

# Ligand-Free Pd/C-Catalyzed One-Pot, Three-Component Synthesis of Aryl-Substituted Benzimidazoles by Hydrogen-Transfer and Suzuki Reactions in Water

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An efficient protocol for the ligand-free and heterogeneous Pd/C-catalyzed one-pot, three-component synthesis of aryl-substituted benzimidazoles from benzyl alcohols by using

Introduction

Benzimidazoles are an important class of N-containing heterocyclic compounds for organic and medicinal chemistry.<sup>[1]</sup> Commonly, they are prepared from 1,2-diaminoarenes by condensation of carboxylic acids or aldehydes (Scheme 1, a) under relatively harsh conditions that include the use of strong acidic conditions and high reaction temperatures.<sup>[2]</sup> Thus, efforts have been made to develop new strategies to synthesize benzimidazoles by metal-catalyzed intramolecular C-N cross-coupling reactions (Scheme 1, b) under mild<sup>[3]</sup> and metal-free conditions.<sup>[2e,3g]</sup> However, these methods require multistep reactions for the preparation of the starting materials. Recently, there has been significant interest in metal-catalyzed hydrogen-transfer reactions by alcohols as a more benign alternative to aldehydes.<sup>[4]</sup> This strategy can improve both the atom efficiency and the regioselectivity of the process by producing only water as a side product. Several groups have reported the use of homogeneous Ir<sup>[5]</sup> and Ru<sup>[6]</sup> catalysts for the synthesis of benzimidazoles from alcohols and 1,2-diaminoarenes by hydrogen transfer (Scheme 1, c). However, in most cases the catalysts employed need to be used with high loadings and their recovery is poor, which negates the advantages associated with the use of alcohols. From economic and practical points of view, a process featuring an efficient and recyclable catalyst in combination with the use of an inexpensive solvent would be highly desirable. Water is known

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water as the solvent was developed. The reaction involves hydrogen-transfer and Suzuki reactions. This method is quite convenient and environmentally friendly.

as a "green solvent" and has clear advantages as a solvent in organic synthesis, because it is cheap, readily available, and nontoxic.<sup>[7]</sup> To the best of our knowledge, there are no reports concerning a heterogeneous catalyst for the synthesis of benzimidazoles from alcohols in water.

On the other hand, multicomponent reactions (MCRs) are ideal synthetic tools to generate complex molecules from readily available starting materials in a single synthetic operation; hence, they minimize waste generation and this renders the transformations green.<sup>[8]</sup> We also developed Ir/ Pd- and Pd/Cu-cocatalyzed three-component reactions for the synthesis of arylquinolines from aminobenzyl alcohols through hydrogen-transfer/Suzuki reactions.<sup>[9]</sup> However, the reaction requires two different metals/ligands and the use of organic solvents. Therefore, the development of a ligandfree and single-metal-catalyzed MCR with the use of water as the solvent is desired. Considering that Pd/C is a common heterogeneous catalyst for hydrogen-transfer<sup>[10]</sup> and Suzuki reactions,<sup>[11]</sup> we speculated that Pd/C would be able to catalyze the above-two distinct reactions in a MCR. In this context, herein, we report the recyclable Pd/C-catalyzed three-component reaction of 1,2-diaminoarenes, alcohols, and arylboronic acids in water to provide a series of arylsubstituted benzimidazoles (Scheme 1, d).

### **Results and Discussion**

Initially, the reaction of 1,2-diaminobenzene with (4methoxyphenyl)methanol was selected as the model reaction to probe the optimal reaction conditions by using Pd/C (5 mol-% as Pd metal) as the catalyst and water as the solvent at 100 °C for 24 h; the results are shown Table 1. It was disappointing to find that the yield of isolated product 1 was only 14% in the absence of a base (Table 1, entry 1). However, the yield was greatly improved by adding a base. After screening a variety of bases, NH<sub>4</sub>HCO<sub>3</sub> was found

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Scheme 1. Main strategies for accessing benzimidazole.

to give the best result (Table 1, entry 12).  $(NH_4)_2CO_3$  and KHCO<sub>3</sub> afforded moderate yields of the product (72 and 63%, respectively). Under the same conditions, dioxane also gave a moderate yield of the product (Table 1, entry 13). Other organic solvents such as toluene, xylene, and DMF afforded the product in lower yields (Table 1, entries 14–16). Additionally, we examined the reusability of the Pd/C catalyst in the above reaction. After initial experimentation, the reaction mixture was filtered, washed, and dried, and the catalyst was used in a subsequent run. This experiment and the three subsequent experiments provided a consistent yield of the product (Table 1, entry 17). It was observed that Pd/C could be recycled and reused four times without any significant loss of activity.

