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Tandem oxidation–oxidative C–H/C–H cross-coupling: synthesis of arylquinones from hydroquinones†

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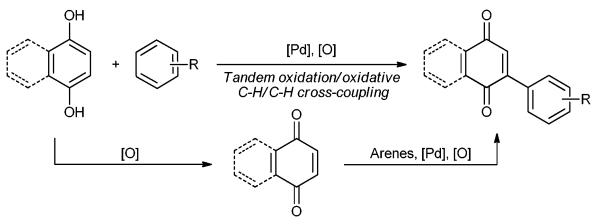
A concise and efficient approach to arylquinones from widely available hydroquinones has been developed through a tandem reaction involving the oxidation of hydroquinones and subsequent oxidative C–H/C–H cross-coupling of the resulting quinones with arenes.

The quinone derivatives are widely distributed in natural products[1] and exhibit various biological activities.[2] They are also involved in many bioenergetic processes due to the electron-transport properties.[3] Furthermore, aryl substituted quinones are very useful in the dye industry owing to their important coloring properties.[4] Thus, the synthesis of aryl substituted quinones has attracted significant attention and many methods have been developed. Among these, the reaction of quinones with aryl radicals has become an important protocol. Traditionally, diazonium salts are used as the aryl radical sources,[5] which are usually unstable, synthetically difficult, and sometimes explosive. To address this issue, commercially available, non-toxic, and stable boronic acids are found to be ideal radical sources to react with quinones in the presence of catalytic amounts of $AgNO_3$, which is to date the most efficient, general, and mild synthetic route to arylquinones.[6] Alternative approaches to arylquinones include the Lewis acid-catalyzed nucleophilic addition of arenes to quinones,[7] the transition-metal-catalyzed addition of boronic acids or their salts to quinones,[8] and the palladium-catalyzed cross-coupling of halogenated quinones with boronic acids or stannanes.[9] However, these addition approaches often require an oxidation step to convert the resulting arylated hydroquinones to quinones. Besides, the Lewis acid-catalyzed addition approach is limited to electron-rich arenes such as amino and/or methoxy-substituted arenes due to the low nucleophilicity of electron-deficient arenes. The palladium-catalyzed cross-coupling reactions require tedious prefunctionalization of both substrates.[9]

A more efficient approach to arylquinones is probably the transition-metal-catalyzed oxidative C–H/C–H cross-coupling of quinones with arenes that does not need preactivation of each coupling partner. However, the capability of quinones to oxidize and coordinate with transition metals[10] makes this type of coupling challenging, and thus very limited success has been obtained in the past years,[11] although the transition-metal-catalyzed oxidative Heck coupling has made significant progress.[12] Given the fact that many quinones are synthesized *via* the oxidation of hydroquinones[13] and oxidation conditions are necessary for the oxidative C–H/C–H cross-coupling of quinones with arenes, we rationalized that these two reactions could be conducted in one pot and thus enhance the synthetic efficiency of arylquinones. Herein, we report a one-pot synthesis of arylquinones starting from hydroquinones through the tandem reaction of oxidation of hydroquinones–oxidative C–H/C–H cross-coupling of quinones with arenes (Scheme 1). It is noteworthy that the reactions can be carried out under an air atmosphere.

The reaction of 1,4-naphthalenediol **1a** with benzene **2a** was used to optimize the reaction conditions (eqn (1); Table S1, ESI†). After screening various parameters, it was found that oxidant, palladium species and PivOH were crucial for this tandem reaction to proceed smoothly. The yield of the desired product 2-phenyl-1,4-naphthoquinone **3a** could reach 97% in the presence of 5 mol% $Pd(acac)_2$, 3.0 equiv. of Ag_2CO_3, 3.5 equiv. of DMSO, and 2.0 equiv. of PivOH using benzene as the solvent. The addition of DMSO was beneficial to the reaction. Using more economical $Cu(OAc)_2$, $PhI(OAc)_2$, or O_2 as oxidant could not provide the desired arylquinone **3a** in satisfactory yields due to the inefficiency of the second-step oxidative coupling,



Scheme 1 The one-pot synthesis of arylquinones from hydroquinones.

