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Communication

Palladium-catalyzed Suzuki cross-couplings of *N*'-mesyl arylhydrazines via C–N bond cleavage†

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An efficient palladium-catalyzed Suzuki cross-coupling reaction of *N*'-mesyl arylhydrazine with aryl boronic acid is described, which affords the corresponding biaryl compounds in high yields. This transformation proceeds through C–N bond cleavage under mild conditions.

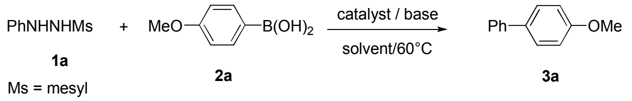
Substituted biaryls are important structural motifs because of their presence in many natural products pharmaceuticals, agrochemicals, and functional materials.[1] Thus, the development of new and efficient methods for synthesizing these structures is crucial to the work of organic chemistry, and several useful reactions have been developed during the last century.[2]

Transition-metal-catalyzed cross-coupling reactions are among the most powerful methods for the formation of (hetero)aryl–aryl bond.[3] The Suzuki cross-coupling is, unarguably, of the greatest practical importance of these methods.[4] Although aryl halides and pseudo-halides are the most commonly employed electrophilic partners, broadening the scope of electrophiles would be significant to practitioners of chemical synthesis. In recent years, metal-catalyzed cross-coupling reaction via C–N bond cleavage of arylhydrazine has attracted renewed interest in this reagent.[5] This strategy utilizing arylhydrazine as arylating reagent has provided powerful methods for constructing biaryls[5a] and aryl substituted olefins,[5b] indoles,[5c] ketones[5d] and glycals[5e]. Very recently, we developed a novel palladium-catalyzed Suzuki cross-coupling of *N'*-tosyl arylhydrazine, which also demonstrated its generality as a readily available and efficient coupling partner in a number of coupling reactions.[6]

Meanwhile, in view of the deficient atom-economy of *N*'-tosyl arylhydrazines as arylating reagents in the coupling procedure, to pursue other more economic and efficient coupling partners is necessary. *N*'-Mesyl arylhydrazines are relatively unreactive but atom-economic compared to the corresponding *N*'-tosyl arylhydrazines counterparts. However, to the best of our knowledge, no reports have appeared for the cross-coupling of *N*'-mesyl arylhydrazines with arylboronic acids. In this paper, as a continuation of our ongoing study on novel and green coupling processes,[6,7] we investigated whether or not the Suzuki reaction could be carried out by employing *N*'-mesyl arylhydrazines via C–N bond cleavage.

To verify our hypothesis, a set of experiments were carried out using *N*'-mesyl phenylhydrazine **1a** and 4-methoxyphenyl boronic acid **2a** as model substrates. Various conditions were screened and the results were summarized in Table 1. When 5 mol % of $Pd(OAc)_2$ was used as the palladium source and K_2CO_3 (2.0 equiv) as the base, the reaction of **1a** with **2a** proceeded smoothly, and 73% yield of product **3a** was achieved in MeOH at 60 °C (Table 1, entry 1). Encouraged by this result, we examined more Pd catalysts and found that $PdCl_2(PPh_3)_2$ was the best Pd source, affording 94% yield of the desired product **3a** (Table 1, entry 3). Various bases were then screened for this reaction. However, none of them was more efficient than K_2CO_3 (Table 1, entries 5–9). Other solvents, such as EtOH, H_2O, DMSO, toluene and THF, were also investigated; however, moderate yields were obtained (Table 1, entries 10–14). In addition, the reaction temperature was examined and the results showed that 60 °C was the best choice (Table 1, entry 3 *versus* 15 and 16). Increasing the amount of Pd catalyst loading to 10 mol % resulted in a comparable yield (Table 1, entry 17 *versus* 3). However, a significant drop in yield was observed when 2 mol% of $PdCl_2(PPh_3)_2$ was used (Table 1, entry 18). Palladium catalyst is necessary for the cross-coupling and no product was observed in the absence of any Pd-catalyst (Table 1, entry 19).

Table 1 Influence of the reaction conditions in Suzuki cross-coupling of *N*'-mesyl phenylhydrazine **1a** with 4-methoxyphenyl boronic acid **2a**.[a]



