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Cyclopropylmethyl Palladium Species from Carbene Migratory Insertion: New Routes to 1,3-Butadienes

Lei Zhou,[†,‡] Fei Ye,[†] 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 School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, China

wangjb@pku.edu.cn

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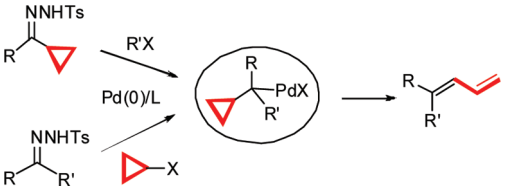
ABSTRACT



Cyclopropylmethyl palladium species can be accessed by Pd-catalyzed reaction of either cyclopropyl *N*-tosylhydrazone with halide or *N*-tosylhydrazone with cyclopropyl halide. In both approaches migratory insertion of Pd carbene is the key process. These transformations constitute new approaches toward 1,3-butadiene derivatives.

Molecules bearing cyclopropyl groups are versatile building blocks in organic synthesis.[1] Their unique structural and electronic properties give rise to an array of very interesting and characteristic transformations. Among these small ring compounds, reactions of highly strained methylenecyclopropanes (MCPs) with various reactants, catalyzed by transition metals such as Pd,[2] Ni,[3] and Pt,[4] have attracted much attention. One of the characteristic reaction patterns of MCPs is the formation of cyclopropylmethyl metal species, followed by cyclopropyl ring opening through β-carbon elimination, which ultimately leads to homoallylic compounds (Scheme 1). In general, the cyclopropylmethyl metal species is generated upon the addition of M−M′ or R−M intermediates to the double bond of MCPs, and palladium is the most commonly used transition metal for this transformation (path ***a***, Scheme 1).[1a,f,2] For an earlier example, de Meijere and co-workers have demonstrated that Pd-catalyzed ring opening of MCPs affording polyenes in a cascade reaction consisting of intramolecular Heck-type coupling.[2f] Suginome and co-workers have developed transition-metal-catalyzed silaborative C−C bond cleavage of MCPs.[2c,d] Palladium-catalyzed ring

[†] Peking University.
[‡] Sun Yat-Sen University.

(1) For selected reviews, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493. (c) Patai, S. *The Chemistry of the Cyclopropyl Group*, Part 2; John Wiley & Sons: New York, 1987; Vol. 1. (d) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1. (e) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013. (f) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (g) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (h) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867. (i) Ma, S. *Pure Appl. Chem.* **2008**, *80*, 695.

(2) For recent Pd-catalyzed reactions of MCPs, see: (a) Jiang, M.; Mei, Y.; Shi, M. *Eur. J. Org. Chem.* **2010**, 3307. (b) Shao, L.; Li, J.; Wang, B.; Shi, M. *Eur. J. Org. Chem.* **2010**, 6448. (c) Ohmura, T.; Taniguchi, H.; Suginome, M. *Org. Lett.* **2009**, *11*, 2880. (d) Ohmura, T.; Taniguchi, H.; Kondo, Y.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 3518. (e) Shi, M.; Liu, L.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430. (f) Braese, S.; de Meijere, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 2545.

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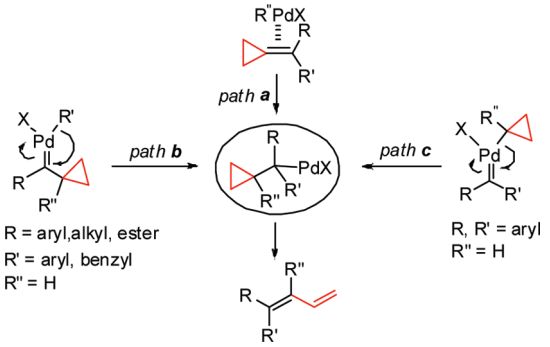
Scheme 1. Routes to the Cyclopropylmethyl Palladium Species



opening of MCPs with alcohols or amines as the nucleophile have been reported by Yamamoto[5] and Shi.[6]

In the previous studies, the regioselectivity of palladation across the C=C bond of MCPs is usually substrate-dependent, which in some cases results in the formation of isomeric products. This may limit the wide application of this type of transformations. Thus, the methods for the generation of cyclopropylmethyl metal species through alternative approaches are highly desirable.