With the optimized reaction conditions established, we then investigated the scope of the reaction with various arylmethanols and 1,2-diaminoarenes (Table 2). Good yields (84–85%) were obtained in the reaction of phenylmethanol or 1-naphthalenemethanol. The electronic nature of the substituents on the arylmethanols had an effect on the reaction. Electron-donating substrates reacted to give corresponding products 2c and 2d, the yields (86–87%) of which were clearly higher than the yields (43–48%) obtained for products 2e and 2f resulting from substrates containing electron-withdrawing groups. For the substrate containing an *ortho*-methyl group, the yield of 2g decreased slightly. The reactions of heteroarylmethanols proceeded efficiently to form expected products 2h and 2i in good yields. Similar

Table 1. Optimization of the reaction conditions.<sup>[a]</sup>

$ \underbrace{ \left( \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$			
Entry	Base	Solvent	Yield [%] <sup>[b]</sup>
1	_	water	14
2	NaOH	water	18
3	КОН	water	34
4	CsOH	water	37
5	$Na_2CO_3$	water	36
6	$K_2CO_3$	water	44
7	$Cs_2CO_3$	water	30
8	$(NH_4)_2CO_3$	water	72
9	$(NH_4)_2C_2O_4$	water	50
10	NaHCO <sub>3</sub>	water	54
11	KHCO <sub>3</sub>	water	63
12	NH <sub>4</sub> HCO <sub>3</sub>	water	88
13	NH <sub>4</sub> HCO <sub>3</sub>	dioxane	75
14	NH <sub>4</sub> HCO <sub>3</sub>	toluene	30
15	NH <sub>4</sub> HCO <sub>3</sub>	xylene	44
16	NH <sub>4</sub> HCO <sub>3</sub>	DMF	trace
17	Entry 12, runs 2,	3, 4	85, 80, 73

[a] Reaction conditions: Pd/C (5 mol-%), 1,2-diaminobenzene (0.5 mmol), (4-methoxyphenyl)methanol (0.55 mmol), base (1 mmol), solvent (3 mL), 100 °C, 24 h. [b] Yield of isolated product.

to the results of 1,2-diaminobenzene, good yields (80–90%) were also obtained in the case of 1,2-diamino-3-methylbenzene, 3,4-diaminotoluene, and 3,4-diaminoanisole.

Table 2. Pd/C-catalyzed synthesis of 2-arylbenzimidazoles from 1,2-diaminoarenes and arylmethanols. $^{[a]}$ 



[a] Reaction conditions: Pd/C (5 mol-%), 1,2-diaminoarene (0.5 mmol), arylmethanol (0.55 mmol), NH<sub>4</sub>HCO<sub>3</sub> (1 mmol), water (3 mL), 100 °C, 24 h, yields of isolated products are given.

It is known that biaryls are important structural moieties of biologically active compounds and organic functional materials. However, 2-biarylbenzimidazoles are less explored,<sup>[12]</sup> which were not synthesized through a multicomponent reaction but by a classical step-by-step approach. Given that Pd/C can catalyze Suzuki reactions to form a variety of biaryls in water,<sup>[11,13]</sup> we were interested to see whether Pd/C could catalyze the three-component reaction for the synthesis of 2-biarylbenzimidazoles. To our delight, the three-component reaction of 1,2-diaminobenzene, (4bromophenyl)methanol, and arylboronic acids gave 2-biarylbenzimidazoles in moderate to good yields by using Pd/ C in the presence of NH<sub>4</sub>HCO<sub>3</sub> (5 equiv.) in water (Table 3).

To understand the reaction pathway, several control experiments were undertaken, and two possible pathways are given in Scheme 2. For example, 2-biarylbenzimidazole 3c was obtained from the hydrogen-transfer reaction of (4bromophenyl)methanol followed by a Suzuki reaction. The hydrogen-transfer reaction only gave 2e in low yield (48%). However, 3c was obtained in good yield (86%) by the onepot transformation. As an alternative to this reacting sequence, both reactions afforded good yields. We also investigated the above two reactions of (4-bromophenyl)methanol for just 3 h and 2e was obtained in 16% yield. These results indicate that the Suzuki reaction should be faster than the hydrogen-transfer reaction. Moreover, by using 4-(hydroxymethyl)phenylboronic acid instead of (4-bromophenyl)methanol, this method was also successfully applied to the one-pot synthesis of 3c (Scheme 3). Clearly, the hydrogen-transfer product was not obtained by the reaction of 4-(hydroxymethyl)phenylboronic with 1,2-diaminobenzTable 3. Three-component reaction for the synthesis of 2-biarylbenzimidazoles.<sup>[a]</sup>



[a] Reaction conditions: Pd/C (5 mol-%), 1,2-diaminobenzene (0.5 mmol), (4-bromophenyl)methanol (0.55 mmol), arylboronic acid (0.75 mmol), NH<sub>4</sub>HCO<sub>3</sub> (2.5 mmol), water (3 mL), 100 °C, 24 h, yields of isolated products are given.

ene, whereas the Suzuki reaction gave a good yield (89%). On the basis of the above results and related processes,<sup>[14]</sup> it is highly probable that the reaction pathway involves first the reaction of the arylboronic acid with the aryl bromide to give the biarylmethanol, which further reacts with the 1,2-diaminoarene to afford the desired benzimidazole through a hydrogen-transfer reaction.<sup>[5,6]</sup>



Scheme 2. Control experiments and possible pathway.

