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# Cationic Palladium(II)-Catalyzed Addition of Arylboronic Acids to Nitriles. One-Step Synthesis of Benzofurans from Phenoxyacetonitriles

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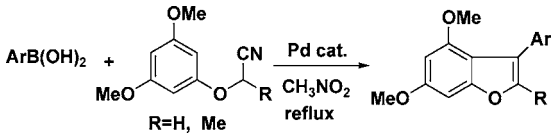
## ABSTRACT




**A cationic palladium complex catalyzed addition of arylboronic acids to nitriles to yield aryl ketones with moderate to good yields was developed. A one-step synthesis of benzofurans from phenoxyacetonitriles under the catalysis of $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ or $[(bpy)Pd^{2+}(H_2O)_2](^{-}OTf)_2$ was developed which showed that the cationic palladium catalyst is highly active for these addition reactions.**

Addition of carbon−metal species to carbon−heteroatom multiple bonds, such as the carbonyl, imino, and nitrile groups, is an important reaction of carbon−carbon bond formation. However, in contrast to the many reports using stoichiometric amounts of organometallic reagents, catalytic reactions using transition-metal catalysts received scant attention.[1] In general, the organometallic compounds of late transition metals are less nucleophilic than other organometallics. Although the arylpalladium species are usually used as electrophiles in carbon−carbon coupling reactions and reaction with alcohols and amines,[1,2] only few reports on the use of the arylpalladium species as nucleophiles to react with the polar electrophilic multiple bonds exist.[2]

In general, nitriles are stable to organopalladium species. Thus, acetonitrile or benzonitrile can be used as the solvent in the palladium-catalyzed reactions. $PdCl_2(RCN)_2$ (R = Me, Ph) is widely used as Pd catalysts. Recently, Larock's group reported a series of papers dealing with the addition of arylpalladium species to the nitrile group using Pd(0)-catalyzed reactions in the presence of DMF.[3a−e] They also used the Pd(II) species as the catalyst in the presence of DMSO to study the addition of arenes to nitriles.[3f,g] In the same paper, the first example of the addition of arylboronic acids to nitriles was reported. Vicente has also reported the

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insertion of nitriles into a C−Pd bond assisted by the *ortho*-hydroxy group.[3k]

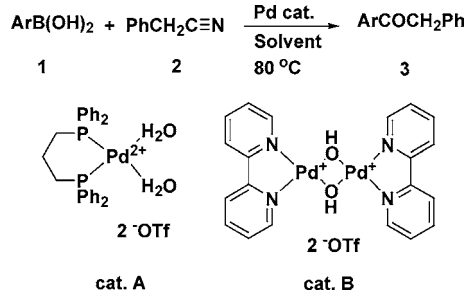
Our group has reported the Pd(II)-catalyzed intramolecular addition of vinylpalladium species to the nitrile groups in the presence of 2,2′-bipyridine (bpy) as the ligand.[4] Recently, we also reported the $Pd(OAc)_2$-catalyzed addition of arylboronic acids to nitriles in the presence of bpy.[5] In both reactions, bpy is crucial for the reactions implying that the presence of bpy can stabilize the arylpalladium species and increase its reactivity.

Compared to the neutral palladium species, the cationic palladium species has vacant coordination sites and shows a harder metal property.[6,7] It occurred to us that the cationic palladium complexes might also catalyze the addition of arylboronic acids to nitriles due to their high Lewis acid property. We report herein the cationic palladium complex catalyzed addition of arylboronic acids to nitriles and the one-step synthesis of benzofuran derivatives.

First, $(dppp)Pd^{2+}(H_2O)_2(^-OTf)_2$ (catalyst **A**)[8] was used as the catalyst in this reaction. Unfortunately, the reaction mixtures became dark quickly in THF or in $CH_3NO_2$ with low yields of products (Table 1, entries 1 and 2). In our previous work, we reported that the ligand bpy is crucial for the reaction.[4] The cationic palladium complexes containing bpy as the ligand, $[(bpy)Pd^+(\mu\text{-}OH)]_2(^-OTf)_2$ (catalyst **B**) and $[(bpy)Pd^{2+}(H_2O)_2](^-OTf)_2$ (catalyst **C**), were chosen as the catalysts.[9,10a] To our delight, the catalysts were effective and the reaction could take place without any protection from air and moisture. After screening the solvent, we found that the best result could be obtained in $CH_3NO_2$ (Table 1, entry 9). It is worth noting that water could be used as the solvent for this reaction (Table 1, entry 8).

