ORGANIC LETTERS

2013
Vol. 15, No. 18
4814–4817

Pd-Catalyzed Heck-Type Cascade Reactions with *N*-Tosyl Hydrazones: An Efficient Way to Alkenes via in Situ Generated Alkylpalladium

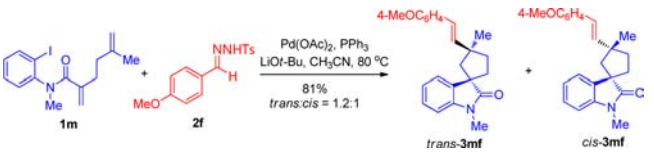
Xianglei Liu, Xinna Ma, Yunze Huang, and Zhenhua Gu*

Department of Chemistry, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, People's Republic of China

zhgu@ustc.edu.cn

Received August 4, 2013

ABSTRACT



A palladium-catalyzed Heck-type cascade reaction of aryl halides and *N*-tosyl hydrazones is reported. The neopentylpalladium species, generated from an intramolecular Heck-type insertion reaction of aryl halides, could efficiently react with carbenes to form highly functionalized alkenes. The synthesis of spiro compounds was also explored via a multiple Heck-type insertion reaction with *N*-tosyl hydrazone.

Since the discovery of transition-metal-catalyzed asymmetric cyclopropanation of alkenes with diazo compounds in the 1960s,[1] various useful transformations involving active metal−carbene intermediates have been discovered, which played an important role in the revolution of modern organic synthetic methods.[2] In contrast to the well-documented rhodium-, copper-, and ruthenium-catalyzed reactions, palladium-catalyzed transformations that involve Pd carbene intermediates so far have received less attention. Studies indicated that the reactivity of palladium−carbene species are fairly different from that of the corresponding Rh(II) and Cu(I) compounds.[3] Although several decades ago Pd carbenes as active intermediates were already proposed in some reactions of nondiazo compounds,[4] the Pd carbene migration/insertion process was first proposed by Van Vranken and co-workers in their seminal report in the palladium-catalyzed reaction of benzyl halides and (trimethylsilyl)diazomethane in 2001.[5]

Subsequently, contributions from the groups of Van Vranken,[6] Barluenga and Valdés,[7] Wang,[8] and others[9] greatly enriched the chemistry of palladium-catalyzed

(1) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *7*, 5239.

(2) (a) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998, pp 163−220. (d) Evans, P. A. *Modern Rhodium-Catalyzed Organic Reactions*; Wiley-VCH: Weinheim, Germany, 2005. (e) Nishiyama, H. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

(3) (a) Anciaux, A. J.; Hubert, A. J.; Noel, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem.* **1980**, *45*, 695. For a review, see: (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

(4) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *Tetrahedron Lett.* **1985**, *26*, 5143.

(5) Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219.

(6) (a) Greenman, K. L.; Van Vranken, D. L. *Tetrahedron* **2005**, *61*, 6438. (b) Devine, S. K.; Van Vranken, D. L. *Org. Lett.* **2007**, *9*, 2047. (c) Devine, S. K.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909. (d) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677. (e) Khanna, A.; Maung, C.; Johnson, K. R.; Luong, T. T.; Van, Vranken, D. L. *Org. Lett.* **2012**, *14*, 3233. (f) Kudirka, R.; Van Vranken, D. L. *J. Org. Chem.* **2008**, *73*, 3585.

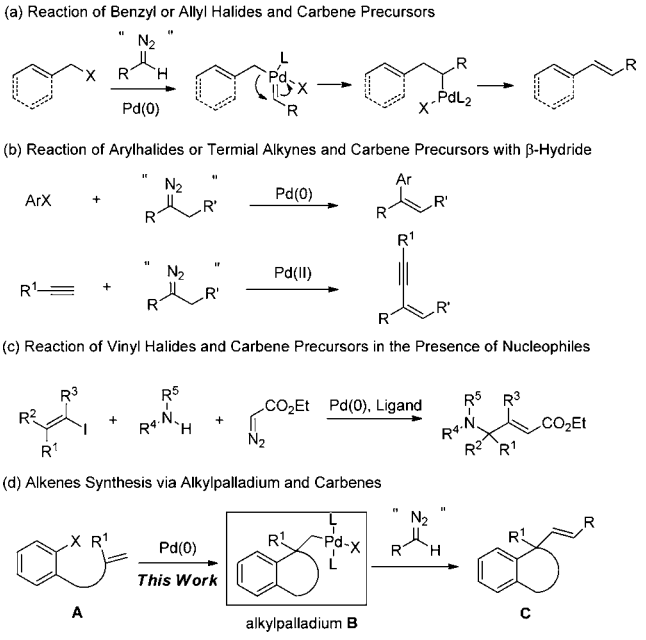
(7) (a) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587. (b) Barluenga, J.; Tomás-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem. Eur. J.* **2008**, *14*, 4792. (c) Barluenga, J.; Escribano, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem. Eur. J.* **2009**, *15*, 13291. (d) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Chem. Eur. J.* **2010**, *16*, 12801. (e) Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6856. (f) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2010**, *352*, 3235. (g) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510. (h) Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2012**, *14*, 2323.

