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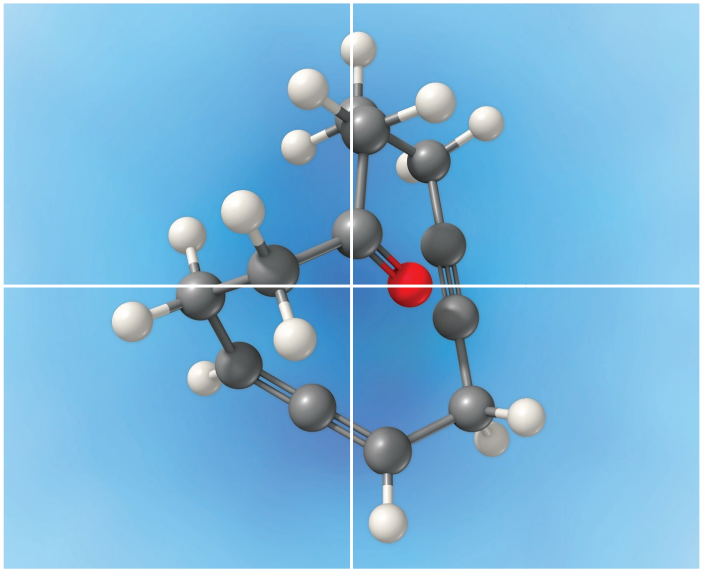

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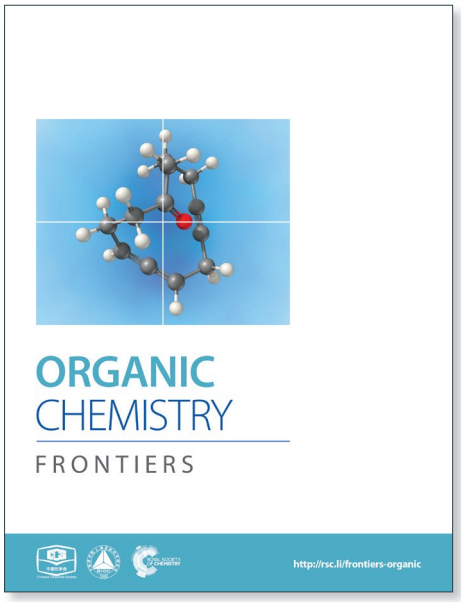

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ARTICLE

$K_2S_2O_8$-Mediated Metal-Free Direct C-H Functionalization of Quinones Using Arylboronic Acids

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Direct C-H functionalization of quinones with arylboronic acids is achieved using $K_2S_2O_8$ as the sole and efficient green catalytic system. This method provides a straight forward and sustainable way to construct arylquinones via radical pathway in moderate to good yields under metal-free conditions.

Introduction

Arylated benzoquinone, naphthoquinone and heterocyclic ring systems form important skeletal framework of several biologically active compounds and natural products (Figure 1).[1a-d] Unique electronic and visual properties of arylated quinones make them act as useful dyes and photoactive materails.[2a-b] Recent developments on C-C bond forming methods made it possible to carryout direct C-H functionalization of quinones using different aryl counter parts. Consequently, several new procedures were reported for the synthesis of arylated quinones. Employing stannyl quinone for Stille type coupling[3a] or halogenetaed quinones for Suzuki-Miyaura type coupling[3b] have their own drawbacks as they require pre-functionalization of quinones. Haloquinones or stannyl quinones are hard to access due to chemo and regioselectivity issues. Heck type cross coupling fails in case of quinones due to the fact that quinones can co-ordinate with Pd and usually acts as a catalyst for reoxidation Pd(0) species[4a-b]