The influence of the amount of the phenylboronic acids is shown in Table 2. A high yield was also obtained even using 2 equiv of phenylboronic acid reacting at 80 °C (Table 2, entry 3). Under reflux conditions, the amount of phenylboronic acid could be reduced to 1.5 equiv and the loading of the catalyst could be reduced to 1 mol % with not much change in the yield (Table 2, entry 6).

**Table 1.** Optimization of Reaction Conditions for the Addition of $PhB(OH)_2$ to Phenylacetonitrile[a]




| entry | Pd catalyst | solvent | yield[c] (%) |
|---|---|---|---|
| 1 | **A**[b] | THF | 21 |
| 2 | **A**[b] | $CH_3NO_2$ | 19 |
| 3 | **B** | HOAc/THF/$H_2O$ (0.5:0.25:0.15, v/v/v) | 67 |
| 4 | **B** | HOAc | 23 |
| 5 | **B** | THF | 78 |
| 6 | **B** | dioxane | 43 |
| 7 | **B** | $^i$PrOH | 51 |
| 8 | **B** | $H_2O$ | 85 |
| 9[d] | **B** | $CH_3NO_2$ | 94 |
| 10 | **B** | $CH_3NO_2$/dioxane (8:1, v/v) | 73 |
| 11 | **B** | DMF | 36 |
| 12 | **B** | DMSO | 26 |

[a] Reaction conditions: $PhB(OH)_2$ (1.5 mmol), phenylacetonitrile (0.5 mmol), $[(bpy)Pd^+(\mu\text{-}OH)]_2(^-OTf)_2$ (catalyst **B**, 3.5 mol %) in solvent (2 mL) at 80 °C for 2 days. [b] 5 mol %. [c] Isolated yield. [d] 30 h.

With the optimized conditions in hand, the scope of the reaction was studied as shown in Table 3. The yields in most cases are higher than that using $Pd(OAc)_2$ as the catalyst as we reported recently.[5] Arylboronic acids with electron-donating groups gave better yields than those with electron-withdrawing groups (Table 3, entries 2, 3, and 6). It is worth noting that those groups, which are reactive in the presence of Grignard reagents or lithium reagents such as the nitro, hydroxyl, and acetate groups (AcO−), could tolerate the reaction conditions (Table 3, entries 9−12). It is especially attractive that the reaction behaves with high chemoselectivity between nitrile groups and Br− or TfO− groups which

**Table 2.** $[(bpy)Pd^+(\mu\text{-}OH)]_2(^-OTf)_2$-Catalyzed Addition of $PhB(OH)_2$ to Phenylacetonitrile[a]

| entry | $PhB(OH)_2$ (equiv) | catalyst (mol %) | $t$ (°C) | time (h) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 3.0 | 3.5 | 80 | 48 | 94 |
| 2 | 2.5 | 3.5 | 80 | 48 | 89 |
| 3 | 2.0 | 3.5 | 80 | 48 | 87 |
| 4 | 1.5 | 3.5 | 80 | 48 | 77 |
| 5 | 1.5 | 3.5 | reflux | 24 | 92 |
| 6 | 1.5 | 1.0 | reflux | 24 | 91 |

[a] Reaction conditions: $PhB(OH)_2$, phenylacetonitrile (0.5 mmol), $[(bpy)Pd^+(\mu\text{-}OH)]_2(^-OTf)_2$ (catalyst **B**) in $CH_3NO_2$ (2 mL). [b] Isolated yield.

(4) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343.
(5) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 6765.
(6) For reactions catalyzed by cationic palladium species, see: (a) Yamamoto, A. *J. Organomet. Chem.* **1995**, *500*, 337. (b) Coates, G. W. *Chem. Rev.* **2000**, *100*, 1223. (c) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, *35*, 905. (d) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941. (e) Mikami, K.; Hatano, M.; Akiyama, K. *Top. Organomet. Chem.* **2005**, *14*, 279 and references therein.
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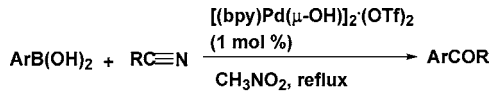
(8) Stang, P. J.; Cao, D. H.; Poulter, G. T.; Arif, A. M. *Organometallics* **1995**, *14*, 1110.
(9) Catalyst **B** is very stable to air and moisture. $^1$H NMR spectra showed clearly the bridged OH in catalyst **B** at 3.34 and 2.79 ppm. Its structure was confirmed by X-ray crystallography (see Supporting Information).[10a] Catalyst **C** showed $^1$H NMR spectra identical with those of the reported data.[10b] Catalyst **B** and catalyst **C** can be converted to each other under the acidic or basic conditions according to the literature.[10c]
(10) Complex $[(bpy)Pd^+(\mu\text{-}OH)]_2(^-OTf)_2$ has been reported in the literature, but no X-ray crystallographic data were given. See: (a) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *Organometallics* **1996**, *15*, 3509. (b) Aeby, A.; Consiglio, G. *Inorg. Chim. Acta* **1999**, *296*, 45. (c) Wimmer, S.; Castan, P.; Wimmer, F. L.; Johnson, N. P. *Inorg. Chim. Acta* **1988**, *142*, 13.

