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Carbon–Carbon Bond Formation: Palladium-Catalyzed Oxidative Cross-Coupling of *N*-Tosylhydrazones with Allylic Alcohols

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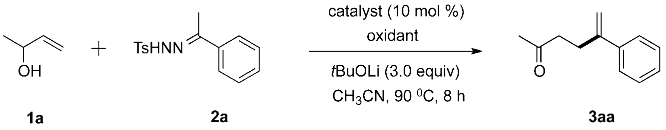
Over the past few decades, the development of palladium-catalyzed carbon–carbon bond-forming reactions has dramatically advanced "state-of-the-art" organic synthesis.[1] The most commonly applied palladium-catalyzed carbon–carbon bond-forming reactions in synthesis are the Heck, Stille, Suzuki, Sonogashira, Tsuji–Trost, and the Negishi reactions. In particular, the development of alternative methodologies that could be advantageous in terms of the selectivity and the availability of starting materials prior to the carbon–carbon bond-forming event is of interest.[2] Recently, Pd-catalyzed cross-coupling reactions of diazo compounds have emerged as a new type of cross-coupling reaction for the construction of carbon–carbon bonds.[3] An alternative route that makes use of *N*-tosylhydrazones as nucleophiles, which are an in situ source of diazo compounds for this transformation, has attracted much attention. The required *N*-tosylhydrazones are easily generated from carbonyl compounds, and the reaction can be seen as a cross-coupling of carbonyl groups, a process of high synthetic relevance that involves several steps and other methodologies. Recently, the groups of Barluenga and Wang have made significant progress towards palladium-catalyzed coupling reactions by using *N*-tosylhydrazones as the coupling partner.[4,5,6] A migratory insertion involving a palladium–carbene is proposed to account for these cross-coupling reactions.[7] However, palladium-catalyzed oxidative cross-coupling reactions using *N*-tosylhydrazones as the nucleophile are less developed.[5] Herein, we report a new palladium-catalyzed oxidative cross-coupling reaction of *N*-tosylhydrazones with allylic alcohols for the formation of carbon–carbon bonds. The reaction proceeds with readily available starting materials and affords substituted alkenes in a highly stereoselective manner.

Initially, we explored the Pd-catalyzed reaction of allylic alcohol **1a** with *N*-tosylhydrazone **2a** (Table 1). We found that a small amount of product **3aa** was obtained when oxygen was used as an oxidant (Table 1, entry 1). This result peaked our interest and we then screened for suitable reaction conditions for the synthesis of product **3aa**. Subsequently, we tested a series of oxidants in the reaction; however, inferior results were obtained when using *tert*-butyl hydroperoxide (TBHP), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), Ag_2CO_3, $PhI(OAc)_2$, or $Cu(OAc)_2$ as an oxidant (Table 1, entries 2–6). To our delight, the use of benzoquinone (BQ) as the oxidant greatly promoted the $Pd(OAc)_2$-catalyzed reaction of **1a** with **2a**, leading to the corresponding product **3aa** in 88% GC yield (Table 1, entry 7). Notably, none of the desired product **3aa** was detected when $Cu(OAc)_2$ was used as the metal catalyst (Table 1, entry 8). The reaction did not occur without the palladium catalyst (Table 1, entry 9); thus, the optimal reaction conditions for the cross-coupling of *N*-tosylhydrazones with allylic alcohols involved the treatment of allylic alcohol **1a** with *N*-tosylhydrazone **2a** in acetonitrile at 90 °C in the presence of palladium acetate (10 mol%) and lithium *tert*-butoxide (3.0 equiv) using BQ (2.0 equiv) as an oxidant.

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Oxidant	Yield [%][b]
1	$[Pd(OAc)_2]$	O_2 (1 atm)	8
2	$[Pd(OAc)_2]$	TBHP	5
3	$[Pd(OAc)_2]$	DDQ	0
4	$[Pd(OAc)_2]$	Ag_2CO_3	11
5	$[Pd(OAc)_2]$	$PhI(OAc)_2$	5
6	$[Pd(OAc)_2]$	$Cu(OAc)_2$	15
7	$[Pd(OAc)_2]$	BQ	88 (84)
8	$Cu(OAc)_2$	BQ	0
9	–	BQ	0

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), catalyst (10 mol%), and oxidant (2.0 equiv) in MeCN (3 mL) for 8 h. [b] Yields determined by GC; number in parentheses is the yield of isolated product.

