



Palladium(II)/2,2'-bipyridine-catalyzed addition of arylboronic acids to *N*-tosyl-aryaldimines

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ABSTRACT

A Pd(II)/NO₂-bpy-catalyzed addition of the arylboronic acids to *N*-tosylaldimines to yield diarylmethylamines with moderate to excellent yield was developed. The use of bipyridines as the ligands is crucial in this reaction. The asymmetric version of the reaction also showed that a moderate high yield and ee value can be obtained using the pymox ligands.

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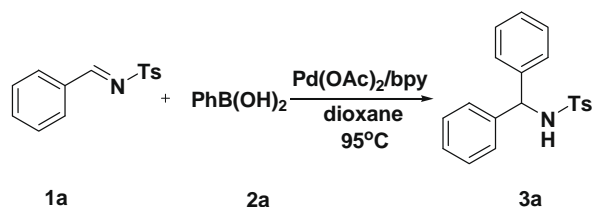
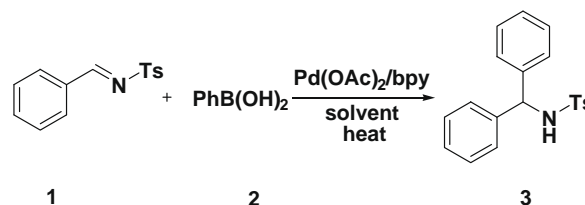
The insertion of carbon–carbon multiple bonds into the carbon–transition–metal bonds is an important fundamental reaction in organotransition–metal chemistry. However, in contrast to the numerous reports about the insertion of carbon–carbon multiple bonds into carbon–transition–metal bonds, direct insertion of the carbon–heteroatom multiple bonds, such as carbonyl, imino, and cyano groups, without using stoichiometric organometallic reagents, has received scant attention.¹ Among these carbon–heteroatom multiple bonds, the addition of the metallic reagents to imines attracts much attention from the chemists because it provides a powerful method to afford useful amines which are important in the biological and pharmaceutical fields.²

However, the difficulties aroused in the addition of imines because of the poor electrophilicity of the azomethine carbon and

the tendency of enolizable imines to undergo deprotonation.³ Recently, some progress has been achieved centered on the catalytic

Table 1

Palladium(II)/bpy-catalyzed reaction of the addition of phenylboronic acid to benzaldimine in different solvents^a



Scheme 1.

Entry	Solvent	T (°C)	Yield ^b (%)
1	Dioxane	95	53
2	THF	Reflux	43
3	DME	Reflux	46
4	DCE	Reflux	36
5	Toluene	Reflux	11
6	Xylene	110	Trace
7	DMSO	110	Trace
8	HMPA	110	31
9	HOAc	110	NR
10	Isopropanol	Reflux	NR


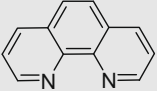
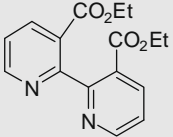
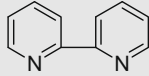
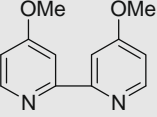
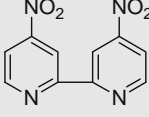
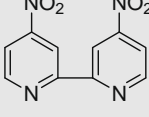
^a Reaction conditions: *N*-tosylbenzaldimine **1** (0.25 mmol), phenylboronic acid **2** (0.5 mmol) in the presence of Pd(OAc)₂ (5 mol %), bpy (20 mol %), and solvent (1 mL) at the temperature for 2 days.

^b Isolated yield.

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Table 2

The ligand effect of the addition of phenylboronic acid to *N*-tosylbenzalimine catalyzed by Pd(II) species^a

Entry	Ligand (equiv of Pd)	Yield ^b (%)
1	None	NR
2		NR
3	(8 equiv) Bu ₄ NCl (4 equiv)	NR
4	 (4 equiv)	Trace
5	 (4 equiv)	Trace
6	 (4 equiv)	53
7	 (4 equiv)	66
8	 (4 equiv)	82
9	 (1.2 equiv)	95

^a Reaction conditions: *N*-tosylbenzalimine **1** (0.25 mmol), phenylboronic acid **2** (0.50 mmol), Pd(OAc)₂ (0.0125 mmol), and ligand in dioxane (1 mL) at 95 °C for 2 days.

^b Isolated yield.

arylation of imines. The most well-known examples are the addition of diphenylzinc to *N*-formylimines,⁴ and the addition of arylstannanes,⁵ aryltitanium,⁶ and arylboron⁷ reagents to *N*-sulfonylimines mediated by rhodium complexes. In palladium chemistry, only few examples have been reported.⁸ The reason may be that the arylpalladium species are more electrophilic and were commonly used in the carbon–carbon coupling reactions or in the reactions with alcohols and amines.⁹ Herein, we wish to report the palladium-catalyzed addition of arylboronic acids to *N*-tosylaldimines in the presence of 2,2'-bipyridine as the ligands.