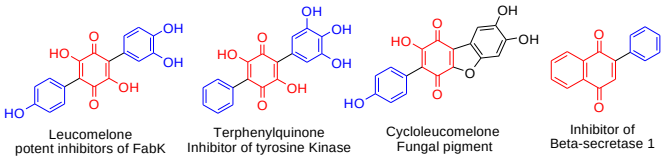

Fig 1. Bioactive arylquinone motifs

Direct C-H/C-H cross coupling is highly advantageous, as this avoids involvement of functionalized starting materials. Rh(III) together with expensive re-oxidant ($AgSbF_6$-AgOAc) worked well for C-H/C-H of quinones using with directing group.[5] Similarly, stochiometric quantity of $Pd(OAc)_2$ or catalytic quantity of $Pd(OAc)_2$-$Na_2S_2O_8$ was used for direct C-H/C-H cross coupling.[6a] $Pd(acac)_2$ with large excess of Ag_2CO_3 as co-oxidant was found useful for the synthesis of arylated quinone from hydroquinone.[6b] $Pd(TFA)_2$ with $(NH_4)_2S_2O_8$ as the co-oxidant is yet another useful catalytic system reported for arylation of quinones as well as olefins.[6c] Direct C-H/C-H cross coupling is mainly applicable for electron rich aryl counterparts, thus making it substrate specific[5,6a,6c] and less attractive.

Arylation of quinones using radical is a successful approach. Although Meerwein arylation of quinone was reported earlier,[7a-b] improved methods were reported only later. It requires hydroquinone or a reducing metal like copper for the homolytic decomposition of the diazonium functionality to form aryl radical. Aryl diazonium salts are very unstable, sometimes explosive above 0 °C and require highly acidic condition for its synthesis, thus not suitable for large scale applications.[7c] Recently, application of metal-free methods for making C-C or C-heteroatom bonds gained attention of chemists.[8] However, methods involving metal-free generation of radicals are only in scarce.[9] Aryl radicals obtained from phenyl hydrazine-IBX was used for arylation of naphthoquinones to get products in moderate to good yields.[9a] Different Ar_2IOTf salts were also used successfully to generate aryl radical for arylation benzoquinoine and naphthoquinone.[9b] The scarce availability of substituted phenyl hydrazine and Ar_2IOTf salts make these approaches of limited substrate scope and hence less attractive.

Arylboronic acids are highly stable, even in water and readily available in variety of substituted forms, making it a convenient precursor for building compounds of wide substrate scope. After Molina et al demonstrated that naphthoquinones can be directly arylated using arylboronic acids in the presence of Pd/Cu catalyst and $FeCl_3$ co-oxidant,[10] a series of reports appeared on application of arylboronic acids for arylation of quinones using different metal salts such as $AgNO_3$,[11a] FeS,[11b] $FeNO_3$,[11c] $FeSO_4$,[11d] $Fe(acac)_2$,[11e] all in combination with large excess of $K_2S_2O_8$ as co-oxidant. ($Pd(OCOCF_3)_2$ with large excess of 2,6-dichlorobenzoquinone (2.5 equiv.) as co-oxidant was also reported for diarylation of quinonens using arylboronic acids.[12] Analysis of methods reported so far reveals that except few reagents (IBX and

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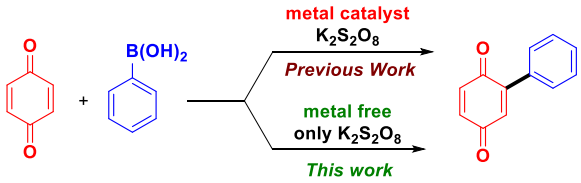
Ar_2IOTf)[9a-b] almost all the methods reported require metal salts and a re-oxidant (Scheme 1).



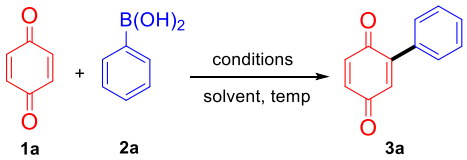
Scheme 1. Arylation of quinones

It is well known that $K_2S_2O_8$ decomposes at higher temperature to generate radical.[13a-b] However, in the presence of metal salts, decomposition of $K_2S_2O_8$ takes place at room temperature to generate sulphate radical.[11d,14] Thus we envisaged that aryl radical could be generated from arylboronic acids using $K_2S_2O_8$ at higher temperature and used for arylation of quinones. $K_2S_2O_8$ is a versatile oxidant available at much cheaper price and can be used for the regeneration of quinone from hydroquinone. Avoiding metallic reagents is advantageous in terms of elimination of metal toxicity, cost saving and minimization of environmental pollution. Herein, we present a simple method for arylation of quinones and heterocycles using arylboronic acid under metal free condition.

