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Microwave-Assisted, Pd(0)-Catalyzed Cross-Coupling of Diazirines with Aryl Halides

Xia Zhao,[†] Guojiao Wu,[†] Chong Yan,[†] Kui Lu,[†] Hui Li,[†] Yan Zhang,[†] and Jianbo Wang*[,†,‡]

Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China, and State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

wangjb@pku.edu.cn

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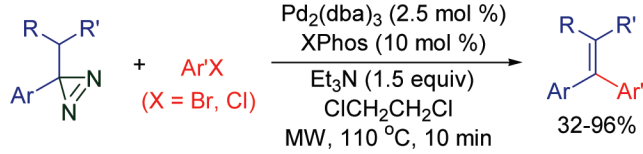
ABSTRACT

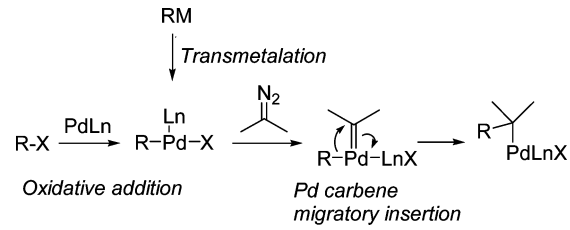


Pd(0)-catalyzed cross-coupling reactions of diazirines with aryl halides under microwave heating conditions afford a series of substituted olefins. A reaction mechanism involving the migratory insertion of the Pd carbene intermediate is proposed.

In recent years, Pd-catalyzed cross-coupling reactions of diazo compounds have emerged as a new type of synthetic method for constructing C−C double bonds.[1] In related studies, Barluenga and co-workers first reported the Pd-catalyzed cross-coupling of *N*-tosylhydrazones with aryl halides.[2a−c] Recently, we have reported related coupling reactions with *N*-tosylhydrazones.[2d−g] *N*-Tosylhydrazones are commonly used as precursors for in situ generation of diazo compounds (eq 1).[3] In all the transformations mentioned above, migratory insertion of Pd carbene is proposed as the key step in the catalytic cycle (Scheme 1).

On the other hand, diazirines are important carbene precursors, and their reaction mechanism upon photolysis and thermolysis has been studied extensively over the past decades.[4] Diazirines are also widely used as photosensitive groups of photoaffinity labeling techniques in biochemical studies.[5] Moreover, reactions of diazirines with transition metal complexes have been documented in the literature.[6]

Scheme 1. Migratory Insertion of Pd Carbene



[†] Peking University.
[‡] Chinese Academy of Sciences.

(1) (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) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909. (e) Kudirka, R.; Van Vranken, D. L. *J. Org. Chem.* **2008**, *73*, 3585. (f) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566. (g) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198. (h) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469. (i) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677.

(2) (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*, 3291. (d) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732. (e) Zhao, X.; Jing, J.; Lu, K.; Zhang, Y.; Wang, J. *Chem. Commun.* **2010**, 1724. (f) Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1139. (g) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590.

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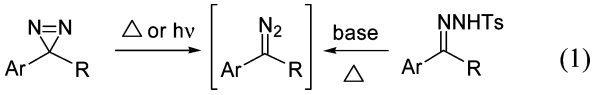
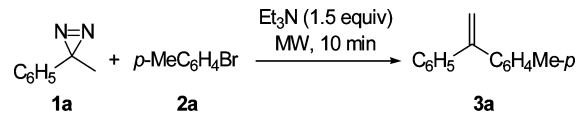
However, to the best of our knowledge, the transition-metal-catalyzed reaction of diazirines has not been reported. Since diazirine can be converted into a diazo compound or carbene upon photolysis or thermolysis (eq 1),[7] we conceived that diazirine might replace *N*-tosylhydrazone in a Pd-catalyzed cross-coupling reaction. Herein we report the Pd(0)-catalyzed cross-coupling of diazirines with aryl halides, which affords substituted olefins in good yields.



