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Pd-Catalyzed Oxidative Annulation of Aryl Ethers with Alkynes: Synthesis of Functionalized Spirocycles and Naphthalenes

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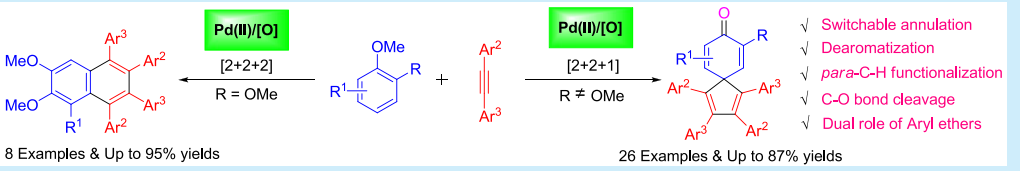


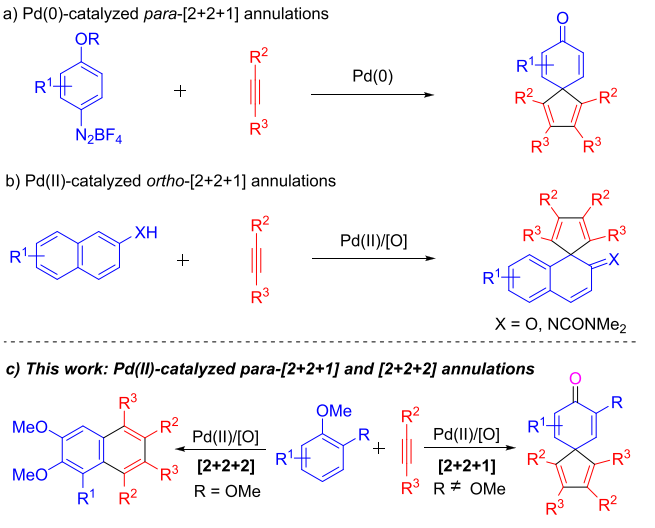
ABSTRACT: Palladium-catalyzed dearomative [2+2+1] annulations of aryl ethers with alkynes are reported via *para*-selective C−H functionalization, providing highly functionalized spirocyclohexadienones in moderate to excellent yields under mild reaction conditions. Importantly, mechanistic investigation indicated an unusual C−O bond cleavage was involved. Moreover, polyarylated naphthalenes could be obtained via oxidative [2+2+2] annulation by tuning aryl ethers from monomethoxybenzenes to polymethoxybenzenes under an identical catalytic system.

Spirocycles and naphthalenes represent long-standing targets for synthetic chemists because they are common skeletons of diverse natural products, biologically active molecules, and functional materials.[1] Spirocyclohexadienones, unique structural units in the spirocarbocycles, widely exist in medicinal molecules with remarkable biological activities and pharmaceutical interest.[2] Also, polyarylated aromatic compounds, commonly found in functional materials, are always used as semiconductors, fluorescent and luminescent tools, and materials.[3] Thus, developing efficient and versatile routes toward spirocyclohexadienone frameworks and polyarylated aromatic substrates via identical catalytic conditions is highly desirable.

Within the rapidly growing realm of transition-metal catalysis, dearomative annulation of alkynes with substrates featuring versatile functional groups has emerged as a powerful tactic in the synthesis of diverse spirocycles.[4] Among the various catalytic strategies, the annulation of alkynes with readily available aromatic starting materials such as phenol diazonium salts, phenols, and naphthols to deliver a broad range of heterocycles via a dearomative process has been widely explored.[5] However, these dearomative annulations always achieved spirocycles through prefunctional aromatic substrates. The assembly of spirocarbocycles via dearomative annulations from nonprefunctionalized aromatic starting materials such as alkyl aryl ethers remains a challenge.

Recently, palladium-catalyzed intermolecular dearomative [2+2+1] cycloaddition processes have been recognized as powerful strategies for constructing spirocyclohexadienones.[5a,6−8] In 2011, Schmidt and co-workers developed a palladium(0)-catalyzed dearomative *para*-[2+2+1] coupling of alkynes with phenol diazonium salts to synthesize spirocyclohexadienones (Scheme 1a).[5a] Compared with such a palladium(0)-catalyzed method with functionalized substrates, a

Scheme 1. Pd-Catalyzed Oxidative Annulations



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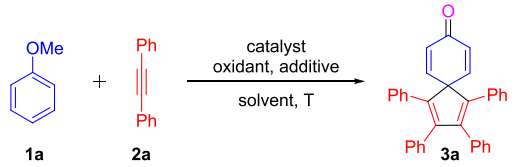
palladium(II)-catalyzed oxidative [2+2+1] dearomatization process is a more efficient strategy with respect to step economy (Scheme 1b). In 2014, Luan and co-workers reported the palladium(II)-catalyzed oxidative *ortho*-[2+2+1] dearomatizations of free naphthols with two alkynes to provide a variety of spirocyclic compounds.[6] Recently, Jiang and co-workers realized palladium(II)-catalyzed oxidative *ortho*-[2+2+1] dearomatizations of *N*-aryl ureas with two alkynes to provide spirocyclic imine derivatives.[7] However, there has been no report of palladium(II)-catalyzed oxidative *para*-[2+2+1] dearomatizations for spirocyclohexadienone synthesis.