Recently, Pd-catalyzed cross-coupling reactions of diazo compounds have been proven as an efficient method for the formation of C=C double bonds.[7] The characteristic steps of these reactions are the formation of a Pd-carbene complex and the subsequent migratory insertion of the carbene. The carbenoid ligand can migrate into the aryl-,[8,9] benzyl-,[10] vinyl-,[11] allyl-,[12] acyl-,[13] alkynyl-,[14] and allenyl-palladium bonds.[15] The application of *N*-tosylhydrazones as nonstabilized diazo precursors in this type of Pd-catalyzed cross-coupling reactions, pioneered by Barluenga and co-workers,[7b,c,8a] has significantly expanded this chemistry. As a continuation of our interest in the exploration of Pd-carbene migratory insertion as a key process in the development of new synthetic transformations, we have conceived that the cyclopropylmethyl palladium species may be accessed by the migratory insertion of carbene. Herein we wish to report the Pd-catalyzed cross-coupling of cyclopropyl *N*-tosylhydrazones with aryl halide, which leads to the 1,1-disubstituted 1,3-butadienes *via* cyclopropylmethyl palladium species (Scheme 1, path ***b***). Moreover, we observed that the Pd-catalyzed coupling of *N*-tosylhydrazones with bromocyclopropane led to the formation of same palladium intermediate. This latter reaction involves a migratory insertion of a carbenoid ligand into the cyclopropyl-palladium bond (Scheme 1, path ***c***).

Initially, the path ***b*** process was explored by the reaction of iodobenzene and cyclopropyl *N*-tosylhydrazone **2a** in 1,4-dioxane at 80 °C with various palladium catalysts (Table 1). It was observed that Pd(II) complexes such as $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ were not effective, while $Pd(PPh_3)_4$ gave 10% of product **3a** (Table 1, entries 1−3). When $Pd_2(dba)_3$ was employed with P(2-furyl)$_3$ as the ligand, 1,3-diene product **3a** was obtained in a slightly higher yield (15%). Encouraged by this result, we then decided to optimize the reaction conditions with $Pd_2(dba)_3$ and various phosphine ligands (Table 1, entries 5−8).We were delighted to find that an 81% yield of the desired product **3a** could be obtained when the reaction was carried out in the presence of 2.5 mol % of $Pd_2(dba)_3$ and 5 mol % of Xphos (Table 1, entry 8). The effect of solvents was subsequently examined, and the reactions were found to proceed more efficiently in polar solvents (Table 1, entries 8−11), whereas a nonpolar solvent such as toluene was found to be unfavorable (Table 1, entry 12). The reaction at 80 °C provided the optimal results; either higher or lower temperatures resulted in diminished yields (Table 1, entries 13 and 14).

With the acceptable conditions in hand (Table 1, entry 8), we next explored the scope of the reaction with a variety of aryl halides and cyclopropyl *N*-tosylhydrazones (Table 2). The reaction is general with respect to the structure of aryl halides, and both iodides and bromides could be employed as substrates with similar results (Table 2, entries 2 and 3). Chloride was also effective, albeit providing the product with a slightly diminished yield (Table 2, entry 3). The reaction with *ortho*-, *meta*-, and *para*-substituted aryl halides all proceeded efficiently (Table 2, entries 2−10). 2-Iodo naphthalene was also a suitable substrate for the coupling, leading to the 1,3-butadiene **3i** in good yield (85%) (Table 2, entry 11). When 1,4-diiodobenzene was used as a substrate, double cross-coupling occurs, affording the corresponding butadiene derivative **3j** in 70% yield (Table 2, entry 12). To further examine the scope of the reaction, *N*-tosylhydrazone **2d** and **2e** were employed to react with aryl halides, and they all gave the cross-coupling products in good yields (Table 2, entries 13−16).

