

# Palladium–bipyridine catalyzed conjugate addition of arylboronic acids to $\alpha,\beta$ -unsaturated carbonyl compounds in aqueous media

Shaohui Lin 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**—Palladium/bipyridine catalyzed conjugate addition of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds in aqueous media was developed with high yields.

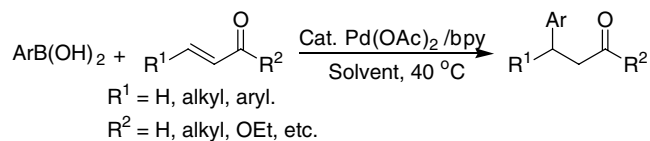
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A significant amount of research has been devoted recently in the pursuit of alternative solvents that are more environmentally benign. The use of aqueous systems for carrying out traditional organic transformations was the first choice because of its cost, safety and environmental concerns.<sup>1</sup> In general, due to the low water solubility of most organic compounds and the water-sensitivity of some reagents especially for organometallic reagents, organic reactions can not proceed in aqueous media easily.<sup>2</sup> Recently, with the development of environmentally benign reactions, there has been increasing interests for chemists to perform the reactions in aqueous media.<sup>2c</sup> The use of water as solvent for organic reactions is advantageous in many respects which may include the cost, safety, synthetic efficiency, simple operation and environmental concerns.<sup>2b</sup> Thus, basic research on aqueous organic reactions could provide the foundation for the development of environmentally friendly synthetic processes.

The conjugate addition of organometallic reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds is a powerful tool for the construction of C–C bonds.<sup>3</sup> While the Rh(I)-catalyzed conjugate addition of organo-boron, silicon, and tin reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds has been well developed,<sup>3d</sup> the reports on Pd-

catalyzed conjugate addition are rare because the later were troubled by the formation of Heck type coupling products by  $\beta$ -hydride elimination. Recently, Miyauro reported the use of cationic Pd(II) complexes to catalyze the conjugate addition of arylboronic acids to enones with excellent yields<sup>4</sup> and our group also developed the use of Pd(OAc)<sub>2</sub>/2,2'-bipyridine(bpy) catalyst system for the conjugate addition of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds with high yields (Scheme 1).<sup>5</sup> The key point may be that the presence of bpy can inhibit the  $\beta$ -hydride elimination and promote the protonolysis of the carbon–palladium bond.<sup>6</sup>

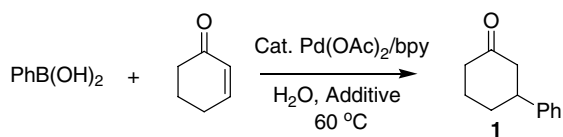
In the Pd(OAc)<sub>2</sub>/bpy catalyzed conjugate addition of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds developed by our group,<sup>5</sup> water is necessary for high yields. It occurred to us that whether water could be used as the solvent in this reaction. The air and moisture stability of divalent palladium catalyst, arylboronic acids, and  $\alpha,\beta$ -unsaturated carbonyl compounds makes this reaction in aqueous media possible.



**Scheme 1.** Conjugate addition of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds.

**Keywords:** Palladium; Arylboronic acids;  $\alpha,\beta$ -Unsaturated carbonyl compounds; Aqueous media; Conjugate addition.

\* Corresponding author. Tel.: +86 21 54925158; fax: +86 21 64166128; e-mail: [xylu@mail.sioc.ac.cn](mailto:xylu@mail.sioc.ac.cn)

**Table 1.** Pd(II)-Bipyridine catalyzed conjugate addition of phenylboronic acid to 2-cyclohexen-1-one in water<sup>a</sup>