Herein, we report a palladium(II)-catalyzed dearomative [2+2+1] annulation of aryl ethers with alkynes via *para*-selective C−H functionalization and C−O cleavage, providing highly functionalized spirocyclohexadienones in moderate to excellent yields under mild reaction conditions. Via the tuning of aryl ethers from monomethoxybenzenes to polymethoxybenzenes, polyarylated naphthalenes could be constructed via oxidative [2+2+2] annulation transformations with high efficiency (Scheme 1c).

Initially, anisole **1a** and diphenylacetylene **2a** were utilized as model substrates to optimize the reaction conditions (Table 1).

Table 1. Optimization of Reaction Conditions[a]



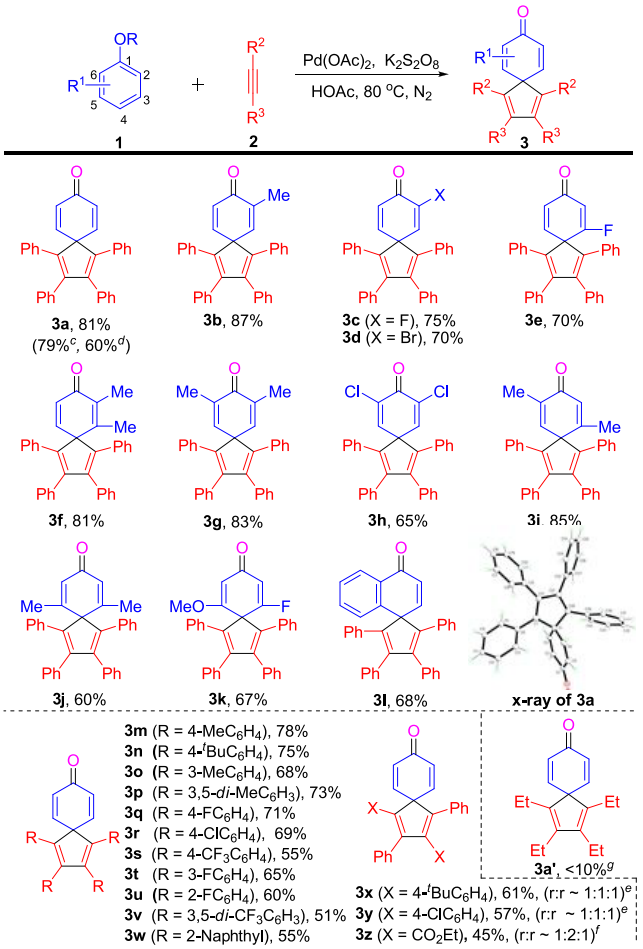
entry	catalyst	oxidant	additive	T (°C)	yield (%)[b]
1	$Pd(OAc)_2$	oxone	–	100	60
2	$Pd(OAc)_2$	$PhI(OAc)_2$	–	100	12
3	$Pd(OAc)_2$	$K_2S_2O_8$	–	100	67
4	$Pd(OAc)_2$	$AgSbF_6$	–	100	–
5	$Pd(OAc)_2$	$CuCl_2$	–	100	–
6[c]	$Pd(OAc)_2$	$K_2S_2O_8$	–	100	49
7[d]	$Pd(OAc)_2$	$K_2S_2O_8$	–	100	31
8	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH	100	70
9	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH	120	72
10	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH	80	81
11	$Pd(OAc)_2$	$K_2S_2O_8$	PivOH	80	79
12	$Pd(TFA)_2$	$K_2S_2O_8$	TFA	80	64

[a]Reaction conditions: **2a** (0.2 mmol), catalyst (10 mol %), **1a** (1.0 mL), oxidant (0.4 mmol), additive (0.4 mmol), 24 h, N_2. [b]Isolated yields after flash chromatography. [c]AgOAc (0.4 mmol) as the co-oxidant. [d]$Cu(OAc)_2$ (0.4 mmol) as the co-oxidant.

