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Two C−O Bond Formations on a Carbenic Carbon: Palladium-Catalyzed Coupling of *N*-Tosylhydrazones and Benzo-1,2-quinones To Construct Benzodioxoles

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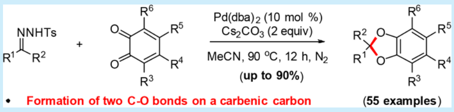
Supporting Information

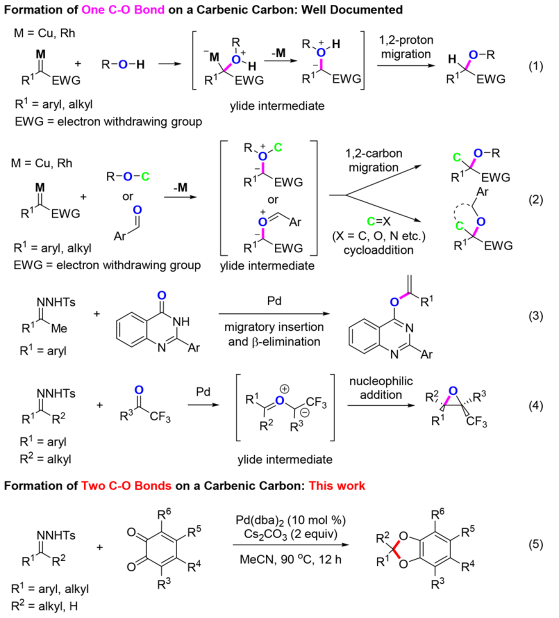
ABSTRACT: A novel and efficient method for the formation of two C−O bonds on a carbenic carbon is reported. This palladium-catalyzed coupling of *N*-tosylhydrazones and benzo-1,2-quinones were involved the process of carbonyl ylides generation, aromatization, and intramolecular nucleophilic addition, delivering various useful benzodioxoles in high yields.



Since carbon−heteroatom bonds (C−X) are ubiquitous motifs that broadly exist in both natural and artificially synthesized molecules, the development of new and efficient methods for the construction of carbon−heteroatom bonds is one of the most active research topics in synthetic chemistry.[1] Transition-metal catalyzed X−H (X = O, N, S, P, B, Si, etc.) insertion of metal carbene has represented one of the most promising methods to construct carbon−heteroatom bonds.[2] In particular, the diverse O−H insertion of metal carbenes for the construction of C−O bond has attracted considerable attention in the past decades.[3−6] In general, these extensively investigated O−H insertion reactions usually employ diazo compounds bearing electron-withdrawing groups as carbene precursors and are treated with highly active copper and rhodium catalysts to ensure the reactivity and selectivity. Mechanistically, these O−H insertions of metal carbenes undergo a stepwise ylide formation and subsequent 1,2-proton migration pathway (Scheme 1, eq 1).[4] When the H atom is replaced by a carbon, the corresponding insertion reactions are also involved in the formation of ylide intermediates initially, but followed by the 1,2-carbon migration or cycloaddition process (Scheme 1, eq 2).[5] These O−H insertions of metal carbene have also found broad applications in the construction of bioactive compounds and the total synthesis of natural products.[6] Despite this progress, however, these transformations inevitably lead to the formation of one C−O bond on the carbenic carbon, while the method for the formation of two C−O bonds on the carbenic carbon in the O−H insertion of metal carbenes has still not been reported.

