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# COMMUNICATION

# Palladium-Catalyzed Heck Coupling of Arylhydrazines via C– NHNH<sub>2</sub> Bond Activation

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A novel palladium-catalyzed Heck coupling reaction of arylhydrazines with olefins is described, which affords various styrenes with high efficiency. This transformation proceeds through a C–NHNH<sub>2</sub> bond activation under mild conditions.

Transition-metal-catalyzed C–C coupling reactions have been recognized as powerful tools in multiple organic transformations. One of the most important C–C coupling reactions is the palladium-catalyzed Heck coupling reaction,<sup>1</sup> such as the arylation of olefins by aryl halides. The reaction has been applied to many areas, including bioactive compounds,<sup>2</sup> fine chemicals,<sup>3</sup> and organic materials synthesis.<sup>4</sup> Although aryl (pseudo)halides are the most commonly and successfully employed electrophilic partners, broadening the scope of electrophiles would be significant to practitioners of chemical synthesis.

In recent years, C-N compounds have been utilized as another candidate for electrophilic components in some cross-coupling reactions. Generally, the C-N bonds are activated by conversion to diazonium salts,<sup>5</sup> ammonium salts,<sup>6</sup> or triazenes.<sup>7</sup> However, existing methods are still plagued with problems such as the explosive and unstable nature of the substrates, harsh reaction conditions, limited substrate scope, and the need to use strong acids, etc. To expand this substrate scope, What's more, to make this novel coupling reaction practically useful in organic synthesis, other sources such as hydrazines have attracted our attention.<sup>8,9</sup> Notably, Loh and coworkers developed the first Heck coupling of arylhydrazines with olefins under the condition of an excessive amount of acid (Scheme 1a).<sup>8a</sup> In the process, palladium-assisted aryl C–N bond cleavage in arylhydrazines together with subsequential Heck reactions was involved, resulting in various styrenes with high efficiency. Very recently, we also described a novel Suzuki cross-coupling between

<sup>+</sup> Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

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arylhydrazine and aryl boronic acid, using *p*-toluenesulfonyl chloride (TsCl) as the activation reagent under alkaline conditions (Scheme 1b).<sup>9a,c</sup> Prompted by our continuous interest in palladium-catalyzed hydrazine-based cross-coupling reactions, we envisioned that a small library of substituted styrenes could be constructed starting from arylhydrazines via a C–NHNH<sub>2</sub> bond activation. Herein, we reported the Heck coupling of arylhydrazines with olefins activated by TsCl (Scheme 1c).



**Scheme 1** (a) Heck coupling of arylhydrazines under acidic conditions; (b) Suzuki cross-coupling of arylhydrazines via C–NHNH<sub>2</sub> bond activation; (c) Heck coupling of arylhydrazines via C–NHNH<sub>2</sub> bond activation discussed in this work.

During our initial studies, phenylhydrazine **1a** and *tert*-butyl acrylate 2a were selected as substrates for the model reaction. Various conditions were screened and the results are summarized in Table 1. At the outset, the model reaction was carried out in the presence of 5 mol % of PdCl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub> (2.2 equiv), and TsCl (1.2 equiv) in MeOH at room temperature. Gratifyingly, the expected tert-butyl cinnamate 3a was isolated in 52% yield (entry 1). Encouraged by this result, more Pd-catalysts were surveyed [Pd(OAc)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, and PdCl<sub>2</sub>(PhCN)<sub>2</sub>] (entries 2-4). We found that Pd(OAc)<sub>2</sub> was the best Pd source, affording 60% yield of the product 3a (entry 2). The effect of bases in this reaction was then investigated (entries 5-9), and the use of Et<sub>3</sub>N as the base led to higher yield for this Heck coupling (entry 7 versus entries 2, 5-6, and 8-9). Other solvents, such as EtOH, CH<sub>2</sub>Cl<sub>2</sub>, toluene, DMSO, and THF, were also investigated (entries 10-14); however, none of them was more efficient than MeOH. In addition, the reaction temperature was examined and the results showed that 40 °C was the best choice (entry 15 versus entries 7 and 16). Increasing the amount of Pd

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catalyst loading to 10 mol % resulted in a comparable yield (entry 17 *versus* entry 15). However, a significant drop in yield was observed when 2 mol % of Pd(OAc)<sub>2</sub> was used (entry 18). TsCl was necessary for the C–NHNH<sub>2</sub> bond activation procedure, and no product was observed in the absence of TsCl (entry 19).

