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Three-Component Oxyarylation of Alkenes Enables Access to C_3-Substituted Dihydrobenzofurans

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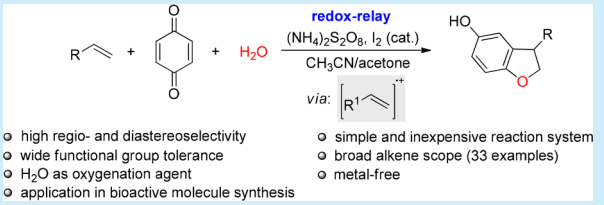
Supporting Information

ABSTRACT: A practical and modular three-component alkene oxyarylation with benzoquinone and H_2O to rapidly access C_3-substituted dihydrobenzofurans has been developed. The $(NH_4)_2S_2O_8$-mediated redox-relay process has an excellent regioselectivity and functional group tolerance and exhibits a broad scope of simple alkenes, rapidly furnishing a variety of the substructures that would require multiple steps to prepare with traditional methods. Mechanistic studies revealed a dual role of benzoquinone serving as both the arylation agent and the origin of dihydroquinone for the reductive cyclization step.



C_3-Substituted dihydrobenzofurans (DHBs) are key motifs in a number of bioactive natural molecules and have been used for many pharmaceutical applications (Figure 1a).[1] The most frequently employed approach to access such motifs relies on intramolecular arylation of an allylic ether of *o*-halophenol either through organotin-mediated radical cyclization or through transition-metal-catalyzed Heck-type cyclization, both of which require multiple steps for substrate prefunctionalization (Figure 1b).[2,3] On the other hand, acid-catalyzed [3 + 2] cycloaddition of alkenes with benzoquinone (BQ) represents one of the most practical methods for rapid DHB skeleton construction (Figure 1c).[4] Due to the innate alkene polarization, the biomimetic oxyarylation process follows Markovnikov's rule, predominantly giving C_2-substituted DHBs with oxygen bonding to the more substituted olefinic carbon.[5,6] Moreover, the reaction mechanism requires electron-rich alkenes such as styrenes and enol ethers, with the widely existing simple olefins intact. Accordingly, direct access to C_3-substituted DHBs by reversing the alkene polarization in oxyarylation with BQ would be an attractive, but challenging, project to pursue.[7]

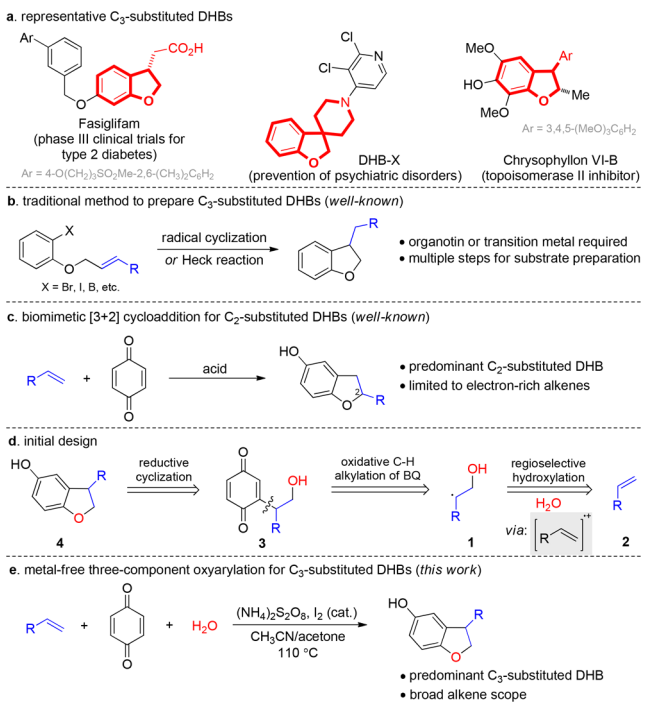


Figure 1. Overview of the access to C_3-substituted DHBs through alkene arylation reaction.