**Table 3.** $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$-Catalyzed Addition of Arylboronic Acids to Nitriles[a]



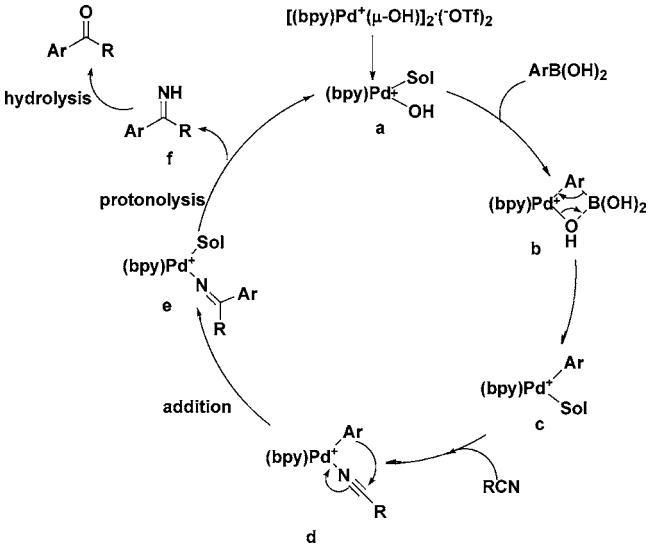

| entry | Ar | R | product | yield (%)[d] |
|---|---|---|---|---|
| 1[b] | Ph | Bn | **3a** | 91 |
| 2 | 4-Me-$C_6H_4$ | Bn | **3b** | 86 |
| 3 | 4-MeO-$C_6H_4$ | Bn | **3c** | 87 |
| 4 | α-naphthyl | Bn | **3d** | 63 |
| 5 | β-naphthyl | Bn | **3e** | 89 |
| 6 | 4-F-$C_6H_4$ | Bn | **3f** | 80 |
| 7 | Ph | Ph | **3g** | 88 |
| 8 | Ph | 4-MeO-$C_6H_4$ | **3h** | 78 |
| 9 | Ph | 4-$NO_2$-$C_6H_4$ | **3i** | 86 |
| 10 | Ph | 3-$NO_2$-$C_6H_4$ | **3j** | 92 |
| 11 | Ph | 4-HO-$C_6H_4$ | **3k** | 91 |
| 12 | Ph | 4-AcO-$C_6H_4$ | **3l** | 82 |
| 13 | Ph | 4-Br-$C_6H_4$ | **3m** | 78 |
| 14 | Ph | 4-TfO-$C_6H_4$ | **3n** | 91 |
| 15 | Ph | $PhOCH_2$ | **3o** | 91 |
| 16[c] | Ph | $C_2H_5$ | **3p** | 52 |
| 17[c] | Ph | $n$-$C_3H_7$ | **3q** | 59 |
| 18[c] | Ph | $n$-$C_5H_{11}$ | **3r** | 72 |
| 19[c] | Ph | $Cl(CH_2)_3$ | **3s** | 35 |

[a] Reaction conditions: $ArB(OH)_2$ (0.38 mmol), RCN (0.25 mmol), $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ (catalyst **B**, 1 mol %) in $CH_3NO_2$ (1 mL) at reflux for about 24 h. [b] See Table 2. [c] Reaction conditions: $PhB(OH)_2$ (1.5 mmol), RCN (0.5 mmol), $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ (catalyst **B**, 3.5 mol %) in $CH_3NO_2$ (2 mL) at 80 °C for 48 h. [d] Isolated yield.

are highly reactive to Pd(0) species[11] (Table 3, entries 13 and 14). For other alkyl nitriles, good results could also be obtained (Table 3, entries 15−19).