**Table 1** Optimization of Reaction Conditions on Heck coupling of phenylhydrazine **1a** with *tert*-butyl acrylate **2a**.<sup>a</sup>

F	PhNHNH⊳ +	CO₂t-Bu	[Pd], TsCl, base		XO₂ <i>t</i> -Bu
	19	20	Solvent, air, rt.	Ph	
	la	2 <b>a</b>		ઝત	
entry	,	[Pd]/base	sol	vent	yield <sup>b</sup> [%]
1	I	PdCl <sub>2</sub> /K <sub>2</sub> CO <sub>3</sub>	M	eOH	52
2	Pd	$(OAc)_2/K_2CC$	0 <sub>3</sub> M	eOH	60
3	Pd	(Ph <sub>3</sub> P) <sub>4</sub> / K <sub>2</sub> C	D <sub>3</sub> M	eOH	50
4	PdCl	2(PhCN)2/ K2	CO <sub>3</sub> M	eOH	51
5	Pd(	OAc) <sub>2</sub> / Na <sub>2</sub> C	O <sub>3</sub> M	eOH	44
6	Pd	(OAc) <sub>2</sub> /Cs <sub>2</sub> Co	D <sub>3</sub> M	eOH	55
7	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	I M	eOH	70
8	Pd	OAc) <sub>2</sub> /DABC	0 M	eOH	43
9	P	d(OAc) <sub>2</sub> /DBL	J M	eOH	30
10	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	J Et	OH	65
11	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	I CH	$I_2CI_2$	56
12	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	l tol	uene	62
13	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	I DI	VISO	<5
14	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	I T	ΉF	11
15 <sup>°</sup>	Po	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	N M	eOH	82
16 <sup>d</sup>	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	I M	eOH	68
17 <sup>c,e</sup>	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	I M	eOH	78
18 <sup>c,f</sup>	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	I M	eOH	56
19 <sup>g</sup>	P	d(OAc) <sub>2</sub> /Et <sub>3</sub> N	I M	eOH	trace

<sup>a</sup> Reaction conditions: **1a** (0.36 mmol), **2a** (0.3 mmol), TsCl (1.2 equiv), [Pd] (5 mol %), base (2.2 equiv), solvent (2 mL), 4-12 h. <sup>b</sup> Isolated yields of **3a**. <sup>c</sup> 40 °C. <sup>d</sup> 60 °C. <sup>e</sup> [Pd] (10 mol %). <sup>f</sup> [Pd] (2 mol %). <sup>g</sup> Without the presence of TsCl.

Then the scope of the Pd-catalyzed Heck coupling of arylhydrazines with acrylates was investigated (Table 2). As already outlined, a wide range of arylhydrazines gave the desired products in good to excellent yields, including ortho-, para-, and metasubstituted arylhydrazines. For example, both 4-methylhydrazine 1b and 4-methoxyhydrazine 1f could react with 2a to provide the Heck coupling products in high yields (entries 2 and 6). The orthosubstituted arylhydrazines also proceeded readily to give the crosscoupling products in good yields (entries 4 and 5). The tolerance of ortho-substituted arylhydrazines is an advantage over the palladium-catalyzed traditional coupling chemistry, which is frequently sensitive to steric hindrance. Notablely, excellent chemoselectivities were observed when chloro- (entries 8 and 9). bromo- (entry 10), and fluorophenylhydrazines (entry 11) were involved in this Heck reaction. This feature affords an opportunity for further functionalization at the halide group. To further illustrate the utility of this coupling reaction, other acrylates were evaluated under the optimal reaction conditions, and showed little influence on the reaction efficiency (entries 12-15). Arylhydrazine 11 with a long-range electron-withdrawing substituent was also

tolerant in this reaction and gave good yield (entry 15). But, unfortunately, when 1, 1-disubtituted acrylate such as butyl methacrylate **2e**, or electron-rich alkene such as butyl vinyl ether **2f** was used as the substrate under the optimized conditions, few Heck coupling product was obtained (entries 16 and 17). We supposed that these alkenes were too reactive for this hydrazine-based Heck coupling reaction.