(1)

At the outset of this investigation, we explored the Pd-catalyzed cross-coupling of 3-methyl-3-phenyldiazirine **1a** with *p*-bromotoluene **2a** under oil bath heating conditions. To our delight, cross-coupling product could indeed be formed, albeit in low yield, by heating at 90 °C for 4 h (Table 1, entry 1). The yield could not be further improved regardless of extensive optimization attempts.[8] We observed that the main side product was styrene, which was derived from diazirine decomposition through a carbene 1,2-hydrogen shift.[4,9] Further optimization experiments revealed that microwave irradiation could slightly improve the yield with $Pd(PPh_3)_4$ as catalyst (entry 2).[10] Switching the catalyst to $Pd_2(dba)_3$/Xphos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) further improved the reaction (entry 3). Since microwave-assisted reactions are generally affected by solvents, we next attempted to optimize the reaction by examining a series of solvents, including 1,2-dichloroethane (DCE), *N*-methyl-2-pyrrolidinone (NMP), THF, and $CHCl_3$ (entries 4−7). DCE

Table 1. Reaction Condition Optimization with Pd-Catalyzed Cross-Coupling of **1a** and **2a**



1a **2a** **3a**

entry	cat. (mol %)	*t* (°C)	solvent	yield (%)[a]
1[b,c]	$Pd_2(dba)_3$(2.5)/Xphos (10)	90	DCE	32
2[b]	$Pd(PPh_3)_4$ (5)	100	MeCN	27
3[b]	$Pd_2(dba)_3$(2.5)/Xphos (10)	100	MeCN	33
4[b]	$Pd_2(dba)_3$(2.5)/Xphos (10)	100	THF	11
5[b]	$Pd_2(dba)_3$(2.5)/Xphos (10)	100	$CHCl_3$	–[d]
6[b]	$Pd_2(dba)_3$(2.5)/Xphos (10)	100	NMP	–[d]
7[b]	$Pd_2(dba)_3$(2.5)/Xphos (10)	100	DCE	37
8[e]	$Pd_2(dba)_3$(2.5)/Xphos (10)	100	DCE	40
9[e]	$Pd_2(dba)_3$(2.5)/Xphos (10)	110	DCE	64
10[e,f]	$Pd_2(dba)_3$(2.5)/Xphos (10)	110	DCE	78
11	Xphos (10)	110	DCE	–[g]

[a] Isolated yields. [b] **1a**:**2a** = 1.1:1; concentration of **1a** is 0.17 mol/L. [c] Reaction was heated by an oil bath for 4 h. [d] Product **3a** was not detected. [e] Concentration of **1a** is 1.0 mol/L. [f] **1a**:**2a** = 1.5:1. [g] **2a** remained unchanged while **1a** decomposed to afford a complex mixture.

afforded better results compared with MeCN (entry 7), while other solvents all gave inferior results (entries 4−6). Subsequent experiments indicated that higher concentration and higher reaction temperature could improve the reaction (entries 8 and 9). Finally, the reaction was found to afford optimal results by further changing the substrate ratio of **1a** to **2a** from 1.1:1 to 1.5:1 (entry 10).

With the optimized reaction conditions in hand, the substrate scope was examined with a series of diazirines **1a**−**g** and halides **2a**−**n** (Table 2). All the reactions were complete within 10 min and afforded substituted olefins in moderate to excellent yields. For the aromatic bromides, the reactions demonstrated high functional group tolerance. The reaction proceeded smoothly with *ortho*-, *meta*-, and *para*-substituted aryl bromides (entries 1, 12, and 20). Both electron-donating and -withdrawing groups of the aryl bromides were tolerated (entries 2−6). Heterocyclic aryl bromides could be employed in the coupling reaction (entry 7). Highly sterically hindered mesityl bromide (**2j**) could also afford the coupling products **3m** and **3p** in good yields (entries 13 and 18).

