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Palladium-catalyzed reductive homocoupling of *N*′-tosyl arylhydrazines†

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A novel procedure for the preparation of biaryl compounds by Pd-catalyzed homocoupling of *N*′-tosyl arylhydrazine has been described. *N*′-Tosyl arylhydrazine, as a readily available and stable coupling partner, demonstrated its generality in the homocoupling reactions. The scope of the reaction and possible mechanism have also been investigated.

The aryl–aryl bond-forming reaction is an important transformation in synthetic organic chemistry because the biaryl unit is found in a large number of natural products, pharmaceuticals, biologically significant agrochemicals, and conducting polymers.[1] Numerous studies have been carried out, and several efficient reactions for the synthesis of biaryls have been developed during the last century.[2] Symmetrical biaryls have traditionally been prepared through copper-mediated Ullmann reductive homocoupling of aryl halides,[3] but its requirement of high temperature has spawned the recent development of milder palladium-[4] and nickel-[5] mediated reductive homocouplings. The latter reactions have already provided powerful access to synthetic biaryls despite excess external reducing reagents (a hydrogen donor and/or an electron source) usually being needed to regenerate the Pd(0) active species.

In recent years, considerable attention has been focused on the transition metal-catalyzed cross-coupling reactions that utilize arenediazonium salts as aryl electrophilic components.[6] However, metal-catalyzed routes to symmetrical biaryls from arenediazonium salts have not received much attention, although stoichiometric cupric[7a] or ferrous salt[7b]-promoted methods have been introduced. Furthermore, Hanna *et al.* reported palladium-catalyzed homocoupling of arenediazonium salts for the synthesis of symmetrical biaryls; however, a significant amount of by-products complicated the purification process.[8] Notably, aryl diazonium salts are dangerously explosive and prone to decomposition upon storage. To expand this substrate scope, and more importantly, to make this novel coupling reaction practically useful in organic synthesis, other sources that can generate nonstabilized diazo compounds *in situ* have attracted our attention. *N*′-Tosyl arylhydrazine has been considered as another safe and effective source of active diazo compound in a Suzuki cross-coupling reaction (Scheme 1a).[9] In this paper, as part of our ongoing study on palladium-catalyzed cross-coupling processes, we report the symmetrical aryl–aryl bond formation *via* homocoupling of *N*′-tosyl arylhydrazine under mild conditions (Scheme 1b).

First, *N*′-tosyl phenylhydrazine **1a** derived from phenylhydrazine was selected as the model substrate for the reaction condition screening. The results are summarized in Table 1. When $Pd(OAc)_2$ was used as the palladium source and K_2CO_3 as the base, the reaction of **1a** proceeded smoothly, and 58% yield of product **2a** was achieved in DMSO at room temperature (Table 1, entry 1). Encouraged by this result, we examined more Pd catalysts and found that $PdCl_2$ was the best Pd source, affording 91% yield of the desired product **2a** (Table 1, entry 4). Various bases were then screened for this reaction. However, none of them was more efficient than K_2CO_3 (Table 1, entries 4–10). Other solvents, such as MeOH, dioxane and toluene, were also investigated; however, moderate yields were obtained (Table 1, entries 11–13). Increasing the amount of Pd catalyst loading to 5 mol% resulted in a comparable

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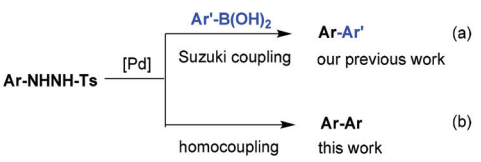
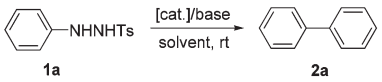


Scheme 1 (a) Suzuki cross-coupling reaction of *N*′-tosyl arylhydrazine; (b) Homocoupling of *N*′-tosyl arylhydrazine.

Table 1 Influences of the reaction conditions in the homocoupling of *N*′-tosyl phenylhydrazine **1a**[a]



1a **2a**

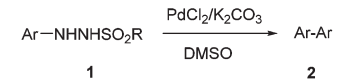
Entry	[Cat.]/base	Solvent	Yield[b] [%]
1	$Pd(OAc)_2/K_2CO_3$	DMSO	58
2	$Pd(PPh_3)_4/K_2CO_3$	DMSO	52
3	$PdCl_2(PPh_3)_2/K_2CO_3$	DMSO	45
4	**$PdCl_2/K_2CO_3$**	**DMSO**	**91**
5	$PdCl_2/Na_2CO_3$	DMSO	70
6	$PdCl_2/K_3PO_4$	DMSO	58
7	$PdCl_2$/KOH	DMSO	35
8	$PdCl_2/Et_3N$	DMSO	75
9	$PdCl_2$/DABCO	DMSO	26
10	$PdCl_2$/DBU	DMSO	33
11	$PdCl_2/K_2CO_3$	MeOH	48
12	$PdCl_2/K_2CO_3$	Dioxane	40
13	$PdCl_2/K_2CO_3$	Toluene	55
14[c]	$PdCl_2/K_2CO_3$	DMSO	78
15[d]	$PdCl_2/K_2CO_3$	DMSO	91
16	$-/K_2CO_3$	DMSO	Trace
17[e]	$PdCl_2/K_2CO_3$	DMSO	84
18[f]	$PdCl_2/K_2CO_3$	DMSO	71

