Organic Chemistry |Hot Paper|

Using N-Tosylhydrazone as a Double Nucleophile in the Palladium-Catalyzed Cross-Coupling Reaction to Synthesize Allylic Sulfones

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Abstract: Without extra addition of sulfinate salt, allylic sulfones were synthesized by palladium-catalyzed cross-coupling of aryl iodide with *N*-tosylhydrazone. In this transformation, not only the diazo compound but also the sulfinate salt, which were both generated in situ from base-mediated decomposition of the *N*-tosylhydrazone, was used as nucleophilic partner.

The allylic sulfone skeleton has been found in numerous of compounds exhibiting important biological activities, such as treatment of Alzheimer's disease, cancer, antibacterial agents, and herbicides etc.^[1] Moreover, because of the activation of $\alpha\text{-}$ sulfonyl carbanions, allylic sulfones are used as efficient tools for carbon-carbon bond-forming reactions (Ramberg-Bäcklund reaction, Julia olefinations etc.).^[2] Much attention has been paid to prepare allylic sulfones. The oxidation of sulfides to the corresponding sulfones is the most favored method. However, this method often needs to employ high oxidant loading to control the synthesis of sulfoxides and sulfones.^[3] Allylic substitution reaction with sulfinate salts is also a general approach. But these transformations have their own drawbacks, such as expensive catalysts, high catalyst loading, and excess additive.^[4] In light of those limitations, a new, efficient, environmental, and atom economic way to synthesize allylic sulfones is highly desirable.

Recently, diazo compounds have been considered as a new type of nucleophilic coupling partner in the palladium-catalyzed cross-coupling reaction. The initial work of the palladi-

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	Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201405172.

um-catalyzed stabilized diazo compound insertion reaction was reported by Van Vranken and co-workers in 2001.^[5,6] Diazo compounds without an electron-withdrawing group on the diazo carbon, such as diazoalkanes and aryldiazomethanes, are generally highly reactive and difficult to handle. To expand the scope of this type of reaction and the practical utility of this protocol, Barluenga and co-workers reported the first example of using N-tosylhydrazones as precursors of unstabilized diazo substrates in the palladium-catalyzed cross-coupling reaction in 2007.^[7] Since then, a series of palladium-catalyzed insertions of *N*-tosylhydrazones were developed.^[8] For example, Wang and co-workers demonstrated that under oxidative conditions, N- tosylhydrazones could also undergo cross-coupling with terminal alkynes.^[9] They also reported a three-component coupling of aryl halides, N-tosylhydrazones, and terminal alkynes for the synthesis of propargylarenes.^[10] The palladium-catalyzed carbenylative amination with N-tosylhydrazones was shown by Van Vranken.^[11] Jiang described a Pd-catalyzed intermolecular cross-coupling reaction of terminal alkenes and Ntosylhydrazones.^[12] In 2014, we reported the example of utility N-tosylhydrazones as a coupling partner in the Catellani-Lautens reaction.^[13] For all of those reactions, decomposition of the tosylhydrazone generated the sulfinate salt. As we all know, sulfinate salt is also a good nucleophilic coupling partner in the palladium-catalyzed reaction.^[14] However, using diazo compound and sulfinate salt, which are generated in situ from Ntosylhydrazone, both as nucleophilic coupling partners in one reaction has not been reported in the literature to date. From an environmental and atom economic view and for our interest in this field,^[13,15] here we report a new palladium-catalyzed N-tosylhydrazones insertion reaction, in which not only diazo compounds (generated in situ from N-tosylhydrazone) but also the byproduct sulfinate salt (generated in situ from N-tosylhydrazone) is used as a nucleophilic coupling partner.

To demonstrate the feasibility of this hypothesis, we began our investigation by employing iodobenzene **1 a** and α , β -unsaturated *N*-tosylhydrazones **2 a** as the substrate. At the outset of this investigation, the reaction was catalyzed by [Pd₂(dba)₃]·CHCl₃ (2.5 mol%)/PPh₃ (15 mol%) (dba=dibenzylideneacetone) in the presence of Cs₂CO₃ and BnNEt₃Cl in toluene at 50 °C for 10 h (Table 1, entry 1). However, only a small amount of product **3 a** was detected. Different mono- and bidentate phosphine ligands were envisioned and it was found that the yield was not improved (entries 2–6). Further inspec-

