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Pd-Catalyzed Three-Component Coupling of *N*-Tosylhydrazone, Terminal Alkyne, and Aryl Halide

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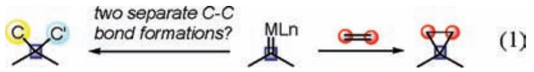
Abstract: A Pd-catalyzed three-component reaction of *N*-tosylhydrazone, terminal alkyne, and aryl halide follows a mechanism involving a sequence of Pd carbene migratory insertion−transmetalation−reductive elimination, leading to the formation of one sp^2-sp^3 C−C bond and one $sp-sp^3$ C−C bond.

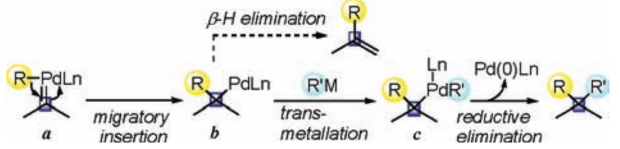
Typical reactions of electron-deficient metal carbenes, such as Rh carbene and Cu carbene, are C−H insertion, cyclopropanation, and ylide generation.[1] Cyclopropanation is the formation of two C−C bonds between a carbenic carbon and a double bond of olefin. However, the formation of two separate C−C bonds on a carbenic carbon from two substrates will not be possible in conventional metal carbene transformations, as restricted by their reaction pattern (eq 1).



(1)

Recently, Pd-catalyzed cross-coupling of diazo compounds, pioneered by Van Vranken, has been proven to be a reliable methodology for the formation of $C(sp^2)-C(sp^2)$ bonds.[2−5] Furthermore, Barluenga first employed *N*-tosylhydrazone in Pd-catalyzed cross couplings, which significantly expanded the scope of this type of reaction.[3,4] In these transformations, the migratory insertion of Pd carbene species ***a*** is suggested as the key step in the mechanism, leading to intermediate ***b*** which is followed by β-H elimination to afford olefin (Scheme 1). In 2001 Van Vranken and co-workers reported a Pd-catalyzed three-component reaction of trimethylsilyldiazomethane, aryliodide, and tributylphenyltin, affording benzhydryl derivatives.[2a] Although the yields of three-component coupling are rather low due to side reactions, this seminal work indicates that the transmetalation from intermediate ***b*** and thus the formation of two separate C−C bonds in a carbenic center are indeed possible. More recently, the same group reported a Pd carbene migratory insertion−carbopalladation sequence in the intramolecular reaction, in which two C−C bonds were also formed in a carbenic center.[2e]

Scheme 1. Formation of Two C−C Bonds on Metal Carbene

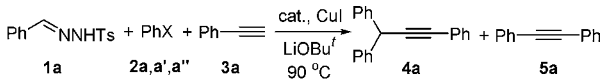


The challenge in the development of an efficient sequence of migratory insertion−transmetalation−reductive elimination lies in the restraint of possible side reactions, such as overinsertion, direct coupling, and β-H elimination. Obviously, a judicious choice of reaction conditions, in particular a suitable R′M for efficient transmetalation, is crucial for the reaction to proceed along the desired pathway. In this context, we hypothesized that copper acetylide might be a good candidate for this purpose. Herein, we wish to report a Pd-catalyzed three-component coupling of *N*-tosylhydrazone, terminal alkyne, and aryl halide, leading to the formation of two separate C−C bonds (one sp^2-sp^3 bond, one $sp-sp^3$ bond[6]).

Initially, we studied the three-component reaction of *N*-tosylhydrazone **1a**, iodobenzene **2a′** (X = I), and phenylacetylene **3a** with catalytic $Pd_2(dba)_3$ and CuI at 90 °C (Table 1, entry 1). An anticipated competing process in such a reaction system is the direct Sonogashira coupling reaction between **2a′** and **3a**.[7] Indeed, the direct coupling product **5a** was obtained in 55% yield. To our delight, the desired three-component coupling product **4a** was also obtained, albeit in low yield (37%).