After extensive investigations, spirocyclohexadienone **3a** was obtained in 60% yield when the reaction was performed at 100 °C with anisole as the solvent, oxone as the oxidant, and $Pd(OAc)_2$ as the catalyst (entry 1). Next, different oxidants were examined, and potassium persulfate ($K_2S_2O_8$) resulted in a better yield (entries 2−7). When AcOH was used as an additive, the efficiency of the reaction was remarkably increased (entry 8). An evaluation of temperature revealed that 80 °C was suitable for the reaction (entries 8−10). It was noted that the erosive yield was observed when employing PivOH as an additive or using $Pd(TFA)_2$ as a catalyst and trifluoroacetic acid as an additive (entries 11 and 12).

Having the optimal conditions in hand, we first evaluated the scope of anisoles (Scheme 2). It is worth noting that the same

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: **2** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), **1** (2.0 mL), $K_2S_2O_8$ (0.8 mmol), AcOH (0.4 mmol), 80 °C, 24−48 h, N_2. [b]Isolated yields after flash chromatography. [c]Phenetole was used. [d]On a 10 mmol scale. [e]The ratio of regioisomers was based on isolated yields. [f]The ratio of regioisomers was based on ^1H NMR. [g]Confirmed by GC-MS.

product **3a** was formed when using phenetole (**1b**) instead of anisole (**1a**). Then, all reactions of diphenylacetylene **2a** with different substituted anisoles bearing electron-donating or electron-withdrawing substituents at the aryl moiety proceeded smoothly to afford the desired products in moderate to excellent yields (**3b−e**). Additionally, different disubstituted anisoles and 1-naphthol-derived aryl ether were also well tolerated for the reaction (**3f−l**). Gram-scale synthesis was examined under standard reaction conditions and gave product **3a** in 60% yield. The structure of **3a** was confirmed by X-ray diffraction analysis (CCDC 1953883).

Then, various symmetric and asymmetric diaryl alkynes were subjected to this reaction. Symmetric diaryl alkynes with both electron-deficient and electron-rich substituents could be converted to the corresponding spirocyclic products in good yields (**3m−w**). Moreover, unsymmetrical alkynes were explored and delivered the desired spirocyclohexadienones with high efficiency (**3x** and **3y**). However, **3z** was produced as a mixture of inseparable regioisomers. Also, only a trace amount of product was formed when the symmetrical aliphatic alkyne was used as the substrate (see the Supporting Information).

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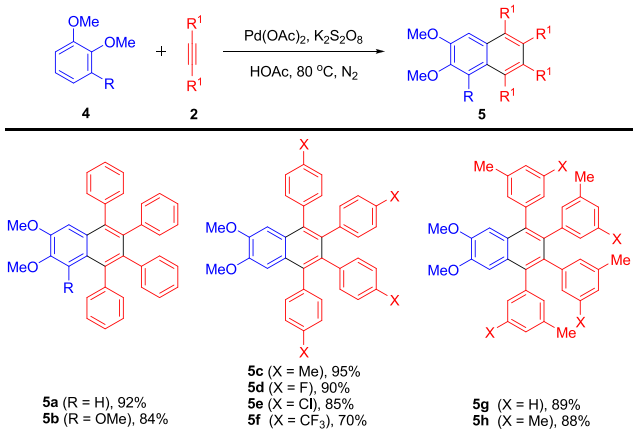
Interestingly, as shown in Scheme 3, when polymethoxybenzenes were used as substrates, functionalized naphthalenes

Scheme 3. Functionalized Naphthalene Synthesis[a,b]

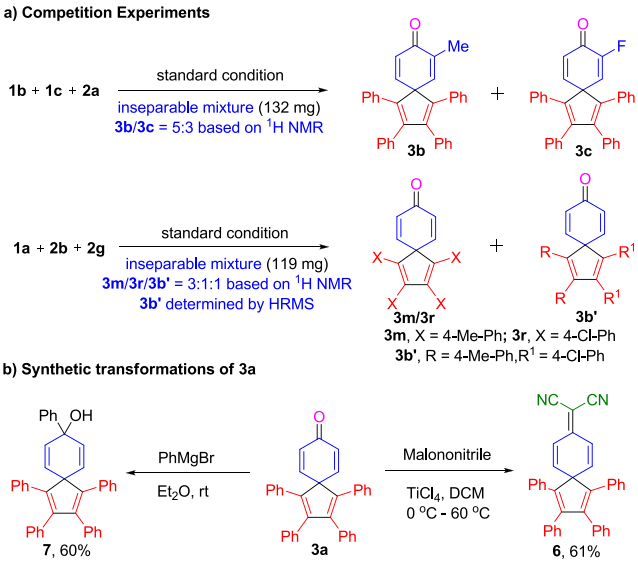


[a]Reaction conditions: **2** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), **4** (2.0 mL), $K_2S_2O_8$ (0.8 mmol), AcOH (0.4 mmol), 80 °C, 24−36 h, N_2. [b]Isolated yields after flash chromatography.