Readily available *N*-tosylhydrazones, as an alternative and safe source of diazo compounds that do not bear electron-withdrawing groups, have emerged as attractive metal carbene precursors,[7] especially under palladium catalysis.[8−12] Those palladium carbene intermediates derived from *N*-tosylhydrazones usually undergo migratory insertion,[7c] carbonylation,[8] cyclopropanation,[9] and N−H insertion,[10] which exhibit diverse transformation properties. In 2017, Nagaiah and co-workers reported the O−H insertion reactions of palladium carbenes derived from *N*-tosylhydrazones, which lead to the construction of one C−O bond on the carbenic carbon via the migratory insertion and *β*-elimination process (Scheme 1, eq 3).[11] We also documented the formation of one C−O bond on the carbenic carbon of palladium carbene derived from *N*-tosylhydrazone involving the ylide intermediate pathway (Scheme 1, eq 4).[12] Inspired by these works, as well as a part of our continuous effort toward exploiting the potential reactivity of *N*-tosylhydrazones,[9,10,12,13] herein, we report the palladium-catalyzed coupling reaction of *N*-tosylhydrazones with benzo-1,2-quinones, which leads to the formation of two

Scheme 1. C−O Bond Formations on a Carbenic Carbon



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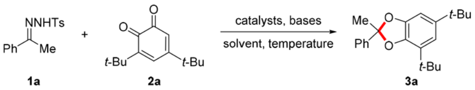
C−O bonds on the carbenic carbon and delivers various useful benzodioxoles in high yields (Scheme 1, eq 5).[14]

When we investigated the palladium-catalyzed oxidative coupling of N-tosylhydrazones,[13a,b] an experiment was carried out with N-tosylhydrazone **1a** and benzo-1,2-quinone **2a** in toluene at 90 °C in the presence of $Pd(OAc)_2$ and Cs_2CO_3 under N_2 (Table 1, entry 1). Surprisingly, a new species was detected by GC-MS with a peak m/z = 324.33, which was tentatively assumed as benzodioxole **3a** via two C−O bond formations on the carbenic carbon, and it was obtained in 74% isolated yield (Table 1, entry 1). To optimize the reaction conditions, various inorganic bases such as K_2CO_3, Li_2CO_3, *t*-BuOK, *t*-BuOLi, and MeONa and organic bases such as DABCO and DBU were examined; however, no superior results were obtained (Table 1, entries 2−8). The absence of bases was fatal to this transformation (Table 1, entry 9). Next, diverse organic solvents were screened, and a solvent of MeCN enhanced the GC-MS yield of the product to 81% (Table 1, entries 10−14). Furthermore, different types of palladium salts were investigated (Table 1, entries 15−19). A catalyst of $Pd(dba)_2$ was found to be optimal, and gave the desired product **3a** in 86% isolated yield. With CuI or $Rh_2(OAc)_4$ as the catalyst, the yields of **3a** decreased significantly (Table 1, entries 20−21). Furthermore, changing the reaction temperature in either direction eroded the yield of **3a** slightly (Table 1, entries 22−23). Additionally, when ethyl diazoacetate instead of N-tosylhydrazone **1a** was tested under $Pd(dba)_2$, CuI, or $Rh_2(OAc)_4$ catalysis, no corresponding benzodioxole product was detected.