Chem. Eur. J. **2014**, 20, 1–5

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Table 1. Optimization of reaction conditions. ^[a]						
la la	+ Line NNHTs 2a	Pd/L, base BnNEt ₃ Cl solvent { 50°C, 10h	Ja Ta	s		
Entry	Cat.	Base	Solvent	Yield		
1	[Pd ₂ (dba) ₃]·CHCl ₃ /PPh ₃	Cs ₂ CO ₃	toluene	<10%		
2	[Pd ₂ (dba) ₃]·CHCl ₃ /TFP	Cs ₂ CO ₃	toluene	n.r.		
3	[Pd ₂ (dba) ₃]•CHCl ₃ /Xphos	Cs ₂ CO ₃	toluene	n.r.		
4 ^[b]	[Pd ₂ (dba) ₃]•CHCl ₃ /dppb	Cs ₂ CO ₃	toluene	n.r.		
5 ^[b]	[Pd ₂ (dba) ₃]•CHCl ₃ /Xantphos	Cs ₂ CO ₃	toluene	n.r.		
6 ^[b]	[Pd ₂ (dba) ₃]·CHCl ₃ /DPEphos	Cs ₂ CO ₃	toluene	trace		
7	[Pd ₂ (dba) ₃]•CHCl ₃ /PPh ₃	<i>t</i> BuOLi	toluene	n.r.		
8	[Pd ₂ (dba) ₃]•CHCl ₃ /PPh ₃	tBuONa	toluene	n.r.		
9	[Pd ₂ (dba) ₃]•CHCl ₃ /PPh ₃	<i>t</i> BuOK	toluene	12		
10	[Pd ₂ (dba) ₃]•CHCl ₃ /PPh ₃	Na ₂ CO ₃	toluene	69		
11	[Pd ₂ (dba) ₃]•CHCl ₃ /PPh ₃	K ₂ CO ₃	toluene	42		
12	[Pd ₂ (dba) ₃]·CHCl ₃ /PPh ₃	Na ₂ CO ₃	DCE	51		
13	[Pd ₂ (dba) ₃]·CHCl ₃ /PPh ₃	Na ₂ CO ₃	THF	48		
14	[Pd ₂ (dba) ₃]·CHCl ₃ /PPh ₃	Na ₂ CO ₃	dioxane	60		
15	[Pd ₂ (dba) ₃]·CHCl ₃ /PPh ₃	Na ₂ CO ₃	MeCN	84		
16 ^[c]	[Pd(CH ₃ CN) ₂ Cl ₂]/PPh ₃	Na ₂ CO ₃	MeCN	73		
17 ^[c]	Pd(OAc) ₂ /PPh ₃	Na ₂ CO ₃	MeCN	68		
18 ^[c]	PdCl ₂ /PPh ₃	Na ₂ CO ₃	MeCN	63		
19	[Pd ₂ (dba) ₃]/PPh ₃	Na ₂ CO ₃	MeCN	77		
20 ^[c]	[Pd(PPh ₃) ₄]/PPh ₃	Na ₂ CO ₃	MeCN	67		
[a] Palladium-catalyzed cross-coupling of 1 a with <i>N</i> -tosylhydrazones 2 a . Reaction conditions: 1 (0.3 mmol, 1.0 equiv), 2 (0.6 mmol, 2.0 equiv), [Pd.(dba).]-CHCL, (2.5 mol%), PPb, (15 mol%), Na ₂ CO, (0.75 mmol						

[Pd₂(dba)₃]-CHCl₃ (2.5 mol%), PPh₃ (15 mol%), Na₂CO₃ (0.75 mmol, 2.5 equiv), BnNEt₃Cl (0.3 mmol, 1.0 equiv), solvent (3 mL), 50 °C, 10 h. Yield is of the isolated product. [b] ligand (7.5 mol%). [c] Pd (5 mol%).

tion of the reaction conditions revealed that base had a notable effect on the reaction yield. No reaction occurred when Cs_2CO_3 was switched to *t*BuOLi or *t*BuONa (entries 7–8). To our delight, product **3a** was isolated in 12% yield in the presence of *t*BuOK (entry 9). Use of Na₂CO₃ furnished the corresponding product in 69% yield, but the yield was not improved when K₂CO₃ was used as a base (entries 10–11). A number of solvents, including DCE, THF, dioxane, and MeCN were then examined. DCE and THF gave low yield (entries 12–13). The reaction was found to proceed more efficiently in MeCN compared with toluene and dioxane (entries 14–15). Finally, no better results were afforded when other palladium catalysts were screened (entries 16–20).

Under the optimized conditions, we explored the substrate scope of this reaction. As summarized in Table 2, both electron-withdrawing and -donating groups on the aromatic ring worked well to afford **3** in good to excellent yields with sulfones as the sole product (no ester was observed through the O-allylation reaction, which is due to the ambident of sulfinate anion).^[14b] However, reaction of 1-iodo-2-methylbenzene with *ortho*-substituted $\alpha_{,}\beta$ -unsaturated *N*-tosylhydrazones gave a low yield of product **3h**, which might be due to the steric hindrance.