were obtained with high efficiency under standard reaction conditions (**5a** and **5b**).[5a,9] Then, the scope of symmetric diaryl alkynes was examined in this transformation, providing the corresponding naphthalene products in good to excellent yields (**5c**−**h**). The structure of **5a** was confirmed by X-ray diffraction analysis (CCDC 1953747).

To further understand this dearomative process, two competition experiments were conducted (Scheme 4). Elec-

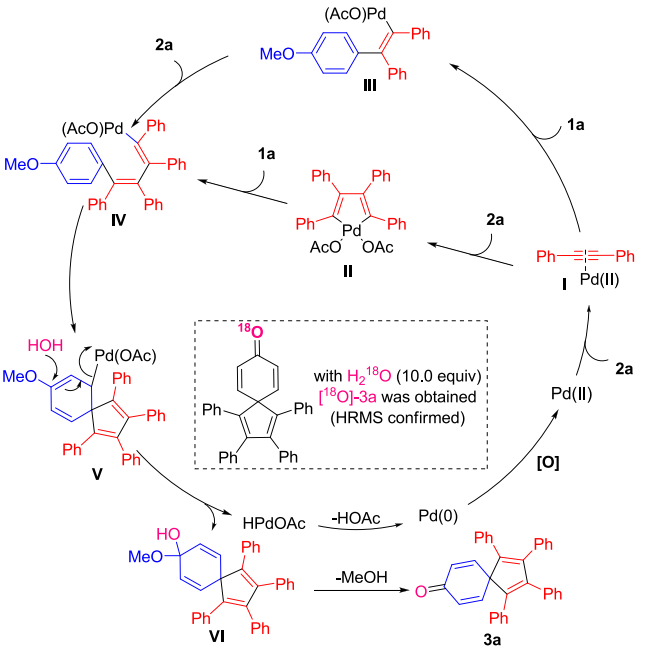
Scheme 4. Competition Experiments and Synthetic Transformations



tron-donating aryl ethers **1b** reacted more quickly than electron-withdrawing aryl ethers **1c** (Scheme 4a). Similarly, electron-rich alkyne **2b** reacted more quickly in this reaction than electron-deficient alkyne **2e** together with a new cross-annulated product **3b′** (Scheme 4b). Additionally, KIE studies indicated that this reaction involves a C−H activation process (see the Supporting Information).[10] Due to the various bioactivities of spirocycles, we turned our attention to transform the achieved spirocycles. The condensation of **3a** with malononitrile was accomplished in the presence of $TiCl_4$, smoothly affording the functionalized spirocycle **6** in 60% yield. Upon treatment of product **3a** with PhMgBr in Et_2O at room temperature, 1,2-addition product **7** was obtained in 61% yield.

On the basis of former investigations, a plausible mechanism for this spirocycles synthesis is given in Scheme 5.[11] The

Scheme 5. Proposed Reaction Mechanism



formation of spirocyclohexadienones begins with the palladation of **2a** to yield intermediate **I** or **II**. Then, vinyl-palladium intermediate **IV** is formed from intermediate **III** with the second alkyne unit inserted or intermediate **II** via a *para*-C−H functionalization process. At this point, the dearomatization occurs from this intermediate and generates spirocyclic species **V**, which then furnishes intermediate **VI** via H_2O attack and forms spirocyclohexadienone **3a** together with the regeneration of a Pd(II) catalyst. To further confirm the C−O bond cleavage process, the postulated product [^{18}O]-**3a** was detected via HRMS via the addition of 10.0 equiv of $H_2{}^{18}O$ to the reaction system (see the Supporting Information), which further supports the possible mechanism for the C−O bond cleavage process.

In conclusion, we have developed a palladium-catalyzed dearomatization reaction of aryl ethers with alkynes to afford spirocyclohexadienones in moderate to excellent yields. Additionally, when polymethoxybenzenes are used to react with alkynes under identical reaction conditions, functionalized naphthalenes can be obtained with good to excellent yields. This protocol represents a pathway for expanding the repertoire of palladium-catalyzed oxidative annulations for assembling spirocyclohexadienones and functionalized naphthalenes from readily available starting materials.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00970.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1953747 and 1953883 contain 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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(11) The mechanism proposed for naphthalene formation is given in the Supporting Information.

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