In contrast to arylboronic acids, the Suzuki reactions of 2-*N*-heteroarylboronic acids are less explored,<sup>[15]</sup> and this may be attributed to their instability.<sup>[15b,15c]</sup> Thus, the cou-

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Scheme 3. An alternative method for the synthesis of 3c.

pling of 2-*N*-heteroaryl halides with arylboronic acids provided a valuable complement for the preparation of the corresponding 2-aryl-*N*-heterocycles. Accordingly, the threecomponent reaction of 1,2-diaminobenzene, 4-HOCH<sub>2</sub>-PhB(OH)<sub>2</sub>, and 2-*N*-heteroaryl bromides was investigated under the same reaction conditions (Table 4). Gratifyingly, the desired products **4a**–**h** were isolated in good yields. To broaden the substrate scope, we further investigated this MCR under the same reaction conditions by using 4bromo-1,2-diaminobenzene instead of 1,2-diaminobenzene. As depicted in Table 5, corresponding 2-aryl-5-arylbenzimidazoles **5a**–**h** were also obtained in good yields. Moreover, the detailed structure of **5b** was confirmed by single-crystal X-ray crystallography (Figure 1).

Table 4. Three-component reaction for the synthesis of 2-(1-aryl-4-heteroaryl)benzimidazoles.  $\ensuremath{^{[a]}}$ 



[a] Reaction conditions: Pd/C (5 mol-%), 1,2-diaminobenzene (0.5 mmol), 4-HOCH<sub>2</sub>PhB(OH)<sub>2</sub> (0.55 mmol), 2-*N*-heteroaryl bromide (0.75 mmol), NH<sub>4</sub>HCO<sub>3</sub> (2.5 mmol), water (3 mL), 100 °C, 24 h, yields of isolated products are given.

Table 5. Three-component reaction for the synthesis of 2-aryl-5-arylbenzimidazoles.  $^{\left[ a\right] }$ 



[a] Reaction conditions: Pd/C (5 mol-%), 4-bromo-1,2-diaminobenzene (0.5 mmol), (4-methoxyphenyl)methanol (0.55 mmol), arylboronic acid (0.75 mmol),  $NH_4HCO_3$  (2.5 mmol), water (3 mL), 100 °C, 24 h, yields of isolated products are given.



Figure 1. Molecular structure of **5b**. H atoms are omitted for clarity.

Finally, this newly developed protocol was applied to the synthesis of larger conjugated 2-biaryl-5-arylbenzimid-



azoles through the three-component reactions of 4-bromo-1,2-diaminobenzene, (4-bromophenyl)methanol, and arylboronic acids. As shown in Table 6, desired products **6a**–**j** were isolated in moderate to good yields by using arylboronic acids (3 equiv.) and the Pd/C catalyst (8 mol-%). Electron-donating arylboronic acids reacted to give the corresponding products, and the yields were clearly higher than those obtained with electron-withdrawing arylboronic acids.

Table 6. Three-component reaction for the synthesis of 2-biaryl-5-arylbenzimidazoles.  $^{\left[ a\right] }$ 



[a] Reaction conditions: Pd/C (8 mol-%), 4-bromo-1,2-diaminobenzene (0.5 mmol), (4-bromophenyl)methanol (0.55 mmol), arylboronic acid (1.5 mmol), NH<sub>4</sub>HCO<sub>3</sub> (4 mmol), water (3 mL), 100 °C, 24 h, yields of the isolated products are given.

#### Conclusions

In summary, we developed a green and sustainable method for the synthesis of 2-arylbenzimidazoles from alcohols and 1,2-diaminoarenes in water catalyzed by recyclable Pd/C. This method was also successfully applied to the one-pot, three-component synthesis of 2,5-diarylbenz-imidazoles through hydrogen-transfer and Suzuki reactions. The advantages of the present process include operational simplicity, high efficiency, convenience, the use of an inex-

pensive and reusable catalyst, no need for an additional ligand, the use of water as a solvent, and environmental friendliness.

## **Experimental Section**

General Procedure for the Synthesis of 2-Biaryl-5-arylbenzimidazoles: A Schlenk tube containing a mixture of the 4-bromo-1,2-diaminobenzene (0.5 mmol), (4-bromophenyl)methanol (0.55 mmol), arylboronic acid (1.5 mmol), NH<sub>4</sub>HCO<sub>3</sub> (4 mmol), and Pd/C (8 mol-% as Pd metal) in water (3 mL) was evacuated and charged with nitrogen. The mixture was heated at 100 °C for 24 h and then cooled to room temperature. After vacuum evaporation of the solvent, the resulting residue was purified by silica gel column chromatography to provide the desired product.

**Supporting Information** (see footnote on the first page of this article): Experimental details, characterization data, and copies of the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of all key intermediates and final products.

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