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Pd-Catalyzed C=C Double-Bond Formation by Coupling of *N*-Tosylhydrazones with Benzyl Halides

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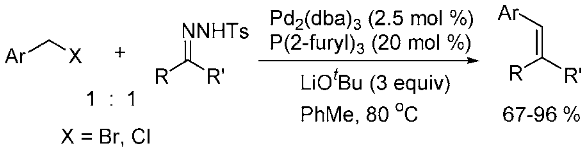
ABSTRACT



Pd-catalyzed reaction of *N*-tosylhydrazones with benzyl halides affords di- and trisubstituted olefins in high yields with excellent stereoselectivity. This coupling reaction is supposed to proceed through a migratory insertion of Pd carbene species.

C=C double-bond formation is one of the most fundamental transformations in synthetic organic chemistry. Among the various methods for constructing C=C double bonds from ketone and halide, the Wittig reaction and its modified versions are the most applicable and efficient choices.[1] In recent decades, Pd-catalyzed reactions have received increasing attention in C−C single bond formation.[2,3] However, to our knowledge, no example of a Pd-catalyzed cross-coupling reaction has been reported in the literature which can construct C=C double bonds directly, except the recent reports which involve Pd carbene species (vide infra). In the Pd-catalyzed cross-coupling of organometallic reagents with halides or triflates, the mechanism follows a common catalytic cycle that involves oxidative addition, transmetalation, and reductive elimination. It is thus not possible with this type of reaction to construct a C=C bond in conjunction with the coupling process.

Recent reports on a Pd-catalyzed cross-coupling reaction of α-diazocarbonyl compounds, in which the migratory insertion of Pd carbene species is suggested as the key step in the mechanism, have demonstrated such a possibility of

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(2) For selected reviews, see: (a) Negishi, E.-I. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002. (b) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (d) Tsuji, J. *Palladium Reagents and Catalysts, New Perspectives For the 21st Century*, 2nd ed.; Wiley: Chichester, 2004. (e) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (f) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (g) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (h) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366. (i) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (j) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622. (k) Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838. (l) Liebscher, J.; Yin, L. *Chem. Rev.* **2007**, *107*, 133. (m) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (n) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

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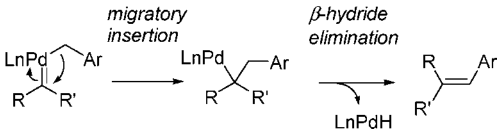
constructing C=C double bonds through Pd catalysis (Scheme 1).[4] Van Vranken et al. first reported the Pd-catalyzed cross-coupling of trimethylsilyldiazomethane with benzyl halides, affording styrene derivatives in low to moderate yields.[4a] More recently, Yu and co-workers reported a Pd-catalyzed reaction of benzyl bromide and α-aryldiazoacetate.[4i]

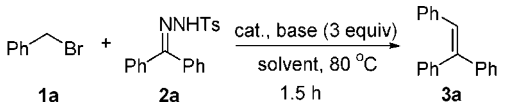
Scheme 1. Pd-Catalyzed C=C Bond Formation



In Yu's reports, α-diazocarbonyl compounds,[5] which are relatively stable due to the presence of an electron-withdrawing carbonyl group, serve as substrates. Diazo compounds without an electron-withdrawing substituent are usually unstable and thus difficult to handle. This significantly limits the scope of the above-mentioned Pd-catalyzed C=C double-bond-forming reaction. However, it has been well documented that unstable diazo compounds can be generated in situ from *N*-tosylhydrazones or *N*-tosylhydrazone salts through the Bamford−Stevens−Shapiro reaction.[6,7] This procedure of generating a diazo compound may be compatible to the Pd-catalyzed reaction conditions. Indeed, Barluenga and co-workers have recently reported the Pd-catalyzed cross-coupling reaction of *N*-tosylhydrazones and aromatic halides.[4d,e] Encouraged by those reports and in connection with our interest in this field,[4g,h,8] we report here the Pd-catalyzed cross-coupling reaction of *N*-tosylhydrazones and benzyl halides which affords olefins with excellent yields and stereoselectivity.