With the optimized reaction conditions identified, the *N*-tosylhydrazone substrate scope was then investigated as shown in Table 2. The cross-coupling reaction of aromatic *N*-tosylhydrazones containing electron-withdrawing or electron-donating groups afforded the desired products (**3aa**–**3ah**) in moderate to good yields. We also found no significant effect on the reactivity when compounds were used which had substituents at the *para*-, *meta*-, and *ortho* positions of the aromatic ring (products **3ad**–**3af**). The naphthyl

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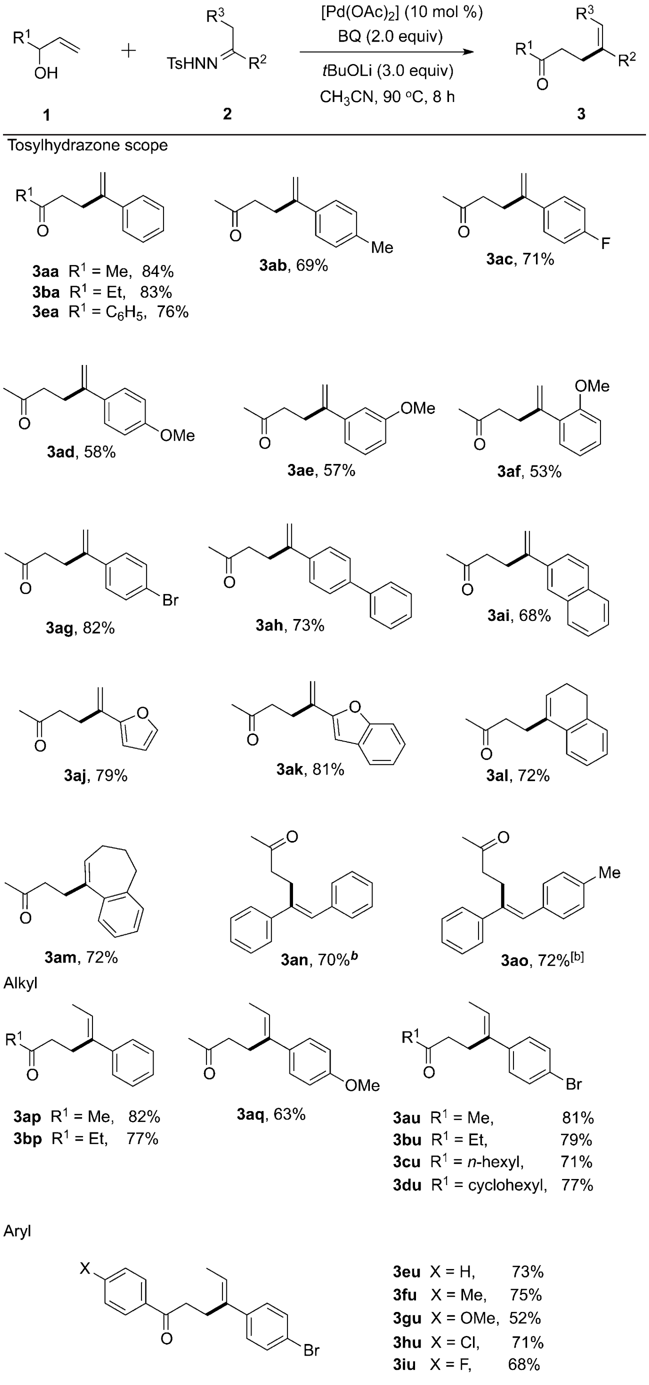
Table 2. Scope of reaction.[a]



1 + **2** → **3**

Tosylhydrazone scope

3aa R^1 = Me, 84%
3ba R^1 = Et, 83%
3ea R^1 = C$_6$H$_5$, 76%
3ab, 69%
3ac, 71%
3ad, 58%
3ae, 57%
3af, 53%
3ag, 82%
3ah, 73%
3ai, 68%
3aj, 79%
3ak, 81%
3al, 72%
3am, 72%
3an, 70%^{b}
3ao, 72%[b]

Alkyl

3ap R^1 = Me, 82%
3bp R^1 = Et, 77%
3aq, 63%
3au R^1 = Me, 81%
3bu R^1 = Et, 79%
3cu R^1 = n-hexyl, 71%
3du R^1 = cyclohexyl, 77%