[a] Reaction conditions: **1a** (0.3 mmol), $PdCl_2$ (2.5 mol%), base (1.0 equiv.), solvent (1 mL), rt, 2–12 h, under air. [b] Isolated yields. [c] $PdCl_2$ (1.25 mol%). [d] $PdCl_2$ (5 mol%). [e] K_2CO_3 (0.5 equiv.). [f] K_2CO_3 (2.0 equiv.).

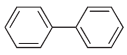
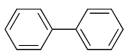
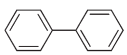
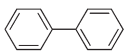
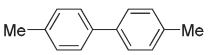
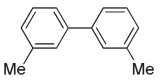
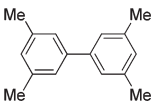
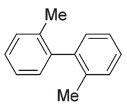
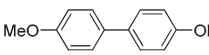
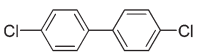
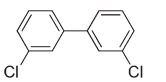
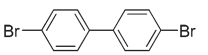
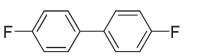
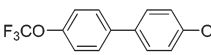
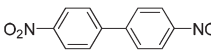
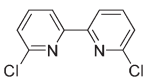
yield (Table 1, entry 15 *versus* entry 4). However, a significant drop in yield was observed when 1.25 mol% of $PdCl_2$ was used (Table 1, entry 14). A palladium catalyst was necessary for this homocoupling, and a trace product was observed in the absence of any Pd catalyst (Table 1, entry 16). The amount of K_2CO_3 was also important for this reaction (Table 1, entries 4, 17 and 18). The optimized homocoupling reaction conditions were as follows: **1a** (0.3 mmol), $PdCl_2$ (2.5 mol%) and K_2CO_3 (1.0 equiv.) in DMSO at room temperature.

The scope of the Pd-catalyzed homocoupling of *N*′-sulfonyl arylhydrazine was then investigated (Table 2). *N*′-Sulfonyl arylhydrazine with substituted groups, such as phenylsulfonyl and methylsulfonyl, could also afford the desired products in high yields (Table 2, entries 2 and 3). However, the strong electron-deficient nitro group lowered the yield significantly even at higher temperature (Table 2, entry 4). *N*′-Tosyl arylhydrazines with both electron-donating and electron-withdrawing groups attached to the aromatic ring all contributed to this transformation. For example, methyl and methoxyl substituents on phenyl rings can be successfully converted into the desired products in high yields (Table 2, entries 5–7 and 9). In addition, substrates with halogen, trifluoromethoxy, and nitro-substituents at the aryl moiety participated in the desired homocoupling process at a higher temperature (60 °C) (Table 2, entries 10–15). Interestingly, the homocoupling of 4-chlorophenyl and 4-bromophenyl sulfonylhydrazide led to the exclusive formation of **2g** and **2i** in 78% and 74% yield, respectively (Table 2, entries 10 and 12), indicating excellent chemoselectivity in contrast to the traditional Ullmann

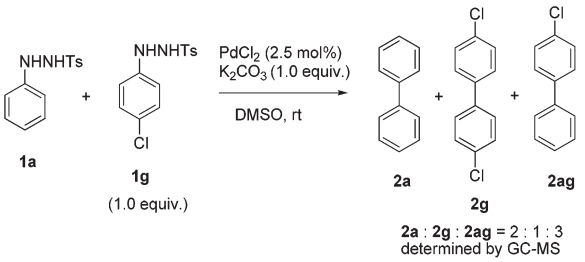
Table 2 Pd-catalyzed homocoupling of *N*′-tosyl arylhydrazines[a]



