Proton Catalysis Hot Paper

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Trifluoromethanesulfonic Acid Catalyzed Synergetic Oxidative/[3+2] Cyclization of Quinones with Olefins**

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Dedicated to Professor Xiyan Lu on the occasion of his 85th birthday

Oxidative coupling reaction has received considerable attention in recent years, as it provides novel routes for retrosynthetic analysis and has become a versatile approach in organic synthesis.[1] Among oxidative coupling reactions, direct oxidative coupling of C–H bonds is of particular interest, owing to its green and economical nature. Most oxidative coupling reactions have been achieved using transition-metal catalysts; however, few examples have been reported on metal-free oxidative direct C–H functionalization under mild conditions.[2] Furthermore, most of the oxidative C–H functionalization reactions have been focused on the aromatic, vinylic C_{sp^2}–H, C_{sp}–H bonds, and activated C_{sp^3}–H bonds, whereas the direct oxidative C–H transformation of quinones has rarely been reported, owing to the unique electronic properties of quinones.[3]

Because of their biological and pharmacological activity, hydrofurans have attracted considerable attention, and they have also been found to exist in many natural products.[4] In the past decade, transition-metal-catalyzed reactions have been used for the synthesis of hydrofuran and hydrobenzofuran,[5] whereas few examples have been reported for the synthesis of tetrahydrobenzodifuran by direct C–H bond functionalization; thus, establishing a novel and green method for tetrahydrobenzodifuran synthesis from quinones would be appealing.

Herein, we present the first transition-metal-free oxidative C–H transformation of quinones for the synthesis of tetrahydrobenzodifuran. Our idea is shown in Figure 1: [3+2] cyclization of the strongly electrophilic 1,4-benzoquinone with an olefin would generate 2,3-dihydrobenzofuran-5-ol **B** (Figure 1, step 1) followed by the oxidative cyclization of **B** with another olefin molecule to generate the tetrahydrobenzodifuran (Figure 1, step 2).

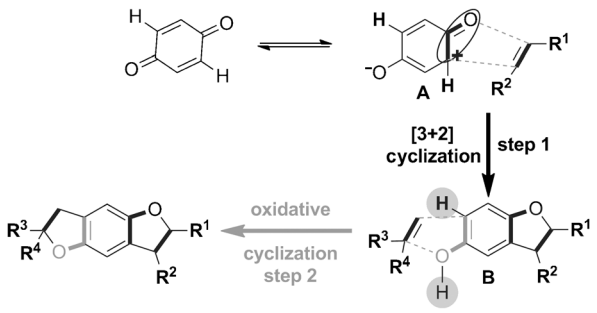
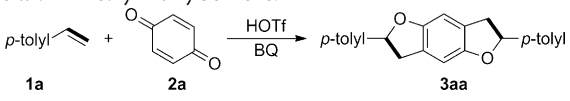


Figure 1. Synthesis of tetrahydrobenzodifuran from 1,4-benzoquinone with olefins.

To test the above hypothesis, our experiment started with treating 1-methyl-4-vinylbenzene (**1a**) with benzoquinone (**2a**) in the presence of catalytic amount of trifluoromethanesulfonic acid (HOTf; Table 1). The addition of HOTf was expected to activate benzoquinone and facilitate the reaction. By optimizing various reaction parameters, the best results were found to be HOTf (10 mol%) in MeCN under N_2 (Table 1, entry 1). Under these reaction conditions, a 78% yield of 2,6-di-*p*-tolyl-2,3,6,7-tetrahydrobenzo[1,2-b:4,5-b′]difuran (**3aa**) was obtained after 2 h. When the reaction

Table 1: Impact of reaction parameters on the cyclization of benzoquinone with 1-methyl-4-vinylbenzene.[a]



1a 2a 3aa

Entry	Variation from standard conditions[a]	Yield [%][b]
1	none	78
2	in air	53
3	HOTf (0.01 mmol)	64
4	without HOTf, 12 h	0
5	TFA instead of HOTf, 12 h	< 5
6	PTSA instead of HOTf, 12 h	71
7	$Zn(OTf)_2$ instead of HOTf, 12 h	0
8	LiOTf instead of HOTf, 12 h	0

[a] Standard reaction conditions: **1** (0.30 mmol), **2a** (0.45 mmol), MeCN (2 mL), HOTf (0.03 mmol), at RT for 2 h, under N_2. [b] Yield of isolated product. PTSA = *para*-toluenesulfonic acid, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