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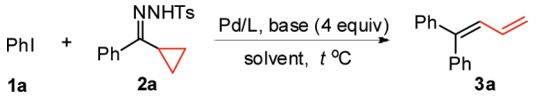
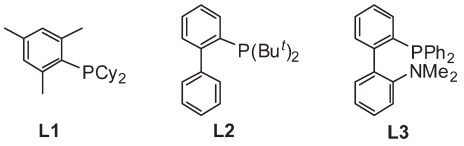
Table 1. Palladium-Catalyzed Cross-Coupling of Iodobenzene with *N*-Tosylhydrazone **2a**[a]



entry	catalyst	L	solvent	*t* (°C)	yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	dioxane	80	0
2	$PdCI_2(PPh_3)_2$	–	dioxane	80	0
3	$Pd(PPh_3)_4$	–	dioxane	80	10
4	$Pd_2(dba)_3$[c]	P(2-furyl)$_3$	dioxane	80	15
5	$Pd_2(dba)_3$	**L1**	dioxane	80	<10
6	$Pd_2(dba)_3$	**L2**	dioxane	80	20
7	$Pd_2(dba)_3$	**L3**	dioxane	80	37
8	$Pd_2(dba)_3$	Xphos[d]	dioxane	80	81
9	$Pd_2(dba)_3$	Xphos	MeCN	80	51
10	$Pd_2(dba)_3$	Xphos	DCE	80	40
11	$Pd_2(dba)_3$	Xphos	DMF	80	33
12	$Pd_2(dba)_3$	Xphos	toluene	80	<10
13	$Pd_2(dba)_3$	Xphos	dioxane	60	45
14	$Pd_2(dba)_3$	Xphos	dioxane	100	75

[a] All of the reactions were carried out by using iodobenzene (0.5 mmol), **2a** (1 mmol), and ^{t}BuOLi (2 mmol) with 2.5 mol % of palladium as the catalyst and 5 mol % of ligand in 5 mL of solvent for 16 h. [b] Yields were determined by using GC/MS methods with *n*-dodecane as the internal standard. [c] $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0). [d] Xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

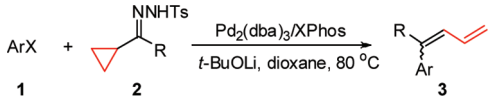


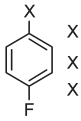
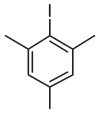
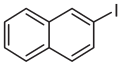
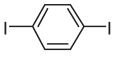
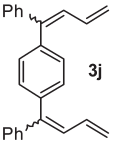
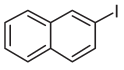
L1 L2 L3

The stereochemical outcome of the reaction seems to be directed by the steric bulkiness of the substituents. When the steric hindrances are similar for both *E* and *Z* products, the *E*/*Z* selectivity is poor (Table 2, entries 6–8 and 12). However, when there are substituents at the *ortho*-position of aryl halides, or Ar groups are much larger than the R group, the *Z*-isomers are obtained as the major products. The configuration of **3h** is confirmed by its X-ray crystal diffraction, and the configurations of other major products are assumed to be same as that of **3h**.

To further expand the scope of the reaction, *N*-tosylhydrazone **4** was prepared and was subjected to the Pd-catalyzed coupling with iodobenzene under the same reaction conditions (Scheme 2). Interestingly, 1,4-diene **5** was obtained as the major product instead of the expected 1,3-diene **6**. This result can be rationalized as follows. The *β*-carbon elimination, which is driven by strain release, requires *syn*-periplanar alignment of the C–Pd bond with the proximal C–C bond of the cyclopropyl ring, as depicted in **A**. This leads to the exclusive formation of *cis*-(2-vinylcyclohexyl)palladium species **B**. The intermediate **B** is unable to undergo *syn*-*β*-hydride elimination to form a conjugate diene **6**, thus producing **5** as the major product.