Aryl

3eu X = H, 73%
3fu X = Me, 75%
3gu X = OMe, 52%
3hu X = Cl, 71%
3iu X = F, 68%

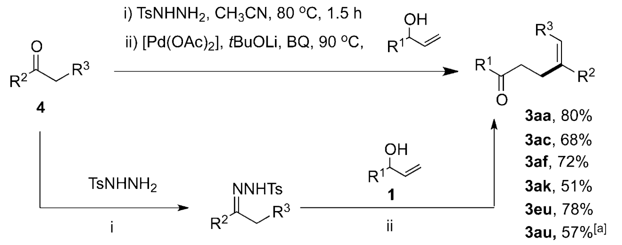
[a] All reactions were conducted on a 0.3 mmol scale: **1** (0.3 mmol), **2** (0.3 mmol), [Pd(OAc)$_2$] (10 mol %), BQ (2.0 equiv), and tBuOLi (3.0 equiv) in MeCN (3 mL) at 90 °C for 8 h; yields of isolated products are given. [b] $Z/E > 10{:}1$; the Z/E selectivity was determined by ^{1}H NMR spectroscopy; for product **3au**, the configuration was further confirmed by NOESY and COSY spectra.

N-tosylhydrazone (**2i**) was also a suitable substrate for this reaction (product **3ai**). The reaction of heterocyclic *N*-tosylhydrazones, such as furan and benzofuran, with allylic alcohol **1a** under similar conditions also proceeded well (products **3aj** and **3ak**). Notably, cyclic *N*-tosylhydrazones (**2l** and **2m**) also underwent smooth reactions to afford the corresponding products (**3l** and **3m**) in good yield.

Next, we used *N*-tosylhydrazones **2p**, **2q**, and **2u** to examine the cross-coupling reaction with a series of allylic alcohols (Table 2, allylic alcohol scope). Electron-rich and electron-poor benzene derivatives, as well as alkyl-substituted allyl alcohols, can be used. Notably, halide substituents were tolerated on the aromatic ring and furnished the products **3hu** and **3iu** in good yields.

Stereochemistry is a very important issue in the synthesis of polysubstitued olefins, and various trisubstituted olefins were obtained in this reaction with high stereoselectivity ($Z/E > 10{:}1$) (Table 2, see products **3an**, **3ao**, and allylic alcohol scope).

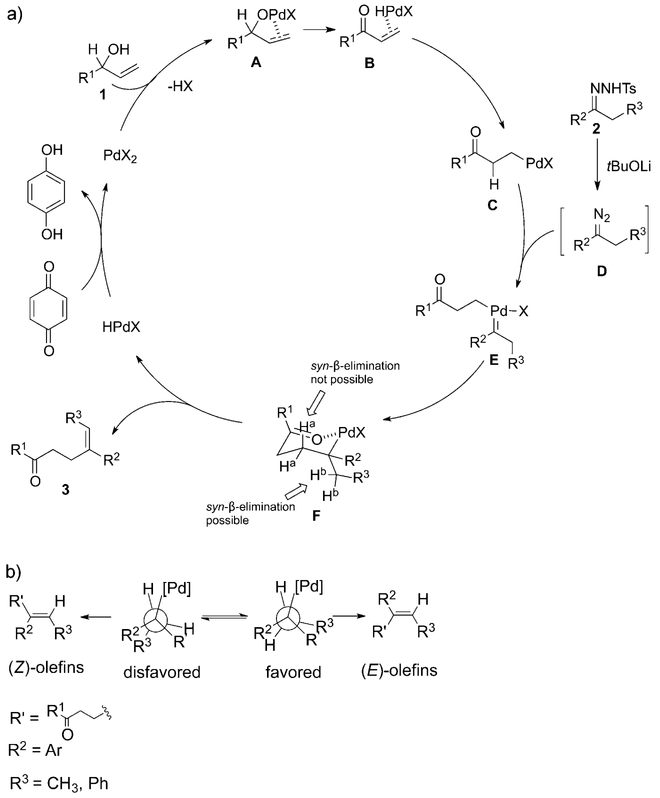
We succeeded in performing the reaction in a one-pot fashion by simply heating the carbonyl compound **4** with tosylhydrazide prior to the addition of the allyl alcohol; the oxidative coupling products were obtained in similar yields, but without the need to isolate the intermediate tosylhydrazone. Selected examples are shown in Scheme 1. It is worth noting that the reaction can be carried out on a multigram scale. For example, the reaction using 10 mmol (1.98 g) of 4-bromoacetophenone resulted in 1.44 g of the coupling product **3au** (Scheme 1, 57 % yield of isolated product). Moreover, the one-pot process can be considered a direct oxidative coupling of a carbonyl compound, a type of transformation without precedent and of great synthetic interest.