Results and Discussion

Our studies began with optimization of condition for reaction between quinone **1a** (1.0 equiv.) and arylboronic acid **2a** (1.5 equiv.) in the presence of $K_2S_2O_8$ as an oxidant in DCE/H_2O. Various reaction parameters were studied and the results are summarized in Table 1. No reaction was observed at room temperature (rt) with 1.0 equiv. of $K_2S_2O_8$, in DCE. However when the solvent system was changed to DCE/H_2O, we were delighted to see the formation of **3a** in traces (entry 2). Increase in temperature to 80 °C lead to formation of product **3a** in 30% isolated yield (entry 1 and 3). It was concluded that temperature is the key factor for the reaction to take place. Increasing the amount of $K_2S_2O_8$ to 2.0 equiv. had beneficial effect and the product **2a** was obtained in highest yield (72%) in shortest reaction time (entry **4**). Further, increase in the quantity of $K_2S_2O_8$ to 3.0 equiv. had no improvement on the yield (entry 5). However, when the quantity of $K_2S_2O_8$ was increased further to 5.0 equiv. the yield of the product **3a** decreased (entry 6). Similarly, increasing or decreasing the temperature from 80 °C only provided the product **3a** in low yield (entry 7 and 8). Likewise, when the quantity of the arylboronic acid **2a** was decreased to 1.0 equiv. the yield decreased (entry 9). In the absence of $K_2S_2O_8$ no desired product was formed, indicating that $K_2S_2O_8$ is crucial to this reaction (entry 10). Other oxidants TBHP, H_2O_2 and oxone as catalysts were ineffective for the reaction (entries 11-13). Among the different solvent systems, DCE:H_2O furnished highest yield (entries 14-18). Thus a systematic screening study revealed that **1** (1.0 equiv.), **2a** (1.5 equiv.) and $K_2S_2O_8$ (2.0 equiv.) in DCE-H_2O at 80 °C is the optimum condition for arylation.