Table 2. Palladium-Catalyzed Cross-Coupling of Aryl Halides with Various *N*-Tosylhydrazones[a]



entry	halide **1**	R (**2**)	product **3**	yield (%)[b]	*Z*/*E*[c]
1	PhI	Ph (**2a**)	**3a**	74	-
2	 X = I		**3b**	82	-
3	X = Br	*p*-FC_6H_4 (**2b**)	**3b**	77	-
4	X = Cl		**3b**	45	-
5	*p*-$CH_3OC_6H_4I$	*p*-$CH_3OC_6H_4$ (**2c**)	**3c**	75	-
6	*p*-$CH_3C_6H_4I$	Ph (**2a**)	**3d**	77	1:1
7	*m*-$CH_3OC_6H_4I$	Ph (**2a**)	**3e**	66	1.2:1
8	*p*-$(CH_3)_2NC_6H_4Br$	*p*-FC_6H_4 (**2b**)	**3f**	86	4:1
9		Ph (**2a**)	**3g**	62	>10:1
10		Ph (**2a**)	**3h**[d]	87	>10:1
11		Ph (**2a**)	**3i**	85	8:1
12		Ph (**2a**)	 **3j**	70	1:1
13	*p*-$CH_3OC_6H_4I$	CH_3 (**2d**)	**3k**	84	>10:1
14		CH_3 (**2d**)	**3l**	54	>10:1
15	PhI	CO_2Me (**2e**)	**3m**	62	>10:1
16	*p*-$CH_3C_6H_4I$	CO_2Me (**2e**)	**3n**	73	>10:1

[a] All the reactions were carried out by using *N*-tosylhydrazone (0.5 mmol), aryl halide (0.25 mmol), and *t*-BuOLi (3.5 equiv) in the presence of $Pd_2(dba)_3$ (2.5 mol %) and Xphos (5 mol %) in 1,4-dioxane (2 mL) at 80 °C for 12 h. [b] Isolated yields. [c] The ratio of *E*/*Z* selectivity was determined by the crude ^{1}H NMR and GC MS. [d] The *Z*-configuration was confirmed by X-ray diffraction.

The observation of a minor amount of **6** can be explained by the double bond migration, which is likely the result of hydropalladation/dehydropalladation processes promoted by HPdX, which is often observed in Pd-catalyzed reactions.[16] Alternatively, **6** may be formed through the conformational change of **B**.

Since we have previously reported the Pd-catalyzed cross-coupling of benzyl halides with *N*-tosylhydrazone,[10c] we next conceived that benzyl halide might also be employed in this type of reaction. We are delighted to find that

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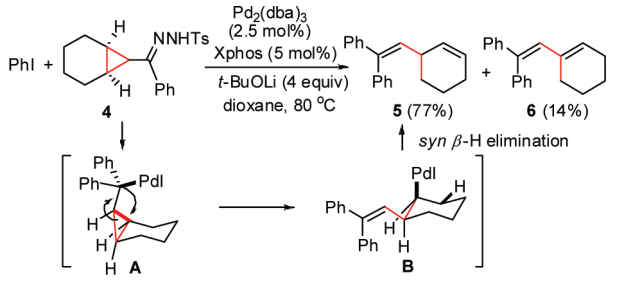
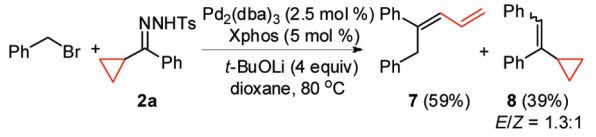
Scheme 2. Cross-Coupling of Iodobenzene with **4**