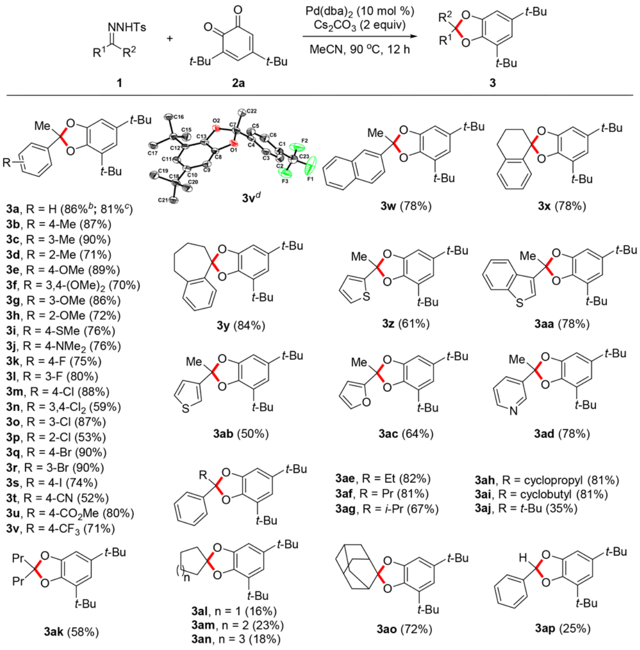
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	solvent	*t* (°C)	yield[b] (%)
1	$Pd(OAc)_2$	Cs_2CO_3	toluene	90	78 (74)
2	$Pd(OAc)_2$	K_2CO_3	toluene	90	54
3	$Pd(OAc)_2$	Li_2CO_3	toluene	90	33
4	$Pd(OAc)_2$	*t*-BuOK	toluene	90	38
5	$Pd(OAc)_2$	*t*-BuOLi	toluene	90	76
6	$Pd(OAc)_2$	MeONa	toluene	90	34
7	$Pd(OAc)_2$	DABCO	toluene	90	<5
8	$Pd(OAc)_2$	DBU	toluene	90	<5
9	$Pd(OAc)_2$	–	toluene	90	<5
10	$Pd(OAc)_2$	Cs_2CO_3	MeCN	90	81
11	$Pd(OAc)_2$	Cs_2CO_3	THF	90	45
12	$Pd(OAc)_2$	Cs_2CO_3	DCE	90	52
13	$Pd(OAc)_2$	Cs_2CO_3	dioxane	90	34
14	$Pd(OAc)_2$	Cs_2CO_3	DMF	90	63
15	$PdCl_2$	Cs_2CO_3	MeCN	90	71
16	$Pd(TFA)_2$	Cs_2CO_3	MeCN	90	84
17	$Pd(CH_3CN)_2Cl_2$	Cs_2CO_3	MeCN	90	81
18	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	90	84
19	$Pd(dba)_2$	Cs_2CO_3	MeCN	90	92 (86)
20	CuI	Cs_2CO_3	MeCN	90	40
21	$Rh_2(OAc)_4$	Cs_2CO_3	MeCN	90	61
22	$Pd(dba)_2$	Cs_2CO_3	MeCN	80	83
23	$Pd(dba)_2$	Cs_2CO_3	MeCN	100	90

[a] A mixture of **1a** (0.4 mmol, 2 equiv), **2a** (0.2 mmol, 1 equiv), base (0.4 mmol, 2 equiv), catalyst (10 mol %), and solvent (2 mL) was sealed in a 25 mL Schlenk tube at 90 °C for 12 h under N_2. [b] Yields were determined by GC-MS with *n*-dodecane as internal standard. The number in the parentheses was isolated yield. dba = dibenzylideneacetone.

Scheme 2. Substrate Scope of N-Tosylhydrazones[a]

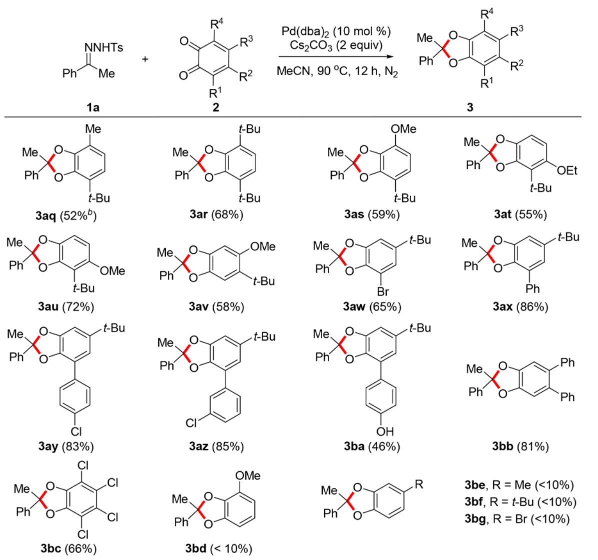


[a] Unless otherwise noticed, the reaction was run at 0.2 mmol scale under standard reaction conditions. [b] The average isolated yields of two parallel runs. [c] On 5 mmol scale. [d] ORTEP representation with 50% probability thermal ellipsoids of a crystal structure of **3v**; H atoms were omitted for clarity.