Table 1. Optimization Studies for the Formation of **3a**



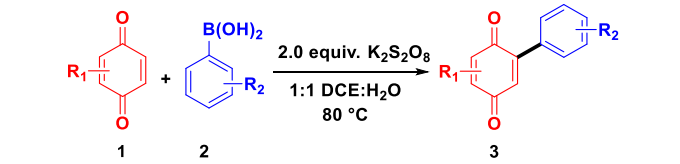
1a **2a** **3a**

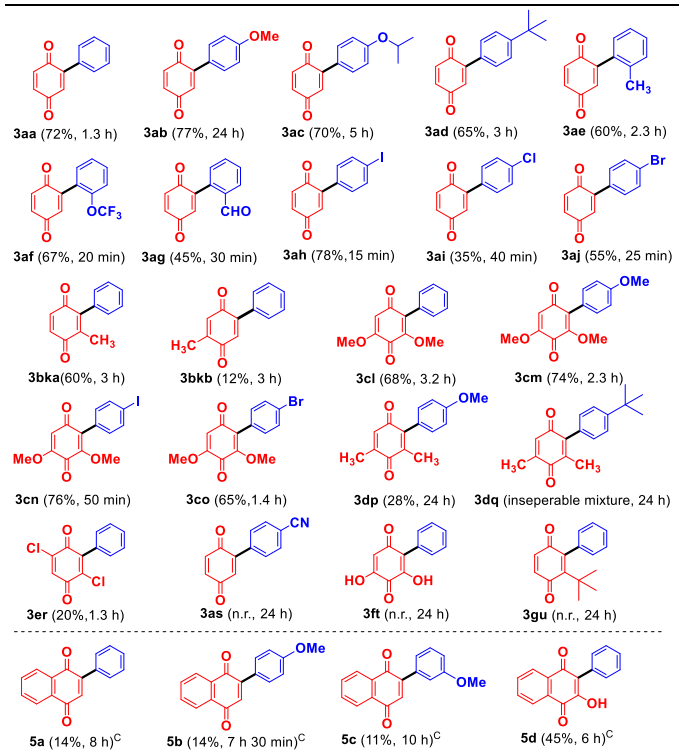
S.NO	additive	solvent	temp (°c)	time	yield (%)[a]
1	$K_2S_2O_8$ (1.0 equiv)	DCE	rt	24 h	nr[b]
2	$K_2S_2O_8$ (1.0 equiv)	DCE/H_2O	rt	24 h	5
3	$K_2S_2O_8$ (1.0 equiv)	DCE/H_2O	80	24 h	30
4	**$K_2S_2O_8$ (2.0 equiv)**	**DCE/H_2O**	**80**	**1h 30 min**	**72**
5	$K_2S_2O_8$ (3.0 equiv)	DCE/H_2O	80	1h 10 min	72
6	$K_2S_2O_8$ (5.0 equiv)	DCE/H_2O	80	1 h	65
7	$K_2S_2O_8$ (2.0 equiv)	DCE/H_2O	60	2 h	60
8	$K_2S_2O_8$ (2.0 equiv)	DCE/H_2O	100	1 h	64
9	$K_2S_2O_8$ (2.0 equiv)	DCE/H_2O	80	2 h 30 min	58[c]
10	-	DCE/H_2O	80	24 h	nr[b]
11	TBHP (2.0 equiv)	DCE/H_2O	80	24 h	nr[b]
12	H_2O_2 (2.0 equiv)	DCE/H_2O	80	24 h	nr[b]
13	Oxone (2.0 equiv)	DCE/H_2O	80	24 h	nr[b]
14	$K_2S_2O_8$ (2.0 equiv)	H_2O	80	24 h	36
15	$K_2S_2O_8$ (2.0 equiv)	DMF/H_2O	80	1h 50 min	45
16	$K_2S_2O_8$ (2.0 equiv)	Toluene/H_2O	80	24 h	50
17	$K_2S_2O_8$ (2.0 equiv)	DMSO/H_2O	80	24 h	nr[b]
18	$K_2S_2O_8$ (2.0 equiv)	MeOH/H_2O	80	24 h	trace

[a]Isolated yield. [b]No reaction. [c]**2a** (1.0 mmol).

With the optimal condition in hand, the scope of quinone arylation reaction was explored on different substrates (Scheme 2). Different arylboronic acids, bearing electron donating groups **2b-2e** reacted well with 1,4-benzoquinone to give corresponding products **3ab-3ae** in moderate to good yields. Similarly, arylboronic acids **2f** and **2g** containing substituents at sterically crowded *ortho* position reacted fast to furnish the products **3af** and **3ag** in moderate yield. Arylboronic acids, **2h-2j** bearing halogen groups were well tolerated and offered **3ah-3aj** in moderate to good yields. Next, the effect of the substituent on quinone was investigated. Mono substituted benzoquinone such as 2-methylcyclohexa-2,5-diene-1,4-dione (**1b**) produced regio isomeric mixture of arylated quinone **3bka** and **3bkb** in 72% overall yield. Similarly, more sterically hindered 2,6-dimethoxybenzoquinone (**1c**) reacted successfully with different aryl boronic acids **2a**, **2b**, **2h**, and **2j** to provide corresponding products **3cl-3co** in good yields. However, 2,6-dimethylbenzoquinone (**1d**) and 2,5-dichlorobenzoquinone (**1e**) delivered the desired products **3dp, 3dq** (inseparable mixture) **and 3er** in low yield. The arylboronic acid **1q** containing strong electron withdrawing -CN group on reaction with simple benzoquinone (**1a**) failed to produce the desired product **3as.** This may be due to the unstable nature of cyano aryl radical.[11a] Similarly, 2,6-dihydroxybenzoquinone (**1f**) and *t*-butylbenzoquinone (**1g**) on treatment with phenyboronic acid (**2a**) also failed to produce the expected arylated products **3t** and **3u**, even after prolonged reaction time.