Entry	Catalyst/Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2/K_2CO_3$	MeOH	73
2	$PdCl_2/K_2CO_3$	MeOH	60
3	$\mathbf{PdCl_2(PPh_3)_2/K_2CO_3}$	MeOH	**94**
4	$PdCl_2(PhCN)_2/K_2CO_3$	MeOH	61
5	$PdCl_2(PPh_3)_2/\ Na_2CO_3$	MeOH	70
6	$PdCl_2(PPh_3)_2/K_3PO_4$	MeOH	54
7	$PdCl_2(PPh_3)_2/KF$	MeOH	50
8	$PdCl_2(PPh_3)_2/KOAc$	MeOH	45
9	$PdCl_2(PPh_3)_2/Et_3N$	MeOH	68
10	$PdCl_2(PPh_3)_2/K_2CO_3$	EtOH	75
11	$PdCl_2(PPh_3)_2/K_2CO_3$	H_2O	37
12	$PdCl_2(PPh_3)_2/K_2CO_3$	DMSO	55
13	$PdCl_2(PPh_3)_2/K_2CO_3$	PhMe	48
14	$PdCl_2(PPh_3)_2/K_2CO_3$	THF	35
15[c]	$PdCl_2(PPh_3)_2/K_2CO_3$	MeOH	79
16[d]	$PdCl_2(PPh_3)_2/K_2CO_3$	MeOH	58
17[e]	$PdCl_2(PPh_3)_2/K_2CO_3$	MeOH	87

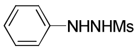
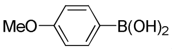
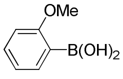
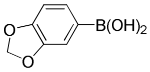
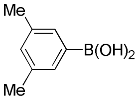
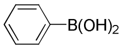
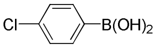
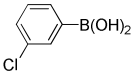
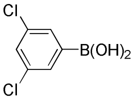
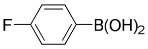
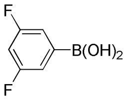
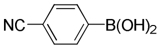
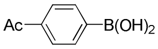
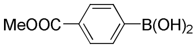
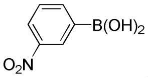
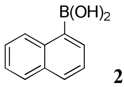
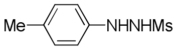
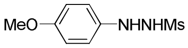
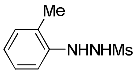
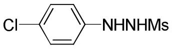
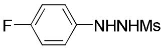
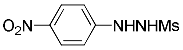
18[f]	$PdCl_2(PPh_3)_2/K_2CO_3$	MeOH	63
19	$-/K_2CO_3$	MeOH	trace

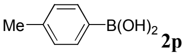
[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.36 mmol), Pd catalyst (5 mol %), base (2.0 equiv.), solvent (2 mL), 60°C, 4-8 h, under air. [b] Isolated yields. [c] at 80 °C. [d] at room temperature. [e] Pd catalyst (10 mol %). [f] Pd catalyst (2 mol %).

Then the scope of the Pd-catalyzed Suzuki cross-coupling of *N*'-mesyl arylhydrazines with aryl boronic acids was investigated (Table 2). For all cases, *N*'-mesyl arylhydrazines reacted with arylboronic acid **2** leading to the corresponding products **3** in good to excellent yields. Arylboronic acids with both electron-donating and electron-withdrawing groups attached to the aromatic ring were all good partners in this transformation. For example, *N*'-mesyl phenylhydrazines **1a** reacted with **2e** to provide the cross-coupling biaryl product in excellent yield (Table 2, entry 5). High yields could also be obtained for arylboronic acids **2c** and **2d** (Table 2, entries 3 and 4). In addition, **2b** with *ortho*-substituent at aryl moiety also participated in the desired cross-coupling process, and slightly lower yield was obtained for its larger steric hindrance of methoxy substituent (Table 2, entry 2). Halogen substituents on phenyl rings (Table 2, entries 6-10) were observed to be tolerant in this reaction, indicating good chemoselectivity in contrast to the traditional Suzuki cross-coupling of aryl chloride and aryl fluoride. Arylboronic acids **2k-n** with electron-withdrawing groups attached to the aromatic ring all could participate in the desired cross-coupling process smoothly (Table 2, entries 11-14). Not only aryl- but also heteroarylboronic acid gave high yield (Table 2, entry 15). Besides **1a**, other substituted *N*'-mesyl arylhydrazines **1b-g** were all effective in this kind of reaction (Table 2, entries 16-22). For instance, *N*'-mesyl arylhydrazines **1b** and **1c** with electron-donating groups could be employed in the coupling reaction in good yields (Table 2, entries 16, 17 and 22). Interestingly, 83% yield could be obtained with **1d** even for its large steric hindrance of *ortho*-methyl substituent (Table 2, entry 18).

Table 2 Pd-catalyzed Suzuki cross-coupling of *N*'-mesyl arylhydrazines with arylboronic acids.[a]

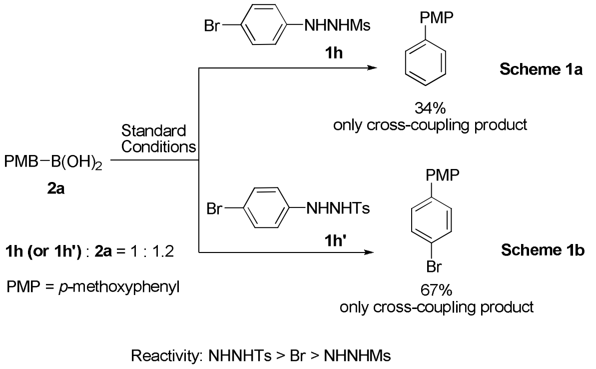
$$\underset{\mathbf{1}}{\text{ArNHNHMs}} + \underset{\mathbf{2}}{\text{Ar'B(OH)}_2} \xrightarrow[\text{MeOH/60°C}]{\text{PdCl}_2(\text{PPh}_3)_2/\text{K}_2\text{CO}_3} \underset{\mathbf{3}}{\text{Ar}-\text{Ar'}}$$