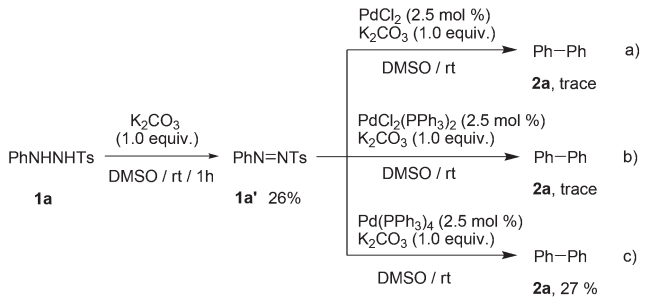
1 **2**

Entry	R =	Product	Yield[b] [%]
1	4-Tolyl	 **(2a)**	91
2	Phenyl	 **(2a)**	88
3[c]	Methyl	 **(2a)**	85
4[c]	4-Nitrophenyl	 **(2a)**	20
5	4-Tolyl	 **(2b)**	90
6	4-Tolyl	 **(2c)**	85
7	4-Tolyl	 **(2d)**	80
8[c]	4-Tolyl	 **(2e)**	Trace
9	4-Tolyl	 **(2f)**	92
10[c]	4-Tolyl	 **(2g)**	78
11[c]	4-Tolyl	 **(2h)**	82
12[c]	4-Tolyl	 **(2i)**	74
13[c]	4-Tolyl	 **(2j)**	68
14[c]	4-Tolyl	 **(2k)**	60
15	4-Tolyl	 **(2l)**	50
16[c]	4-Tolyl	 **(2m)**	44

[a] Reaction conditions: **1** (0.3 mmol), $PdCl_2$ (2.5 mol%), K_2CO_3 (1.0 equiv.), DMSO (1 mL), rt, 2–12 h, under air. [b] Isolated yields. [c] 60 °C.



Scheme 2 Cross-coupling between **1a** and **1g**.



Scheme 3 Control experiments.

homocoupling of aryl chlorides and aryl bromides. Unfortunately, the *ortho*-substituent of arylhydrazine was not compatible with the reaction conditions (Table 2, entry 8). The aryl-substituted, as well as the heteroaryl-substituted tosylhydrazide, provided moderate yields (Table 2, entry 16).

We also performed the Pd-catalyzed cross-coupling reaction between *N*′-tosyl arylhydrazines **1a** and **1g**, and detected both homocoupling products **2a**, **2g** and cross-coupling product **2ag** in a ratio of 2 : 1 : 3 (Scheme 2). The current chemoselectivity was only moderate, and more experiments were still needed to understand the mechanism, to optimize the reaction conditions for the desired pathway and to explore its potential applications in organic synthesis.

To explain the mechanism of this homocoupling reaction, three control experiments were carried out (Scheme 3). Initially, 1-phenyl-2-tosyldiazene **1a**′ can be isolated in 26% yield from *N*′-tosyl phenylhydrazine **1a** under basic conditions, but the direct homocoupling reaction of **1a**′ can only afford trace biphenyl **2a** under the aforementioned standard conditions ($PdCl_2$ as the catalyst, without any external reductants) (Scheme 3a). Other Pd(II) catalysts as $PdCl_2(PPh_3)_2$ also failed to give **2a** (Scheme 3b). In contrast, when $Pd(PPh_3)_4$ was utilized as the catalyst, 27% yield of **2a** could be obtained (Scheme 3c), which indicated that the novel homocoupling reaction of *N*′-tosyl arylhydrazine may proceed *via* a Pd(0)-mediated redox cycle.[10] Moreover, *N*′-tosyl arylhydrazine might have an efficient and special role in the *in situ* regeneration of the reductive Pd(0) active species from the oxidative Pd(II) species.[11]

Based on our results and the research findings from other groups, a possible mechanism for homocoupling reactions has

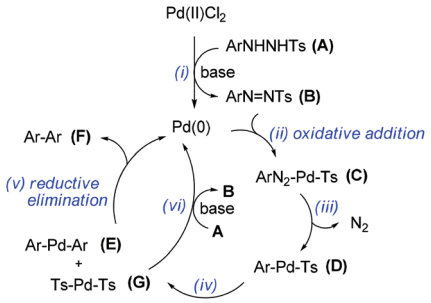


Fig. 1 Proposed mechanism.

been proposed (Fig. 1).[8–11] The *in situ* generated reductive Pd(0) active species from the oxidative Pd(II) species undergoes oxidative insertion to diazene **B** (step **ii**) to form the organopalladium intermediate **D** by N_2 release. Then **D** is converted to diarylpalladium complex **E**, followed by the reductive elimination (step **v**), to afford biaryl **F** and to regenerate the Pd(0) catalyst. *N*′-Tosyl arylhydrazine **A** may have functions on both the initial reduction (step **i**) and the terminal reduction (step **vi**),[12] allowing the homocoupling to be carried out in an operationally simple manner without the addition of a zero-valent metal or other terminal reductant.

In summary, a novel procedure for the preparation of biaryl compounds by Pd-catalyzed homocoupling of *N*′-tosyl arylhydrazine without the addition of zero-valent metal or other terminal reductants was presented. *N*′-Tosyl arylhydrazine, as a readily available and stable coupling partner, demonstrated its generality in the aforementioned homocoupling reactions. Future studies are aimed at extending the scope and synthetic applications.

Acknowledgements

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