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In-Situ Generated Cationic Pd(II)/Bipyridine-Catalyzed Addition of Arylboronic Acids to *N*-Sulfonyl-Arylaldimines

Zhenyu Yang, Yuxin Ni, Rui Liu, Kaixuan Song, Shaohui Lin∗ and Qinmin Pan∗

State and Local Joint Engineering Laboratory for Novel Functional Polymeric Materials, Jiangsu Key Laboratory of Advanced Functional Polymer Design and Application, Key Laboratory of Organic Synthesis of Jiangsu Province, Green Polymer and Catalysis Technology Laboratory (GAPCT), College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Ren'ai Road, Suzhou 215123, P. R. China

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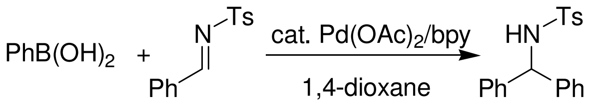
ABSTRACT

An in-situ generated cationic Pd(II)/bipyridine-catalyzed nucleophilic addition of arylboronic acids to *N*-sulfonyl arylaldimines was developed and optimized, and the reaction was proceeded highly efficiently and conveniently in CH_3NO_2. A series of arylboronic acids and *N*-sulfonyl arylaldimines were surveyed, and 12 of 13 examples gave 90~96% yields.

Transition metal catalyzed nucleophilic addition is universal in carbon backbones construction.[1] Hayashi's group developed a series of Rh(I)-catalyzed conjugate addition of organoboron reagents to different α,β-unsaturated compounds,[2] and nucleophilic addition to ketimines,[3] *N*-substituted aldimines,[4] in which excellent asymmetrical inductions had been achieved. Compared with the expensive rhodium catalysts, palladium compounds are more economical but rarely investigated in the nucleophilic addition of arylboronic acids. Uemura[5a] and Miyaura[5b-e] started Pd-catalyzed conjugate addition of organoboron reagents to enones and enals, and in Miyaura's research, cationic Pd(II) complexes with biphosphine ligands were used as highly reactive catalysts. Compared with neutral Pd(II) species, cationic Pd(II) has very weak and non-coordinating counter anions, and this coordination vacancy favors the transmetallation and alkenes insertion.[6] Cationic Pd(II) catalysts were extensively used in the copolymerization of alkenes,[6b,7] C-H activations[8] and other C-C bond formations.[9]

In our systematic survey of Pd(II)-catalysis,[10] a series of Pd(II)/bipyridine(bpy) catalyzed conjugate addition of arylboronic acids to α,β-unsaturated aldehydes, ketones, esters,[10d,10e] and amides had been realized. In 2007, we reported a highly efficient cationic Pd(II) catalyzed 1,2-addition of arylboronic acids to aldehyde to produce diarylmethols,[10c] in which nitromethane was proved to be an excellent solvent. It's found that cationic Pd(II) is more active than neutral species in this nucleophilic addition reactions, and all carbon quaternary carbon centers can be constructed with this method.[10b] Then several groups studied imine type substrates with this nucleophilic addition strategy,[11] and Lu reported a Pd(II)/bpy-catalyzed addition of arylboronic acids to *N*-tosylaldimines (Scheme 1) with 4,4'-dinitro-[2,2']-bipyridine as the best ligand.[12] This neutral $Pd(OAc)_2$ catalyzed reaction gave modest to good yields at high temperature with a prolonged reaction time. Now we reinvestigated this reaction with our cationic Pd(II) catalysis strategy, and a highly efficient and mild reaction system was achieved to realize the nucleophilic addition to imines under base-free conditions.



