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Cationic Pd(II)/Bipyridine-Catalyzed Conjugate Addition of Arylboronic Acids to α,β-Unsaturated Carboxylic Acids in Aqueous Media

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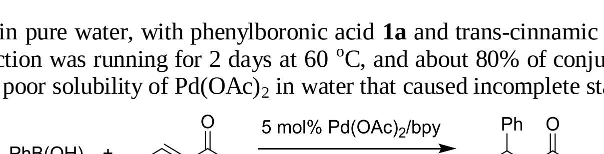
Abstract

An in-situ generated cationic Pd(II)/bipyridine-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carboxylic acids in water was developed and optimized. For most substrates, nearly quantitative yields were given, and the products can be purified by simple washing without column chromatography. The reaction can be scaled up to 1.0 g easily with excellent yields. Also the loading of catalyst can be lowered to 1.0 mol% with modest yields, and the reaction provided a mild and easy way to synthesize β-disubstituted carboxylic acids.

Keywords:
Cationic Pd(II)/Bipyridine
Aqueous Media
Arylboronic acid
Unsaturated carboxylic acid
Conjugate addition

The conjugate addition of organometallic reagents to α,β-unsaturated comounds in the presence of transition metal catalysts is a useful strategy to construct carbon-carbon bonds.[1] Organocopper reagents have been used in conjugate addition[2], for which Corey's group gave the first report.[3] Meanwhile, Hayashi developed the highly efficient Rh(I)-catalyzed asymmetric conjugate addition of arylboronic acids to a variety of α,β-unsaturated compounds.[1b, 1e, 4] However, Cu(I)-catalyzed conjugate addition is limited to only alkylation, and Rh(I)-catalysts are very expensive. Relatively, Pd(II)-catalyzed conjugate addition is more economic and practical but rarely surveyed.[5-10] In Uemura[6] and Miyaura's[7] pioneering research, they developed Pd(II)-catalyzed conjugate addition of organoboron reagents to enones and enals, which sparked scientist's inspiration of conjugate addition with Pd(II)-catalysis. In the previous decade, our group has been concentrating on Pd(II)-catalysis with bidentate nitrogen compounds as ligands[8]. We have developed a series of Pd(II)/bipyridine(bpy)-catalyzed conjugate additions of arylboronic acids to α,β-unsaturated ketones, aldehydes, esters[8a-8c] and amides,[8e] under mild and efficient ambient conditions. With this methodology, quaternary carbon centers were built firstly by conjugate addition of arylboronic acids to α,β-disubstituted enones via cationic Pd(II)/bpy-catalysis.[8d] At the same time, Minnaard finished Pd(II)-catalyzed asymmetric conjugate addition of arylboronic acids to enones.[9] And Stoltz's group used chiral pyridinooxazoline ligands to construct highly enantioselective quaternary stereocenters.[10] Also the mechanism of this reaction has been explored.[11] In our recent research, the $Pd(OAc)_2$/bpy-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carboxylic acids and β-disubstituted unsaturated carboxylic acids has been realized.[8f] Actually, no report of conjugate addition of arylboronic acids to α,β-unsaturated carboxylic acids was found in Pd(II)-catalysis before our research, and the only publication found in Rh(I)-catalysis was by Breit[12], in which acrylic acid was the only reactive substrate. In our reaction, good yields were obtained with $Pd(OAc)_2$/bpy in HOAc. As arylboronic acids and α,β-unsaturated carboxylic acids are all water soluble, and the reaction is insensitive to air and moisture, it's highly promising to perform this reaction in water. Compared with organic solvents, water has many advantages such as natural abundance, low cost, simple operation, synthetic efficiency.[13] In fact, we have reported Pd(II)/bpy-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds in aqueous media[8b] in 2006, in which the presence of surfactants was key to improve the yields. In this case, the direct conjugate addition to α,β-unsaturated carboxylic acids is rare and highly efficient, which would avoid the use of excess reactive organometallic reagents and the neutralizatoin step during work-up.[14] Performing the reaction in water efficiently could simplify the conditions as far as possible.

Then we tried this reaction in pure water, with phenylboronic acid **1a** and trans-cinnamic acid **2a** as starting materials, $Pd(OAc)_2$/bpy as the catalysts (Scheme 1). The reaction was running for 2 days at 60 °C, and about 80% of conjugate addition product was isolated (Table 1, entry 1). We thought it might be the poor solubility of $Pd(OAc)_2$ in water that caused incomplete starting materials conversion.



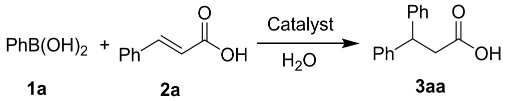
Scheme 1.