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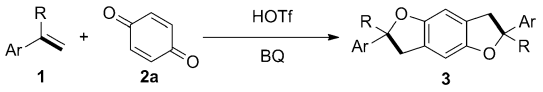
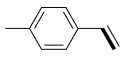
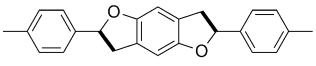
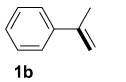
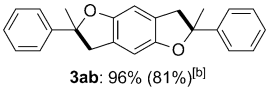
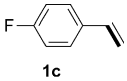
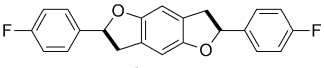
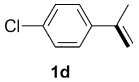
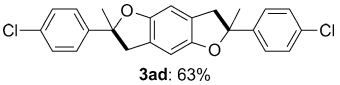
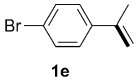
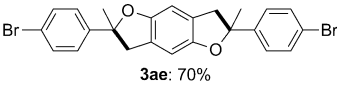
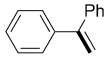
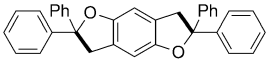
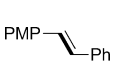
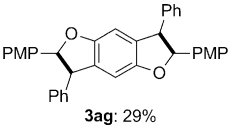
was carried out under air, the yield decreased to 53% (Table 1, entry 2). A lower loading of the catalyst also led to a decreased yield and no reaction occurred in the absence of HOTf (Table 1, entries 3 and 4), thus indicating that the choice of catalyst is essential. Although both trifluoroacetic acid (TFA) and *para*-toluenesulfonic acid (PTSA) also worked, a longer reaction time was needed and the yields were lower (Table 1, entries 5 and 6). Lewis acids $Zn(OTf)_2$ and LiOTf were not efficient for the reaction (Table 1, entries 7 and 8).

With the optimized conditions established, a number of olefins were tested in this oxidative cyclization reaction (Table 2). Moderate to excellent yields were obtained. Prop-1-en-2-ylbenzene **1b** afforded the corresponding product **3ab**

Table 2: Substrate scope of the cyclization reaction of benzoquinone with olefins.[a]



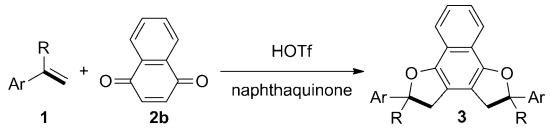
Entry	Substrate	Product
1	 1a	 **3aa**: 78%
2	 1b	 **3ab**: 96% (81%)[b]
3	 1c	 **3ac**: 58%
4	 1d	 **3ad**: 63%
5	 1e	 **3ae**: 70%
6	 1f	 **3af**: 55%
7	 1g	 **3ag**: 29%

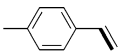
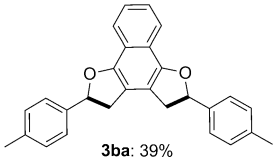
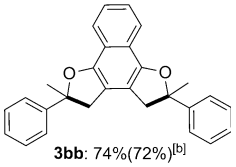
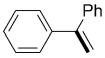
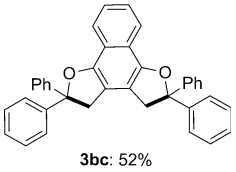
[a] Unless otherwise noted, the reaction was carried out with **1** (0.30 mmol), **2a** (0.45 mmol), HOTf (0.03 mmol), MeCN (2 mL), at RT for 2 h. Yields shown are of isolated products. [b] **1** (10 mmol), **2a** (12 mmol), HOTf (0.1 mmol), MeCN (12 mL), at RT for 2 h. BQ = benzoquinone, PMP = *para*-methoxyphenyl.

in 96% yield. Moreover, halogen groups (F, Cl, and Br) were well tolerated, and α-phenyl-substituted styrene **1f** could also be used in our system, affording the corresponding product **3af** in 55% yield (Table 2, entry 6). When 1,2-disubstituted olefin **1g** was tested, the desired product **3ag** could be obtained, albeit with a lower yield (Table 2, entry 7).

Next, the substrate scope with regard to the quinone moiety was examined. The results for the cyclization of naphthoquinone with olefins are listed in Scheme 3. A 39%

Table 3: Substrate scope of the cyclization reaction of naphthoquinone with olefins.[a]



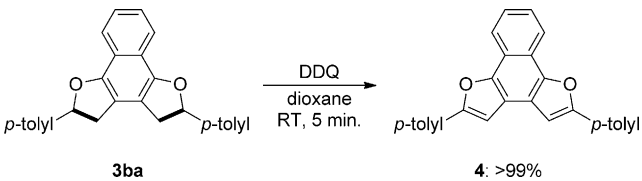
Entry	Substrate	Product
1	 1a	 **3ba**: 39%
2	 1b	 **3bb**: 74%(72%)[b]
3	 1f	 **3bc**: 52%

