Organic LETTERS

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Pd-Catalyzed Site-Selective *p*-Hydroxyphenyloxylation of Benzylic α-C(sp^3)−H Bonds with 1,4-Benzoquinone

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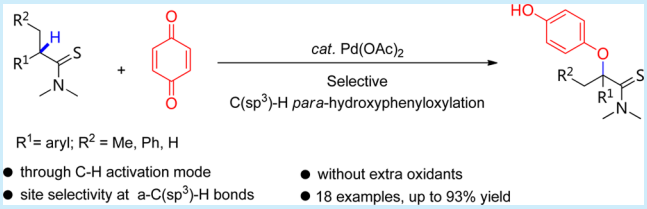
Supporting Information

ABSTRACT: A Pd-catalyzed, site-selective *p*-hydroxyphenyloxylation of benzylic α-C(sp^3)−H bonds with 1,4-benzoquinone using thioamide as a directing group is reported. 1,4-Benzoquinone is employed as the *p*-hydroxyphenyloxy source without extra oxidants. This method exclusively gives site selectivity at α-C(sp^3)−H bonds rather than the usual β-C(sp^3)−H bonds through C−H activation mode. The reactions proceed with high functional group tolerance in yields of 42−93%.

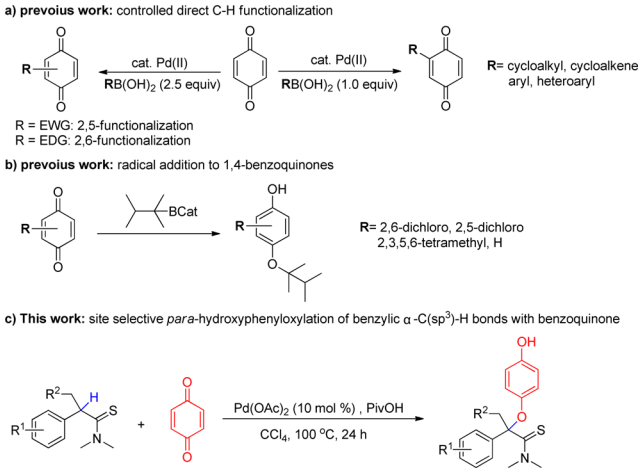


Since benzoquinone and its derivatives have wide application in many fields and are ubiquitous in organic chemistry, functionalization of benzoquinones is still highly desirable.[1] Despite the significant progress achieved for the Pd-catalyzed cross-coupling reactions, only scattered examples of Pd-catalyzed coupling with benzoquinone have been attained. Stille or Suzuki coupling is an indirect strategy to functionalization of benzoquinones.[2] This procedure requires first installing a Br, I, or OTf group and suffers from chemo- and regioselectivity during prefunctionalization. In 2014, Lee first reported Pd-catalyzed direct C−H functionalization of benzoquinone (Scheme 1a).[3] The direct functionalization of benzoquinones was so far mainly based on a radical pathway such as Meerwein arylation,[4] Ag-catalyzed C−H monofunctionalization,[5] and so on. However, the direct functionalization of benzoquinone exclusively at the oxygen atom leading to hydroquinone derivatives is still rare. In 2006, Renaud et al. developed a radical addition to 1,4-benzoquinones at the oxygen atom when bulky secondary and tertiary alkyl radicals were used (Scheme 1b).[6] It is noteworthy that the products of addition at oxygen and carbon are both found.

In fact, benzoquinones often play as an oxidant or ligand instead of a substrate in Pd catalysis.[7] An early report that benzoquinone can coordinate with Pd(0), followed by a redox process to regenerate Pd(II) and hydroquinone.[8] However, hydroquinone was usually released from the metal prior to act as a coupling partner in the presence of other ligand, nucleophile, and steric effect.[8a] To the best of our knowledge, hydroquinones originated from benzoquinones couple with other atoms has not been explored yet. Over the past decades, chelation-assisted transition-metal-catalyzed direct functionalization of C−H bonds has been well developed.[9] However, functionalization of C(sp^3)−H bonds is still a fundamental and ongoing challenge, especially in regioselectivity due to the inertness of aliphatic C−H bonds.[10]

