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Palladium-Catalyzed Insertion of *N*-tosylhydrazones and Trapping with Carbon Nucleophiles

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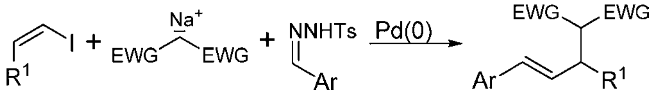
ABSTRACT



A Pd-catalyzed three-component cross-coupling reaction of vinyl iodide, *N*-tosylhydrazone, and carbon nucleophiles is reported, and a one-pot procedure is also developed. The cross-coupling is proposed to proceed through a palladium−carbene migratory insertion, carbopalladation other than classic palladium−carbene migratory insertion, and β-H elimination. Moreover, the reaction proceeds under mild conditions and with high stereoselectivity.

Transition-metal-catalyzed cross-coupling reactions have been recognized as a powerful and efficient method for C−C bond construction.[1] Despite the wide applicability of these reactions, most of these cross-coupling transformations involve the participation of a stoichiometric organometallic reagent, which are usually expensive, toxic, and moisture-sensitive.[2] Moreover, highly reactive organometallic reagents often suffer from a problem of functional group tolerance. Thus, it is highly desirable to further develop a novel coupling process.

The utility of *N*-tosylhydrazones in organic synthesis has a long history. Bamford and Stevens initially demonstrated that *N*-tosylhydrazones can be employed as a source of diazo compounds.[3] The first example of showing their utility in a palladium-catalyzed cross-coupling reaction was reported by Barluenga.[4] Since then, palladium-catalyzed insertion of *N*-tosylhydrazones has been emerging as a new type of cross-coupling reaction and has attracted increasing attention. In 2009, Wang reported a palladium-catalyzed cross-coupling of benzyl halides with tosylhydrazones to generate a variety of polysubstituted olefins.[5] Recently, Barluenga reported the first examples of the use of alkenyl halides in cross-coupling reactions with tosylhydrazones to give linear dienes (Scheme 1, eq 1).[6] However, all of these catalytic cycles involve Pd carbene migratory insertion followed by β-hydride elimination, and only one C(sp^2)−C(sp^2) bond is formed.[7] If we can combine Pd-catalyzed insertion of *N*-tosylhydrazones and Pd-catalyzed cascade reactions, it would provide new possibilities for the development of more novel coupling processes. Indeed, a three-component coupling of aryl halides, *N*-tosylhydrazones,

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(2) (a) Komiya, S. *Synthesis of Organometallic Compounds: A Practical Guide*; Wiley-VCH: Chichester, 1997. (b) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545–1554. (c) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492.

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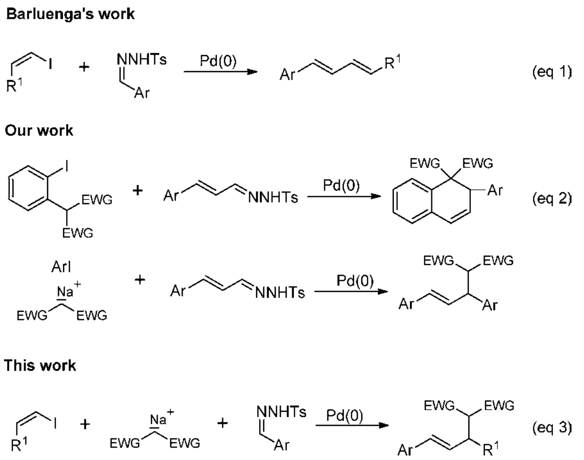
10.1021/ol402457h

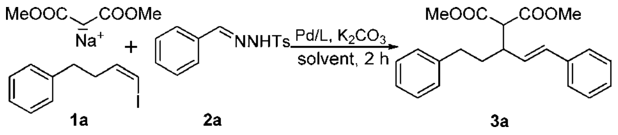
and terminal alkynes for the synthesis of propargylarenes was developed by Wang, in which two separate C−C bonds (one sp^2−sp^3 bond, one sp−sp^3 bond) were formed via a sequential palladium carbene migratory insertion and transmetalation process.[8] We also reported palladium-catalyzed cross-coupling reactions of *N*-(2-iodobenzyl)-anilines with α,*β*-unsaturated tosylhydrazones to afford isoindolines.[9] In this reaction, a C−C bond and a C−N bond were formed via carbene migratory insertion and C−N bond formation. Recently, we demonstrated that stabilized carbon nucleophiles can also be used as partners in cross-coupling with α,*β*-unsaturated *N*-tosylhydrazones (Scheme 1, eq 2).[10] In connection with the common η^3-allylpalladium intermediates in Barluenga's and our work, we wish to report a palladium-catalyzed cross-coupling of alkenyl halides, tosylhydrazones and carbon nucleophiles involving a carbopalladation other than *β*-hydride elimination (Scheme 1, eq 3).