[a] Unless otherwise noted, the reaction was carried out with **1** (0.30 mmol), **2b** (0.45 mmol), HOTf (0.03 mmol), MeCN (2 mL), at RT for 2 h. Yields shown are of isolated products. [b] **1** (1 mmol), **2b** (1.5 mmol), HOTf (0.1 mmol), MeCN (8 mL), at RT for 2 h.

yield of **3ba** was obtained when 1-methyl-4-vinylbenzene **1c** was reacted with naphthoquinone (Table 3, entry 1). A good yield of the corresponding product **3bb** could also be obtained when prop-1-en-2-ylbenzene **1b** was used (Table 3, entry 2). When ethene-1,1-diyldibenzene was applied, 52% of the corresponding product **3bc** was obtained (Table 3, entry 3).

In recent years, benzodifurans have been found to be functional as hole-transporting materials in organic light-emitting diodes.[6] With these tetrahydrobenzodifurans in hand, efforts have been made to synthesize benzodifurans from these tetrahydrobenzodifurans. A quantitive yield of benzodifuran **4** could be obtained from **3ba** when 3 equivalents of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as the oxidant (Scheme 1), thus demonstrating that the present method is a powerful tool for the synthesis of opto-electronic materials.

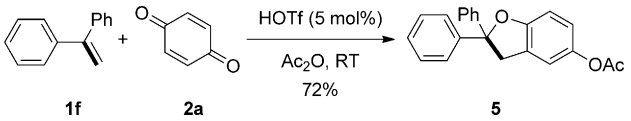
To get a preliminary understanding of the reaction mechanism, we tried to identify the intermediates in the reaction. As 2,3-dihydrobenzofuran-5-ol **B** was proposed as



3ba **4**: >99%

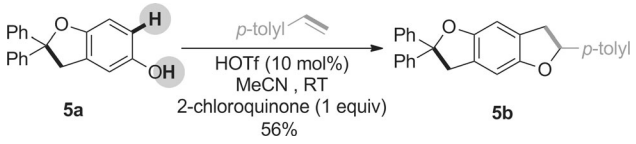
Scheme 1. Dehydrogenation of tetrahydrobenzodifuran. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

an intermediate (Scheme 1), we began by attempting to trap it. Upon addition of acetic anhydride to the reaction, 2,3-dihydrobenzofuran-5-ol acetate was observed. When acetic anhydride was used as the solvent, 2,3-dihydrobenzofuran-5-ol acetate **5** could be obtained in 72% yield (Scheme 2). The following experiments were then conducted to confirm that



Scheme 2. Cyclization/esterification of quinones with olefins. Ac_2O = acetic anhydride.

2,3-dihydrobenzofuran-5-ol could be converted into the final product under the standard conditions: When 2,3-dihydrobenzofuran-5-ol **5a** was applied under the reaction conditions with 1 equivalent of 2-chloroquinone as the oxidant, 56% of the desired product **5b** was obtained (Scheme 3), which confirmed that **5a** was indeed an intermediate.



Scheme 3. Oxidative cyclization of dihydrobenzofuranol with 1-methyl-4-vinylbenzene.

The above results demonstrated that cyclization reaction proceeded through a two-stage process. The intermediate 2,3-dihydrobenzofuran-5-ol was first generated, followed by an oxidative cyclization with the olefin to generate the tetrahydrobenzodifuran final product. Operando IR experiments were also carried out to get more mechanistic insight. Hydroquinone was immediately observed after the reaction started, whereas no 2,3-dihydrobenzofuran-5-ol was detected by operando IR (Figure 2), which indicates that the oxidative cyclization took place immediately after 2,3-dihydrobenzofuran-5-ol was generated, and thus that the oxidative cyclization is faster than the acid-catalyzed [3+2] cyclization.

On the basis of the above results and previous work in our group and others, a mechanism for this reaction was proposed (Figure 3).[7] The first step is the HOTf-catalyzed [3+2] cyclization of benzoquinone (BQ) with the olefin to generate 2,3-dihydrobenzofuran-5-ol **I**.[8] The following steps could proceed either through a cationic pathway or a radical pathway. In the cationic pathway, **I** is oxidized to cation **II** by BQ/HOTf.[9] Cyclization of cation **II** with a second olefin followed by deprotonation yields the final product and regenerates the HOTf catalyst.[7c,d] In the radical pathway, under HOTf catalysis, **I** is oxidized by BQ to radical **IV**. Radical **IV** then isomerizes into radical **V** and cyclizes with a second olefin to generate radical **VI**.[10] Oxidation of radical **VI** by BQ/HOTf gives the final product and regenerates the HOTf catalyst.[9]