10.1021/ol402210a
Published on Web 09/09/2013

cross-coupling reactions with carbenes,[10] especially the introduction of *N*-tosyl hydrazones as carbene precursors by Barluenga and Valdés. *N*-Tosyl hydrazones now are known as valuable and convenient synthons for carbenes and are used frequently in both metal-catalyzed and metal-free cross-coupling reactions.[11] However, there are still limited reaction patterns for the construction of C=C double bonds from Pd carbenes: (1) the reaction of benzyl/allyl halides and carbene precursors can deliver styrene or 1,3-diene derivatives (Scheme 1a);[5,6a,8a,b] (2) the reaction of aryl halides or terminal alkynes with carbene precursors bearing β-hydride can construct polysubstituted alkenes (Scheme 1b);[7,8d−f,9i−l] (3) the reaction of vinyl halides and carbene precursors can generate an (η^3-allyl)-palladium intermediate, which can be terminated with both inter- or intramolecular nucleophiles (Scheme 1c).[6b−e] Thus, the exploration of new reaction patterns for Pd carbene involved reactions is still important and necessary.

Even though significant attention has been paid to *N*-tosyl hydrazones as carbene precursors in Pd-catalyzed cross-coupling reactions over the past decade, examples of the reactions between alkylpalladium and carbenes are rare,[9f] which might be a new way to synthesize functionalized alkenes. The well-developed intramolecular Heck-type reaction provides a good platform to study the reaction between carbene and alkylpalladium.[12] Despite the fact that Heck reaction based cascades are very well known, the integration of the chemistry of a cascade Heck reaction with Pd carbenes obtained from diazo compounds or tosyl hydrazones has rarely been explored.[6f] We reasoned that alkylpalladium species **B**, which was extensively studied by Overman and co-workers in the control of further chemoselective transformations,[13] could be formed efficiently via classical oxidative addition and insertion reactions of **A** (Scheme 1d). Subsequently the reaction of **B** with carbenes could deliver the functionalized alkene **C** via a Pd carbene migration/insertion and β-hydride elimination process.

Scheme 1. Reaction Patterns of Pd Carbene Involved Alkene Synthesis



We began our initial studies with the readily available acrylamide **1a**[14] and benzaldehyde derived *N*-tosyl hydrazone **2a**. Delightfully, heating a mixture of **1a** and 2.0 equiv of **2a** in the presence of 5 mol % $Pd(OAc)_2$ and 15 mol % of tri(2-furyl)phosphine (TFP) in toluene gave the expected product **3aa** in 73% yield, and no corresponding *Z* isomer was detected (Table 1, entry 1). Both THF and CH_3CN are good solvents, with the yields being 95% and 98%, respectively (entries 2 and 3). However, it was found by crude ^1H NMR analysis that the reaction in CH_3CN is cleaner than that in THF, and the isolated product from the reaction in THF was contaminated with small amounts of uncharacterized byproducts. Triphenylphosphine (PPh_3) is found to be as efficient as TFP (entry 4), while *rac*-BINAP and dppe greatly decrease the reaction rate and the reaction becomes complicated with prolonged reaction times (entries 5 and 6). In the absence of a palladium source there was no conversion of **1a**. The reaction gave limited conversion of the iodide to the desired product

(8) (a) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198. (b) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732. (c) Zhou, F.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590. (d) Zhao, X.; Wu, G.; Yan, C.; Lu, K.; Li, H.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 5580. (e) Zhou, L.; Ye, F.; Ma, J.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3510. (f) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 922.