Table	2	Pd-catalyzed	Heck	coupling	of	arylhydrazines	1	with
acryla	tes	<b>2</b> . <sup>a</sup>						

R	$1 \qquad 2^{1}$	Pd(OAc) <sub>2</sub> 5 mol % TsCl 1.2 equiv Et <sub>3</sub> N 2.2 equiv MeOH, air, 40 °C	R	→R' 3		
entry	R	R'	3	yield of $3^{b}$		
1	H ( <b>1a</b> )	CO <sub>2</sub> t-Bu ( <b>2a</b> )	3a	82		
2	4-Me ( <b>1b</b> )	2a	3b	85		
3	3-Me ( <b>1c</b> )	2a	3c	84		
4	2-Me ( <b>1d</b> )	2a	3d	80		
5	2-OMe ( <b>1e</b> )	2a	3e	84		
6	4-OMe ( <b>1f</b> )	2a	3f	91		
7	3,5-diMe ( <b>1g</b> )	2a	3g	82		
8	4-Cl ( <b>1h</b> )	2a	3h	78		
9	3-Cl (1i)	2a	3i	80		
10	4-Br ( <b>1j</b> )	2a	3j	76		
11	4-F ( <b>1k</b> )	2a	3k	79		
12	1a	CO <sub>2</sub> <i>n</i> -Bu ( <b>2b</b> )	31	78		
13	1a	CO <sub>2</sub> Et ( <b>2c</b> )	3m	78		
14	1a	CO <sub>2</sub> Me ( <b>2d</b> )	3n	80		
15	4-OCF <sub>3</sub> (11)	2c	Зо	70		
16	1a		Зр	<5		
17	1a	л-BuO ( <b>2f</b> )	3q	trace		

<sup>a</sup> Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), TsCl (1.2 equiv), Pd(OAc)<sub>2</sub> (5 mol %), Et<sub>3</sub>N (2.2 equiv), MeOH (2 mL), 4-12 h. <sup>b</sup> Isolated yields of **3**.

We have also tried the Heck coupling reaction between arylhydrazine and styrene; however, unexpected products were obtained as shown in Scheme 2. A mixture was obtained when phenylhydrazine reacted with styrene **2g** (Scheme 2a). We proposed that the *p*-tolyl substituent of product **3s** was derived from the TsCl, as similar results have been reported in literatures.<sup>10</sup> Intriguingly, the only product **3s** was isolated in moderate yields when hydrazines with electron-withdrawing groups such as Cl and Br were employed as the reactants (Scheme 2b). The current selectivity and efficiency were poor, and we are still screening the reaction conditions in detail to further improve the chemoselectivity and to explore its practical applications in organic synthesis.



Scheme 2 Heck coupling of arylhydrazine with styrene.

To explore the mechanism of this Heck reaction, two control experiments were carried out (Scheme 3). We conceived that phenylhydrazine derivatives 1a' and 1a'' would be generated as the key intermediates for this C–NHNH<sub>2</sub> bond activation process. As described in Scheme 3, 1-phenyl-2-tosyldiazene 1a'' could be isolated in 24% yield from N'-tosyl phenylhydrazine 1a'' under basic conditions, and the direct Heck coupling between 1a'' and 2a smoothly afforded 3a in 84% yield.



Scheme 3 Control experiments.

Based on these results and the research findings from other groups, a possible mechanism for this Heck reaction via C–NHNH<sub>2</sub> bond activation was proposed (Fig. 1). Firstly, arylhydrazine could quickly react with TsCl to form *N'*-tosyl arylhydrazine I, which was dehydrogenated in the presence of base and Pd(II)-catalyst to provide the diazene II, accompany with the *in situ* generation of Pd(0) active species. In addition, diazene II was in equilibrium with the corresponding diazonium ion III, when it was dissolved in solvent.<sup>11</sup> Then oxidative addition of III to the Pd(0) gave the organopalladium intermediate IV, which could be transformed to intermediate V in the presence of olefin. Degeneration of intermediate V gave a coupling product and regenerated [Pd(0)]. The catalytic cycle was closed upon reoxidation of Pd(0) to Pd(II) by air.



Fig. 1 Proposed mechanism.

## Conclusions

In summary, we have developed a novel palladium-catalyzed Heck coupling of arylhydrazines via aryl C–NHNH<sub>2</sub> bond activation with olefins. By employing the commercially available arylhydrazine as the coupling partner and the cheap and manageable TsCl as the activation reagent, this effective methodology will be attractive for both academia and industry. This new methodology can be used as a complement for the classical Heck coupling reaction.

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