To avoid the use of surfactants to improve the materials solubility as in our previous publication,[8b] we tried highly water-soluble cationic palladium catalyst $[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2NO_3^-$ in this reaction (Table 1, entry 2). With weaker coordinating counter anions, cationic Pd(II) is easier to achieve transmetallation and alkenes insertion than neutral Pd(II) species,[15] which was also extensively used in copolymerization of alkenes,[15a,16] C-H activations[17] and other C-C bond formations.[18] Surprisingly, the reaction gave a complete conversion in only 10 h which was much faster than with $Pd(OAc)_2$/bpy in H_2O (Table 1, entry 1) or HOAc[8f], and a 98% yield was given. At the same time, it was found that the product was precipitated in cold water, so the pure product could be isolated simply by filtration and washing, and column chromatography could be avoided. At this point, the conjugate addition of arylboronic acids to α,β-unsaturated carboxylic acids in pure water has been realized. Since the preparation of this cationic palladium is a multi-step synthesis and the yield is very low, we tried to prepare the cationic palladium in-situ in this reaction, and actually this methodology has been used successfully in our previous work of nucleophilic addition to imines.[8f] Then $PdCl_2$-bpy and $AgNO_3$ were directly mixed in reaction at 60 °C, and this method afforded a 96% isolation yield (Table 1, entry 4). So in our optimized conditions, the aforehand preparation of cationic palladium is unnecessary and the purification is very simple. All the reaction components were air-stable and mixed in water, and the products could be isolated by filtration. In the control experiment, no reaction happened in the absence of $AgNO_3$ (Table 1, entry 6). For the temperature effect, no product was observed at 40 °C (Table 1, entry 3). At 80 °C, palladium black was observed (Table 1, entry 5) although an excellent yield could be also obtained. Then, we tried to scale up the cinnamic acid to 1.0 g with only 2.5 mol% catalyst loading, and the reaction gave a 95% yield after 2 days (Table 1, entry 7). When the catalyst loading was decreased to 1.0 mol%, a 70% yield was still given after 3 days (Table 1, entry 8). Compared with the conjugate addition in organic solvents, the reaction carried in water is much faster, and the reaction temperature is lower.[8f]

With this optimal conditions, we started to explore the scope of different arylboronic acids and α,β-unsaturated carboxylic acids (Table 2). Firstly, arylboronic acids with electron donating group were investigated. The best yield was obtained with *p*-tolyboronic acid (Table 2, entry 2). The yield decreased sharply when *p*-methoxyphenylboronic acid was used (Table 2, entry 3), it is because the electron donating groups on phenyl ring accelerate the Pd(II)-catalyzed hydrolyzation of arylboronic acid in water. And the *o*-methoxyphenylboronic acid also gave a very low yield (Table 2, entry 4). Meanwhile, *m*-methoxyphenylboronic acid could gave a modest yield (Table 2, entry 5) in which *m*-methoxyphenyl group is less electron donating. In the case of *p*-fluorophenylboronic and *p*- chlorophenylboronic acid with electron withdrawing groups, the yields were nearly quantitative (Table 2, entries 6 and 7). And *m*-chlorophenylboronic acid and *o*-chlorophenylboronic acid also tend to proceed completely to give excellent yields (Table 2, entries 8 and 9). But for the less reactive 2-fluoro-5-pyridylboronic acid, the reaction was very slow and yield was also low, and the reactants still could be observed after two days (Table 2, entry 10). 1-naphthylboronic acid (Table 2, entry 11) gave a low yield (44%) after 48 h for its steric hinderance. For 2-naphthyboronic acid (Table 2, entry 12), the reaction gave a 92% yield due to smaller steric hindrance. For the highly sterically hindered phenanthrylboronic acid, no reaction could be observed (Table 2, entry 13). Also the alkenylboronic acid ((*E*)-1-pentenylboronic acid) was tested, and no expected product was detected with only palladium black formation (Table 2, entry 14). Then, we screened a series of α,β-unsaturated carboxylic acids with different substitutes on β-aryl groups, and whether for the carboxylic acids with electron donating groups (Table 2, entries 15 and 16) or electron withdrawing groups (Table 2, entries 17 and 18), excellent to quantitative yields were given in all examples. In the case of β-alkyl-substituted unsaturated carboxylic acids (Table 2, entry 19), 55% of the conjugate addition product was isolated; and for acroleic acid (Table 2, entry 20), 50% yield can be obtained, meanwhile some 3,3-diphenylpropanoic acid **3aa** can also be detected in this reaction, which was supposed to be formed by the subsequent conjugate addition to the Heck-type side product (cinnamic acid).[8a]

In summary, we have developed a convenient and economic Pd(II)/bpy catalyzed conjugate addition of arylboronic acid to α, β-unsaturated carboxylic acid in aqueous media. Compared with the reaction in organic solvents, water accelerates the conjugate addition and gave a green and safe option. This reaction can be scaled up to 1.0 g easily, and for most substrates, excellent to quantitative yields were given, and the products can be purified by simple filtration and washing.