Given these developments, we envisaged that benzoquinone was reduced to hydroquinone through a Pd(0)/Pd(II) mode, followed by Pd(II) activation of C−H bonds under assistance of a directing group to form cyclometalated intermediate, which would facilitate the subsequent coupling (Scheme 1c). This method is different from previous C−H activation reactions. Palladium plays dual roles in this reaction, including reduction of benzoquinone to the hydroquinone coupling partner via a redox process and activation of the C−H bonds by the resulting Pd(II) species. The protocol can allow for convenient synthesis of aryl alkyl ethers, which are widely found in numerous biologically molecules and natural products (Figure 1).[11]

Scheme 1. Site-Selective Functionalization of Benzoquinone



Received: September 15, 2016

DOI: 10.1021/acs.orglett.6b02782
Org. Lett. XXXX, XXX, XXX−XXX

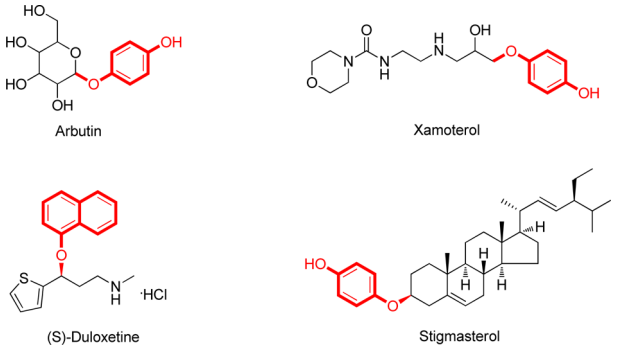


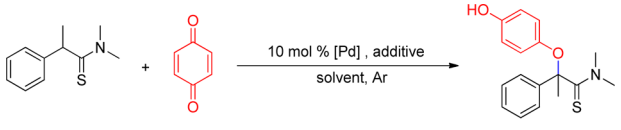
Figure 1. Drugs and natural products containing aryl alkyl ethers.

In recent years, amides have been developed to use as directing groups in metal-catalyzed C−H activation.[12] At the outset of our studies, 2-phenylpropanamide was used as the model substrate, and different Pd catalysts, additives, and solvents were systematically examined (see the Supporting Information). Although our initial efforts to achieve Pd-catalyzed *p*-hydroxyphenyloxylation of C(sp^3)−H bonds with 1,4-benzoquinone were generally unsuccessful, we were inspired by a report by Yu in 2015 using thioamide as a directing group.[13] Fortunately, the desired product **3a** was achieved in 40% yield (Table 1, entry 1). To our surprise, it gives regioselectivity at *α*-C(sp^3)−H bonds rather than the usual *β*-C(sp^3)−H bonds. This result implies that coordination behavior of thioamide is essential for the reaction to proceed. While numerous transformations can be achieved with various coupling partners, the specific directing group and catalyst serve a single reaction in most cases.[14]

Encouraged by achieving the desired promise, we attempted to optimize the reaction conditions. When surveying the effect of solvents, we found that the yield was improved to 88% in CCl_4 (Table 1, entry 8). PivOH and K_2CO_3 can promote the reaction (Table 1, entries 8, 12, 13, and 18).This may be attributed to both of them as promoters of proton abstraction as reported by Echavarren and Fagnou.[15] Using a Pd(0) instead of $Pd(OAc)_2$ precatalyst resulted in a lower yield (entries 10 and 11). A superior outcome was provided by 1,4-benzoquinone (4.0 equiv), PivOH (5.0 equiv), and $Pd(OAc)_2$ (0.1 equiv) at 100 °C (Table 1, entry 8). Argon is beneficial to the coupling; this is probably because both oxygen and 1,4-benzoquinone can oxidate Pd(0) to Pd(II).[8]

Under the optimized reaction conditions, we explored the scope of thioamides (Scheme 2). First, we examined different substitutions on the aryl using 1,4-benzoquinone as the partner. Substrates containing all kinds of functional groups work well to provide good to excellent yields in which electron-donating groups are superior to withdrawing groups. When electron-rich arenes are used, the methoxy- and *para*-substituted methyl are much better groups than others. Among halogen-substituted arenes, *para*-substituted chlorine is worse than *meta*-substituted