1a **2a** **3aa**

Scheme 1

We reproduced the reaction with $Pd(OAc)_2$/bpy as the catalyst in 1,4-dioxane, and only a 64% yield was obtained at 95 °C after 2 days (Table 1, entry 1), with incomplete imine conversion. As cationic Pd(II) catalyst **A** showed higher activity in our previously reported nucleophilic addition to aldehydes,[10c] it's tested in this model reaction and a little higher yield (70%) was given (Table 1, entry 2). Temperature tests (Table 1, entries 3-6)

∗ Corresponding author. Tel.: +86-512-67060327; fax: +86-512-65880089; e-mail: linshaohui@suda.edu.cn

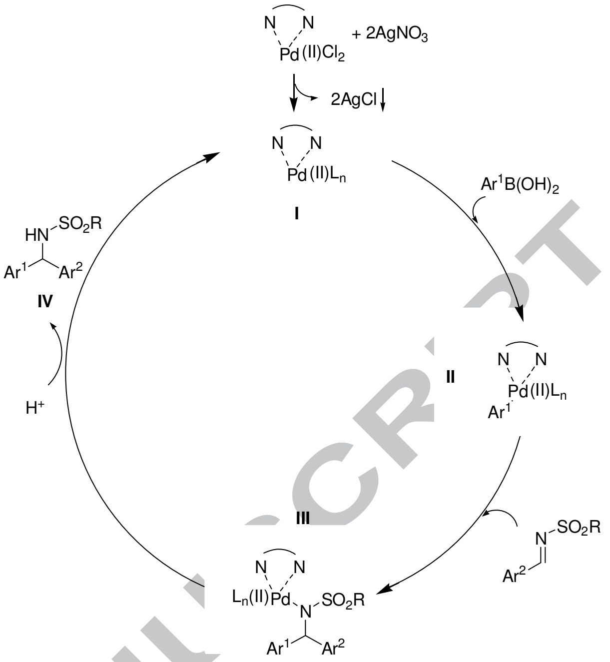
∗ Corresponding author. Tel.: +86-512-65882062; fax: +86-512-65880089; e-mail: qpan@suda.edu.cn

revealed that 60 °C was optimal to give an 82% yield, and no reaction was observed at room temperature. Palladium metal precipitate was observed at 95 °C with cationic Pd(II) catalyst (Table 1, entry 2). It's speculated that the 1,4-dioxane solvent might cause a competing coordination to Pd(II) catalyst, and it would obstruct the coordination of imine substrates to Pd(II), which retarded the nucleophilic addition to imines. Since CH_3NO_2 has been proved to be a good solvent for cationic Pd(II) catalyzed nucleophilic addition due to its polarity and low coordinating ability,[10c] CH_3NO_2 was examined and nearly quantitative yield was obtained (Table 1, entry 7). At the same time, the reaction was accelerated and finished in 24 h. Meanwhile, CH_3OH and toluene as solvents only provided 56% and 20% yields (Table 1, entries 8 and 9).

At this point, combining cationic Pd(II) catalyst with CH_3NO_2 as the solvent accelerated the addition of arylboronic acid to *N*-tosylbenzaldimine with complete starting materials conversion. However, the preparation of cationic Pd(II) catalysts was still a multi-step and low-yielded process. So we tried to synthesize the cationic Pd(II) in-situ, in which bpy-$PdCl_2$ complex and silver trifluoromethanesulfonate were mixed in the reaction. To our surprise, no side reaction was detected and the expected product was synthesized highly selectively with a 95% yield (Table 1, entry 10). The much cheaper silver nitrate was also tired in the reaction to precipitate the chloride anions, and the same high yield was obtained (Table 1, entry 11). ^{1}H NMR and HRMS analysis revealed that cationic $[(bpy)Pd^+(\mu\text{-}OH)]_2\cdot(NO_3^-)_2$ was generated in the presence of $AgNO_3$. It means the catalyst activity was maintained by in-situ preparation of cationic Pd(II), which was more economic by avoiding the waste of rare metal in the step-wise synthesis. No reaction happened in the absence of silver salts (Table 1, entry 12).