Scheme 1. Combine Pd-Catalyzed Insertion of *N*-Tosylhydrazone and Pd-Catalyzed Cascade Reactions



The three-component reaction was started by employing vinyl iodide **1a**, *N*-tosylhydrazone **2a**, and carbon nucleophiles as substrates in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %), PPh_3 (15 mol %), and K_2CO_3 (3.0 equiv) in THF (6 mL) at 70 °C for 2 h. To our delight, the cross-coupling product **3a** was delivered in 37% yield (Table 1, entry 1). Encouraged by this preliminary result, we proceeded to optimize the reaction. First, we investigated the effect of the additive. In order to prevent the undesired *β*-hydride elimination, 2.0 equiv of LiCl was added; however, **3a** was afforded in comparable yield (data not shown in Table 1).[11] When 2.0 equiv of BTAC was used as an additive to enhance the solubility of the sodium dimethyl malonate, it was found to be ineffective (data not shown in Table 1). Next, we inspected the stoichiometry of solvent, PPh_3, carbon nucleophiles, and the effect of temperature. Decreasing the amount of solvent led to a slight improvement in yield (Table 1, entry 2). The yield could be further improved when the reaction was carried out at a lower temperature (Table 1, entry 3). Notably, when the PPh_3 loading was added, a better yield was obtained (Table 1, entry 4). In a similar study, Van Vranken and co-workers showed that using excess inexpensive sodium malonate could significantly improve the yield.[12] Indeed, by increasing the amount of malonate, the product yield was increased to 79% (Table 1, entry 5). Then, we went on to screen other reaction parameters, such as different solvents, catalysts, and ligands. Other solvents including DMF, MeCN, dioxane, and toluene were examined (Table 1, entries 6−9). However, they were found to be unfavorable. Further inspection of the reaction conditions revealed that ligand was essential for this reaction (Table 1, entries 10−13). No reaction occurred when Phen or $[\mathrm{HP}^t\mathrm{Bu}_3]\mathrm{BF}_4$ was used, and a lower yield was observed when

Table 1. Conditions for the Palladium-Catalyzed Reaction of **1a** and **2a**[a]



entry	catalyst	ligand	solvent	yield[b] (%)
1	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3[c]	THF[d]	37[e,f]
2	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3[c]	THF	42[e,f]
3	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3[c]	THF	46[f]
4	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3	THF	52[f]
5	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3	THF	79
6	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3	toluene	NR
7	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3	dioxane	22
8	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3	MeCN	66
9	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3	DMF	NR
10	$Pd_2(dba)_3 \cdot CHCl_3$	Phen	THF	NR
11	$Pd_2(dba)_3 \cdot CHCl_3$	dppb	THF	61
12	$Pd_2(dba)_3 \cdot CHCl_3$	$[\mathrm{HP}^t\mathrm{Bu}_3]\mathrm{BF}_4$	THF	NR
13	$Pd_2(dba)_3 \cdot CHCl_3$		THF	16
14	$Pd_2(dba)_3$	PPh_3	THF	70
15	$Pd(PPh_3)_4$[g]	PPh_3	THF	74
16	$Pd(OAc)_2$[g]	PPh_3	THF	74
17	$Pd(PPh_3)_2Cl_2$[g]	PPh_3	THF	71
18		PPh_3	THF	NR

[a] **1a** (0.3 mmol, 1.0 equiv), **2a** (0.675 mmol, 2.25 equiv), carbon nucleophiles (3.6 mmol, 12.0 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %), ligand (10 mol %), K_2CO_3 (0.9 mmol, 3.0 equiv), solvent (2 mL), 46 °C, 2 h. [b] Yield of isolated product. [c] 15 mol % PPh_3 was employed. [d] 6 mL of THF was employed. [e] The reaction was carried at 70 °C. [f] Carbon nucleophiles (1.8 mmol, 6.0 equiv). [g] Pd (5 mol %).

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(10) Ye, Y.-Y.; Zhou, P.-X.; Luo, J.-Y.; Zhong, M.-J.; Liang, Y.-M. *Chem. Commun.* **2013**10.1039/C3CC45583A.