At the outset of this investigation, we used benzyl bromide **1a** and diphenylmethylene tosylhydrazone **2a** as the substrates (Table 1). When **1** and **2a** were catalyzed with $Pd(PPh_3)_4$ in toluene in the presence of LiO^{t}Bu, the coupling product triphenylethene **3a** was isolated in 28% yield (entry 1). Encouraged by this initial result, we proceeded to optimize the reaction. We were delighted to find that adding P(2-furyl)$_3$ as ligand could significantly improve the reaction (entries 2 and 3). With $Pd(OAc)_2$/P(2-furyl)$_3$, we went on to screen other reaction parameters. The reaction was found to proceed more efficiently in a nonpolar solvent such as toluene than in polar solvent (entries 3−6). The inorganic bases, such as K_2CO_3 and Cs_2CO_3, afforded poor results (entries 7 and 8). Surprisingly, although KO^{t}Bu and NaO^{t}Bu are similar to LiO^{t}Bu, they afforded little coupling products (entries 9 and 10). Several other palladium catalysts and the ratio of substrates were then examined (entries 11−14). $Pd_2(dba)_3$ (2.5 mmol %)/P(2-furyl)$_3$ (20 mmol %) and **1a**/**2a** = 1:1 led to the highest yield of **3a** (entry 13). It is worth noting that the ligand P(2-furyl)$_3$ plays a very important role in the reaction (entries 14 and 15). Without the ligand, only trace coupling product could be detected (entry 15). Finally, a control experiment showed that in the absence of palladium catalysts no product **3a** could be detected under otherwise identical conditions (entry 16).

Table 1. Conditions on Pd-Catalyzed Reaction of **1a** and **2a**[a]

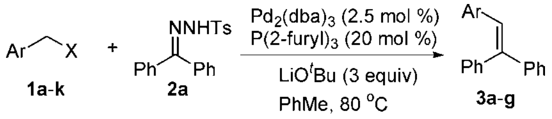


entry	cat. (mol %)/L[b] (mol %)	solvent	base	yield[c] (%)
1	$Pd(PPh_3)_4$(5)	PhMe	LiO^{t}Bu	28
2	$Pd(PPh_3)_2Cl_2$(5)/L(10)	PhMe	LiO^{t}Bu	53
3	$Pd(OAc)_2$(5)/L(20)	PhMe	LiO^{t}Bu	80
4	$Pd(OAc)_2$(5)/L(20)	DCE	LiO^{t}Bu	75
5[d]	$Pd(OAc)_2$(5)/L(20)	THF	LiO^{t}Bu	47
6	$Pd(OAc)_2$(5)/L(20)	dioxane	LiO^{t}Bu	72
7	$Pd(OAc)_2$(5)/L(20)	PhMe	Cs_2CO_3	25
8	$Pd(OAc)_2$(5)/L(20)	PhMe	K_2CO_3	12
9	$Pd(OAc)_2$(5)/L(20)	PhMe	KO^{t}Bu	trace
10	$Pd(OAc)_2$(5)/L(20)	PhMe	NaO^{t}Bu	17
11	$Pd_2(dba)_3$(2.5)/L(20)	PhMe	LiO^{t}Bu	92
12	$[Pd(C_3H_5)Cl]_2$(2.5)/L(20)	PhMe	LiO^{t}Bu	68
13[e]	**$Pd_2(dba)_3$(2.5)/L(20)**	PhMe	LiO^{t}Bu	**94**
14[e]	$Pd_2(dba)_3$(2.5)/L(8)	PhMe	LiO^{t}Bu	67
15	$Pd_2(dba)_3$(2.5)	PhMe	LiO^{t}Bu	trace
16	None	PhMe	LiO^{t}Bu	0

[a] The reactions were carried out in 0.3 mmol scale of **2a** in 5.0 mL solvent. Ratio of **1a** to **2a** is 1.2:1 if not otherwise indicated. [b] L = P(2-furyl)$_3$. [c] Isolated yield. [d] The reaction was run at 66 °C. [e] Ratio of **1a** to **2a** is 1:1.

A series of benzyl bromides were then subjected to the optimized reaction conditions with diphenylmethylene tosylhydrazone **2a** (Table 2).[9] Benzyl bromide and chloride are both effective substrates, although a slightly lower yield was observed for chloride (entries 1 and 2). The reaction with *ortho*-, *meta*-, and *para*-substituted benzyl halides all proceeded efficiently (entries 3−10). The reaction was found to be not notably affected by electronic

Table 2. Pd-Catalyzed Reaction of **1a**−**k** with **2a**[a]