In-situ preparation of cationic Pd(II) provided a very convenient way to perform nucleophilic additions of arylboronic acids to imines. A series of arylboronic acids were examined under the optimal conditions, and the scope of *N*-sulfonyl arylaldimines was surveyed. For the arylboronic acids with electron donating groups, *p*-tolyboronic acid and *p*-methoxyphenyl-boronic acid, excellent 92% and 95 yields were obtained (Table 2, entries 2 and 3). For *p*-chloro and *p*-fluoro substituted phenylboronic acids, >90% yields were also given (Table 2, entries 4 and 5). As for 1-naphthylboronic acid (Table 2, entry 6), only 62% of the product was isolated after 48 h with starting materials remained, and it's proposed that the steric hindrance of this arylboronic acid caused incomplete conversion. For 2-naphthylboronic acid with smaller steric hindrance, the reaction yielded 90% of the addition product (Table 2, entry 7).

Setting phenylboronic acid as the invariable, electron donating and withdrawing substitutes were introduced into the *N*-sulfonyl-arylaldimines (Table 2, entries 8-11), and they all gave perfect yields in the nucleophilic additions. Even for *N*-tosyl-*p*-nitrobenzaldimine (Table 2, entry 12), 93% of the addition product was given. Also the *N*-tosyl group was changed to *N*-mesyl group, and a 92% yield was obtained (Table 2, entry 13). All these results demonstrated that this cationic Pd(II) catalyzed reaction was insensitive to electronic properties on the aryl groups on the substrates, and most reactions were finished in 24 h.

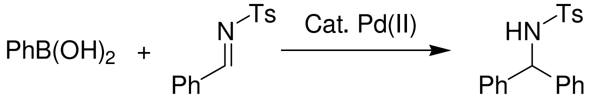


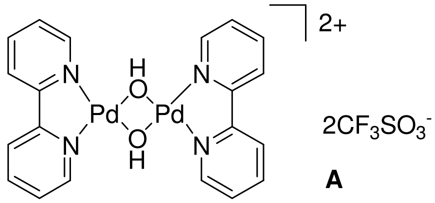
Scheme 2. A proposed mechanism of in-situ generated cationic Pd(II)-catalyzed addition to *N*-sulfonylarylaldimines.

The proposed mechanism of in-situ generated Pd(II)-catalyzed addition was shown in Scheme 2. The chlorides on bpy-$PdCl_2$ were removed by $AgNO_3$ to generate the cationic Pd(II) species **I**. Transmetallation and C=N bonds insertion were accelerated by cationic Pd(II)'s intrinsic properties of vacant coordination sites and high Lewis acidity. The protonolysis of intermediate **III** produced the addition product **IV** and regenerated the cationic Pd(II) catalyst.

In conclusion, an in-situ generated cationic Pd(II) catalyzed nucleophilic addition of arylboronic acids to *N*-Sulfonyl-arylaldimines was developed and optimized. The reaction was performed smoothly under air and *N*-Sulfonyl-arylamines were produced highly efficiently and conveniently. 12 of 13 examples gave >90% yields, which showed very high tolerance of functional groups.

Table 1. Pd(II)-bipyridine catalyzed addition of phenylboronic acid to *N*-tosylbenzaldimine[a]