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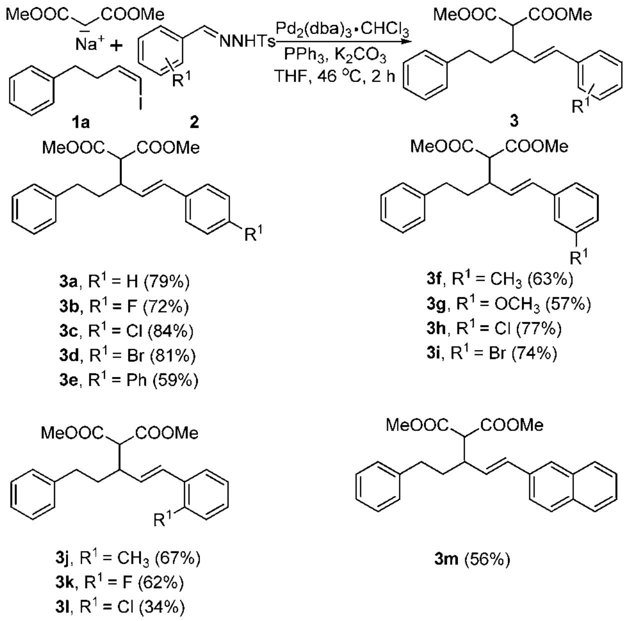
(12) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909–1911.

the reaction was performed in the absence of PPh_3. Employing dppb as a ligand could not further improve the yield. Various palladium catalysts including Pd(II) and Pd(0) were investigated and showed they are less efficient than $Pd_2(dba)_3 \cdot CHCl_3$ (Table 1, entries 14–17). Finally, the reaction could not proceed without palladium catalysis (Table 1, entry 18).

With the optimized conditions, the scope of this reaction was then explored. For meta- or para-substituted *N*-tosylhydrazones, both electron-donating and electron-withdrawing groups were tolerated and reacted smoothly with **1a** to afford the desired products in moderate to good yields (Scheme 2). For ortho-substituted *N*-tosylhydrazones, the yield was found to decrease with increasing size of the substituent. When R^1 is a small methyl group, **3j** is given in comparable yield with **3f**. With a sterically bulky Cl group, the product **3l** was obtained in lower yield. Additionally, using naphthyl *N*-tosylhydrazone as substrate, the reaction worked efficiently to afford **3m** in 56% yield. Notably, the halogen group was tolerated under the Pd-catalyzed conditions, which allowed a transition-metal-catalyzed coupling reaction. However, no reaction occurred when alkyl tosylhydrazones were utilized as coupling partners.

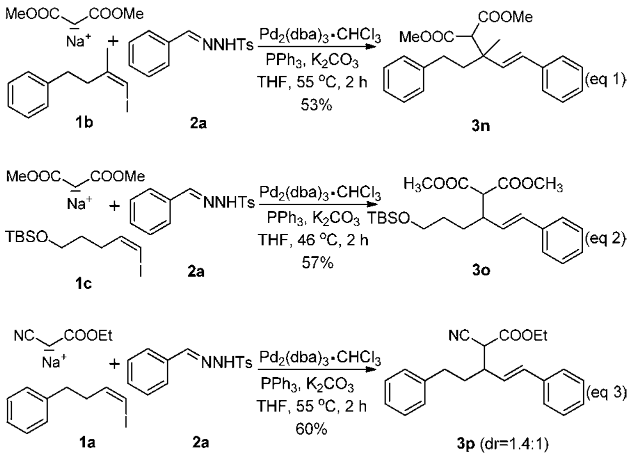
Scheme 2. Palladium-Catalyzed Reactions of **1a** with **2**[a]



[a] Reaction conditions: vinyl iodide **1a** (0.3 mmol, 1.0 equiv), *N*-tosylhydrazone **2** (0.675 mmol, 2.25 equiv), sodium malonate (3.6 mmol, 12.0 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %), PPh_3 (10 mol %), K_2CO_3 (0.9 mmol, 3.0 equiv), THF (2 mL), 46 °C, 2 h. Yields are calculated on isolated products.

