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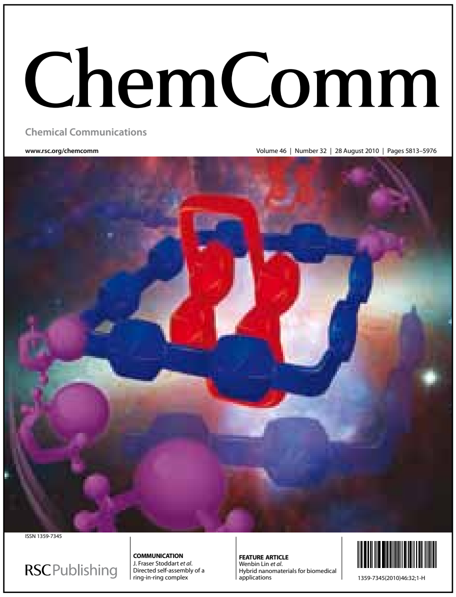

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Communication

Palladium-catalyzed Suzuki cross-coupling of *N*'-tosyl arylhydrazines†

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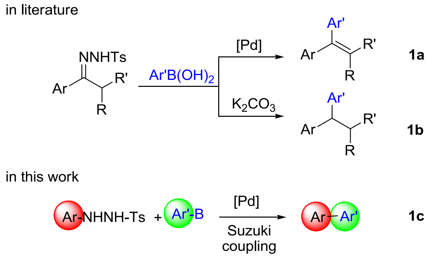
The first palladium-catalyzed Suzuki cross-coupling of *N*'-tosyl arylhydrazines with various organoboron reagents has been developed for the preparation of biaryl compounds in high yields. *N*'-tosyl arylhydrazine as a readily available and stable electrophile also demonstrated its generality in a number of coupling reactions.

The transition-metal-catalyzed cross-coupling reactions are among the most powerful methods for the formation of carbon-carbon and carbon-heteroatom bonds.[1] Although aryl halides and triflates are the most commonly employed electrophilic partners, broadening the scope of electrophiles would be significant to practitioners of chemical synthesis. Carbon-nitrogen compounds may be another candidate of electrophilic components, for example, aryl diazonium salt,[2] aryltrimethylammonium salt[3] and aryltriazene[4] have been utilized in some cross-coupling reactions. However, aryl diazonium salts are often dangerously explosive and prone to decomposition upon storage. The use of highly corrosive $BF_3·OEt_2$[4] or some strong protic acids[5] to activate aryltriazenes and the unavailability of aryltrimethylammonium salts have also respectively restrict their general uses.

The recent development of metal-catalyzed cross-coupling reaction using tosylhydrazone as coupling partner has attracted renewed interest in this reagent (Scheme **1a**).[6] Moreover, Barluenga *et al*. reported a new C–C bond-forming reaction between tosylhydrazones and boronic acids via a metal-free reductive coupling procedure (Scheme **1b**).[7] However, the commonly used tosylhydrazones made this methodology only suitable for the synthesis of polysubstituted olefins and diarylalkanes. Inspired by these pioneering work, we speculated that *N*'-tosyl arylhydrazine (another safe and effective source of active diazo compounds), which can be easily prepared from arylhydrazine and TsCl under mild condition,[8] might also be utilized as proper electrophile in cross-coupling reactions to form aryl-aryl bonds. Herein, we reported the first Suzuki reaction of *N*'-tosyl arylhydrazines with various organoboron reagents (Scheme **1c**). This new methodology may be used as a complement for the classical Suzuki cross-coupling reaction.

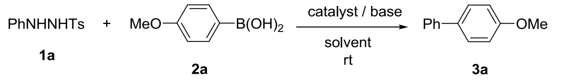
At first, *N*'-tosyl arylhydrazine **1a** and 4-methoxyphenyl boronic acid **2a** were chosen as substrates for the model reaction. Various conditions were screened and the results were summarized in Table 1. When $Pd(OAc)_2$ was used as the palladium source and K_2CO_3 as the base, we were pleased to find that the reaction proceeded smoothly to offer the desired product **3a** in 56% yield in DMSO at room temperature (Table 1, entry 1). Encouraged by this result, more Pd-catalysts and bases were examined. However, none of them was more efficient than the combination of $Pd(OAc)_2/K_2CO_3$ for this reaction (entries 2-9). Moreover, we observed a significant solvent effect in this process (entries 9-15). Although DMSO and MeOH showed comparable results, we adopted MeOH as the optimal solvent for its simplification on the separation of the product. Higher temperature was advantageous for this reaction, and the coupling product **3a** could be obtained in 83% yield in 60 °C (entry 16 versus 12). The amount of Pd-catalyst can even be decreased to 2 mol% without compromising the yield (entry 18 versus 16). Palladium catalyst is necessary for the cross-coupling and no product was observed in the absence of any Pd-catalyst (entry 19).