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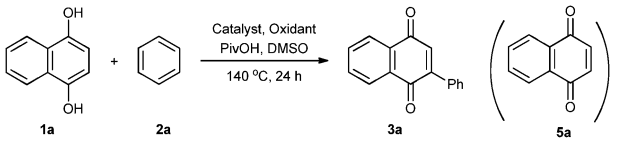
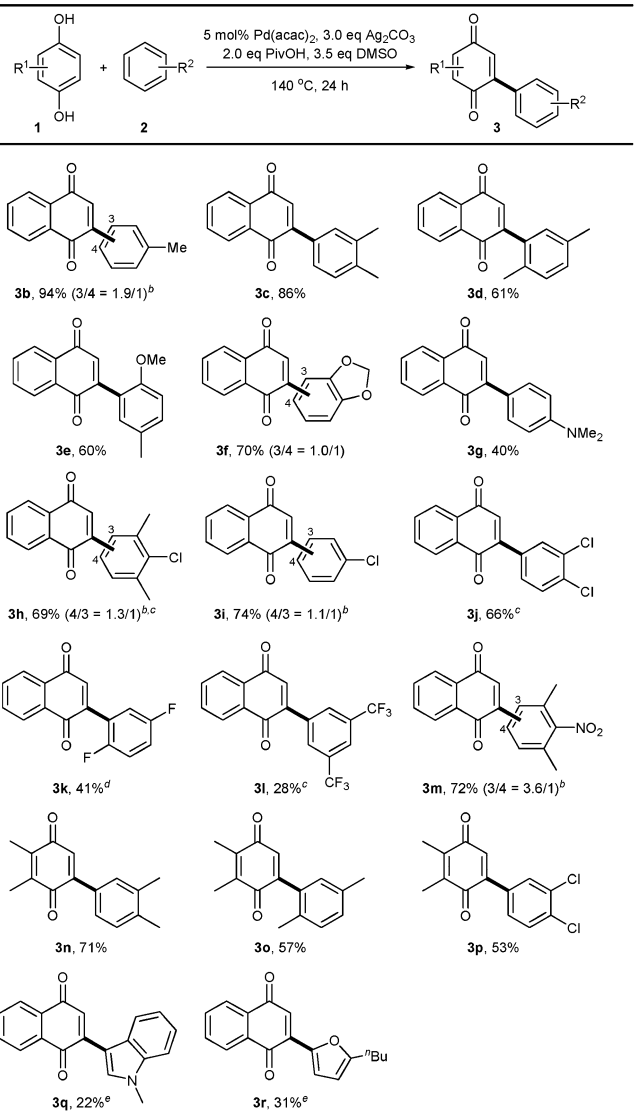
although they could oxidize 1,4-naphthalenediol **1a** to 1,4-naphthoquinone **5a**.



(1)

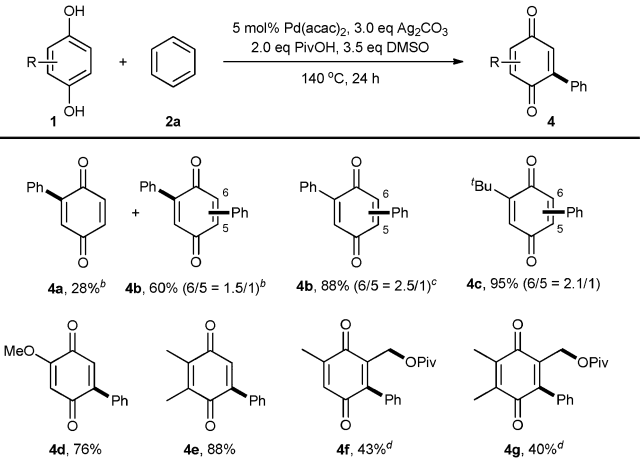
The scope of arene coupling partners was examined next under the optimal conditions (Table 1). Arenes with electron-rich or neutral groups such as methyl and methoxy groups could all couple with the *in situ* generated 1,4-naphthoquinone **5a** to afford the desired arylquinones in good to excellent yields (Table 1, **3b–3f**). However, a moderate yield of 40% was obtained when *N*,*N*-dimethylaniline was employed as the substrate (Table 1, **3g**).

Table 1 The scope of different arenes[a]



[a] Reaction conditions: hydroquinone **1** (0.4 mmol), $Pd(acac)_2$ (5 mol%), Ag_2CO_3 (1.2 mmol), PivOH (0.8 mmol), DMSO (1.4 mmol) and arene **2** (3.0 mL) at 140 °C for 24 h. [b] The ratio of two isomers was determined using ^1H NMR. [c] 10 mol% of $Pd(acac)_2$. [d] 10 mol% of $Pd(acac)_2$, 4.0 equiv. of PivOH, 48 h. [e] 2.0 equiv. of heteroarenes, 1,2-dichloroethane as solvent.

Table 2 The tandem reaction of various 1,4-hydroquinones with benzene[a]

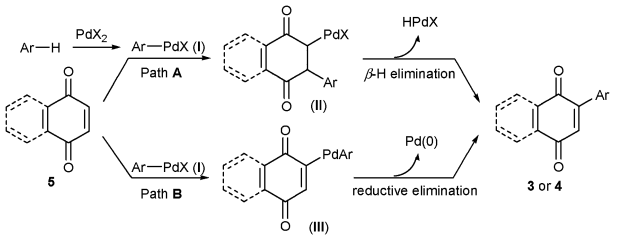


[a] Reaction conditions: hydroquinone **1** (0.4 mmol), $Pd(acac)_2$ (5 mol%), Ag_2CO_3 (1.2 mmol), PivOH (0.8 mmol), DMSO (1.4 mmol) and benzene **2a** (3.0 mL) at 140 °C for 24 h. [b] Starting from 1,4-hydroquinone. [c] Starting from 2-phenyl-1,4-hydroquinone. [d] 10 mol% of $Pd(acac)_2$, 4.0 equiv. of PivOH, 48 h.