Recently, we have disclosed an $(NH_4)_2S_2O_8$-mediated three-component oxyalkynylation of alkenes using H_2O as an oxygenation agent.[8] Notably, the method exhibited reversed regioselectivity to the existing three-component carbooxygenation of alkenes. Mechanistic studies revealed that the reversed regioselectivity was dictated by an alkene radical cation species that underwent hydration to give anti-Markovnikov β-oxyl radical **1** for the subsequent alkynylation process. Given the electron-deficient property of BQ toward radical addition,[9] a two-step redox-relay approach for C_3-substituted DHBs was initially designed: (1) alkene **2** proceeds through regioselective hydroxylation to generate an anti-Markovnikov β-oxyl radical **1** that participates in oxidative C−H alkylation of BQ to yield quinone **3**, and (2) **3** undergoes reductive cyclization to furnish the expected C_3-substituted DHB **4** (Figure 1d). Herein, we report an $(NH_4)_2S_2O_8$-mediated metal-free three-component oxyarylation of alkenes

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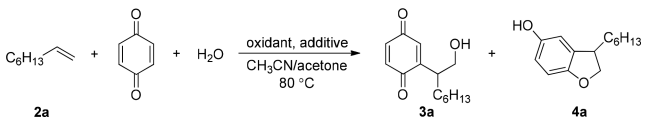
with BQ and H_2O that furnishes C_3-substituted DHBs with high regio- and diastereoselectivities (Figure 1e).

Initially, a three-component reaction of 1-octene (**2a**), BQ, and H_2O was selected for optimization (Table 1, also see the Supporting Information). An exploration of common single-electron oxidants revealed that $Na_2S_2O_8$ promoted the reaction, furnishing the expected alkylated quinone **3a** in 14% yield after 6 h (entries 1 and 2). To our surprise, a considerable amount of C_3-substituted DHB **4a** was also observed in 8% yield. Moreover, **3a** was found to be converted to **4a** when the reaction ran longer (entry 3). Examination of the counterion effect of peroxydisulfate as well as the additive effect identified $(NH_4)_2S_2O_8$ and a catalytic amount of I_2 to be the best candidates (entries 3−8). Reaction with **2a** as a limiting agent afforded an inferior result (entry 9). Variation of reaction temperature indicated that reaction at 110 °C provided **4a** in optimal 46% yield (entry 10). No regioisomeric C_2-substituted DHB was detected. The commercial availability of alkenes and BQ combined with the low cost of $(NH_4)_2S_2O_8$ (less than $0.04 per gram) make the three-component oxyarylation of alkenes more attractive for access to C_3-substituted DHBs than previously reported methods that require prefunctionalization and expensive reagents.

Table 1. Reaction Condition Optimization[a]