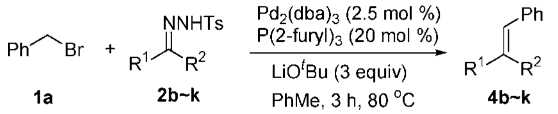


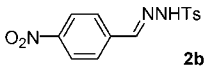
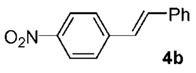
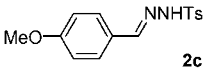
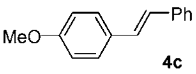
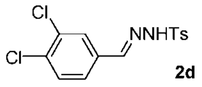
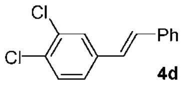
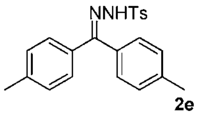
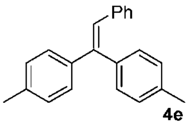
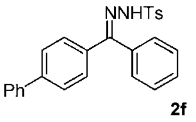
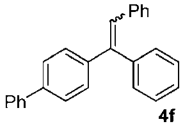
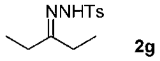
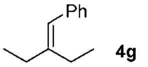
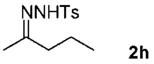
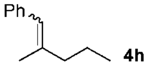
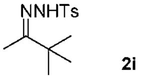
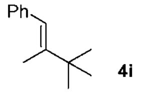
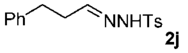
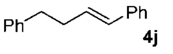
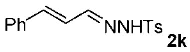
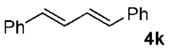
entry	**1**, Ar	X	**3**, yield[b] (%)
1	**1a**, Ph	Br	**3a**, 94
2	**1b**, Ph	Cl	**3a**, 84
3	**1c**, *p*-MeC_6H_4	Br	**3b**, 87
4	**1d**, *p*-MeC_6H_4	Cl	**3b**, 83
5	**1e**, *p*-PhC_6H_4	Br	**3c**, 84
6	**1f**, *m*-ClC_6H_4	Br	**3d**, 87
7	**1f**, *m*-ClC_6H_4	Cl	**3d**, 74
8	**1h**, 2,4-$Cl_2C_6H_3$	Br	**3e**, 83
9[c]	**1i**, *p*-$NO_2C_6H_4$	Br	**3f**, 87
10[c]	**1j**, *p*-$NO_2C_6H_4$	Cl	**3f**, 87
11[d]	**1k**, 2-naphthyl	Br	**3g**, 80

[a] The reactions were carried out on a 0.3 mmol scale of **1a**−**k** and 0.3 mmol of **2a** in 5.0 mL of PhMe. [b] Isolated yield. [c] The reaction was run for 5 h with1.5 equiv of **2a**. [d] The conversion of **1k** was 68%.

effects of the substituents of benzyl halides (entries 3−10), while 1.5 equiv of **2a** was needed and a longer reaction time was required when the substituent was *p*-NO_2 (entries 9 and 10). It is noteworthy that chloro substituents are tolerated in the reaction conditions, which is advantageous for further transformations with palladium catalysis (entries 6−8). Finally, for 2-(bromomethyl)naphthalene **1k**, the reaction became sluggish with lower substrate conversion (entry 11).

Table 3. Pd-Catalyzed Reaction of **1a** with **2b**−**k**[a]

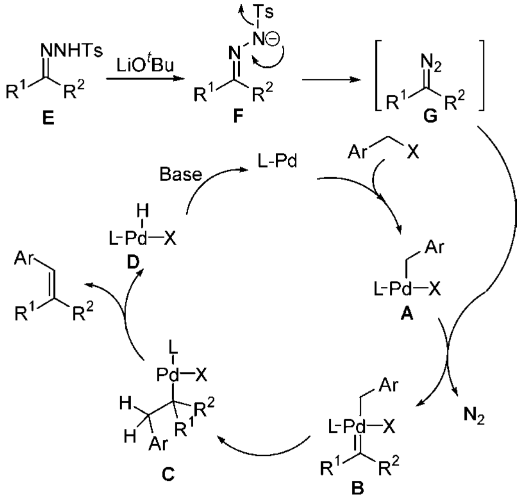


entry	2b~k	product	yield (%)[b]
1	 2b	 4b	83
2	 2c	 4c	75
3	 2d	 4d	96
4	 2e	 4e	78
5[c]	 2f	 4f	82
6[d]	 2g	 4g	75
7[d,e]	 2h	 4h	67
8[d]	 2i	 4i	69
9[d]	 2j	 4j	77
10	 2k	 4k	87

[a] The reactions were carried out in 0.3 mmol scale of **1a** and 0.3 mmol of **2b**−**k** in 5.0 mL of PhMe. [b] Isolated yield. [c] The ratio of 1:1 (*Z*/*E*) determined by GC. [d] The reactions were run in refluxing PhMe. [e] The *Z*/*E* ratio is 1:2 as determined by ^1H NMR of the crude product.