Entry	PhB(OH) <sub>2</sub> /enone	Additive	1 Yield (%) <sup>b</sup>
1	3.0	None	85
2	3.0	Sodium laurylsulfonate <sup>c</sup>	92
3	3.0	Sodium dodecyl benzene sulfonate <sup>c</sup>	93
4	2.0	Sodium laurylsulfonate <sup>c</sup>	86
5	2.0	Sodium dodecyl benzene sulfonate <sup>c</sup>	85
6	2.5	Sodium laurylsulfonate <sup>c</sup>	92

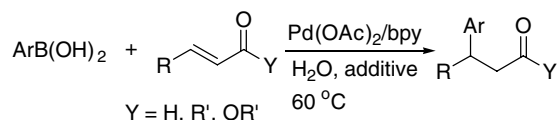
<sup>a</sup> Reaction conditions: 2-cyclohexen-1-one (0.5 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol) and bpy (0.10 mmol) in water (1.0 mL) at 60 °C for 48 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Additive: 20 mg.

In our initial study, we used our previously developed optimal conditions to try this reaction. The only difference is the use of water as the only solvent. Thus, when PhB(OH)<sub>2</sub> (1.5 mmol), 2-cyclohexen-1-one (0.5 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), bpy (0.1 mmol) in water (1 mL) were reacted at 60 °C for 48 h, the reaction afforded 85% yield of conjugate addition product **1** (Table 1, entry 1).

Although phenylboronic acid is soluble in hot water, the palladium/bipyridine catalyst and 2-cyclohexen-1-one are only slightly soluble. With the suggestion that the addition of surface active agents may ameliorate the reaction, some sodium laurylsulfonate was added. To our delight, the reaction system was more homogeneous and the yield was improved to 92% (Table 1, entry 2). Sodium dodecyl benzene sulfonate worked as well as sodium laurylsulfonate (Table 1, entry 3). The yield dropped to 86% when PhB(OH)<sub>2</sub> was decreased (Table 1, entries 4 and 5). Finally, 2.5 equiv of PhB(OH)<sub>2</sub> main-

**Table 2.** Pd(II)-Bipyridine catalyzed conjugate addition of aryl boronic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>a</sup>

Entry	ArB(OH) <sub>2</sub>	$\alpha,\beta$ -Unsaturated carbonyls	Product	Yield (%) <sup>b</sup>
1			<b>1</b>	92
2			<b>2</b>	65
3			<b>3</b>	73
4			<b>4</b>	99
5			<b>5</b>	66
6			<b>6</b>	41
7			<b>7</b>	63
8			<b>8</b>	50

Table 2 (continued)

Entry	ArB(OH) <sub>2</sub>	α,β-Unsaturated carbonyls	Product	Yield (%) <sup>b</sup>
9			<b>9</b>	82
10			<b>10</b>	87
11			<b>11</b>	55
12			<b>12</b>	63
13			<b>13</b>	96
14			<b>14</b>	95
15			<b>15</b>	78
16			<b>16</b>	85

<sup>a</sup> Reaction conditions: arylboronic acid (1.25 mmol), olefin (0.5 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), sodium laurylsulfonate (20 mg) and bpy (0.10 mmol) in water (1.0 mL) at 60 °C for 48 h.

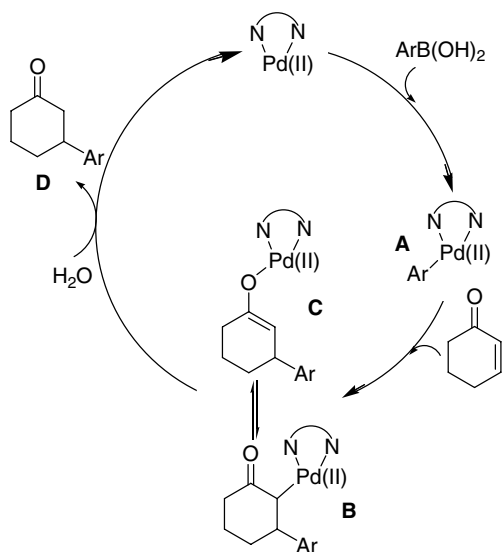
<sup>b</sup> Isolated yield.