Scheme 1 a) Palladium-catalyzed cross-coupling of tosylhydrazones with arylboronic acids; **b)** Metal-free reductive coupling of tosylhydrazones with arylboronic acids; **c)** Pd-catalyzed cross-coupling of *N*'-tosyl arylhydrazines with organoboron reagents discussed in this work. Ts = tosyl.

Then the scope of the Pd-catalyzed Suzuki cross-coupling of *N*'-tosyl arylhydrazines with aryl boronic acids was investigated (Table 2). 4-Methoxyphenylboronic acid **2a** can react with various *N*'-tosyl arylhydrazines to afford the corresponding products in good to excellent yields (Table 2, entries 1-8). *N*'-Tosyl arylhydrazines with both electron-donating and electron-withdrawing groups attached to the aromatic ring were all good partners in this transformation. For example, *N*'-tosyl *p*-tolylhydrazine **1b** reacted with **2a** to provide the coupling biaryl product in 85% yield (entry 2). Good yield (78%) could also be obtained for *N*'-tosyl 4-nitrophenylhydrazine **1h** (entry 8). In addition, **1d** with *ortho*-methyl substituent at aryl moiety also participated in the desired cross-coupling process (entry 4). Besides **2a**, other substituted aryl boronic acids **2b-e** were all effective in this kind of reaction and high yields of products were observed (entries 9-15). Heteroaryl-substituted (entry 13) and halogen-substituted boronic acids (entries 12 and 14) were also tolerant in this reaction and showed good yields.

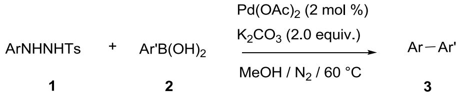
Table 1 Influence of reaction conditions in Suzuki reaction of **1a** with **2a**.[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	$Pd(OAc)_2/K_2CO_3$	DMSO	56
2	$PdCl_2/K_2CO_3$	DMSO	54
3	$PdCl_2(PPh_3)_2/K_2CO_3$	DMSO	43
4	$Pd (PPh_3)_4/K_2CO_3$	DMSO	40
5	$Pd(OAc)_2/KF$	DMSO	50
6	$Pd(OAc)_2/K_3PO_4$	DMSO	44
7	$Pd(OAc)_2/KOAc$	DMSO	40
8	$Pd(OAc)_2/Na_2CO_3$	DMSO	41
9	$Pd(OAc)_2/Et_3N$	DMSO	40
10	$Pd(OAc)_2/K_2CO_3$	DMF	50
11	$Pd(OAc)_2/K_2CO_3$	MeCN	30
12	$Pd(OAc)_2/K_2CO_3$	MeOH	57
13	$Pd(OAc)_2/K_2CO_3$	THF	trace
14	$Pd(OAc)_2/K_2CO_3$	DME	trace
15	$Pd(OAc)_2/K_2CO_3$	toluene	36
16[c]	$Pd(OAc)_2/K_2CO_3$	MeOH	83
17[c,d]	$Pd(OAc)_2/K_2CO_3$	MeOH	80
18[c,e]	**$Pd(OAc)_2/K_2CO_3$**	**MeOH**	**84**
19[c,f]	$Pd(OAc)_2/K_2CO_3$	MeOH	75
20[c]	K_2CO_3	MeOH	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Pd catalyst (5 mol %), base (2.0 equiv.), solvent (2 mL), rt, 4-24 h, under N_2. [b] Isolated yields. [c] 60 °C. [d] Pd catalyst (10 mol %). [e] Pd catalyst (2 mol %). [f] Pd catalyst (1 mol %).

Table 2 Suzuki reaction of *N*'-tosyl arylhydrazines with arylboronic acids.



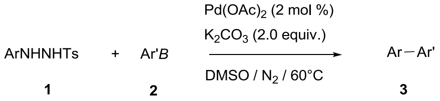
$$\underset{\mathbf{1}}{\text{ArNHNHTs}} + \underset{\mathbf{2}}{\text{Ar'B(OH)}_2} \xrightarrow[\text{MeOH / N}_2\text{ / 60 °C}]{\text{Pd(OAc)}_2\text{ (2 mol \%)},\ \text{K}_2\text{CO}_3\text{ (2.0 equiv.)}} \underset{\mathbf{3}}{\text{Ar}-\text{Ar'}}$$