Entry	1	2	Yield (%)[b]
1	 **1a**	 **2a**	94
2	**1a**	 **2b**	65
3	**1a**	 **2c**	70
4	**1a**	 **2d**	76
5	**1a**	 **2e**	95
6	**1a**	 **2f**	88
7	**1a**	 **2g**	76
8	**1a**	 **2h**	75
9	**1a**	 **2i**	94
10	**1a**	 **2j**	80
11	**1a**	 **2k**	72
12	**1a**	 **2l**	73
13	**1a**	 **2m**	65
14	**1a**	 **2n**	77
15	**1a**	 **2o**	69
16	 **1b**	**2a**	85
17	 **1c**	**2a**	92
18	 **1d**	**2a**	83
19	 **1e**	**2a**	70
20	 **1f**	**2a**	76
21	 **1g**	**2a**	71

22	**1c**	 **2p**	76

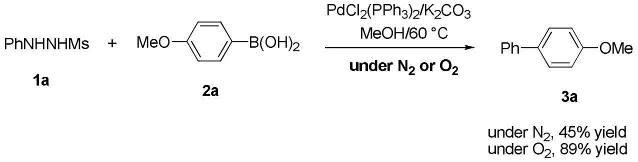
[a] Reaction conditions: **1** (0.30 mmol), **2** (0.36 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), K_2CO_3 (2.0 equiv.), MeOH (2 mL), 60 °C, 4-8 h, under air. [b] Isolated yields.

In our previous work, compared with aryl bromide, *N*'-tosyl arylhydrazines proved to be more efficient and milder electrophiles (Scheme 1b).[6a] Interestingly, for the palladium-catalyzed coupling reaction of bromo-substituted *N*'-mesyl arylhydrazines, a novel chemoselectivity could be observed, and the unexpected 4-methoxybiphenyl was obtained as the only cross-coupling product (Scheme 1a). From the two experiments, we can find that the series of aforementioned electrophiles in decreasing order of reactivity is: *N*'-tosyl arylhydrazine>aryl bromide>*N*'-mesyl arylhydrazine. This practical chemoselectivity can be used for the synthesis of some multi-aryl compounds by stepwise cross-coupling of *N*'-sulfonyl arylhydrazines and halides.



Scheme 1 Suzuki reactions of *N*'-sulfonyl arylhydrazine **1h** and **1h'** with arylboronic acid **2a**.

To explore the mechanism of this Suzuki reaction, we carried out two control experiments (Scheme 2). Compared with the standard conditions, a comparable yield was obtained under O_2 atmosphere, but a significant drop in yield was observed under N_2 atmosphere. From these results, it seems that the oxygen might play an important role as an oxidant in the coupling process.



Scheme 2 Control experiments.

Based on these results and the research findings from other groups, a possible mechanism for this Suzuki reaction via C–N bond cleavage has been proposed (Figure **1**).[6,8] Firstly, *N*'-mesyl arylhydrazine **A** was dehydrogenated in the presence of base and Pd(II)-catalyst to provide the aryl diazonium ion **B**, accompany with the *in situ* generation of Pd(0) active species. Then oxidative addition of diazonium ions to the Pd(0) gave the organopalladium intermediate **C**, which promoted the transmetallation of the arylboronic acid to form the diaryl-palladium species **D**. Finally reductive elimination of **D** afforded the corresponding biaryl product **E** and gave the Pd(0). Meanwhile, oxygen in the air regenerated the Pd(II)-catalyst.

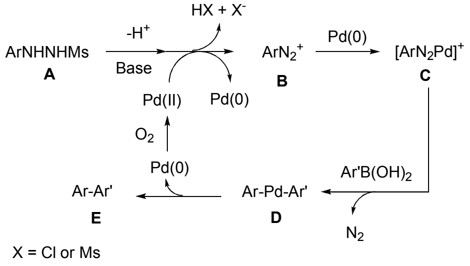


Figure 1 Proposed mechanism for the Suzuki cross-coupling of *N*'-mesyl arylhydrazine with aryl boronic acid.

In summary, we have described a novel C-N bond cleavage for the preparation of biaryl compounds by Pd-catalyzed Suzuki cross-coupling between *N*'-mesyl arylhydrazine and aryl boronic acid. Notably, *N*'-sulfonyl arylhydrazine as a readily available and stable electrophile demonstrated its significant chemo-selectivity in the Suzuki cross-coupling reaction. Efforts are underway to extend the scope of the reaction of *N*'-sulfonyl arylhydrazine.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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