The possible mechanism for this $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ (catalyst **B**) catalyzed addition reaction of arylboronic acids and nitriles is proposed as Scheme 1.

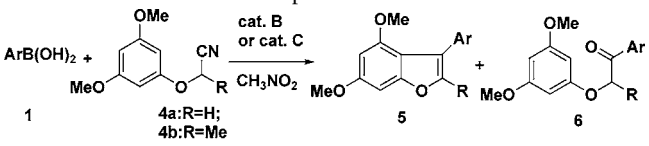
**Scheme 1.** Proposed Mechanism for the Addition of Arylboronic Acids to Nitriles Catalyzed by Catalyst **B**




First, the dimeric catalyst $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ (catalyst **B**) dissociated to the monomeric form **a** in the presence of the solvent or the substrate RCN.[12] Because of the high oxophilicity of boron, the coordination of the hydroxyl group with boronic acid made the transmetalation step (**b**) easily occurring to form the intermediate **c**.[7b] Because of the vacant coordination site on the palladium, nitriles could coordinate with it very easily to generate intermediate **d** and were activated by cationic Pd species due to its higher Lewis acidity. The cationic form made the arylpalladium species more nucleophilic resulting in the smooth addition of the arylpalladium species to the nitrile to form the intermediate **e**. The protonolysis of **e** gave **f** and regenerated the palladium catalyst. Hydrolysis of **f** yielded the aryl ketones as the products.

The important results we found in the study of the reactions of different nitriles encouraged us to study a new area of the reaction. When 3,5-dimethoxyphenoxyacetonitrile (**4a**) was used as the substrate, 4,6-dimethoxy-3-phenylbenzofuran was isolated as the product in 62% yield in one step.

**Table 4.** Synthesis of Benzofurans from the Addition of Arylboronic Acids to Phenoxyacetonitriles under the Catalysis of a Cationic Palladium Complex




1a: Ar=Ph
1b: Ar=4-Me-$C_6H_4$
1c: Ar=4-MeO-$C_6H_4$
1d: Ar= α-Naphthyl
1e: Ar= β-Naphthyl
1f: Ar=4-F-$C_6H_4$
1g: Ar=3-$NO_2$-$C_6H_4$
1h: Ar=4-$CF_3C_6H_4$
1i: Ar=3,5-di$FC_6H_3$
1j: Ar=3-MeO-$C_6H_4$
1k: Ar=2-MeO-$C_6H_4$
1l: Ar=2-Cl-$C_6H_4$

| | substrate | | | | yield (%)[c] | |
|---|---|---|---|---|---|---|
| entry | **1** | **4** | Pd catalyst | time (h) | **5** | **6** |
| 1 | **1a** | **4a** | **B**[a] | 48 | **5aa** (62) | |
| 2 | **1b** | **4a** | **B**[a] | 48 | **5ba** (15) | **6ba** (56) |
| 3 | **1f** | **4a** | **B**[a] | 48 | **5fa** (20) | **6fa** (80) |
| 4 | **1g** | **4a** | **B**[a] | 48 | **5ga** (67) | |
| 5 | **1h** | **4a** | **B**[a] | 48 | **5ha** (52) | **6ha** (35) |
| 6 | **1a** | **4b** | **B**[a] | 9 | **5ab** (82) | |
| | | | **C**[b] | 12 | **5ab** (89) | |
| 7 | **1b** | **4b** | **B**[a] | 21 | **5bb** (58) | **6bb** (42) |
| | | | **C**[b] | 11 | **5bb** (89) | |
| 8 | **1c** | **4b** | **C**[b] | 10 | **5cb** (64) | |
| 9 | **1d** | **4b** | **C**[b] | 18 | **5db** (39) | **6db** (54) |
| 10 | **1e** | **4b** | **C**[b] | 20 | **5eb** (79) | |
| 11 | **1f** | **4b** | **C**[b] | 23 | **5fb** (91) | |
| 12 | **1g** | **4b** | **B**[a] | 14 | **5gb** (65) | |
| 13 | **1h** | **4b** | **C**[b] | 24 | **5hb** (86) | |
| 14 | **1i** | **4b** | **C**[b] | 22 | **5ib** (69) | |
| 15 | **1j** | **4b** | **C**[b] | 12 | **5jb** (84) | |
| 16 | **1k** | **4b** | **C**[b] | 18 | **5kb** (70) | |
| 17 | **1l** | **4b** | **C**[b] | 24 | **5lb** (61) | **6lb** (30) |

[a] $ArB(OH)_2$ (1.5 mmol), **4** (0.5 mmol), catalyst **B** (5 mol %) in $CH_3NO_2$ (2.0 mL) at 80 °C. [b] $ArB(OH)_2$ (0.3 mmol), **4** (0.2 mmol), catalyst **C** (5 mol %) in $CH_3NO_2$ (1.0 mL) at reflux. [c] Isolated yield.