Table 1. Optimization of Reaction Conditions[a]

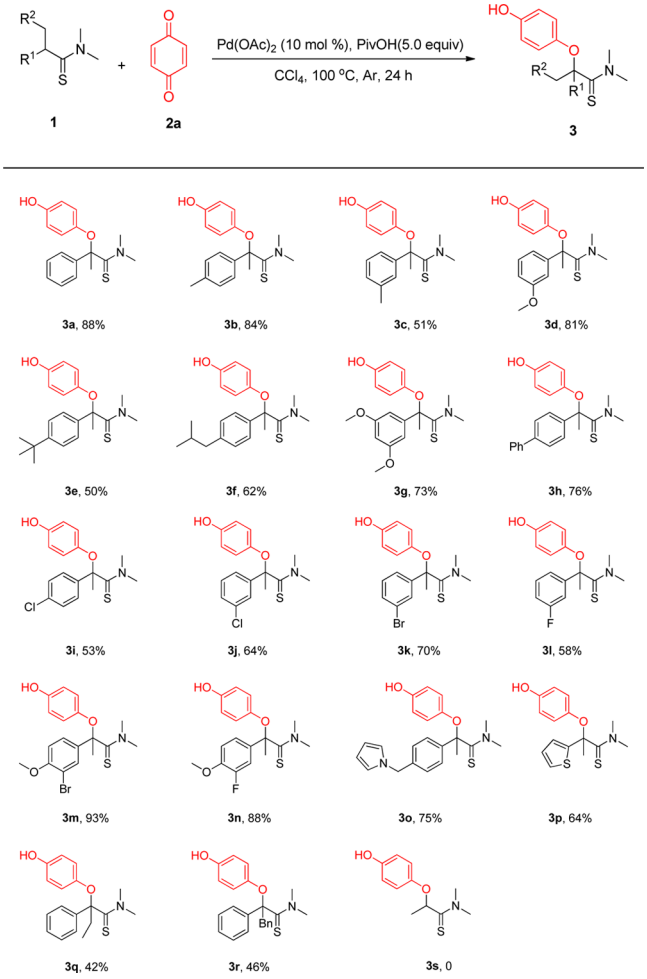


1a 2a 3a

entry	catalyst	solvent	additive (equiv)	yield[b] (%)
1	$Pd(OAc)_2$	DCE	PivOH (5.0)	40
2	$Pd(OAc)_2$	HFIP	PivOH (5.0)	0
3	$Pd(OAc)_2$	ACN	PivOH (5.0)	trace
4	$Pd(OAc)_2$	1,4-dioxane	PivOH (5.0)	0
5	$Pd(OAc)_2$	DMF	PivOH (5.0)	trace
6	$Pd(OAc)_2$	PhMe	PivOH (5.0)	60
7	$Pd(OAc)_2$	PhCl	PivOH (5.0)	47
8	$Pd(OAc)_2$	CCl_4	PivOH (5.0)	88
9	$PdCl_2$	CCl_4	PivOH (5.0)	0
10	$Pd_2(dba)_3$	CCl_4	PivOH (5.0)	31
11	$Pd(PPh_3)_4$	CCl_4	PivOH (5.0)	22
12	$Pd(OAc)_2$	CCl_4	none	55
13	$Pd(OAc)_2$	CCl_4	PivOH (3.0)	72
14	$Pd(OAc)_2$	CCl_4	AcOH (5.0)	43
15	$Pd(OAc)_2$	CCl_4	TFA (5.0)	0
16[c]	$Pd(OAc)_2$	CCl_4	PivOH (5.0)	60
17	$Pd(OAc)_2$	CCl_4	NaOAc (2.0)	56
18	$Pd(OAc)_2$	CCl_4	K_2CO_3 (2.0)	84
19[d]	$Pd(OAc)_2$	CCl_4	PivOH (5.0)	51

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), additive, [Pd] catalyst (0.02 mmol), and solvent (3.0 mL). The mixture was conducted under a Ar atmosphere for 24h. [b]Isolated yields. [c]The reaction was conducted under an air system. [d]The reaction was conducted on 80 °C. PivOH = trimethylacetic acid.