As a part of the study we next examined reactivity of 1,4 naphthoquinone (**4a**) and its derivatives. In case of 1,4 naphthoquinone (**4a**), the desired product **5a** could not be obtained under the optimum reaction condition, however in the presence of triethylamine (TEA, 10.0 equiv.) the expected product **5a** was obtained albeit in low yield (14%). In the presence of disopropylamine the product **5a** was formed only in 5% yield, where as in the presence of inorganic bases such as K_2CO_3 and NaOH the yield was decreased to trace. Similarly, 4-methoxyphenylboronic acid (**2b**) and 3-Methoxy phenylboronic acid (**2l**) furnished the expected products **5b** and **5b** in 14% and 11% respectively. Interestingly, the hydroxyl group in 2-hydroxy naphthaquinone (**4b**) tolerated the reaction condition well and the arylated quinone **5d** was obtained in moderate yield (45%).

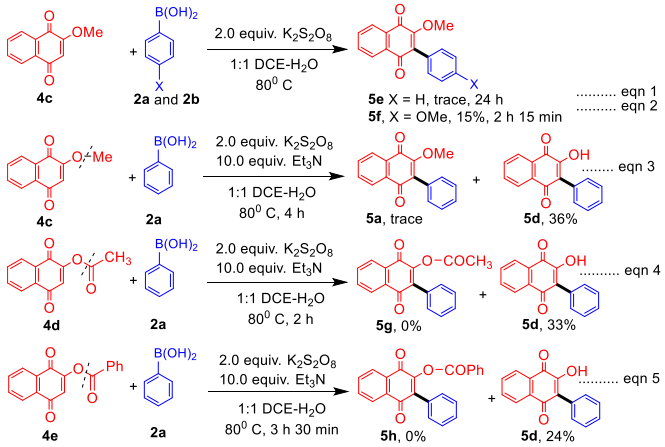




[a]Reaction Conditions: 1 (1.0 mmol), 2 (1.5 mmol), $K_2S_2O_8$ (2.0 equiv.), CH_2Cl_2-H_2O (1:1, v/v, 4 mL) at 80 °C; [b]isolated yields; [C]the reaction was performed in the presence of Et_3N (10.0 equiv.) at 80 °C in CH_2Cl_2-H_2O (1:1, v/v, 4 mL).

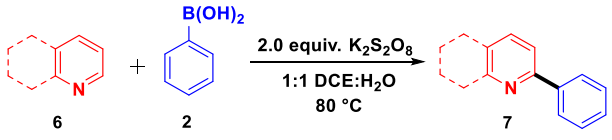
Scheme 2. Scope of quinone and boronic acid coupling partners

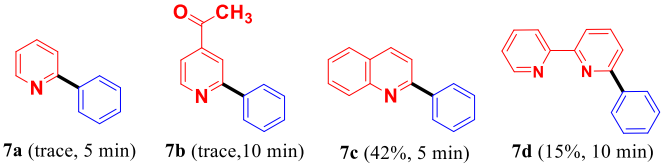
In the absence of TEA, while 2-methoxy naphthaquinone (**4c**) failed to undergo reaction with phenylboronic acid (**2a**, Scheme 3, eqn 1, **5e**), it underwent reaction with 4-methoxy boronic acid (**2b**, Scheme 3, eqn 1) successfully albeit in low yield **5f**. Surprisingly, in the presence of TEA, the -OMe, -$OCOCH_3$ and -OCOPh naphthoquinones **4c-e** underwent C-O bond cleavage reaction to give the corresponding arylated naphthoquinones **5a** and **5d** in low yields (eqn 3-5, Scheme 3). It is interesting to note that in the absence of Et_3N no C-O bond cleavage took place indicating that base plays vital role in C-O bond cleavage (eqn 1 and 2, Scheme 3). To the best of our knowledge, this is for the first time C-O bond cleavage of naphthoquinone derivatives such as **4c**, **4d**, and **4e** was observed in presence of $K_2S_2O_8$ and TEA.