Next, the scope of this reaction was investigated by using various substituted sulfonyl hydrazones. The *ortho-, meta-*, and *para*-substituted substrates can work smoothly. Different functional groups including fluoro, chloro, bromo, and CF₃ were all compatible. It is worth mentioning that halogen-substituted



products could undergo further transition-metal-catalyzed coupling reactions. The benzyl and heterocyclic sulfonyl hydrazones were also suitable substrates for this reaction (Table 3, **3 u**, **3 v**).

Finally, the reaction of iodobenzene **1a** and **1b** with *N*-tosylhydrazones **2b**, **2e**, and **2h** was subsequently studied, respectively (Scheme 1). Treating iodobenzene **1a** with *N*-tosylhydrazones **2b** under standard conditions, two regioisomeric prod-



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Scheme 1. Reaction of iodobenzene 1 a and 1 b with N-tosylhydrazones 2 b, 2 e, and 2 h.

ucts **3w**' and **3w**'' were isolated. The ratio of **3w**'/**3w**'' was approximately 1:1 as indicated by ¹H NMR spectroscopic analysis. Similar results were also obtained for the reaction of **1a** with **2e**. For the reaction of **1a** and **1b** with **2h**, products **3y** and **3z** were afforded with complete regioselectivity. This result is consistent with previous reports.^[15e,16]

According to previous reports,^[8] a possible catalytic cycle is proposed as shown in Scheme 2. Firstly, the oxidative addition of the Pd^0 catalyst to the aryl iodide 1 would produce the Pd^{II} intermediate **A**. Then the palladium–carbene intermediate **B**



Scheme 2. Plausible catalytic cycle.

was afforded though the reaction of Pd^{II} species **A** with the diazo compound **2**' (generated by the base-mediated decomposition of the *N*-tosylhydrazone **2**). Subsequently, aryl group migratory insertion took place to yield the η^1 -allylpalladium **C**. Finally, η^3 -allylpalladium **D**, resulting from isomerization of **C**, would react with the sodium sulfinate **4** (generated in situ by decomposition of the *N*-tosylhydrazone **2**) to furnish the desired product **3**.

In conclusion, we have described a novel palladium-catalyzed cross-coupling of aryl iodide with *N*-tosylhydrazone to

These are not the final page numbers! **77**

access to sulfones. Unlike the previous palladium-catalyzed *N*-tosylhydrazone insertion reaction, in this transformation, not only the diazo compound but also the sodium sulfinate, which are simultaneously formed by base-mediated decomposition of the *N*-tosylhydrazone, were used as the nucleophilic coupling partner. This reaction demonstrates that *N*-tosylhydrazone could be used as a double nucleophile in the palladium-catalyzed reaction. Furthermore, the reaction was carried out under milder conditions with minimal waste and excellent atom economy.

Experimental Section

General procedure for the preparation of the products 3

An oven-dried Schlenk tube under a nitrogen atmosphere was charged with aryl iodide **1** (0.3 mmol, 1.0 equiv), α , β -unsaturated *N*-tosylhydrazones **2** (0.6 mmol, 2.0 equiv),

 $[Pd_2(dba)_3]$ -CHCl₃ (2.5 mol%), PPh₃ (15 mol%), Na₂CO₃ (0.75 mmol, 2.5 equiv), BnNEt₃Cl (0.3 mmol, 1.0 equiv), and CH₃CN (3 mL). The mixture was stirred at room temperature for 15 min and then stirred at 50 °C for 10 h. The resulting mixture was cooled to room temperature and filtered through Celite with EtOAc as the eluent. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel to afford pure **3**.

Acknowledgements

We thank the National Science Foundation (NSF 21072080 and 21272101), National Basic Research Program of China (973 Program) 2010CB833203, "111" program of MOE, and PCSIRT: IRT1138 for financial support.

Keywords: atom economy · carbenes · double nucleophiles · palladium · tosylhydrazone

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Received: September 7, 2014 Published online on

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COMMUNICATION

Ts ∕_Ar¹ $Ar^{1}I + Ar^{1}$

Two for the price of one! Allylic sulfones were achieved through a new palladium-catalyzed cross-coupling of aryl iodide with *N*-tosylhydrazone (see scheme). In this reaction not only the

19 examples up to 93% yield
Without extra addition sulfinate salt
Atom economy
Sulfones as the sole product no ester was observed

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Using N-Tosylhydrazone as a Double Nucleophile in the Palladium-Catalyzed Cross-Coupling Reaction to Synthesize Allylic Sulfones