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol), PivOH (1.0 mmol), Ar, 24 h at 100 °C. [b]Isolated yield.

DOI: 10.1021/acs.orglett.6b02782
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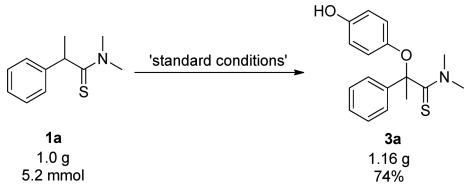
bromine and fluorine. One important feature of this method is that heteroaryls are also compatible with this system. Substrates **1q** and **1r** also proceed smoothly. It is evident that excellent yields can be achieved from **1a**, **1m**, and **1n**, which are probably propitious to stabilize palladium intermediates. The structure of the **3j** was confirmed by X-ray crystallography (see the SI).

The scope of 1,4-benzoquinone derivatives were investigated next (see the SI). Unfortunately, all the substituted benzoquinones are not transformed to the product under optimal conditions. Among many oxidants, 1,4-benzoquinone is most frequently used to recover Pd(II) from Pd(0).[8e] Benzoquinone is a electron-deficient olefin that can coordinate with Pd(0) intermediates then form Pd(II)/hydroquinone.[8] The Pd(0)−alkene complexes proceed via an associative addition/substitution pathway to remove of electron density from the palladium(0).[8b] When stoichiometric palladium is used, the tested benzoquinones are not converted to the desired products and corresponding hydroquinones except DDQ, which can oxidate thioamides. It demonstrates that Pd(0) can not be oxidated by the tested benzoquinone derivatives.

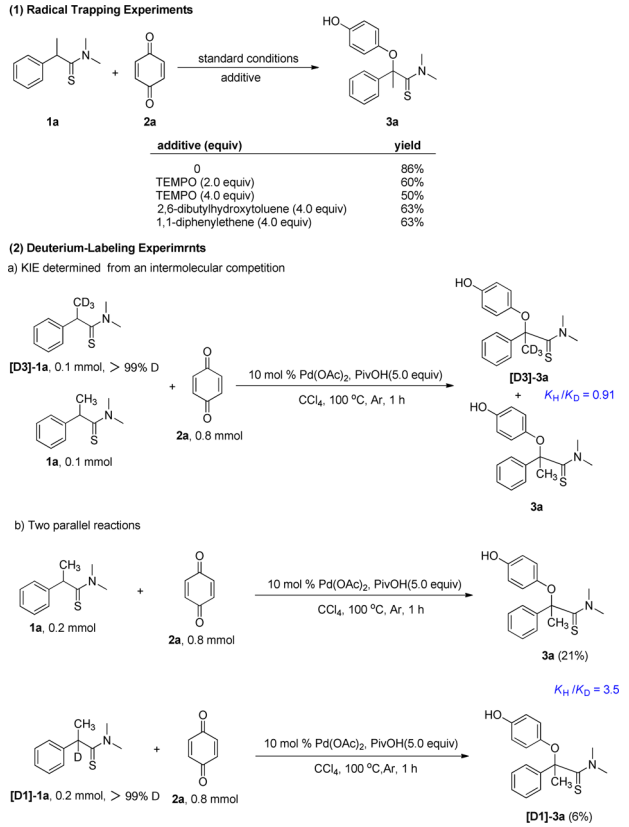
However, this protocol can be readily scaled up, and when it was performed on a gram scale of **1a**, the product **3a** was achieved in 74% yield (Scheme 3).