With the initial results, we proceeded to optimize the reaction conditions. Slow addition of **3a** with a syringe pump over a period of 1 h failed to improve the reaction (entry 2). We conceived that direct Sonogashira coupling could be attributed to slow formation of Pd carbene, presumably due to the low concentration of a diazo substrate which was generated *in situ*. To match the slow Pd carbene formation, we switched the phenyl halide from iodide **2a′** to bromide **2a** which was less reactive in the oxidative addition step. To our delight, the yield of **4a** was improved to 81% and the Sonogashira coupling was reduced to 17% (entry 3). However, none of the

Table 1. Optimization of Reaction Conditions[a]



entry	Pd/ligand	X =	solvent	yield, %[b] **4a** (**5a**)
1	$Pd_2(dba)_3$/Xphos	I	toluene	37 (55)
2[c]	$Pd_2(dba)_3$/Xphos	I	toluene	8 (85)
3	**$Pd_2(dba)_3$/Xphos**	**Br**	**toluene**	**81 (17)**
4	$Pd_2(dba)_3$/Xphos	Cl	toluene	0 (21)
5	$Pd_2(dba)_3$	Br	toluene	0 (39)
6	$Pd_2(dba)_3$/P(furyl)$_3$	Br	toluene	10 (63)
7	$Pd_2(dba)_3$/PPh_3	Br	toluene	0 (70)
8[d]	$Pd_2(dba)_3$/Xphos	Br	toluene	16 (29)
9	$Pd_2(dba)_3$/Xphos	Br	dioxane	50 (23)
10	$Pd_2(dba)_3$/Xphos	Br	MeCN	24 (57)
11	$Pd_2(dba)_3$/Xphos	Br	THF	5 (78)
12[e]	$Pd_2(dba)_3$/Xphos	Br	toluene	65 (26)
13[f]	$Pd_2(dba)_3$/Xphos	Br	toluene	58 (40)
14[g]	$Pd_2(dba)_3$/Xphos	Br	toluene	19 (33)

[a] Unless otherwise noted, reaction conditions are as follows: **1a** (0.2 mmol), **2** (1.1 equiv), **3a** (1.1 equiv), $Pd_2(dba)_3$ (2.5 mol %), ligand (10 mol %), CuI (7.5 mol %), LiOBu^t (3.5 equiv), 90 °C for 1 h. [b] Yield was determined by GC using dodecane as an internal standard. Yield of **5a** was calculated based on **2**. [c] **3a** was added to the reaction mixture over a 1 h period by using a syringe pump. [d] The reaction was carried out in the absence of CuI. [e] **1a**:**2a**:**3a** = 1.0:1.2:1.5. [f] **1a**:**2a**:**3a** = 1.0:1.5:1.5. [g] **1a**:**2a**:**3a** = 1.5:1.0:1.0.

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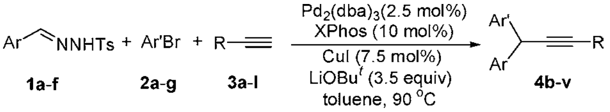
desired product was obtained when chlorobenzene **2a″** was used (entry 4). The ligand also plays an important role in the reaction (entries 5−7). Use of Xphos as the ligand was essential for the three-component coupling. CuI is also essential for the reaction (entry 8). We noted that the reaction was significantly affected by solvent, with toluene giving the best results for the three-component coupling (entries 9−10). Finally, it was found that the reaction could not be improved by adjusting the ratio of the substrates (entries 12−14).

With the optimized reaction conditions, we then studied the scope of this reaction by using various *N*-tosylhydrazones, aryl bromides, and terminal alkynes. As illustrated in Table 2, the three-component cross coupling proceeds smoothly over a wide range of substrates with moderate to good yields. For the aromatic bromide component, the *ortho* substituent has a negative effect on the cross coupling (entries 5, 6). As for the terminal alkyne component, the reaction tolerates a wide range of substituents and functional groups, except in the case when there is an ester substituent, in which none of the desired product was detected except a trace amount of direct Sonogashira coupling byproduct (entry 16). Finally, the cross coupling seems not significantly affected by the substituents on the aromatic moiety of the *N*-tosylhydrazone component (entries 18−22).