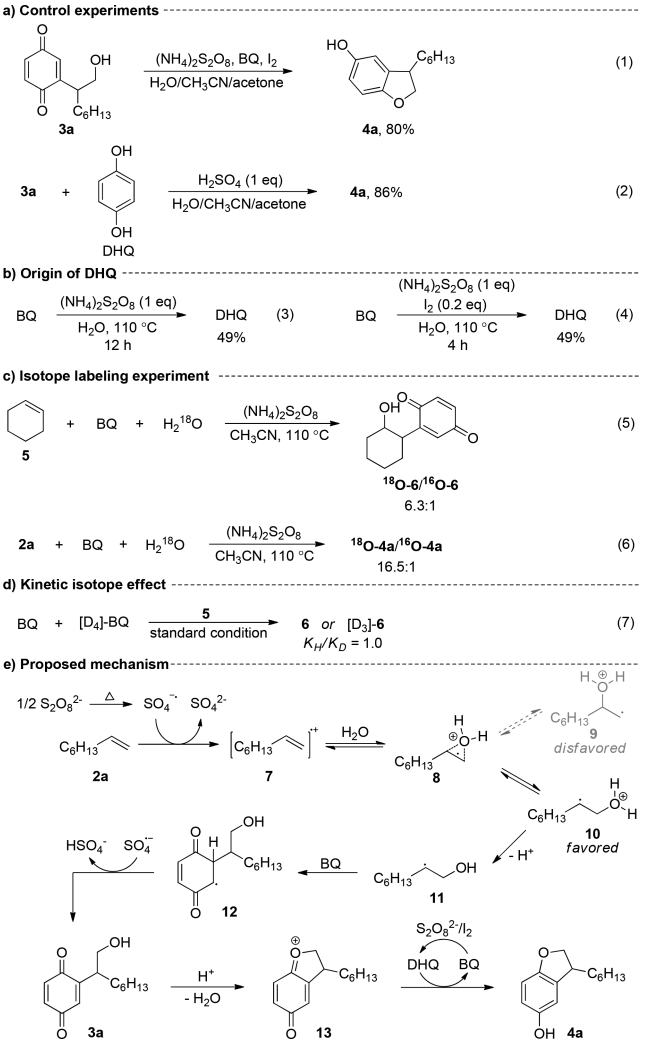


entry	oxidant	additive	yield[b] (%) 3a	4a
1[c]	oxidant		<5	<5
2[d]	$Na_2S_2O_8$		14	8
3[e]	$Na_2S_2O_8$		<5	20
4	$K_2S_2O_8$		<5	15
5	$(NH_4)_2S_2O_8$		<5	24
6	$(NH_4)_2S_2O_8$	$CuSO_4$	<5	31
7	$(NH_4)_2S_2O_8$	NaI	<5	28
8	$(NH_4)_2S_2O_8$	I_2	<5	41
9[f]	$(NH_4)_2S_2O_8$	I_2	<5	9
10[g]	$(NH_4)_2S_2O_8$	I_2	<5	46

[a]**2a** (0.3 mmol), BQ (0.1 mmol), oxidant (0.2 mmol), and additive (0.02 mmol) in H_2O/CH_3CN/acetone (2.1 mL, v/v/v = 1:1:1) at 80 °C for 24 h. [b]Yield of isolated product. [c]$(NH_4)_2Ce(NO_3)_6$, $Mn(OAc)_3$, or TBHP as oxidant. [d]Reaction was analyzed after 6 h. [e]Reaction without H_2O. [f]**2a** used as the limiting agent. [g]Reaction at 110 °C for 4 h.

During the reaction optimization, two interesting observations merited further elucidation: (1) the proposed two-step redox-relay sequence in Figure 1d was actualized in a single step under an oxidative condition, and (2) the optimized reaction yield was less than 50%. Accordingly, a series of experiments were conducted to gain a preliminary understanding of the reaction mechanism (Scheme 1). First, subjecting isolated **3a** to the standard conditions afforded DHB **4a** in good yield, thus implying the intermediacy of **3a** (eq 1). Second, a considerable amount of dihydroquinone (DHQ) was detected during the reaction process. Moreover, the pH value of the reaction solution was less than 7. The transformation of **3a** to **4a** proceeded smoothly in the presence of DHQ and stoichiometric H_2SO_4, suggesting that DHQ might be the species in charge of the reductive cyclization step (eq 2).[10] It has been reported that peroxydisulfate ion can promote the conversion of 2 equiv of BQ to 1 equiv of DHQ and 1 equiv of highly oxidized dark brown materials.[11] Indeed, $(NH_4)_2S_2O_8$ effected the conversion of BQ to DHQ in 49% yield together with other unidentified black materials, though the process required 12 h for complete BQ consumption (eq 3). The reaction with catalytic amount of I_2 was completed in 4 h (eq 4). Accordingly, we envisioned that catalytic amount of I_2 might expedite the formation of DHQ, thus harmonizing the process with the formation of **4a**, though the origin of curious but useful effect has not been elucidated. Third, $H_2{}^{18}O$ isotopic labeling experiments indicated that oxygens in both alkylated quinone **6** and DHB **4a** should originate from H_2O (eqs 5 and 6). Finally, intermolecular KIE for BQ is 1.0, suggesting that C−H cleavage of BQ should be a fast step and might not be involved in the rate-determining step (eq 7). According to the above experiments and previous electron paramagnetic resonance studies, a mechanism is proposed in Scheme 1e.[8] 1-Octene **2a** was oxidized by $SO_4^{\bullet-}$ giving alkene radical cation **7**, which reacted with H_2O, affording a bridged radical cation complex **8**.[12] The regiochemistry was dictated by the relative stabilities of two possible distonic radical cations **9** and **10**. The more stable **10** underwent deprotonation to generate *β*-hydroxyl radical **11**. Radical **11** was added to BQ to provide