Entry	Ar =	Ar'=	Yield (%)[b]
1	phenyl (**1a**)	4-methoxyphenyl (**2a**)	84
2	4-methylphenyl (**1b**)	4-methoxyphenyl (**2a**)	85
3	4-methoxyphenyl (**1c**)	4-methoxyphenyl (**2a**)	75
4	2-methylphenyl (**1d**)	4-methoxyphenyl (**2a**)	82
5	4-(trifluoromethoxy)phenyl (**1e**)	4-methoxyphenyl (**2a**)	86
6	4-chlorophenyl (**1f**)	4-methoxyphenyl (**2a**)	83
7	3-chlorophenyl (**1g**)	4-methoxyphenyl (**2a**)	80
8	4-nitrophenyl (**1h**)	4-methoxyphenyl (**2a**)	78
9	phenyl (**1a**)	phenyl (**2b**)	92
10	4-methylphenyl (**1b**)	4-methylphenyl (**2c**)	93
11	4-methoxyphenyl (**1c**)	phenyl (**2b**)	76
12	4-methoxyphenyl (**1c**)	3-chlorophenyl(**2d**)	70
13	4-methoxyphenyl (**1c**)	2-naphthyl (**2e**)	71
14	3-chlorophenyl (**1g**)	3-chlorophenyl (**2d**)	80
15	4-nitrophenyl (**1h**)	4-methylphenyl (**2c**)	79

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (2 mol %), K_2CO_3 (2.0 equiv.), MeOH (2 mL), 60 °C, 2-12 h, under N_2. [b] Isolated yields.

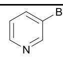
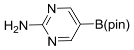
Besides aryl boronic acid, arylborane and boronic ester were also tolerated in this reaction although the solvent need to be re-optimized. When diethyl (3-pyridyl)borane **2f** was employed, no desired product was detected in MeOH while high yield of biaryl product was observed in DMSO (Table 3, entry 1). So we carried out the Suzuki reaction of those organoboron reagents in DMSO at 60 °C. A wide range of *N*'-tosyl arylhydrazines that incorporates electron-donating and electron-withdrawing groups at *ortho*-, *meta*-, and *para*-positions were found to be efficient for this Suzuki reaction (Table 3, entries 1-8). For *ortho*-substituted *N*'-tosyl arylhydrazines, larger amount of Pd-catalyst was needed due to the larger steric hindrance of the substrates (entries 5-6). Boronic ester with an amino-group **2g** also offered the corresponding products in 85% and 81% yield respectively (entries 9-10). We have also tried this reaction with *N*'-tosyl benzylhydrazine and *N*'-tosyl isopropylhydrazine under similar conditions, but observed few cross-coupling products. We attributed this to the low stability of alkyl intermediate.

Table 3 Suzuki reaction of *N*'-tosyl arylhydrazines with alkylborane or boronic ester.



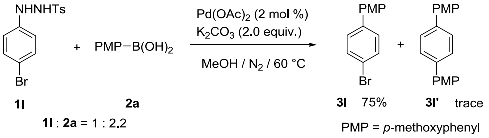
$$\underset{\mathbf{1}}{\text{ArNHNHTs}} + \underset{\mathbf{2}}{\text{Ar'}B} \xrightarrow[\text{DMSO / N}_2\text{ / 60°C}]{\text{Pd(OAc)}_2\text{ (2 mol \%)},\ \text{K}_2\text{CO}_3\text{ (2.0 equiv.)}} \underset{\mathbf{3}}{\text{Ar}-\text{Ar'}}$$

B = BEt_2 or B(pin)

Entry	Ar =	Ar'*B*=	Yield (%)[b]
1	phenyl (**1a**)	 (**2f**)	85
2	4-methylphenyl (**1b**)	**2f**	74
3	3-methylphenyl (**1i**)	**2f**	70
4	4-methoxyphenyl (**1c**)	**2f**	68
5[c]	2-methylphenyl (**1j**)	**2f**	55
6[c]	2-methoxyphenyl (**1k**)	**2f**	64
7	4-chlorophenyl (**1f**)	**2f**	76
8	3-chlorophenyl (**1g**)	**2f**	73
9	phenyl (**1a**)	 (**2g**)	85
10	4-methylphenyl (**1b**)	**2g**	81

[a] Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (2 mol %), K_2CO_3 (2.0 equiv.), DMSO (1 mL), 60 °C, 2-6 h, under N_2. [b] Isolated yields. [c] $Pd(OAc)_2$ (5 mol %).