Next, we studied the scope of the reaction with various tosylhydrazones (Table 3). A series of tosylhydrazones were examined, and all gave the cross-coupling products in good yields. In the cases where di- and trisubstituted olefins were formed, the reaction only afforded the products with *E* selectivity (entries 1−3 and 8−10). However, when the steric hindrances were similar for the *E* and *Z* isomers, the *E* selectivity diminished (entries 5 and 7). Notably, for the tosylhydrazones generated from alkyl aldehydes or ketones, the reactions could be completed in moderate yields (entries 6−9). The reaction also worked well with the tosylhydrazones derived from cinnamaldehyde, affording 1, 3-diene products (entry 10).

Scheme 2. Mechanistic Rationale



A plausible mechanism is proposed as shown in Scheme 2. The reaction is initiated by oxidative addition of Pd(0) to benzyl halide to afford Pd(II) intermediate **A**. Diazo compound **G** is generated in situ from *N*-tosylhydrazone **E** with treatment of base. Decomposition of diazo compound **G** by Pd(II) species **A** leads to palladium carbene intermediate **B**. Migratory insertion of benzyl group to the carbenic carbon gives intermediate from which *β*-hydride elimination affords the olefins and regenerates the catalyst with the aid of base.

In summary, we have reported the first palladium-catalyzed cross-coupling reaction of *N*-tosylhydrazones

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(4) (a) Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219. (b) Greenman, K. L.; Van Vranken, D. L. *Tetrahedron* **2005**, *61*, 6438. (c) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2007**, *9*, 2047. (d) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587. (e) Barluenga, J.; Tomás-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.*−*Eur. J.* **2008**, *14*, 4792. (f) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909. (g) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198. (h) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566. (i) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469. (j) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677.

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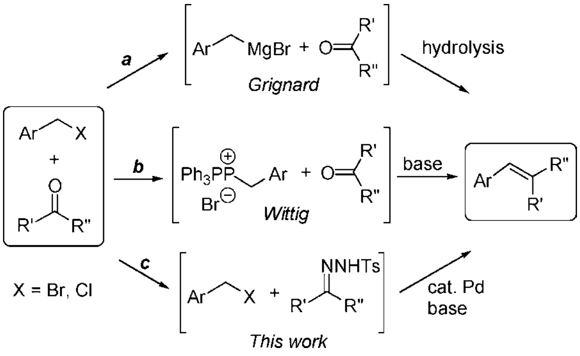
(7) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.

(8) Peng, C.; Cheng, J.; Wang, J. *J. Am. Chem. Soc.* **2007**, *129*, 8708.

with benzyl halides. This reaction represents a case of constructing a C═C double bond by a Pd-catalyzed coupling reaction. As outlined in Scheme 3, starting with ketones and benzyl halides, a classic method of synthesizing aromatic substituted olefins involves (1) converting the halides into Grignard or Gellman reagents, which add to the carbonyl group and then followed by dehydration (path a), and (2) converting benzyl halides into phosphine ylide, followed by a Wittig reaction (path b). The reaction reported in this paper represents an alternative way to achieve such a transformation by converting the ketones or aldehydes into *N*-tosylhydrazones, which are then coupled with benzyl halides with Pd catalysis (path c).

Scheme 3. Different Pathways of Converting Ketones and Benzyl Halides to Olefins



The Pd-catalyzed reaction reported in this paper has the advantages of mild reaction conditions and use of a 1:1 ratio of two coupling partners. Moreover, conversion of carbonyl compounds into *N*-tosylhydrazones is very easy and straightforward. Thus, in addition to the conventional Grignard- and Wittig-type approaches, this reaction provides an alternative method to prepare various di- and trisubstituted olefins. Mechanistically, this reaction again demonstrates the generality and importance of a migratory insertion process of Pd carbene species, which will inspire further exploration of these important intermediates.[3,10]

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Supporting Information Available: Experimental procedure and characterization data. These materials are available free of charge via the Internet at http://pubs.acs.org.

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(9) Typical experimental procedure for the Pd-catalyzed reaction of *N*-tosylhydrazones with benzyl halides: Under a nitrogen atmosphere, to a mixture of $Pd_2(dba)_3$ (7 mg, 0.075 mmol), LiO^tBu (72 mg, 0.9 mmol), and P(2-furyl)$_3$ (14 mg, 0.06 mmol) in PhMe (5 mL) was added benzyl bromide (**1a**, 51 mg, 0.3 mmol) and 1-(diphenylmethylene)-2-tosylhydrazone (**2a**, 105 mg, 0.3 mmol). The mixture was then stirred at 80 °C for 3 h. The reaction was monitored through TLC. Solvent was removed in vacuo to leave a residue which was purified by column chromatography to afford pure **3a** as a white solid (72 mg, 94%).

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