With the optimized reaction conditions in hand, we next turned our attention to the generality of this palladium-catalyzed coupling reaction. The scope of N-tosylhydrazones **1** was first explored with benzo-1,2-quinone **2a** as the reaction partner, and the results are outlined in Scheme 2. In general, N-tosylhydrazones with both electron-donating and -withdrawing substituents at the *para*, *meta*, and *ortho* positions of the phenyl ring delivered the desired benzodioxoles smoothly (**3a−w**). It is worth noting that this palladium-catalyzed system tolerates various valuable functional groups on the phenyl ring of N-tosylhydrazones, such as alkoxy, methylthio, amino, halo, cyano, ester, and trifluoromethyl groups (products **3e−v**), providing ample potential for further synthetic utilities. Significantly, product **3v** was proven to be crystalline, and the structure of these benzodioxoles was further confirmed by means of X-ray crystallographic analysis (CCDC 1588105). Furthermore, 1-tetralone and 1-benzosuberone derived N-tosylhydrazones were perfectly applicable to this catalytic system, providing the corresponding spiro benzodioxoles efficiently (**3x**, **y**). Different heteroaromatic groups such as thienyl, furanyl, and pyridyl were also tolerated on the N-tosylhydrazones, and the desired products were obtained in high yields (**3z−3ad**). Additionally, N-tosylhydrazones derived from other alkyl phenylmethanones, such as ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, and *tert*-butyl phenylmethanones, all afforded the corresponding products smoothly (**3ae−aj**). Acyclic aliphatic heptan-4-one derived N-tosylhydrazone ketone also gave product **3ak** in 58% yield. Although N-tosylhydrazones derived from cyclic aliphatic ketones such as cyclopentanone, cyclohexanone, and cycloheptanone led to lower yields of the corresponding products (**3al**−**an**), *N*-tosylhydrazone derived from cyclic 2-admantanone could provide the desired product **3ao** in 72% yield. Additionally, benzaldehyde derived *N*-tosylhydrazone also gave the corresponding product **3ap** in 25% yield.

To further define the generality of our method, the substrate scope was extended to different benzo-1,2-quinones **2** (Scheme 3). Pleasingly, diverse disubstituted benzo-1,2-quinones with an alkyl, alkoxyl, bromo, and aryl group at different locations of the benzo-1,2-quinone ring all delivered the corresponding benzodioxoles in good to high yields (**3aq**−**bb**). It is worth mentioning that an unprotected hydroxyl group could also been tolerated under the standard reaction conditions, delivering the desired product **3ba** in 46% yield. Furthermore, tetrachloro substituted benzo-1,2-quinone also gave the corresponding product **3bc** in 66% yield. However, monosubstituted benzo-1,2-quinones with both electron-donating groups such as alkoxyl and alkyl and an electron- withdrawing bromo group on the benzo-1,2-quinone ring did not afford the corresponding products **3bd**−**bg** in isolatable yield, as the corresponding aryl-1,2-diols via oxidative aromatization of benzo-1,2-quinones were detected as the major byproduct under our standard reaction conditions.

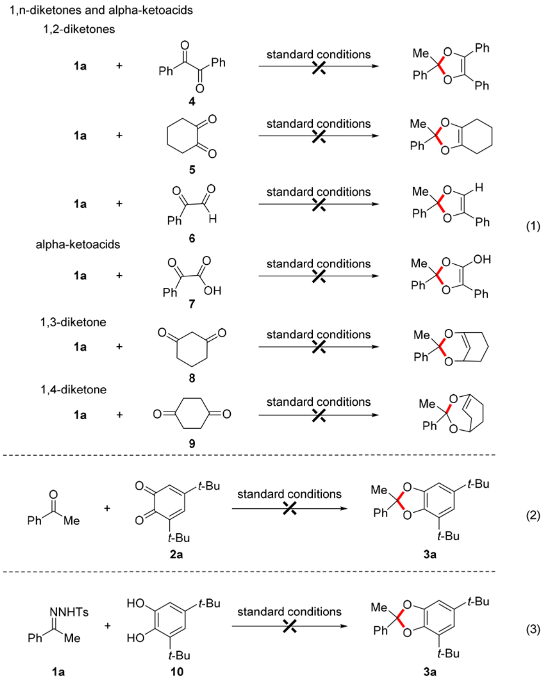
Scheme 3. Substrate Scope of Benzo-1,2-quinones[a]