(9) (a) Albéniz, A. C.; Espinet, P.; Manrique, R.; Pérez-Mateo, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2363. (b) López-Alberca, M. P.; Mancheño, M. J.; Fernández, I.; Gómez-Gallego, M.; Sierra, M. A.; Torres, R. *Org. Lett.* **2007**, *9*, 1757. (c) Goll, J. M.; Fillion, E. *Organometallics* **2008**, *27*, 3622. (d) Zhou, F.; Ding, K.; Cai, Q. *Chem. Eur. J.* **2011**, *17*, 12268. (e) Chen, Z.-S.; Duan, X.-H.; Wu, L.-Y.; Ali, S.; Ji, K.-G.; Zhou, P.-X.; Liu, X.-Y.; Liang, Y.-M. *Chem. Eur. J.* **2011**, *17*, 6918. (f) Chen, H.; Huang, L.; Fu, W.; Liu, X.; Jiang, H. *Chem. Eur. J.* **2012**, *18*, 10497. (g) Meana, I.; Albéniz, A. C.; Espinet, P. *Organometallics* **2012**, *31*, 5494. (h) Meana, I.; Toledo, A.; Albéniz, A. C.; Espinet, P. *Chem. Eur. J.* **2012**, *18*, 7658. (i) Tréguier, B.; Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 6549. (j) Brachet, E.; Hamze, A.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Org. Lett.* **2010**, *12*, 4042. (k) Roche, M.; Hamze, A.; Brion, J.-D.; Alami, M. *Org. Lett.* **2013**, *15*, 148. (l) Roche, M.; Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *J. Org. Chem.* **2013**, *78*, 445.

(10) For some reviews, see: (a) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577. (b) Franssen, N. M. G.; Walters, A. J. C.; Reek, J. N. H.; de Bruin, B. *Catal. Sci. Technol.* **2011**, *1*, 153. (c) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486. (d) Zhang, Z.; Zhang, Y.; Wang, J. *ACS Catal.* **2011**, *1*, 1621. (e) Zhang, Y.; Wang, J. *Top. Curr. Chem.* **2012**, *327*, 239. (f) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015. (g) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (h) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236.

(11) For the migration/insertion process for Cu carbenes, see: (a) Zhou, L.; Shi, Y.; Xiao, Q.; Liu, Y.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 968. (b) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296. (c) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114. (d) Ye, F.; Ma, X.; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2012**, *134*, 5742. (e) Hossain, M. L.; Ye, F.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 1236.

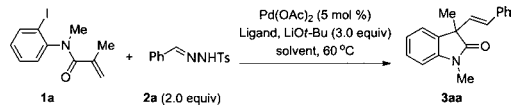
(12) Tsuji, J. *Palladium Reagents and Catalysis—New Perspectives for the 21st Century*; Wiley: Chichester, U.K., 2004; pp 105−430.

(13) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439.

(14) (a) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500. (b) Evans, P.; Grigg, R.; Ramzan, M. I.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1999**, *40*, 3021.

along with a wide range of additional side products in the absence of phosphine ligands.

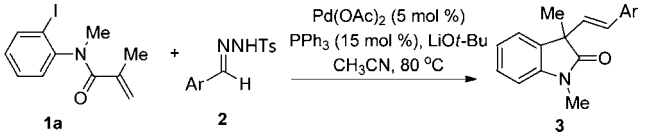
Table 1. Optimization of Reaction Conditions[a]

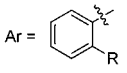
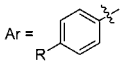


entry	ligand (amt (mol %))	solvent	time (h)	yield of **3aa** (%)[b]
1	TFP (15)	PhMe	3	73
2	TFP (15)	THF	2	95[c]
3	TFP (15)	CH_3CN	1	98
4	PPh_3 (15)	CH_3CN	1	98
5	*rac*-BINAP (7.5)	CH_3CN	5	37
6	dppe (7.5)	CH_3CN	5	31

[a] The reactions were conducted with a 0.15−0.20 mmol amount of **1a**. [b] Isolated yields. [c] The isolated product was contaminated with a small amount of an uncharacterized compound.