Scheme 1. Mechanistic Studies



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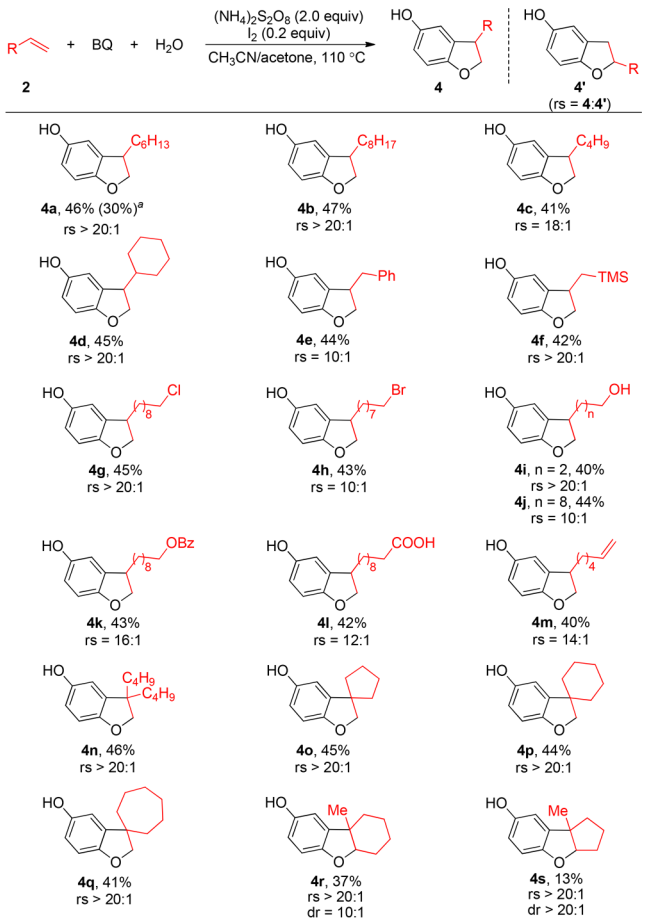
radical **12**, which underwent hydrogen atom abstraction to deliver alkylated quinone **3a**. Under acidic conditions, a kinetically favored intramolecular cyclization followed by dehydration gave oxocarbenium **13**, which was reduced by DHQ, to deliver C_3-substituted DHB **4a** and regenerate BQ.

The scope of three-component oxyarylation of alkenes was then explored (Scheme 2). The reaction proved fairly general

Scheme 2. Scope of Aliphatic Alkenes

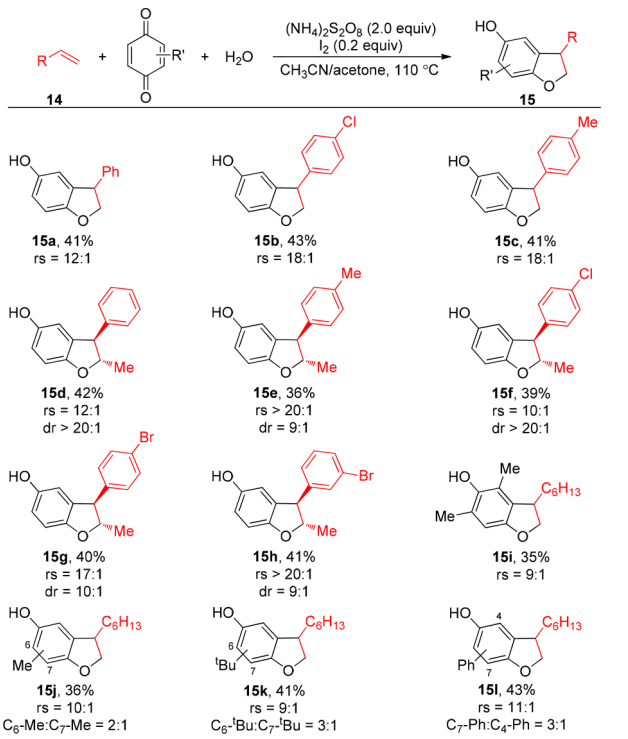


[a]Reaction at 1.0 mmol scale.