Tri- and tetrasubstituted olefins were obtained in good yields by using the diazirines bearing alkyl substituents other than a methyl group (entries 16−23). The stereoselectivity of the olefin products varied depending on the substrates. It was noted that the reaction of diazirines with *ortho*-substituted aryl bromides could afford trisubstituted olefins with high stereoselectivity,

(3) For a review, see: Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.

(4) For reviews, see: (a) Moss, R. A. *Acc. Chem. Res.* **2006**, *39*, 267, and references therein. (b) Liu, M. T. H., Ed. *Chemistry of Diazirines*; CRC Press: Boca Raton, FL, 1987.

(5) For selected recent reports, see: (a) Mayer, T.; Maier, M. E. *Eur. J. Org. Chem.* **2007**, 4711. (b) Kumar, N. S.; Young, R; N. *Bioorg. Med. Chem.* **2009**, *17*, 5388. (c) Chee, G.; Yalowich, J. C.; Bodner, A.; Wu, X.; Hasinoff, B. B. *Bioorg. Med. Chem.* **2010**, *18*, 830. (d) Hashimoto, M.; Furukawa, K.; Tomohiro, T.; Hatanaka, Y. *Chem. Pharm. Bull.* **2010**, *58*, 405.

(6) (a) Albini, A.; Kisch, H. In *Topics in Current Chemistry*; Springer Berlin/Heidelberg Press, 1976; Vol. 65, p 5. (b) Chaloner, P. A.; Gary, D.; Glick, G. D.; Moss, R. A. *J. Chem. Soc., Chem. Commun.* **1983**, 880. (c) Avent, A. G.; Benyunes, S. A.; Chaloner, P. A.; Hitchcock, P. B. *J. Chem. Soc., Chem. Commun.* **1987**, 1285. (d) Benyunes, S. A.; Chaloner, P. A. *J. Organomet. Chem.* **1988**, *341*, C50. (e) Benyunes, S. A.; Chaloner, P. A.; Hitchcock, P. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1491. (f) Avent, A. G.; Benyunes, S. A.; Chaloner, P. A.; Gotts, N. G.; Hitchcock, P. B. *J. Chem. Soc., Dalton Trans.* **1991**, 1417. (g) Moss, R. A.; Fedé, J.; Yan, S. *J. Am. Chem. Soc.* **2000**, *122*, 9878.

(7) For selected literature, see: (a) Amrich, M. J.; Bell, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 292. (b) Liu, M. T. H.; Ramakrishnan, K. *J. Org. Chem.* **1977**, *42*, 3450. (c) Ammann, J. R.; Subramanian, R.; Sheridan, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 7592. (d) Nigam, M.; Platz, M. S.; Showalter, B. M.; Toscano, J. P.; Johnson, R.; Abbot, S. C.; Kirchhof, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 8055. (e) Reinaldo, M.; Frances, L. C. *Org. Lett.* **2004**, *6*, 881. (f) Zhang, Y.; Burdzinski, G.; Kubicki, J.; Platz, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 16134. (g) Zhang, Y.; Vyas, S.; Hadad, C. M.; Platz, M. S. *J. Phys. Chem. A* **2010**, *114*, 5902.

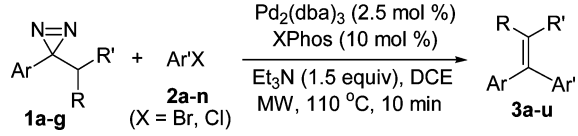
(8) For details, see Supporting Information.