3aa, 80%
3ac, 68%
3af, 72%
3ak, 51%
3eu, 78%
3au, 57%[a]

Scheme 1. One-pot synthesis. Reaction conditions: i) carbonyl compound (0.3 mmol), tosylhydrazide (0.3 mmol), MeCN (3 mL), 90 °C, 90 min. ii) allyl alcohol (0.3 mmol), [Pd(OAc)$_2$] (10 mol %), BQ (2.0 equiv), tBuOLi (3.0 equiv), 90 °C, 8 h. Yields of isolated products are given. [a] Carried out on a 10 mmol scale.

The exact mechanism for the product formation is not clear at the present stage. A plausible mechanism for the oxidative cross-coupling reaction is proposed in Scheme 2. The reaction of allyl alcohol **1** with Pd^{II} leads to palladium alkoxide **A** by an intramolecular coordination of the alkene to the palladium center. Next, palladium alkoxide **A** undergoes a C−H bond cleavage to form intermediate **B**, with the double bond still coordinated to the palladium center. This is followed by insertion of the olefin into the Pd−H bond to give the palladium complex **C**.[8] Then, reaction of the diazo compound **D** (generated by the base-mediated decomposition of the tosylhydrazone **2**) with palladium complex **C** produces the Pd–carbene complex **E**.[3–7] Subsequently, a migratory insertion occurs to give cyclic intermediate **F** (similar to

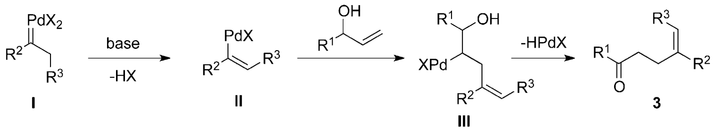


Scheme 2. Plausible mechanism for the oxidative cross-coupling.

cyclohexane), which is promoted by coordination of the carbonyl group to the alkylpalladium intermediate. Finally, the olefin **3** is produced with exclusive regioselectivity by *syn*-β-H^b elimination of **F**, and Pd^0 is oxidized by benzoquinone to regenerate the Pd^{II} species.

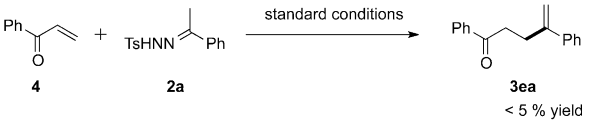
In this reaction pathway, the high stereoselectivity for the formation of (*E*)-olefins can be explained by the transition state of the *syn*-β-H elimination from intermediate **F**: the group R^3 prefers to eclipse with the less-bulky linear alkyl moiety, and this arrangement leads to (*E*)-olefins **3** as the main products (Scheme 2).

Another plausible mechanism starts with the initial formation of a palladium–carbene complex **I** (Scheme 3). After deprotonation by a base, the palladium–carbene complex **I** is transformed into to the alkenylpalladium intermediate **II**. Finally, the product **3** is produced by the traditional Heck route.[9]

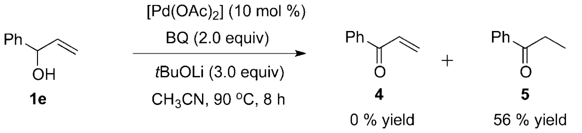


Scheme 3. Another plausible mechanism for the oxidative cross-coupling.

However, it is possible that the allylic alcohol could be oxidized by Pd^{II} to afford vinyl ketone, and then the base-mediated 1,4-addition of hydrazones could occur to give the desired product **3**. To investigate this possible pathway, vinyl ketone **4** and *N*-tosylhydrazone **2a** were treated with lithium *tert*-butoxide at 90 °C [Eq. (1)]. Only a trace amount of product **3ea** was detected in the ^{1}H NMR spectrum of the crude product. Moreover, **1e** was reacted under the optimized reaction conditions but only the ketone product **5** was observed, and no vinyl ketone **4** was detected [Eq. (2)]. Consequently, this pathway can be excluded.[10]



(1)



(2)

In conclusion, we have reported a new type of Pd-catalyzed carbon–carbon bond-forming coupling reaction of *N*-tosylhydrazones with allylic alcohols. The main features of this new methodology are: 1) common and readily available starting materials; (2 the formation of products with high stereoselectivity. Additionally, the reaction can be carried out on a multigram scale and in one pot. For these reasons, this reaction is highly applicable for target-oriented organic synthesis.