Our group has recently reported the Pd(II)-catalyzed conjugate addition of arylboronic acid to α,β -unsaturated carbonyl compounds¹⁰ and the addition of arylboronic acids to nitriles.¹¹ We found that the ligand 2,2'-bipyridine (bpy) is crucial in these

reactions. It occurred to us that bpy may be useful in the addition reaction of arylboronic acids to aldimines catalyzed by palladium(II) species.

Initially, we investigated the reaction of *N*-tosyl-benzaldimine (**1**) (0.25 mmol) with phenylboronic acid (**2**) (0.5 mmol) in the presence of Pd(OAc)₂ (5 mol %) and bpy (20 mol %) in dioxane (1 mL) at 95 °C (Scheme 1). To our delight, the reaction proceeded smoothly, yielding the addition product **3** in 53% yield after two days (based on the aldimine **1**) (Scheme 1).

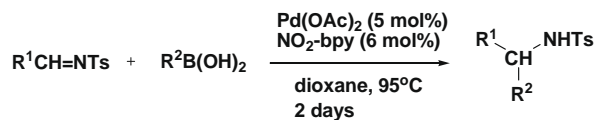
Then, the solvent was screened. It was found that the reaction could also proceed in THF, DME, DCE, and HMPA (Table 1, entries 2–4 and 8), the best result was obtained in dioxane (Table 1, entry 1). Hydrolysis of the imine was the main side reaction, especially in the HOAc, only hydrolysis reaction was observed.

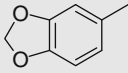
Other phenylboron compounds were tried for this reaction. Arylboronic acid and arylboroxine showed the similar results, but potassium phenyltrifluoroborate gave the lower yield.

Different ligands were surveyed in the reaction. To our surprise, when the 4,4'-dinitro-[2,2']-bipyridine was used as the ligand, the reaction gave the addition product in high yield (82%, Table 2, entry 8). When the ligand decreased to 1.2 equiv based on the palladium, the yield increased to 95% (Table 2, entry 9). In the absence of the ligand, the reaction mixture became black immediately and the aldehyde from the hydrolysis of imine was obtained together with a small amount of the coupling product, diphenyl (Table 2, entry 1). No addition product was obtained when pyridine or Bu₄NCl was used as the ligand (Table 2, entries 2 and 3). Phenanthroline and 2,2'-bipyridinyl-3,3'-dicarboxylic acid diethyl ester only gave trace of the addition products (Table 2, entries 4 and 5). 2,2'-Bipyridine and 4,4'-dimethoxy-2,2'-bipyridine can get the medium yields (Table 2, entries 6 and 7). These results may imply that the ligand plays an important role and is crucial for this reaction. It may stabilize the divalent palladium species and inhibit the coupling reaction of two phenylboronic acids to form the diphenyl.^{10–12} The success of the addition reaction of phenylboronic acid to imines may also imply that the presence of ligand may have the influence to the electrophilicity of the phenylpalladium species.

Table 3

The addition of arylboronic acids to aldimines^a

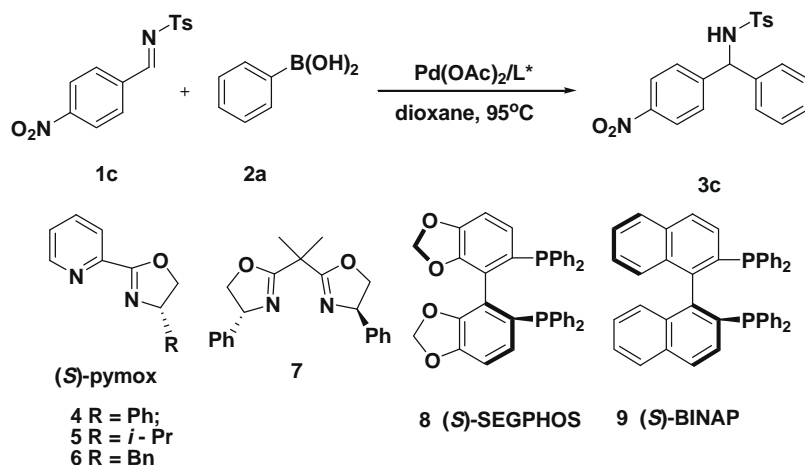


Entry	R ¹	R ²	Yield ^b (%)
1	Ph	Ph	3a (95)
2	4-MeOC ₆ H ₄	Ph	3b (84)
3	4-NO ₂ C ₆ H ₄	Ph	3c (82)
4	4-ClC ₆ H ₄	Ph	3d (82)
5	4-CF ₃ C ₆ H ₄	Ph	3e (75)
6	α -Naphthyl	Ph	3f (69)
7		Ph	3g (71)
8	Ph	4-FC ₆ H ₄	3h (73)
9	Ph	4-MeOC ₆ H ₄	3b (61)
10	Ph	α -Naphthyl	3f (44)
11	Ph	β -Naphthyl	3i (85)

^a Reaction conditions: aldimine (0.25 mmol), arylboronic acids (2 equiv based on the aldimines), Pd(OAc)₂ (0.0125 mmol), and NO₂-bpy (0.015 mmol) in dioxane (1 mL) at 95 °C for 2 days.