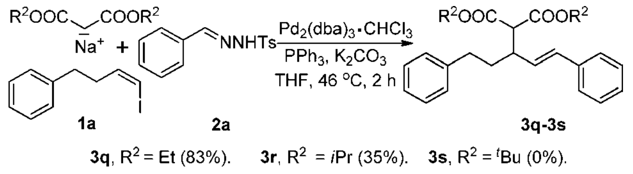
Moreover, the reaction of vinyl iodide **1b** with *N*-tosylhydrazone **2a** was also investigated, and **3n** was obtained in lower yield, with an all-carbon quaternary center. A better result was observed when the reaction was carried out at 55 °C (Scheme 3, eq 1). Addition, vinyl iodide **1c** worked well with **2a.** However, no reaction occurred when (*Z*)-2-iodo-3-phenylacrylaldehyde was employed. The reaction also worked with ethyl cyanoacetate (Scheme 3, eq 3). Dimethyl 2-allylmalonate and dimethyl 2-phenylmalonate were also investigated. To our disappointment, none of desired products was obtained, which is consistent with the previous report.[12]

Scheme 3. Scope of the Palladium-Catalyzed Reactions with **2a**



We further studied the different malonates and found: Diethyl malonate gave good yield, and diisopropyl malonate was less efficient. No reaction occurred when ditertbutyl malonate was used (Scheme 4). Those phenomenon may be may be due to the steric hindrance.

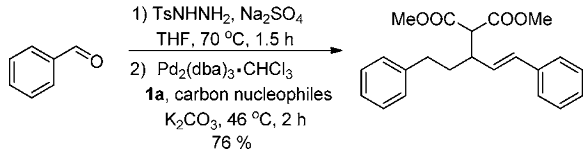
Scheme 4. Reactions of Different Malonates with **2a**



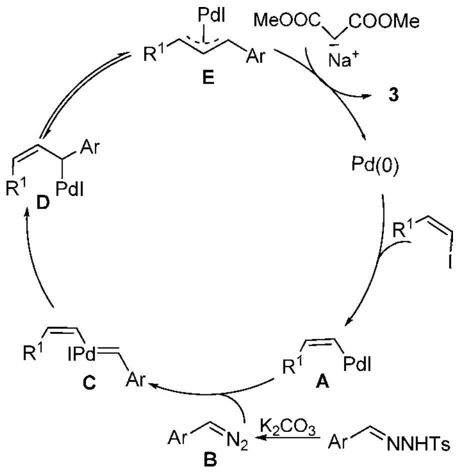
As is known, *N*-tosylhydrazone **2a** is readily formed by the condensation of aldehyde with tosylhydrazide (Scheme 5). Thus, we decided to conduct this reaction in a one-pot fashion. Treatment of the benzaldehyde with tosylhydrazide generated **2a** in situ, then catalyst, ligand, base, and another cross-coupling partner were added. Indeed, product **3a** could be isolated in 76% yield.

A plausible mechanism is proposed as shown in Scheme 6. The cross-coupling starts with oxidative addition of Pd(0)

Scheme 5. One-Pot Cross-Coupling Starting from Aldehyde



Scheme 6. Plausible Catalytic Cycle



to the vinyl iodide to afford intermediate **A**, followed by decomposition of the diazo compound **B** (generated in situ from *N*-tosylhydrazone) to give a palladium carbene complex **C**.[13] Subsequently, migratory insertion of a vinyl group to the carbonic carbon led to the η^1-allylpalladium complex **D**, which can isomerize to the η^3-allylpalladium **E**. This intermediate is then trapped with sodium malonate to generate product **3**.[14]

In conclusion, we have developed a new palladium-catalyzed three-component coupling of vinyl iodide, *N*-tosylhydrazone, and carbon nucleophiles, in which two separate C–C bonds were formed. This reaction proceeds via Pd carbene migratory insertion, followed by carbopalladation instead of classic β-H elimination. This reaction further demonstrates the concept of combination Pd-catalyzed insertion of diazo compounds and Pd-catalyzed cascade reactions, which opens a new avenue for the development of more novel Pd-catalyzed transformations.

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Supporting Information Available. Detailed experimental procedure and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The intermolecular substitution could occur on either end of the η3-allylpalladium and it can generate two regioisomeric products. Three were isolated in complete regioselectivities due to the steric hindrance. For a similar example, see: (a) Deardorff, D. R.; Savin, K. A.; Justman, C. J.; Karanjawala, Z. E.; Sheppeck, J. E., II; Hager, D. C.; Aydin, N. J. *Org. Chem.* **1996**, *61*, 3616–3622. (b) Yamada, Y. M. A.; Watanabe, T.; Torii, K.; Uozumi, Y. *Chem. Commun.* **2009**, 5594–5596. (c) Šebesta, R.; Škvorcová, A.; Horváth, B. *Tetrahedron: Asymmetry* **2010**, *21*, 1910–1915.

The authors declare no competing financial interest.