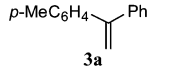
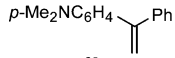
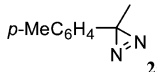
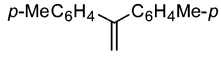
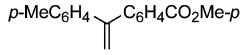
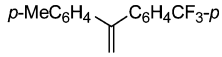
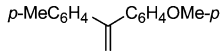
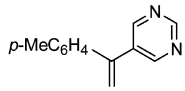
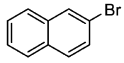
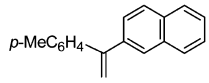
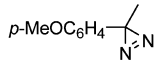
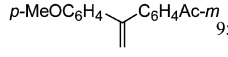
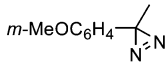
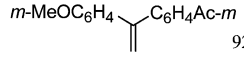
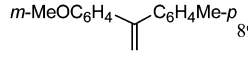
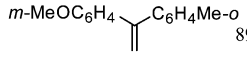
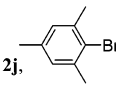
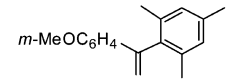
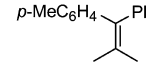
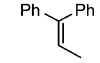
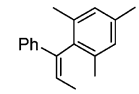
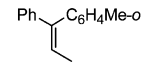
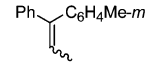
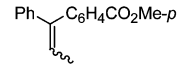
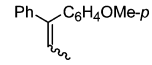
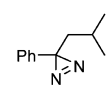
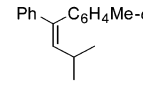
(9) (a) Schaefer, H. F., III *Acc. Chem. Res.* **1979**, *12*, 288. (b) Nikon, A. *Acc. Chem. Res.* **1993**, *26*, 84.

(10) For recent reviews on microwave-assisted reactions, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Appukkuttan, P.; Van der Eycken, E. *Eur. J. Org. Chem.* **2008**, 1133 and references cited therein.

(11) Typical procedure for the Pd(0)-catalyzed cross-coupling. Aryl halide (0.6 mmol), diazirine (0.9 mmol), triethylamine (0.9 mmol), $Pd_2(dba)_3$ (0.015 mmol, 2.5 mol %), XPhos (0.06 mmol, 10 mol %), and dioxane (0.6 mL) were mixed in a microwave tube. The mixture was stirred at 110 °C for 10 min under microwave conditions (the highest power: 200 W; run time: 2 min; hold time: 10 min; temperature: 110 °C). Upon the completion of the reaction, the solution was filtered through a short silica gel column. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography on silica gel.

Table 2. Pd(0)-Catalyzed Cross-Coupling with a Series of Diazirines and Aryl Halides[a] [11]

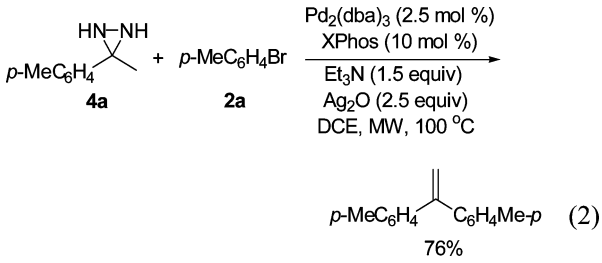


entry	1, diazirine	2, Ar'X	product, 3	yield (%)[b]
1	 **1a**	**2a**, *p*-MeC_6H_4Br	 **3a**	78
2	**1a**	**2b**, *p*-$Me_2NC_6H_4Br$	 **3b**	68
3	 **1b**	**2a**, *p*-MeC_6H_4Br	 **3c**	89
4	**1b**	**2c**, *p*-$MeO_2CC_6H_4Br$	 **3d**	96
5	**1b**	**2d**, *p*-$CF_3C_6H_4Br$	 **3e**	90
6	**1b**	**2e**, *p*-$MeOC_6H_4Br$	 **3f**	92
7	**1b**	**2f**, 	 **3g**	56
8	**1b**	**2g**, 	 **3h**	86
9	 **1c**	**2h**, *m*-AcC_6H_4Br	 **3i**	95
10	 **1d**	**2h**	 **3j**	92
11	**1d**	**2a**	 **3k**	89
12	**1d**	**2i**, *o*-MeC_6H_4Br	 **3l**	89
13	**1d**	**2j**, 	 **3m**	76
14	**1d**	**2k**, *m*-AcC_6H_4Cl	**3j**	50
15	**1d**	**2l**, *p*-MeC_6H_4Cl	**3k**	32
16	 **1e**	**2a**	 **3n**	47
17	 **1f**	**2m**, C_6H_5Br	 **3o**	95
18	**1f**	**2j**	 **3p**, *Z*:*E* = 10:1[c]	68
19	**1f**	**2i**	 **3q**, *Z*:*E* = 10:1[c]	96
20	**1f**	**2n**, *m*-MeC_6H_4Br	 **3r**, *Z*:*E* = 1:1[c]	89
21	**1f**	**2c**	 **3s**, *Z*:*E* = 1:1[c]	95
22	**1f**	**2e**	 **3t**, *Z*:*E* = 1:1[c]	95
23	 **1g**	**2i**	 **3u**, *Z*:*E* = 19:1[c]	87