^b Isolated yield.

Table 4
Screening of the asymmetric version of the reaction^a



Entry	Pd (5 mol %)	L* (6 mol %)	T (days)	Yield ^b (%)	ee ^c (%)
1	Pd(OAc) ₂	5	1	16	87
2	Pd(OAc) ₂	5	4	58	87
3	Pd(CF ₃ CO ₂) ₂	5	4	71	85
4	Pd(OAc) ₂	6	4	56	79
5	Pd(OAc) ₂	4	4	51	53
6	Pd(OAc) ₂	7	4	NR	/
7	Pd(CF ₃ CO ₂) ₂	8	4	NR	/
8	Pd(CF ₃ CO ₂) ₂	9	4	NR	/

^a Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), in dioxane (1 mL), 95 °C.

^b Isolated yields.

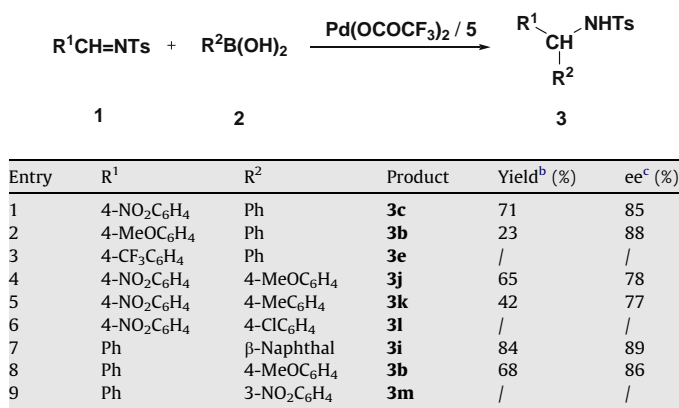
^c Determined by HPLC analysis using a Chiralcel column.

With the optimized condition in hand, the addition of arylboronic acids to different kinds of aldimines was studied. The results are shown in Table 3. It is shown that in aromatic aldimines with both electron-rich and electron-deficient substituents, the addition of arylboronic acids can proceed in high yields. Also there was no large difference in yields between the arylboronic acids with electron-rich and electron-deficient substituents.

Subsequently, the asymmetric version of this reaction was studied. First, we screened some homochiral nitrogen-containing and diphosphine ligands instead of the NO₂-bpy as shown in Table 4. We initially employed the easily available monooxazoline (pymox) and bisoxazoline as ligands. When using the pymox instead of the NO₂-bpy, the reaction can proceed smoothly but the reaction time prolongs to 4 days (Table 4, entry 2), especially, when using the Pd(CF₃CO₂)₂ instead of Pd(OAc)₂, the best result was obtained (Table 4, entry 3). It was also found that the different substituents on the oxazoline ring significantly affected the enantioselectivity of the reaction (Table 4, entries 3–5). While using bisoxazoline and diphosphines as the ligand, no addition product was formed (Table 4, entries 6–8).

On the basis of the optimization of the reaction conditions, the scope of this reaction with various aryl-substituted imines and boronic acids was explored. The combination between the electronic properties of *N*-tosylaldimines and arylboronic acids is very important. *N*-Tosylaldimines with strong electron-withdrawing groups and the arylboronic acids with electron-donating groups are useful for this reaction (Table 5, entries 1, 4–5, and 7–8). *N*-Tosylaldimines with electron-donating groups and the arylboronic acids with electron-withdrawing groups are not so efficient in our reaction (Table 5, entries 2, 6, and 9). The only exception is 4-trifluorobenzaldehyde which showed no reaction in our conditions (Table 5, entry 3).

Table 5
Asymmetric addition of arylboronic acids to *N*-tosylaldimines^a



^a Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), Pd(CF₃CO₂)₂ (5 mol %), and **5** (6 mol %) in dioxane (1 mL), 95 °C, 4 days.

^b Isolated yields.

^c Determined by HPLC analysis using a Chiralcel column.

In conclusion, we developed a Pd(II)/NO₂-bpy-catalyzed addition of the arylboronic acids to *N*-tosylaldimines to yield diarylmethylamines with moderate to excellent yield. The use of bipyridines as the ligands was crucial in this reaction. We also found that this reaction could be influenced by the steric and electronic properties of the ligands. The asymmetric version of the reaction also showed that a moderate high yield and ee value can be obtained using the pymox ligands.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedure, characterization data, copies of ^1H and ^{13}C NMR spectra for new compounds, and copies of HPLC data for ee value determination are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.005.

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