0.15 ml) under argon. The mixture was stirred and heated at 80 °C for 2 days until the substrate disappeared as monitored by TLC. The reaction mixture was neutralized with saturated NaHCO₃ solution and then extracted with Et₂O. The combined ether solution was washed with brine, dried by MgSO₄, and concentrated. The residue was purified by flash chromatography (EtOAc/petroleum ether = 1/50) to give product **1** with 85% yield as a white solid. The detailed characterization data of the products were included in **Supplementary data**.