Scheme 3. $K_2S_2O_8$-Et_3N mediated C-O bond cleavage of naphthoquinones

With these impressive results, we further focused on application of the same oxidant system for arylation of different heterocycles such as pyridine (**6a**), 4-acetyl pyridine (**6b**), quinoline (**6c**) and bipyridine (**6d)** (Scheme 4). Among the different heterocycles, quinoline (**6c**) was successful in undergoing reaction with the aryl radical to give **7c** in moderate yield. While bipyridine (**6d**) produced low yield of the product **7d**, pyridine (**6a**) and 4-acetyl pyridine (**6b**) produced only trace amount of the products **7a** and **7b**. Further attempts to enhance the yield for the formation of expected products **7a** and **7b** was not successful. This may be due to the salt formation of pyridinium ring system during the course of the reaction.



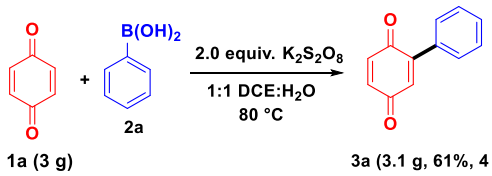


[a]Reaction Conditions: 1 (1.0 mmol), 2 (1.5 mmol), $K_2S_2O_8$ (2.0 equiv.), CH_2Cl_2-H_2O (1:1, v/v, 4 mL) at 80 °C. [b]Isolated yields.

Scheme 4. Scope of heterocycles and boronic acid coupling

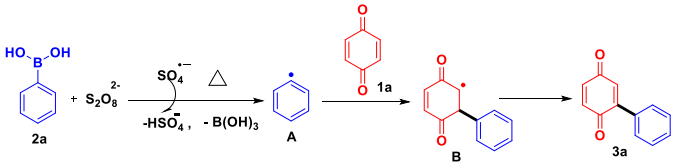
To demonstrate the synthetic utility of the present method, a gram-scale experiment was carried out, under the

optimal reaction condition, on benzoquinone (**1a**, 3.0 g) using phenylboronic acid (**2a,** Scheme 5). The arylated product **3aa** was obtained in 61% isolated yield (3.1 g), which shows that the present method can be easily adopted for the large scale preparations.



Scheme 5. Gram-scale synthesis of aryl benzoquinone

To study the reaction mechanism, radical scavenger effect was investigated by adding TEMPO in the reaction between benzoquinone (**1a**) and phenylboronic acid (**2a**). Obviously, the yield decreased from 72% to 12% when 2.0 equiv. of TEMPO was added. This result shows that the reaction takes place through radical mechanism and complies with reported literature.[10c] Based on these results, a suitable mechanism is proposed (Scheme 6). Initially, $K_2S_2O_8$ thermally decomposes to form sulfate radical (SO4−•),[13a-b] which in turn reacts with arylboronic acid **2a** to give aryl radical **A**.[13c-14] Further, aryl radical **A** reacts with quinone **1a** to give **B**, which on re-oxidation afforded the desired product **3a** (Scheme 6).



Scheme 6. A plausible reaction mechanism

Conclusion

In summary, the present study shows that aryl radicals could be generated from arylboronic acid under metal free condition by means of $K_2S_2O_8$ and used for C-H functionalization of quinones and heterocycles. The radical path way involved in the reaction was established by studying the reaction in the presence of radical scavenger. The present method avoids metal and ligand. $K_2S_2O_8$ is inexpensive, environmentally benign, and found to show high efficiency to generate radical at high temperature. This method is simple, scalable, and do not require any prefunctionalization of quinones. Further study on applications of this reaction is underway in our laboratory.

Acknowledgements

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