tained the yield at 92%, and this was chosen as the optimized conditions (Table 1, entry 6).<sup>7</sup>

The scope of the reaction with different α,β-unsaturated carbonyl compounds is outlined in Table 2. For acyclic and cyclic enones (Table 2, entries 1–5), moderate to excellent yields were obtained, among which 2-cyclopenten-1-one gave the highest yield (Table 2, entry 3). From these results, it seems that enones with bulky groups (4,4-dimethyl cyclohex-2-en-1-one, Table 2, entry 5) showed lower reactivity. Enals provided moderate yields in water (Table 2, entries 6 and 7). It was worth noting that α,β-unsaturated esters also afforded good yields of conjugate addition products (Table 2, entries 8–10). When 2-nitrostyrene was performed under the optimized conditions, 55% yield of addition product was isolated (Table 2, entry 11).

Next, the influence of different arylboronic acids was evaluated. Interestingly, *p*-methoxyphenylboronic acid afforded 63% yield of conjugate addition product (Table 2, entry 12) which only gave very low yield in our previously reported reactions in HOAc media.<sup>5</sup> Maybe, it is the weaker acidity of water that decreased the protonolysis of *p*-methoxyphenylboronic acid and made the yield of conjugate addition better. Among the arylboronic acids tested, *p*-methylphenyl boronic (Table 2, entry 13) acid and *p*-chlorophenyl boronic acid (Table 2, entry 14) provided high yields of conjugate addition products without the detection of β-H elimination products.

A plausible mechanism for the divalent palladium catalyzed conjugate addition is shown in Scheme 2. First, transmetalation between arylboronic acid and palladium catalyst yields the aryl palladium species A



**Scheme 2.** Mechanism of the Pd(II) catalyzed conjugate addition reaction.

followed by insertion of the olefin into the carbon–palladium bond giving palladium enolate **B** or **C**.  $\beta$ -H elimination of the C–Pd bond in **B** is suppressed in the presence of bpy and protonolysis of **B** in water gives the corresponding conjugate addition product **D** with the regeneration of divalent palladium species making the catalytic cycle possible.

In conclusion, we developed a palladium–bipyridine catalyzed conjugate addition of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds in aqueous media. The addition of surface active agent made the reaction system more homogeneous and improved the yields. Moderate to excellent yields of conjugate addition products were obtained even for the reactions of  $\alpha,\beta$ -unsaturated esters.

#### Acknowledgements

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#### Supplementary data

Experimental procedure and characterization data for compounds 1–16 are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.154.

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- Typical procedure for the conjugate addition of phenylboronic acid to 2-cyclohexen-1-one: To a schlenk tube, phenylboronic acid (153 mg, 1.25 mmol), 2-cyclohexen-1-one (48 mg, 0.5 mmol), Pd(OAc)<sub>2</sub> (5.6 mg, 0.025 mmol), bpy (15.6 mg, 0.10 mmol), sodium laurylsulfonate (20 mg) and distilled water (1.0 mL) were added. The mixture was stirred and heated at 60 °C for two days until the substrate disappeared as monitored by TLC. The reaction mixture was extracted with Et<sub>2</sub>O. The combined ether solution was washed with saturated NaCl, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (EtOAc: petroleum ether 1:20) to give the product **1** with 92% yield as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.40–7.17 (m, 5H), 3.09–2.94 (m, 1H), 2.30–2.66 (m, 4H), 2.22–2.01 (m, 2H), 1.94–1.68 (m, 2H); IR (KBr):  $\nu$  2939, 2867, 1710, 1497, 1452, 1224, 756, 700 cm<sup>-1</sup>; MS (70 eV, EI) *m/z* (%): 175 (M<sup>+</sup>+1), 174 (M<sup>+</sup>), 131, 117 (100), 104, 91, 78, 42.