for a wide range of simple monosubstituted aliphatic alkenes with varied alkyl chain lengths, providing C_3-alkyl-substituted DHBs **4a−m** with excellent regioselectivity. A variety of commonly encountered functionalities, including benzyl (**4e**), silyl moiety (**4f**), halide (**4g** and **4h**), alcohol (**4i** and **4j**), acetate (**4k**), carboxylic acid (**4l**), and alkene (**4m**), were tolerated as additional functional handles. 1,1-Disubstituted aliphatic alkenes were also found to be amenable to the reaction, exclusively producing DHBs **4n−q** bearing an all-carbon quaternary center at the C_3 position. In particular, reactions with methylene cycloalkanes bearing different ring sizes proceeded smoothly, rapidly affording 5-, 6-, and 7-membered spirocycles **4o−q** as a single isomer. Because DHB-based spirocycles are prominent structural features in bioactive molecules, and the efficient synthesis of such substructures has been challenging, three-component oxyarylation starting from simple alkenes and BQ would provide a complementary method to the existing spirocyclization approaches.[13] Trisubstituted aliphatic cyclic alkenes were also suitable substrates, as evidenced by rapid access to DHB-fused tricyclic **4r** and **4s** bearing an all-carbon quaternary center at the C_3 position.[14]

The scope of styrenes was next probed (Scheme 3). Electronically varied terminal styrenes were competent

Scheme 3. Scope of Styrenes and BQ



components, yielding C_3-aryl DHBs **15a−c** with high regioselectivity. 1,2-Disubstituted internal styrenes bearing diverse electronic properties were also tolerated, yielding *trans*-2-methyl-3-aryl-DHBs **15d−h** related to chrysophyllon VI-B type natural products shown in Figure 1a with good regio- and diastereoselectivity. Notably, multiple steps were previously required to prepare such skeletons.[3d]

The scopes of the BQs were then examined (Scheme 3). Symmetric dimethyl-substituted BQ proceeded to give **15i** in a slightly reduced yield, presumably due to the steric factor. The regioselectivity on unsymmetric BQs appeared to be controlled by the electronic nature of the substituent. Para and meta selectivities were observed for monoalkyl-substituted BQs (**15j** and **15k**), while monophenyl-substituted BQ gave **15l** with meta and ortho selectivities.[15]

The synthetic utility of the method was further explored (Scheme 4). C_3-Substituted spiro-piperidinyl DHBs such as DHB-X (Figure 1a), **16a**, and **16b** have been demonstrated to possess diverse pharmacological activities.[1b−d] However, they were typically prepared via Bu_3SnH-mediated intramolecular cyclization of a highly functionalized piperidine-based allylic ether of *o*-bromophenol.[16] Under the standard conditions, piperidine-based exocyclic methylenes **17a** and **17b** joined in three-component oxyarylation, directly giving respective spiro-piperidinyl DHBs **18a** and **18b** as a single isomer. The free hydroxyl group could act as a linker for combining diverse bioactive scaffolds for access to **16a**-type compounds. DHBs **18a** and **18b** can also undergo dehydroxylation or Suzuki coupling, giving **19a** and **19b**, respectively, for the synthesis of **16b**-type molecules. Together, these applications further

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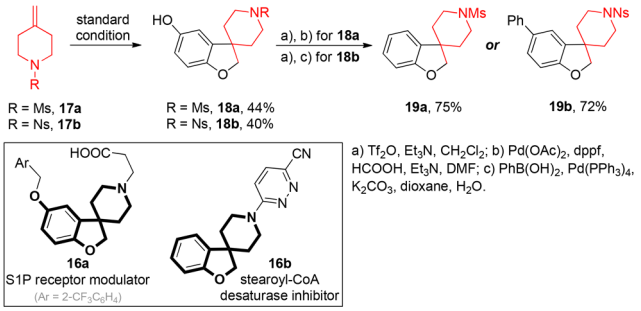
Scheme 4. Synthetic Applications



demonstrate the capability of three-component oxyarylation of alkenes in rapid preparation of complex structural motifs of medicinal relevance that would be difficult to access using other methods.

In summary, a practical and modular method to rapidly access C_3-substituted DHBs through $(NH_4)_2S_2O_8$-mediated metal-free three-component oxyarylation of alkenes with BQ and H_2O has been reported. The redox-relay process has an excellent functional group tolerance and exhibits a broad scope of simple alkenes, thus allowing for highly regio- and diastereoselective access to a variety of the substructures that would require multiple steps to prepare with traditional methods. Mechanistic studies revealed a dual role of BQ serving as both the arylation agent and the origin of DHQ for the reductive cyclization step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03278.

Experimental details and spectral data for new compounds (PDF)

Accession Codes

CCDC 1443601 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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