Table 2. Pd-Catalyzed Three-Component Coupling of Various *N*-Tosylhydrazones, Terminal Alkynes, and Aryl Halides[a]

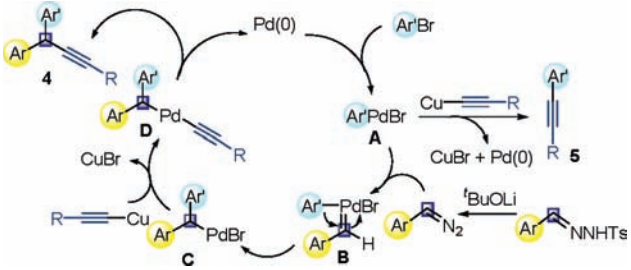


entry	**1**, Ar =	**2**, Ar′ =	**3**, R =	yield, %[b]
1	Ph	*m*-tolyl	Ph	**4b**, 72
2	Ph	*p*-anisyl	Ph	**4c**, 72
3	Ph	*p*-F-C_6H_4	Ph	**4d**, 84
4	Ph	2-naphthyl	Ph	**4e**, 62
5	Ph	*o*-PhC_6H_4	Ph	**4f**, 51
6	Ph	2,6-$Me_2C_6H_3$	Ph	**4g**, 21
7	Ph	Ph	*p*-tolyl	**4h**, 64
8	Ph	Ph	*p*-ClC_6H_4	**4i**, 63
9	Ph	Ph	*p*-anisyl	**4j**, 66
10	Ph	Ph	*p*-$CF_3C_6H_4$	**4k**, 62
11	Ph	Ph	2-(6-MeO)naph	**4l**, 56
12	Ph	2-naphthyl	$PhCH_2CH_2$	**4m**, 47
13	Ph	*o*-PhC_6H_4	*n*-C_4H_9	**4n**, 59
14	Ph	2-naphthyl	TMS	**4o**, 73
15	Ph	Ph	CH_2OTHP	**4p**, 51
16	Ph	Ph	CO_2Et	N.R.[c]
17	Ph	Ph	3-thienyl	**4q**, 84
18	*p*-tolyl	Ph	Ph	**4r**, 73
19	3,4-$(MeO)_2$-C_6H_3	Ph	Ph	**4s**, 60
20	3,4-$Cl_2C_6H_3$	Ph	Ph	**4t**, 41
21	2-hexynlC_6H_4	Ph	Ph	**4u**, 55
22	*p*-tolyl	*p*-anisyl	3-thieny	**4v**, 75

[a] All the reactions were carried out with *N*-tosylhydrazone (0.2 mmol), aryl bromide (1.1 equiv), terminal alkyne (1.1 equiv) in the presence of $Pd_2(dba)_3$ (2.5 mol %), Xphos (10 mol %), CuI (7.5 mol %), and LiOBu^t in 0.8 mL of toluene at 90 °C for 1 h. [b] Isolated yield. [c] N.R.: No reaction.

A plausible mechanism is proposed as shown in Scheme 2.[8] The oxidative addition of Pd(0) to aryl bromide to afford intermediate **A**, which may undergo a competing transmetalation with *in situ* generated copper acetylide. Subsequently, reductive elimination occurs to afford direct Sonogashira coupling product **5**. Conversely, a diazo substrate is generated *in situ* from *N*-tosylhydrazone in the presence of base. Decomposition of the diazo compound by Pd(II) species **A** leads to palladium carbene **B**. Migratory insertion of an aryl group to the carbenic carbon gives intermediate **C**, from which intermediate **D** is generated by transmetalation of **C** with copper acetylide, followed by reductive elimination to afford product **4** and to regenerate the palladium catalyst.

Scheme 2. Plausible Mechanism



In conclusion, we have developed a three-component coupling of *N*-tosylhydrazones, terminal alkynes, and aryl halides *via* a sequential palladium carbene migratory insertion and reductive elimination process, which forms two separate C−C bonds on a carbenic carbon. This reaction provides a novel method for the synthesis of benzhydryl acetylene derivatives from easily available starting materials.[9] More importantly, this study further demonstrates the possibility to incorporate Pd carbene migratory insertion with transmetalation of various metal compounds. Investigation along this line is ongoing in our lab, and the results will be reported in due course.

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Supporting Information Available: Additional mechanistic discussion, experimental procedure, characterization data, and 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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