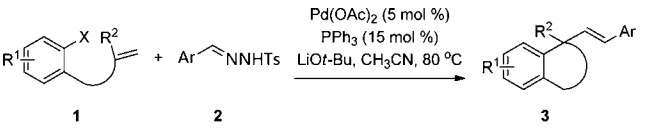
Table 2. Substrate Scope of *N*-Tosyl Hydrazones[a]

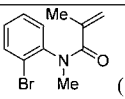
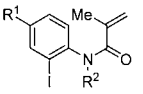
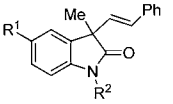
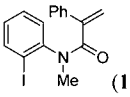
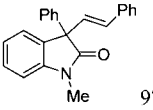
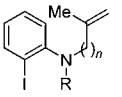
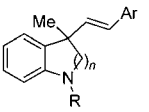
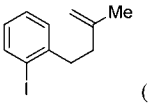
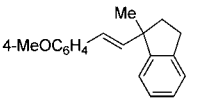
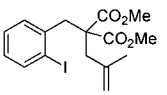
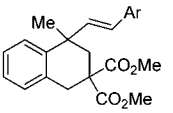


entry	*N*-tosylhydrazone **2**		yield (%)[b]
1		R = Me (**2b**)	99 (**3ab**)
2	Ar = 	R = OMe (**2c**)	99 (**3ac**)
3		R = OMe (**2c**)	89 (**3ac**)[c]
4		R = Br (**2d**)	90 (**3ad**)
5		R = Cl (**2e**)	87 (**3ae**)
6		R = OMe (**2f**)	99 (**3af**)
7		R = *t*-Bu (**2g**)	97 (**3ag**)
8	Ar = 	R = CO_2Et (**2h**)	97 (**3ah**)
9		R = CN (**2i**)	70 (**3ai**)
10		R = CN (**2i**)	<5[c]
11		R = NO_2 (**2j**)	0
12	Ar = 3-$NO_2C_6H_4$	(**2k**)	95 (**3ak**)
13	Ar = 2-furyl	(**2l**)	89 (**3al**)
14	Ar = 2-naphthyl	(**2m**)	72 (**3am**)

[a] The reactions were conducted with 0.20 mmol of **1**; for details see the Supporting Information. [b] Isolated yields. [c] 1 mol % of $Pd(OAc)_2$ was used. Hydrazone **2i** was fully decomposed and **1a** was recovered in 65% yield.

Table 3. Substrate Scope of Organic Halides[a]



entry	halide **1**	**2**	yield of **3** (%)[b]
1	 (**1b**)	**2a**	98 (**3aa**)
			
2	$R^1 = R^2 =$ Me (**1c**)	**2a**	99 (**3ca**)
3	R^1 = Cl, R^2 = Me (**1d**)	**2a**	98 (**3da**)
4	R^1 = H, R^2 = Bn (**1e**)	**2a**	99 (**3ea**)
5	$R^1 = R^2$ = H (**1f**)	**2a**	0 (**3fa**)
6	 (**1g**)	**2a**	 97 (**3ga**)
			
7	R = Ac, *n* = 1 (**1h**)	**2a**	65 (**3ha**), Ar = Ph
8	R = Ts, *n* = 2 (**1i**)	**2f**	77 (87) (**3if**)[c] Ar = 4-$MeOC_6H_4$
9	 (**1j**)	**2f**	 97 (**3jf**)
			
10	(**1k**)	**2f**	Ar = 4-$MeOC_6H_4$: 68 (**3kf**)
11	(**1k**)	**2l**	Ar = 2-furyl; 61 (**3kl**)

[a] The reactions were conducted with 0.15−0.20 mmol of **1**; for details see the Supporting Information. [b] Isolated yields. [c] The conversion is 90%, and the yield in parentheses is based on recovery of SM.

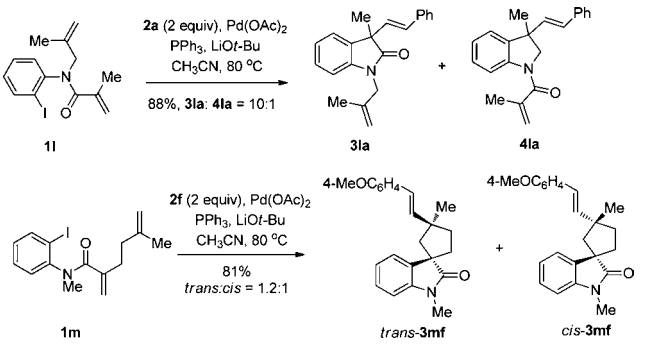
It was found that the scope with respect to the *N*-tosyl hydrazones was expansive, allowing for efficient coupling with **1a** (Table 2). The reaction of aryl hydrazones with ortho substituents on the phenyl ring, i.e., methyl and methoxyl, gave the corresponding products in almost quantitative yields (entries 1 and 2), even when the loading