[a] Reaction conditions: **1a**−**g** (0.9 mmol), **2a**−**n** (0.6 mmol), $Pd_2(dba)_3$ (2.5 mol %), Xphos (10 mol %), Et_3N (0.9 mmol), DCE (0.6 mL), MW 110 °C, Pmax power 200 W, 10 min hold time. [b] Yield of isolated product after silica gel chromatography. [c] Ratio determined by ^1H NMR spectra.

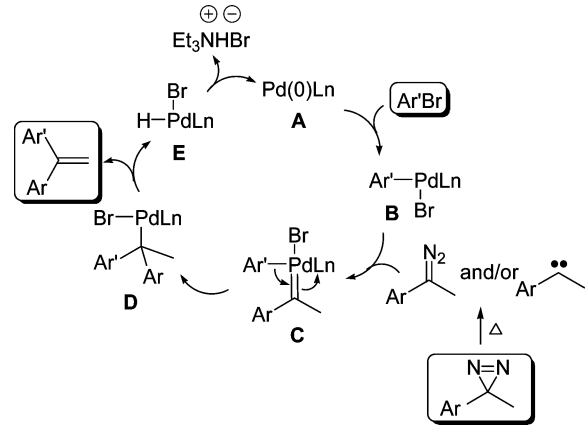
affording predominantly *Z*-isomers (entries 18−19 and 23), while in other cases, the reaction essentially showed no selectivity (entries 20−22). The selectivity was found to be not notably affected by electronic effects of the substituents on the aryl bromide (entries 20−22). Finally, it was noteworthy that aryl chlorides also worked, affording coupling products in moderate yields (entries 14 and 15).

Since diazirines were synthesized by oxidation of diaziridines with oxidants such as Ag_2O and MnO_2,[5b] we explored the possibility of Pd-catalyzed cross-coupling of diaziridines under oxidative conditions. It was demonstrated that such oxidative cross-coupling was indeed possible. As shown in eq 2, the Pd(0)-catalyzed cross-coupling of 4-bromotoluene (**2a**) with diaziridine (**4a**) proceeded smoothly with Ag_2O as oxidant.



A plausible mechanism for this Pd(0)-catalyzed cross-coupling is proposed as shown in Scheme 2. The reaction is initiated by oxidative addition of Pd(0) catalyst **A** to the aryl halide to afford Pd(II) species **B**. On the other hand, diazirine may be converted to a diazo compound or carbene species under the thermolytic conditions,[6] which then reacts with Pd(II) species **B** to afford Pd carbene complex **C**. Migratory insertion of the aryl group to the carbenic carbon affords intermediate **D**, from which β-hydride elimination provides the product and regenerates the Pd(0) species in the presence of triethylamine.

Scheme 2. Mechanistic Rationale



In summary, we have reported a microwave-assisted cross-coupling reaction of diazirines with aryl halides, which provides various substituted olefins efficiently. To our knowledge, this reaction represents the first example of a transition-metal-catalyzed reaction of diazirines, which significantly expands the chemistry of diazirines. Moreover, it further demonstrates the generality and importance of the transformations based on Pd carbene species.

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Supporting Information Available: Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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