Table 1. Pd(II)/bpy catalyzed conjugate addition of phenylboronic acid to cinnamic acid[a]



Entry	Catalyst	Temperature (°C)	Time（h）	Yield (%)[b]
1	$Pd(OAc)_2$/bpy	60	48	80
2	$[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2NO_3^-$.	60	10	98
3	$PdCl_2$-bpy/$AgNO_3$	40	48	trace
4	$PdCl_2$-bpy/$AgNO_3$	60	10	96
5	$PdCl_2$-bpy/$AgNO_3$	80	10	96
6	$PdCl_2$-bpy	60	48	trace
7	$PdCl_2$-bpy/$AgNO_3$	60	48	95[c]
8	$PdCl_2$-bpy/$AgNO_3$	60	72	70[d]

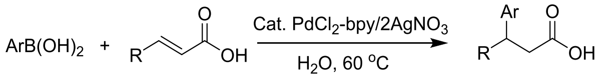
[a] Reaction condition: cinnamic acid (1.0 mmol), phenylboronic acid (2.0 mmol), Pd(II) (0.05 mmol, 5.0 mol%), $AgNO_3$ (0.1 mmol) in water (2 mL).

[b] Isolated yield.

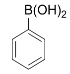
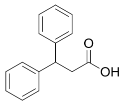
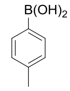
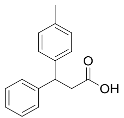
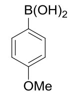
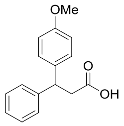
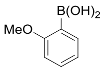
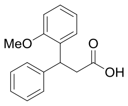
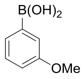
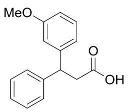
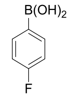
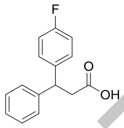
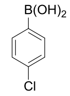
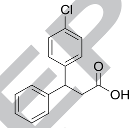
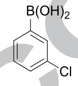
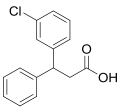
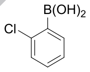
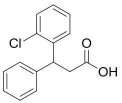
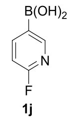
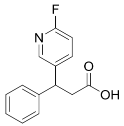
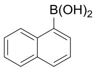
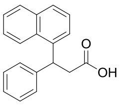
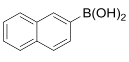
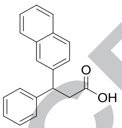
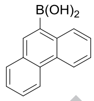
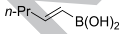
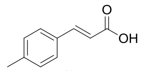
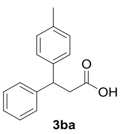
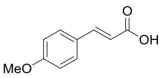
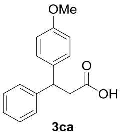
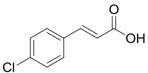
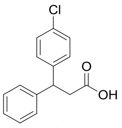
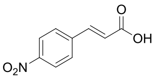
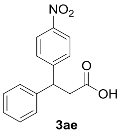
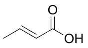
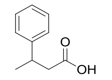
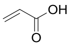
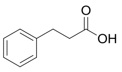
[c] cinnamic acid (1.0 g, 6.75 mmol), phenylboronic acid (13.5 mmol), Pd(II) (0.17 mmol, 2.5 mol%), $AgNO_3$ (0.34 mmol) in water (8 mL).

[d] cinnamic acid (5.0 mmol), phenylboronic acid (10.0 mmol), Pd(II) (0.05 mmol, 1.0 mol%), $AgNO_3$ (0.1 mmol) in water (5 mL).

Table 2. Cationic Pd(II)/bpy catalyzed conjugate addition of arylboronic acids to α, β-unsaturated carboxylic acids[a]



1 2 3

Entry	Substrate	Product	Time (h)	Yield（%）[b]
1	 1a	 3aa	10	96
2	 1b	 3ba	12	96
3	 1c	 3ca	48	36
4	 1d	 3da	48	40
5	 1e	 3ea	12	70
6	 1f	 3fa	12	96
7	 1g	 3ga	12	95
8	 1h	 3ha	12	97
9	 1i	 3ia	12	95
10	 1j	 3ja	48	30
11	 1k	 3ka	48	44
12	 1l	 3la	12	92
13	 1m	--	48	--
14	 1n	--	48	--
15	 2b	 3ba	12	96
16	 2c	 3ca	12	90
17	 2d	 3ga	12	95
18	 2e	 3ae	12	90
19	 2f	 3af	48	55
20	 2g	 3ag	48	50[c]

[a] Reaction conditions: arylboronic acid (2.0 mmol), α, β-unsaturated carboxylic acid (1.0 mmol), $PdCl_2$-bpy (0.05 mmol), $AgNO_3$ (0.1 mmol) in water (2 mL) at 60 °C; Cinnamic acid as the α, β-unsaturated carboxylic acid substrate for entries 1-14; Phenylboronic acid as the arylboronic acid substrate for entries 15-20.

[b] Isolated yield.

[c] Some 3,3-diphenylpropanoic acid can also be found in this reaction.

Acknowledgments

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References and notes

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Highlights

1. Highly efficient Pd(II)-catalyzed conjugate addition in pure water.
2. Easily scaled up 1.0 g. Products easily purified by filtration without columns.
3. Catalyst loading could be lowered to 1.0 mol% with modest yields.
4. Reaction is air and moisture insensitive.
5. 11 of 20 examples yielded >90% with high functional groups tolerance.

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