Arenes with electron-withdrawing substituents including chloro-, fluoro-, nitro- and trifluoromethyl groups could also provide the desired products under the present catalytic conditions, although 10 mol% of $Pd(acac)_2$ was often required to obtain synthetically useful yields (Table 1, **3h–3m**). 2,3-Dimethyl-1,4-hydroquinone showed similar reactivity to 1,4-naphthalenediol **1a** towards the reaction with both electron-rich and electron-deficient arenes (Table 1, **3n–3p**). When heteroarenes such as indoles or furans instead of arenes were subjected to the standard conditions, only the homocoupling products of heteroarenes were obtained.[14] By decreasing the amount of heteroarenes to 2.0 equiv. and changing the solvent to DCE, the desired heteroarylquinones were obtained, albeit in low yields (Table 1, **3q** and **3r**).

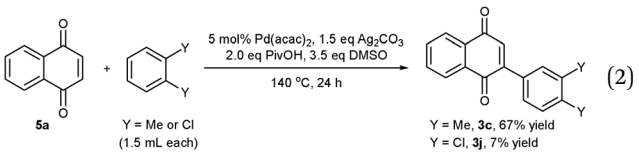
Subsequently, the feasibility of this reaction to other hydroquinones was examined (Table 2). Besides benzannulated hydroquinones, alkyl, aryl, and methoxy substituted hydroquinones could all smoothly undergo the tandem reaction of oxidation–oxidative cross-coupling to afford the desired arylated quinones in good to excellent yields (Table 2, **4a–4e**). Interestingly, the treatment of 2,6-dimethyl-1,4-hydroquinone **1f** and trimethyl-1,4-hydroquinone **1g** with benzene provided the *ortho*-methyl pivaloxylated arylquinones **4f** and **4g** under the standard conditions, respectively. Monitoring of the reaction mixture did not show the phenyl quinone or *ortho*-methyl pivaloxylated quinone intermediates except the final product, implying that the pivaloxyl and phenyl groups might be introduced to the quinone core from the same intermediate.

The study of the mechanism was mainly focused on the second-step oxidative C–H/C–H cross-coupling of quinones with arenes because the oxidation of hydroquinones to quinones is well known.[13] Considering that quinones can react easily with radicals, a radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, 20 mol%) was added to the reaction mixture of 1,4-naphthoquinone **5a** and benzene under standard conditions. A slightly decreased yield of 78% was obtained, indicating that a radical pathway might not be involved in this process.[15]

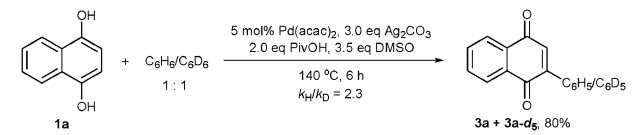


Scheme 2 Proposed mechanism for the oxidative C–H/C–H cross-coupling of quinones with arenes.

The exposure of 1,4-naphthoquinone **5a** to a 1 : 1 mixture of *o*-xylene and 1,2-dichlorobenzene resulted in the formation of the corresponding arylquinones **3c** and **3j** in 67% and 7% yields, respectively (eqn (2)), suggesting that the reaction of quinones with electron-rich arenes was faster than with the electron-deficient arenes. In addition, the primary kinetic isotope effect for benzene (k_H/k_D = 2.3/1) was observed by conducting the competition reaction between benzene and benzene-d_6 (eqn (3)). Therefore, the C–H bond cleavage of benzene might proceed through an electrophilic palladation pathway and might be related to the rate-limiting step.

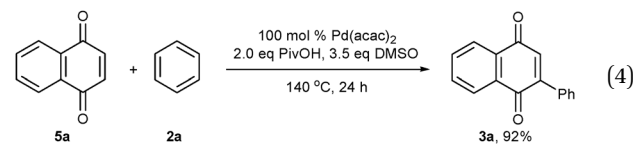


(2)



(3)

Finally, the reaction of **5a** with benzene **2a** and stoichiometric $Pd(acac)_2$ provided **3a** in 92% yield in the absence of the oxidant Ag_2CO_3 (eqn (4)), which suggested that arylquinones were formed directly by the oxidative C–H/C–H cross-coupling rather than generated from the oxidation of arylated hydroquinones.[8]



(4)

As illustrated in Scheme 2, a plausible mechanism was proposed for the oxidative C–H/C–H cross-coupling of quinones with arenes. The S_EAr reaction of arene with Pd(II) produced the arylpalladium complex **I**, followed by two possible pathways: (1) path **A** might involve the Heck-type arylpalladation of quinone **5** with ArPdX **I** and the following β–H elimination to produce the desired arylquinone **3** or **4**; and (2) path **B** might undergo the C–H cleavage of quinone **5a** *via* a carboxylate-assisted concerted metalation–deprotonation (CMD) pathway[16] and subsequent reductive elimination.

In conclusion, a concise and efficient protocol for the synthesis of arylquinones from widely available hydroquinones has been developed. The reaction proceeds through the oxidation of hydroquinones and subsequent oxidative C–H/C–H cross-coupling of the resulting quinones with arenes in one pot. Further studies to apply this methodology to the synthesis of arylquinone-containing natural products are in progress.

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