Experimental Section

General procedure: [Pd(OAc)$_2$] (0.03 mol, 6.7 mg), BQ (0.6 mmol, 64.8 mg), *t*BuOLi (0.9 mmol, 72.1 mg), and *N*-tosylhydrazone **2** were mixed with acetonitrile (3.0 mL) in a glass vial or round-bottom flask equipped with a magnetic stirring bar. Then, allyl alcohol **1** was added and the mixture was stirred at 90 °C for 8 h. After cooling to room temperature, ethyl acetate and brine were added and the layers were separated. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with two portions of brine and then dried over MgSO$_4$ and filtered. The residue was purified by flash chromatography on silica gel to obtain the desired products **3** using light petroleum ether/ethyl acetate (50:1 or 25:1, v/v) as eluent.

Acknowledgements

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Keywords: allylic compounds · C–C coupling · cross-coupling · *N*-tosylhydrazones · palladium

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[1] For monographs on palladium catalysis, see: a) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi),

Wiley, Hoboken, **2002**; b) J.-L. Malleron, J.-C. Fiaud, J.-Y. Legros, *Handbook of Palladium-Catalyzed Organic Reactions*, Academic Press, London, **1997**; c) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **1995**.

[2] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.

[3] a) K. J. Greenman, D. L. Van Vranken, *Tetrahedron* **2005**, *61*, 6438; b) C. Peng, J. Cheng, J. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 8708; c) S. Chen, J. Wang, *Chem. Commun.* **2008**, 4198; d) C. Peng, Y. Wang, J. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 1566; e) W. Y. Yu, Y. T. Tsoi, Z. Zhou, A. S. C. Chan, *Org. Lett.* **2009**, *11*, 469; f) R. Kudirka, S. K. J. Devine, C. S. Adams, D. L. Van Vranken, *Angew. Chem.* **2009**, *121*, 3731; *Angew. Chem. Int. Ed.* **2009**, *48*, 3677; g) Z.-S. Chen, X.-H. Duan, P.-X. Zhou, S. Ali, J.-Y. Luo, Y.-M. Liang, *Angew. Chem.* **2012**, *124*, 1399; *Angew. Chem. Int. Ed.* **2012**, *51*, 1370.

[4] For examples, see: a) J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 5683; *Angew. Chem. Int. Ed.* **2007**, *46*, 5587; b) J. Barluenga, M. Tomás-Gamasa, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2008**, *14*, 4792; c) J. Barluenga, M. Escribano, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2009**, *15*, 13291; d) Q. Xiao, J. Ma, Y. Yang, Y. Zhang, J. Wang, *Org. Lett.* **2009**, *11*, 4732; e) B. Tréguier, A. Hamze, O. Provot, D. J. Brion, M. Alami, *Tetrahedron Lett.* **2009**, *50*, 6549; f) Z. Zhang, Y. Liu, M. Gong, X. Zhao, Y. Zhang, J. Wang, *Angew. Chem.* **2010**, *122*, 1157; *Angew. Chem. Int. Ed.* **2010**, *49*, 1139; g) E. Brachet, A. Hamze, J. F. Peyrat, J. D. Brion, M. Alami, *Org. Lett.* **2010**, *12*, 4042; h) Q. Xiao, Y. Xia, H. Li, Y. Zhang, J. Wang, *Angew. Chem.* **2011**, *123*, 1146; *Angew. Chem. Int. Ed.* **2011**, *50*, 1114; i) L. Zhou, Fe. Ye, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 13590; j) J. Barluenga, L. Florentino, F. Aznar, C. Valdés, *Org. Lett.* **2011**, *13*, 510; k) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Angew. Chem.* **2010**, *122*, 7008; *Angew. Chem. Int. Ed.* **2010**, *49*, 6856; l) J. Barluenga, N. Quiñones, M.-J. Cabal, F. Aznar, C. Valdés, *Angew. Chem.* **2011**, *123*, 2398; *Angew. Chem. Int. Ed.* **2011**, *50*, 2350; m) Z.-S. Chen, X.-H. Duan, L.-Y. Wu, S. Ali, K.-G. Ji, P.-X. Zhou, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2011**, *17*, 6918; n) F. Zhou, K. Ding, Q. Cai, *Chem. Eur. J.* **2011**, *17*, 12268; o) J. Zhang, Y. Liu, L. Ling, Y. Li, Y. Dong, M. Gong, X. Zhao, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 4330; p) L. Zhou, F. Ye, Y. Zhang, J. Wang, *Org. Lett.* **2012**, *14*, 922.