Scheme 3. Large-Scale Synthesis of 3a on a Gram Scale



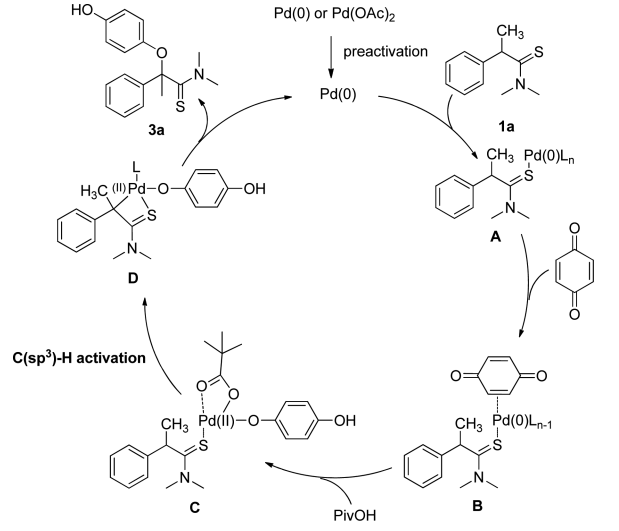
With the aim of gaining mechanistic insights into this reaction, several radical-trapping and deuterium-labeling experiments were performed (Scheme 4). The addition of 2 equiv or 4 equiv of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) as a radical scavenger does not inhibit the reaction (60% and 50% yields, respectively). The addition of 4 equiv of 2,6-dibutylhydroxytoluene (BHT) or 1,1-diphenylethene also has a negligible effect on the yield (63%). A radical pathway was ruled out. The intermolecular competition kinetic isotope effect for C(sp^3)−H of β-methyl is 0.9, and the result indicates that the cleavage C−H bond of β-methyl is a not a rate-determining step. It seems that β-methyls stabilize palladium intermediates.[16] The KIE from two parallel reactions is 3.5, which demonstrates that the cleavage of the α-C(sp^3)−H bond is a rate-determining step. Analysis by ^{1}H NMR showed no hydrogen shift in both experiments (see the SI). β-H elimination of the five-membered metallacycle, followed by bond rotation/insertion to form the four-membered palladacycle, is not involved in this reaction. Pd-catalyzed α-C(sp^3)−H arylation and allylic alkylation of thioamides through an enolate intermediate have been reported.[17] However, this mechanism is probably not suitable to this reaction because acid can promote this coupling reaction, which also proceeds well at neutral conditions. In 2014, Gaunt reported a Pd-catalyzed C−H activation of aliphatic amines through a unique four-membered-ring cyclopalladation for the first time.[16] Zhang then achieved α-C(sp^3)−H bond activation/acetoxylation via a [4,6]-bcyclic metallacycle.[18]

Scheme 4. Deuterium Labeling and Radical-Trapping Experiments



By combining these results, a plausible mechanism is depicted in Scheme 5. First, Pd(0) coordinates with thioamide

Scheme 5. Proposed Mechanism



to serve as a directing group to form intermediate **A**, followed by coordination with 1,4-benzoquinone and then in the presence of PivOH to achieve **C**. The rate-determining step is from **C** to **D** via a concerted metalation−deprotonation mechanism.[19] Subsequent reductive elimination from **D** delivers the product **3a** and releases Pd(0) for the next catalytic cycle.

DOI: 10.1021/acs.orglett.6b02782
Org. Lett. XXXX, XXX, XXX−XXX

In conclusion, we have developed a Pd-catalyzed site-selective *p*-hydroxyphenyloxylation of benzylic α-C(sp^3)−H bonds with 1,4-benzoquinone. The reaction proceeds with high functional group tolerance and provides products exclusively at the α-C(sp^3)−H of thioamides rather than β-C(sp^3)−H. This strategy opens a new avenue for the rapid and efficient synthesis of aryl alkyl ethers from readily available materials. The preliminary reaction mechanism studies demonstrate that this new method is probably through an unusual four-membered palladacycle. Further study of the reaction mechanism, chiral synthesis, and new organic transformations are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02782.

Experimental procedures and spectral data for all new compounds (PDF)

Crystal data and structure for **3j** (ZIP)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the National Natural Science Foundation of China (21476078) and the Science and Technology Commission of Shanghai Municipality (No. 12431900902).

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DOI: 10.1021/acs.orglett.6b02782
Org. Lett. XXXX, XXX, XXX−XXX