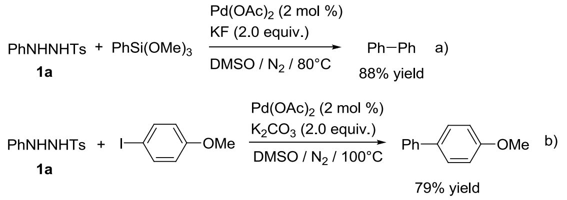
For the palladium catalyzed coupling reaction of bromo-substituted *N*'-tosyl arylhydrazine, a significant chemoselectivity can be observed. For example, **1l** reacted with **2a** to afford **3l** as the major product (Scheme **2**). Here the regioselectivity comes both from the basic condition for *N*'-tosyl arylhydrazine coupling unlike that for halide coupling, and from different Ar-X bond strengths.[2] Compared with aryl bromide, *N*'-tosyl arylhydrazines proved to be more efficient and milder electrophile under the aforementioned reaction conditions. This chemoselectivity may be used for the synthesis of some multi-aryl compounds by stepwise cross-coupling of *N*'-tosyl arylhydrazine and halide.



Scheme 2 Suzuki reaction of *N*'-tosyl arylhydrazine **1l** with arylboronic acid **2a**.

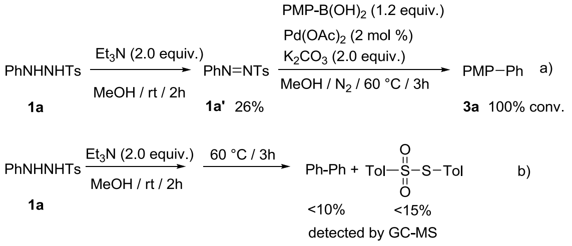
As *N*'-tosyl arylhydrazine is readily available and stable reagent, we also explored whether this substrate could be extended to some other coupling reactions. When *N*'-tosyl phenylhydrazine **1a** was employed in the Hiyama coupling of arylsilane,[9] the biphenyl product could be obtained in 88% yield (Scheme **3a**). *N*'-tosyl arylhydrazine also works well for the coupling reaction with aryl halide, for example, **1a** can react with aryl iodide to produce 4-methoxybiphenyl in 79% yield (Scheme **3b**). Further laboratory studies will be conducted to elucidate its generality in these new coupling reactions.

To explore the mechanism of this Suzuki reaction, we carried out two control experiments. In the first reaction, 1-phenyl-2-tosyldiazene **1a'** could be isolated in 26% yield from *N*'-tosyl phenylhydrazine **1a** under basic conditions, and the direct cross-coupling reaction between **1a'** and 4-methoxyphenylboronic acid



Scheme 3 a) Hiyama reaction of *N*'-tosyl phenylhydrazine with arylsilane. **b)** Cross-coupling of *N*'-tosyl phenylhydrazine with aryl iodide

also afforded 4-methoxybiphenyl **3a** in 100% conversion (Scheme **4a**). In the absence of any palladium catalyst and aryl boronic acid, the *in situ* generated diazene **1a'** would presumably dissociate to give $C_6H_5N_2\cdot$ radical and $TolSO_2\cdot$ radical, the former may release nitrogen and form diphenyl compound, while the latter yields the thiosulfonate (Scheme **4b**).[10a]



Scheme 4 Control experiments. PMP = *p*-methoxyphenyl, Ts = tolylsulfinate, Tol = tolyl.

Based on these experiments, a possible mechanism for this hydrazine Suzuki reaction has been proposed (Figure **1**). *N*'-tosyl arylhydrazine **A** was dehydrogenated in the presence of base to provide the diazene **B**, which was in equilibrium with the corresponding diazonium ion.[10] Then an oxidative addition of diazonium ion to Pd-catalyst gave the organopalladium intermediate **C**, which promoted the transmetallation of the arylboronic acid to form the diaryl-palladium species **D**. Finally a reductive elimination of **D** afforded the corresponding biaryl product **E** and regenerated the Pd-catalyst.

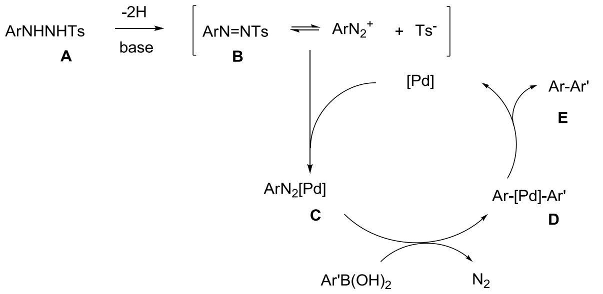


Figure 1 Proposed mechanism for the Suzuki cross-coupling of *N*'-tosyl arylhydrazines with arylboronic acid

In summary, we have described a new procedure for the preparation of biaryl compounds by Pd-catalyzed Suzuki cross-coupling between *N*'-tosyl arylhydrazine and various organoboron reagents. Notably, *N*'-tosyl arylhydrazine as a readily available and stable electrophile demonstrated its generality in a number of coupling reactions. This new methodology can be used as a complement for the classical Suzuki cross-coupling reaction.

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra]. See DOI: 10.1039/b000000x/

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