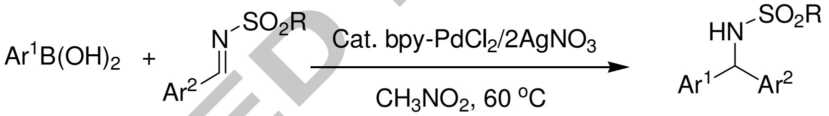
A

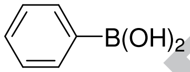
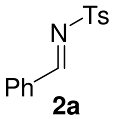
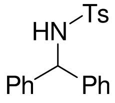
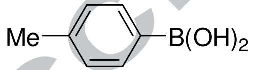
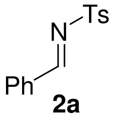
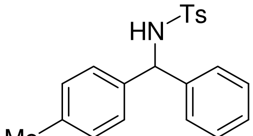
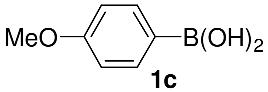
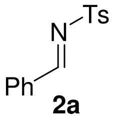
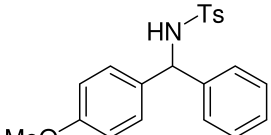
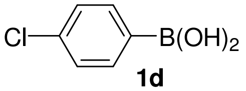
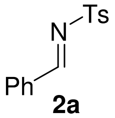
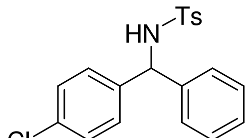
Entry	Catalyst	Solvent	Temperature (°C)	Time (hrs)	Yield (%)[b]
1	Pd(OAc)$_2$/bpy	1,4-dioxane	95	48	64
2	**A**	1,4-dioxane	95	48	70
3	**A**	1,4-dioxane	80	48	80
4	**A**	1,4-dioxane	60	48	82
5	**A**	1,4-dioxane	40	48	53
6	**A**	1,4-dioxane	rt	48	0
7	**A**	CH_3NO_2	60	24	96
8	**A**	Toluene	60	48	56
9	**A**	CH_3OH	60	48	20
10	bpy-PdCl$_2$/2CF$_3$SO$_3$Ag	CH_3NO_2	60	24	95
11	**bpy-PdCl$_2$/2AgNO$_3$**	**CH_3NO_2**	**60**	**24**	**95**
12	bpy-PdCl$_2$	CH_3NO_2	60	24	0

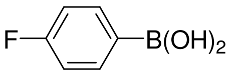
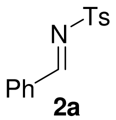
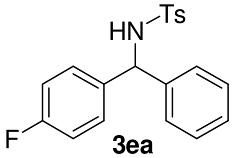
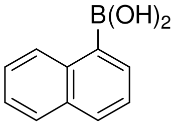
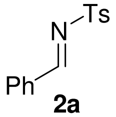
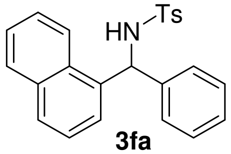
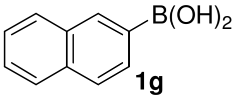
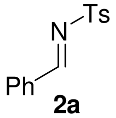
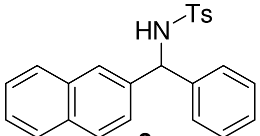
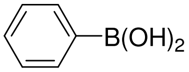
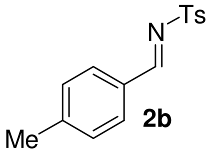
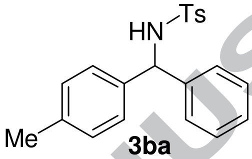
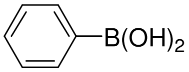
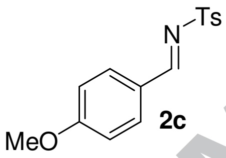
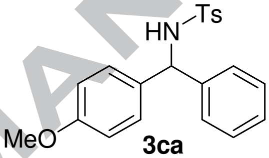
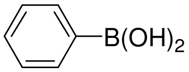
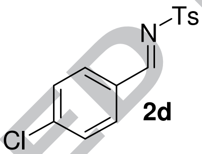
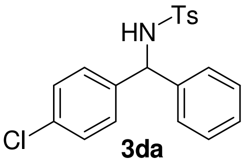
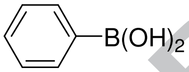
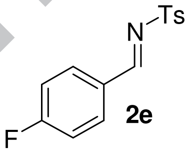
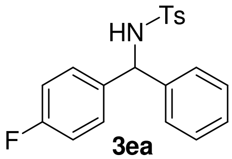
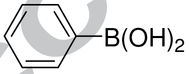
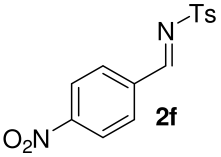
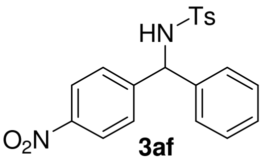
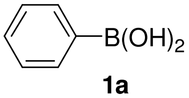
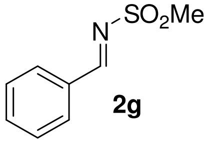
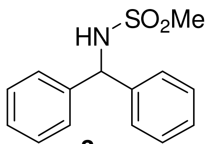
[a] Reaction conditions: *N*-tosylbenzaldimine (1.0 mmol), PhB(OH)$_2$ (2.0 mmol), Pd(II) (0.05 mmol). The optimized conditions highlighted in bold.