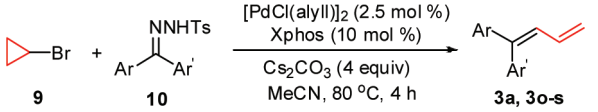
benzyl bromide is a suitable substrate for the cross-coupling with cyclopropyl *N*-tosylhydrazone **2a**, which furnished the ring-opening product **7** in moderate yield (59%). It is noteworthy that alkene **8** was also formed in a considerable amount, which indicates that in the corresponding cyclopropylmethyl palladium intermediate the β-H elimination competes effectively with the ring opening of the cyclopropane moiety.



As shown in Scheme 1, the cyclopropylmethyl palladium intermediate can also be generated by migratory insertion of a carbenoid ligand into a cyclopropyl-palladium bond (path ***c***). To explore such a possibility, Pd-catalyzed reaction of bromocyclopropane and diphenyl *N*-tosylhydrazone was investigated. After extensive optimization experiments by varying palladium catalysts, ligands and solvents, we found that the expected 1,1′-diphenyl-1,3-butadiene **3a** could be obtained in moderate yield as shown in Table 3 (entry 1). The major byproduct is tetraphenylethylene, which is derived from the homo coupling of an *in situ* generated diazo substrate. Upon experimentation, it seems to us that this obstacle is not easily overcome.

Thus, with $[Pd(allyl)Cl]_2$ as the catalyst, Xphos as the ligand, and Cs_2CO_3 as the base in MeCN at 80 °C, the reaction provided the coupling product **3a** in 40% yield. Several other *N*-tosylhydrazones were also examined under the same conditions, and they afforded the cross-coupling products in low to moderate yields. In the cases of coupling with *N*-tosylhydrazones **10d** and **10e**, the ratio of *E*/*Z* isomers was almost 1:1. However, when *N*-tosylhydrazone **10f** was employed to react with bromocyclopropane, only the *Z*-isomer was isolated as the major product. This result indicates that the stereochemical outcome of the reaction is dominated by the steric bulkiness of the substituents.

Table 3. Palladium-Catalyzed Cross-Coupling of Bromide **9** with *N*-Tosylhydrazones **10**[a]



10a, Ar = Ar′ = Ph; **10b**, Ar = Ar′ = *p*-MeC_6H_4
10c, Ar = Ar′ = *p*-PhC_6H_4; **10d**, Ar = Ph, Ar′ = *p*-PhC_6H_4
10e, Ar = Ph, Ar′ = 3,4-diMeC_6H_3; **10f**, Ar = Ph, Ar′ = naphthyl

entry	Ar	Ar′	product **3**	*E*/*Z*[c]	yield (%)[b]
1	Ph	Ph	**3a**	–	40
2	*p*-MeC_6H_4	*p*-MeC_6H_4	**3o**	–	45
3	*p*-PhC_6H_4	*p*-PhC_6H_4	**3p**	–	28
4	Ph	*p*-PhC_6H_4	**3q**	1:1	45
5	Ph	3,4-diMeC_6H_3	**3r**	1:1	36
6	Ph	1-naphthyl	**3s**	>10:1	32

[a] *N*-Tosylhydrazones (0.5 mmol), bromocyclopropane (1 mmol), Cs_2CO_3 (4 equiv), $[Pd(allyl)Cl]_2$ (2.5 mol %), Xphos (10 mol %), CH_3CN (5 mL), 80 °C, 4 h. [b] Isolated yield. [c] *E*/*Z* selectivity was determined by ^1H NMR of the crude product.

In conclusion, we have developed two novel routes toward the cyclopropylmethyl palladium species, which ultimately lead to the formation of 1,3-butadiene derivatives in moderate to good yields.[17] Further studies on the scope and synthetic application of these coupling reactions are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, mechanism, X-ray structure of **3h**, and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For the details of the proposed reaction mechanism, see Supporting Information.

The authors declare no competing financial interest.