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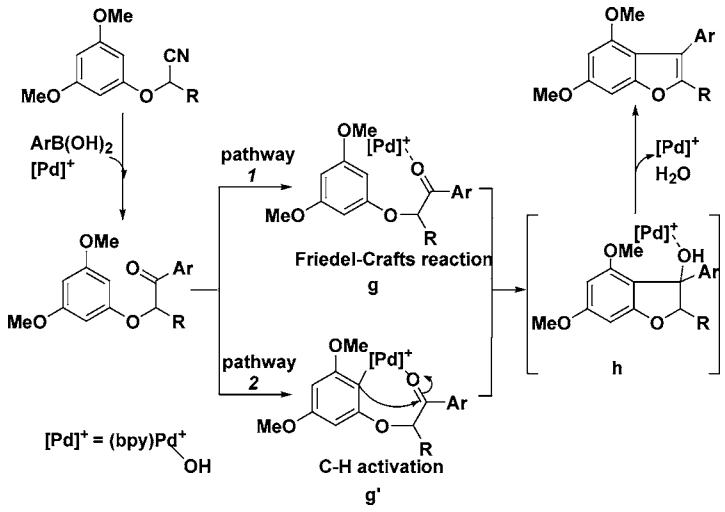
(12) (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (b) Kina, A.; Iwamura, H.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 3904.

**Scheme 2.** Possible Pathways of the Formation of Benzofurans from 3,5-Dimethoxy-phenoxyacetonitriles under the Catalysis of a Cationic Palladium Complex




With this result in hand, we turned our attention to the one-step synthesis of 3-substituted benzofurans from the addition of arylboronic acids to phenoxyacetonitriles under the catalysis of catalyst **B** or catalyst **C**. The results are summarized in Table 4.

From the Table, it was shown that 3-substituted benzofurans were obtained in medium to good yield (up to 91%, Table 4, entry 11). Aryl ketones were obtained as a byproduct in some cases (Table 4, entries 2, 3, 5, 7, 9, and 17) implying that the reaction may proceed with the addition of arylboronic acids to nitriles as the first step. A higher yield was obtained using α-substituted 3,5-dimethoxyphenoxyacetonitrile (**4b**) as the substrate than that using **4a** (Table 4, compare entries 1 and 6). Catalyst **C** is more effective than catalyst **B** in this reaction. Using phenoxyacetonitrile as the substrate, only **3o** was isolated in 91% yield (Table 3, entry 15) implying that the activation of the benzene ring with three alkoxy groups is necessary in this reaction. Using $Pd(OAc)_2$ as the catalyst, no formation of benzofuran occurred, but only the ketone product **6** could be isolated.

Benzofuran derivatives are an important class of heterocyclic compounds that are known to possess important biological properties.[13] In the literature, several methods were reported for the preparation of 3-substituted benzofurans from α-phenoxyacetophenones.[14] The formation of benzofurans may proceed via the following pathways (Scheme 2).

First, arylboronic acids were added to the nitrile group of 3,5-dimethoxy-2-phenoxyacetonitrile forming the aryl ketones. The cationic palladium species acted as a Lewis acid to activate the carbonyl group, and then Friedel−Crafts reaction took place (as shown in **g**) to form the intermediate **h**. Then, benzofuran derivatives were formed after dehydration of **h**. Of course, another pathway (**2**) through the palladium(II)-catalyzed C−H activation of the activated benzene ring forming **g′** first and then nucleophilic attack to the carbonyl group could not be excluded.

In summary, we have developed a cationic palladium complex catalyzed addition of arylboronic acids to nitriles to yield aryl ketones with moderate to good yields. The structure of the catalyst $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ (catalyst **B**) was confirmed by X-ray crystallography. A one-step synthesis of benzofurans from phenoxyacetonitriles under the catalysis of $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ or $[(bpy)Pd^{2+}(H_2O)_2](^{-}OTf)_2$ was developed. The results showed that the cationic palladium catalyst is highly active for these addition reactions.

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**Supporting Information Available:** Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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