[5] For examples of palladium-catalyzed oxidative cross-coupling reactions using *N*-tosylhydrazones as nucleophiles, see: a) X. Zhao, J. Jing, K. Lu, Y. Zhang, J. Wang, *Chem. Commun.* **2010**, *46*, 1724; b) L. Zhou, Fe. Ye, J. Ma, Y. Zhang, J. Wang, *Angew. Chem.* **2011**, *123*, 3572; *Angew. Chem. Int. Ed.* **2011**, *50*, 3510.

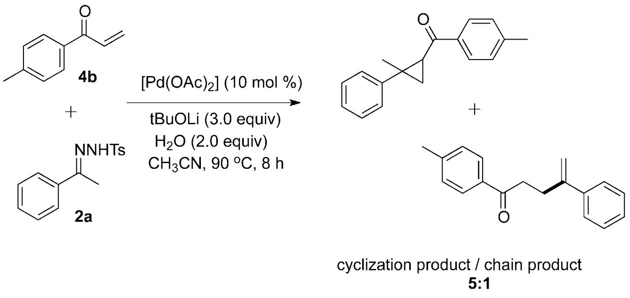
[6] For recent reviews, see: a) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560; b) J. Barluenga, C. Valdés, *Angew. Chem.* **2011**, *123*, 7626; *Angew. Chem. Int. Ed.* **2011**, *50*, 7486.

[7] For reports on the migratory insertion of stable palladium–carbene species, see: a) A. C. Albéniz, P. Espinet, R. Manrique, A. Pérez-Mateo, *Angew. Chem.* **2002**, *114*, 2469; *Angew. Chem. Int. Ed.* **2002**, *41*, 2363; b) M. Bröring, C. D. Brandt, S. Stellwag, *Chem. Commun.* **2003**, 2344; c) D. Solé, L. Vallverdú, X. Solans, M. Font-Bardia, J. Bonjoch, *Organometallics* **2004**, *23*, 1438; d) A. C. Albéniz, P. Espinet, R. Manrique, A. Pérez-Mateo, *Chem. Eur. J.* **2005**, *11*, 1565; e) A. C. Albéniz, P. Espinet, A. Pérez-Mateo, A. Nova, G. Ujaque, *Organometallics* **2006**, *25*, 1293.

[8] a) J. A. Keith, P. M. Henry, *Angew. Chem.* **2009**, *121*, 9200; *Angew. Chem. Int. Ed.* **2009**, *48*, 9038; b) K. M. Gligorich, M. S. Sigman, *Angew. Chem.* **2006**, *118*, 6764; *Angew. Chem. Int. Ed.* **2006**, *45*, 6612; c) K. B. Urkalan, M. S. Sigman, *J. Am. Chem. Soc.* **2009**, *131*, 18042; d) K. B. Urkalan, M. S. Sigman, *J. Am. Chem. Soc.* **2011**, *133*, 11454.

[9] J. B. Melpolder, R. F. Heck, *J. Org. Chem.* **1976**, *41*, 265.

[10] Additionally, vinyl ketone **4b** and *N*-tosylhydrazone **2a** were treated under similar conditions. Both the cyclization product and the chain product were detected in the ^{1}H NMR spectrum of the crude product. These results suggest that the allylic alcohol is not oxidized by Pd^{II} to the vinyl ketone.



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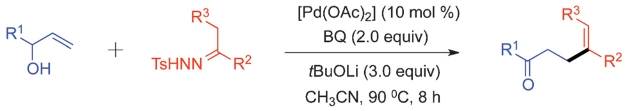
Cross-Coupling

*H. Chen, L. Huang, W. Fu, X. Liu, H. Jiang** .... ▮▮▮▮–▮▮▮▮

Carbon–Carbon Bond Formation: Palladium-Catalyzed Oxidative Cross-Coupling of *N*-Tosylhydrazones with Allylic Alcohols



* C-C bond-forming reaction
* regioselective

In the zone: Pd-catalyzed oxidative cross-coupling of *N*-tosylhydrazones with allylic alcohols leads to C–C bond formation. A palladium–carbene migratory insertion is proposed to play the key role in this transformation. The reaction proceeds with readily available starting materials to afford substituted alkenes in a highly stereoselective manner (see scheme).