[b] Isolated yield.

Table 2. Cationic Pd(II) catalyzed addition of arylboronic acid to N-Sulfonylarylaldimines[a]



Entry	ArB(OH)$_2$	α,β-Unsaturated amide	Product	Time (hrs)	Yield (%)[b]
1	 **1a**	 **2a**	 **3aa**	24	95
2	 **1b**	 **2a**	 **3ba**	24	92
3	 **1c**	 **2a**	 **3ca**	24	95
4	 **1d**	 **2a**	 **3da**	24	92

5	 **1e**	 **2a**	 **3ea**	24	93
6	 **1f**	 **2a**	 **3fa**	48	62
7	 **1g**	 **2a**	 **3ga**	24	90
8	 **1a**	 **2b**	 **3ba**	24	96
9	 **1a**	 **2c**	 **3ca**	24	96
10	 **1a**	 **2d**	 **3da**	24	95
11	 **1a**	 **2e**	 **3ea**	24	95
12	 **1a**	 **2f**	 **3af**	24	93
13	 **1a**	 **2g**	 **3ag**	24	92

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[a] Reaction conditions: *N*-Sulfonylarylaldimines (1.0 mmol), arylboronic acid (2.0 mmol), bpy-$PdCl_2$ (0.05 mmol), $AgNO_3$ (0.10 mmol), CH_3NO_2 4 mL, 60 °C.

[b] Isolated yield.

Acknowledgments

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Supplementary Material

Supplementary data (preparation of substrates, typical experimental procedures, characterization of all products, ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at:

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In-Situ Generated Cationic Pd(II)/Bipyridine-Catalyzed Addition of Arylboronic Acids to *N*-Sulfonyl-Arylaldimines

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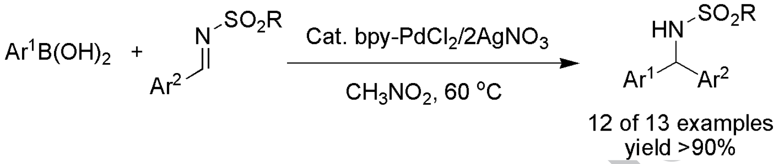
Zhenyu Yang, Yuxin Ni, Rui Liu, Kaixuan Song, Shaohui Lin* and Qinmin Pan*



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In-Situ Generated Cationic Pd(II)/Bipyridine-Catalyzed Addition of Arylboronic Acids to *N*-Sulfonyl-Arylaldimines

Zhenyu Yang, Yuxin Ni, Rui Liu, Kaixuan Song, Shaohui Lin* and Qinmin Pan*

State and Local Joint Engineering Laboratory for Novel Functional Polymeric Materials, Jiangsu Key Laboratory of Advanced Functional Polymer Design and Application, Key Laboratory of Organic Synthesis of Jiangsu Province, Green Polymer and Catalysis Technology Laboratory (GAPCT), College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Ren'ai Road, Suzhou 215123, P. R. China

e-mail: linshaohui@suda.edu.cn

1. Highly reactive cationic Pd(II)-bpy was in-situ generated in CH_3NO_2.
2. High yielded Pd(II)-catalytic addition to arylaldimines was optimized.
3. Air and moisture insensitive Pd(II)-catalysis was developed.
4. 12 of 13 examples yielded >90% and showed high functional groups tolerance.