[a]The reaction conditions were: **1a** (0.2 mmol, 1 equiv), **2** (0.4 mmol, 2 equiv), Cs_2CO_3 (0.4 mmol, 2 equiv), $Pd(dba)_2$ (10 mol %), and MeCN (2 mL) was sealed in a 25 mL Schlenk tube at 90 °C for 12 h under N_2. [b]The average isolated yields of two parallel runs.

To cast some light on the mechanism details of this reaction, some control experiments were performed. First, the reactions of *N*-tosylhydrazone **1a** with diverse 1,*n*-diketones and *α*-ketoacids **4**−**9** were examined under the standard reaction conditions. However, very complex mixtures were obtained for all these reactions, and no desired two C−O bond formation products were detected by GC-MS analysis, indicating the oxidative aromatic potential of benzo-1,2-quinones is very important for the success of this transformation (Scheme 4, eq 1). Furthermore, acetophenone was used as the substrate instead of *N*-tosylhydrazone **1a**. The desired product **3a** was not obtained, implying the generation of palladium carbene was the initial step for this reaction (Scheme 4, eq 2). Additionally,

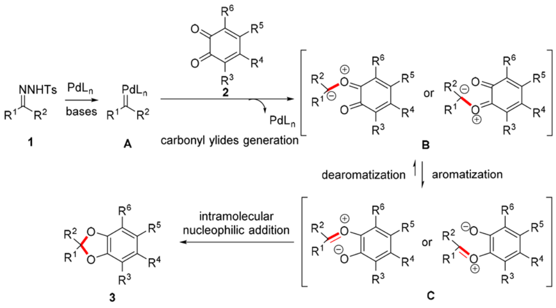
Scheme 4. Control Experiments



3,5-di-*tert*-butylbenzene-1,2-diol **10** was used as the substrate instead of benzo-1,2-quinone **2a**. No desired product **3a** was detected, indicating that **10** was not one of the reaction intermediates, and the formation of carbonyl ylide intermediate might be involved in this transformation (Scheme 4, eq 3).

On the basis of these experimental results, and previous literature,[7−14] we tentatively proposed the reaction mechanism, as illustrated in Scheme 5. First, formation of palladium carbene

Scheme 5. Proposed Mechanism



intermediate **A** via the decomposition of *N*-tosylhydrazones **1** in the presence of palladium catalysts and bases further transformed to the corresponding carbonyl ylide intermediates **B** under the treatment of benzo-1,2-quinones **2**.[12] Subsequent aromatization of the phenyl ring converted intermediates **B** to the more stable carbonyl ylide intermediates **C** via isomerization, which further transformed to the desired benzodioxoles **3** via intramolecular nucleophilic addition.

In summary, we have documented the palladium-catalyzed coupling reaction of *N*-tosylhydrazones with benzo-1,2-quinones, which leads to the formation of two C−O bonds on the carbenic carbon. Various useful benzodioxoles were synthesized in high yields. Primary mechanism studies indicated this reaction involved the process of carbonyl ylides generation, aromatization, and intermolecular nucleophilic addition. Efforts are currently underway in our laboratory to investigate the mechanism details and the applications of these benzodioxoles, the results of which will be reported in the due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00888.

Typical experimental procedures, characterization for all products (PDF)

Accession Codes

CCDC 1588105 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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