



Pd(II)/bipyridine catalyzed conjugate addition of arylboronic acids to α,β -unsaturated amides



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ABSTRACT

The Pd(II)/bipyridine-catalyzed conjugate addition of arylboronic acid to α,β -unsaturated amides was developed and optimized, and the reaction was proceeded smoothly in air. A series of arylboronic acid and α,β -unsaturated amide substrates were surveyed, and modest to excellent yields were given.

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Transition metal catalysis is vital to modern synthesis,¹ and transition-metal-catalyzed conjugate addition has been an efficient approach to C–C bonds formation.² In Hayashi's pioneering work,³ rhodium(I)-catalyzed conjugate addition of arylboronic acids to α,β -unsaturated carbonyl compounds was developed as a powerful strategy, in which air and moisture benign arylboronic acids were performed as excellent nucleophiles. Compared with the high cost of rhodium catalysts, Miyaura provided a more economical option of palladium(II) catalysis, and Pd(II)-catalyzed conjugate addition of arylboronic acids to α,β -unsaturated ketones was reported.⁴

As a part of our research of divalent palladium catalysis, we started the survey of Pd(II)-bipyridine(bpy) catalyzed conjugate addition of arylboronic acids to α,β -unsaturated carbonyl compounds, in which bipyridine played a magnificent role to stabilize Pd(II) species and to inhibit β -H elimination.⁵ We published a series of highly efficient Pd(II)-bpy catalyzed conjugate additions of arylboronic acids to α,β -unsaturated ketones, aldehydes, esters, etc.⁶ Especially for the β,β -disubstituted enones, cationic Pd(II)-bpy complex catalyzed the construction of quaternary carbons.^{6c}

After that, nitrogen ligand-based Pd(II) catalysis attracted more chemists' interest compared with Pd(II)-phosphine catalysis.⁷ Stoltz reported the asymmetric conjugate addition of arylboronic

acids to β -substituted cyclic enones which was catalyzed by Pd(TFA)₂-pyridinooxazoline, and highly enantioselective all carbon quaternary carbon centers were generated.⁸ In the following research by Stoltz, the mechanism of this conjugate addition was studied and explained thoroughly.^{8d,9} Also this Pd(II)-catalyzed conjugate addition was used in some synthesis applications.^{8e}

We reviewed the reports of Pd(II)-catalyzed conjugate additions of arylboronic acids and found that most Michael acceptors were focused on α,β -unsaturated ketones^{4,6,8} esters,^{6a} and nitroalkenes.¹⁰ For α,β -unsaturated amides, Hayashi reported excellent results in his Rh(I)-catalyzed reactions¹¹, but it's rarely surveyed in Pd(II)-catalyzed conjugate addition, which might be the weak electron withdrawing ability of amide groups. Only a few conjugate addition examples of acrylamide can be found in previous publication of Pd(II) catalysis,^{6a,7b} and the Pd(II)-catalyzed oxidative Heck reaction of arylboronic acids with α,β -unsaturated amides was surveyed.¹² Herein, we reported the Pd(II)/bpy-catalyzed conjugate addition to α,β -unsaturated amides.

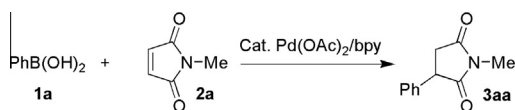
To probe the reaction conditions, phenylboronic acid and *N*-methylmaleimide were chosen as model reactants to optimize the reaction. Firstly, the optimal conditions for conjugate addition to α,β -unsaturated ketones and esters were applied. At 40 °C, only 20% of the expected product was found after 2 days, and most of the starting material *N*-methylmaleimide remained (Table 1, entry 1). In consideration of the fluoride improving the nucleophilicity of organoboronic acids,¹³ KF·2H₂O was added to the reaction, which

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Table 1

Pd(II)-bipyridine catalyzed conjugate addition of phenylboronic acid to *N*-methylmaleimide^a



Entry	Solvent	Ratio 1a:2a	Temperature (°C)	Time (h)	Yield ^b (%)
1	HOAc/THF/H ₂ O = 1 mL/ 2 mL/0.6 mL	3	40	48	20
2	HOAc/THF/H ₂ O = 1 mL/ 2 mL/0.6 mL	3	40	48	27 ^c
3	HOAc/THF/H ₂ O = 1 mL/ 2 mL/0.6 mL	3	60	24	56
4	HOAc/THF/H ₂ O = 1 mL/ 2 mL/0.6 mL	3	80	24	93
5	THF/H ₂ O = 2 mL/0.6 mL	3	80	24	51
6	CH ₃ OH	3	80	24	53
7	Toluene	3	80	24	62
8	HOAc/THF/H₂O = 1 mL/2 mL/0.6 mL	2	80	24	92

^a Reaction conditions: *N*-methylmaleimide (1.0 mmol), Pd(OAc)₂ (0.05 mmol), and bpy (0.20 mmol). The optimized conditions highlighted in bold.

^b Isolated yield.

^c KF·2H₂O (3.0 mmol) as additives, 5% of *N*-methyl-2-phenylmaleimide (**3aa'**) isolated.

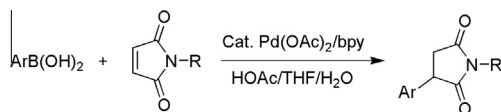
gave a little higher yield but β-H elimination product *N*-methyl-2-phenylmaleimide (**3aa'**) was also observed (Table 1, entry 2).

Then the reaction temperature was increased to 60 °C, and a 56% yield was obtained after 24 h (Table 1, entry 3). When the reaction was heated up to 80 °C, complete starting material conversion was observed and the conjugate addition yield was improved to 93% (Table 1, entry 4). Also the reaction in neutral solvent (THF/H₂O) was tested, and only half of the starting has been converted to the product after 24 h (Table 1, entry 5). Some other solvents (CH₃OH and toluene) were also tested in this reaction (Table 1, entries 6 and 7), only modest yields of conjugate addition were given. It's revealed that acidic conditions were necessary for complete conversion of starting materials. After the reaction in acidic solvent, TLC showed that phenylboronic acid still could be observed. Then the loading of phenylboronic acid was reduced to 2 equiv, and reaction yield was nearly the same (Table 1, entry 8). So far the reaction conditions have been optimized, and no inert gas protection was necessary.

To investigate the substrates scope, different arylboronic acids and α,β-unsaturated amides were tested in the optimized conditions. The reaction of *p*-tolylboronic acid with *N*-methylmaleimide gave excellent conjugate addition yield (Table 2, entry 2). For *p*-methoxyphenyl-, *p*-chlorophenyl- and *p*-fluorophenylboronic acids, high yields were also obtained (Table 2, entries 3–5). But for 1-naphthylboronic acid, the reaction was very slow and only 42% yield of product was isolated after 60 h (Table 2, entry 6). It

Table 2

Pd(II)-bipyridine catalyzed conjugate addition of arylboronic acid to α,β-unsaturated amides^a



Entry	ArB(OH) ₂	α,β-Unsaturated amide	Product	Time (h)	Yield ^b (%)
1	1a	2a	3aa	24	92
2	1b	2a	3ba	22	90
3	1c	2a	3ca	20	83
4	1d	2a	3da	24	74
5	1e	2a	3ea	24	87
6	1f	2a	3fa	60	42

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