of palladium catalyst was decreased to 1 mol % (entry 3). Halogen atoms, i.e. bromide and chloride, at ortho and para positions of the *N*-tosyl hydrazones were compatible with the reaction conditions (entries 4 and 5). Several other functionalities in hydrazones were tolerated, including *p*-methoxyl (**2f**), *p*-*tert*-butyl (**2g**), and ester (**2h**) (entries 6−8). It is worth noting that the efficiency of the reaction greatly depended on the catalyst loading when **2i** was used as the substrate (entries 9 and 10). When 5 mol % of $Pd(OAc)_2$ was used, the reaction afforded the corresponding product in 70% yield, while only a trace amount of product was detected when the amount of $Pd(OAc)_2$ was decreased to 1 mol %. This observation is presumably due to the unmatched rates of different steps in the catalytic cycle: alkylpalladium formation, *N*-tosyl hydrazone decomposition, Pd carbene migration/insertion, etc. The reaction with **2k**, a hydrazone derived from *m*-nitrobenzaldehyde, afforded the product in 95% yield. This stands in contrast with the observation of the reaction with **2j**, a hydrazone derived from *p*-nitrobenzaldehyde, which failed to deliver appreciable amounts of product (entries 11 and 12). **2l**,**m**, hydrazones derived from 2-furylaldehyde and 2-naphthaldehyde, could also smoothly react with **1a** to give the corresponding products in moderate to good yields (entries 13 and 14).

As illustrated in Table 3, the generality of the reaction was additionally explored by subjecting various organic halides to the optimized reaction conditions. Aryl bromide **1b** and *p*-methyl (**1c**)- and *p*-chloro-substituted (**1d**) iodoaniline derivatives efficiently reacted with **2a** to give the corresponding products in almost quantitative yields (Table 3, entries 1−3). The reaction of *N*-benzyl amide **1e** afforded alkene **3ea** in 99% yield, while an amide bearing a free N−H bond failed to undergo this cross-coupling reaction (entries 4 and 5). The reaction of 2-phenylacrylamide **1g** was also highly efficient and delivered the product in 97% yield (entry 6). In addition to acrylamides, we were pleased to find that **1h**,**i** were competent substrates and the reaction furnished the corresponding heterocycles in good yields (entries 7 and 8). The reaction proceeded equally efficiently in the synthesis of a five-membered carbocycle (entry 9). The malonate-derived substrate **1k** could also smoothly couple with *N*-tosyl hydrazones **2f**,**l** to give the coresponding alkenes in moderate yields (entries 10 and 11).

The reaction of **1l**, which bears *N*-allyl and α-methylacryl moieties, forms 2-indolinone **3la** predominantly in good yield (Scheme 2). This method was also applied to the synthesis of spiro compounds via a multiple-insertion process, which has been well studied in classic Heck reactions. Indeed, by the use of diene **1m**, the reaction could smoothly give the spiro compounds **3mf** in 81% combined yield, with a 1.2:1 diastereoselectivity (Scheme 2). The stereochemistry of the products was confirmed by the X-ray analysis of *trans*-**3mf** (see the Supporting Information).

Scheme 2. Reaction of **1l**,**m** with *N*-Tosyl Hydrazones



It is notable that the reaction is scalable, with no impact on the yield, as demonstrated by the reaction of 1.51 g (5.0 mmol) of **1a** with **2a** (2.0 equiv), affording the product in 96% yield (see the Supporting Information for details).

In conclusion we have developed a palladium-catalyzed Heck-type cascade reaction of organic halides with *N*-tosyl hydrazones. It is the first example of the reaction of neopentylpalladium intermediates with carbenes to form steric alkenes. Spiro compounds could also be synthesized efficiently in one step via a multiple Heck-type insertion reaction. This method provided a new route to the divergent synthesis of functionalized alkenes and extended the broad utility of *N*-tosyl hydrazones.

Acknowledgment. This work was financially supported by NSFC (No. 21272221), the Recruitment Program of Global Experts. We thank Prof. K. P. C. Vollhardt (UC Berkeley) for helpful suggestions.

Supporting Information Available. Experimental procedures, crystallographic data and a CIF file for *trans*-**3mf**, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.