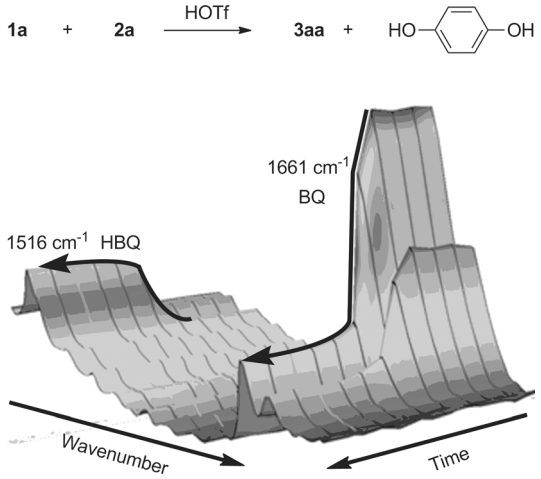


Figure 2. The 3D FTIR profile of the reaction of **1a** (0.5 mmol, **2a** (0.6 mmol), HOTf (0.05 mmol). BQ = benzoquinone, HBQ = hydroquinone.

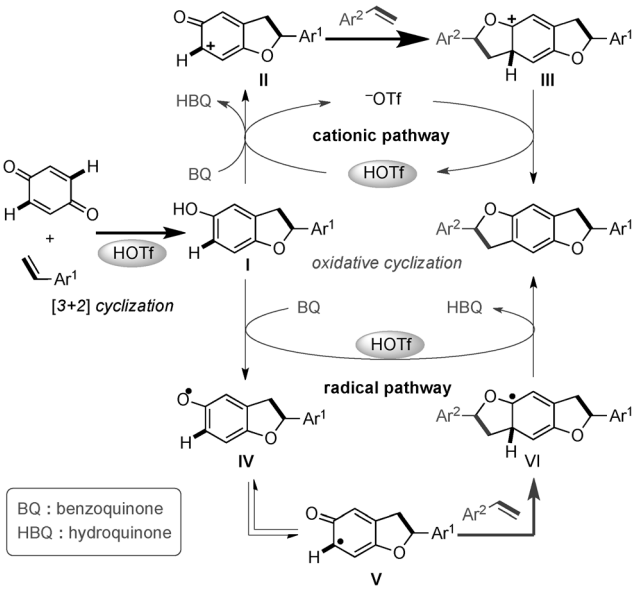
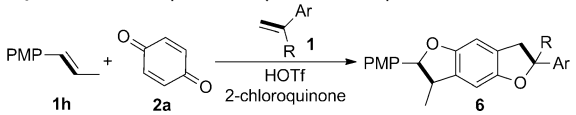


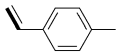
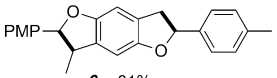
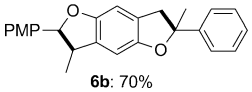
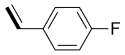
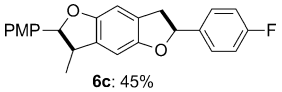
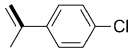
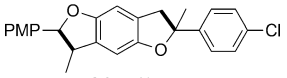
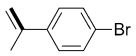
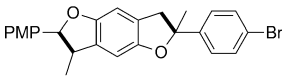
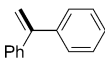
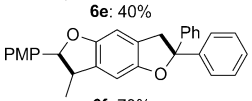
Figure 3. Proposed mechanism.

Based on this mechanistic understanding, we realized that the present method could also be used for the synthesis of asymmetric tetrahydrobenzodifurans through the cyclization of benzoquinone with two different olefins. After further optimization, we found that when (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene was used, 2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran-5-ol could be obtained in a highly selective manner. Then, after adding another olefin and 2-chloroquinone, the asymmetric product could be obtained in one pot with satisfactory yields (Table 4). Halogen groups (F, Cl, and Br) were also well tolerated (Table 4, entries 3–5). Methyl and phenyl substituents on either the aryl ring or in the α-position had little effect on this cyclization, and moderate to good yields were still obtained.

In conclusion, we have demonstrated a HOTf-catalyzed direct oxidative C–H functionalization of benzoquinone with

Table 4: Substrate scope of the cyclization of quinones with olefins.[a]



Entry	Substrate	Product
1	 **1a**	 **6a**: 81%
2	 **1b**	 **6b**: 70%
3	 **1c**	 **6c**: 45%
4	 **1d**	 **6d**: 55%
5	 **1e**	 **6e**: 40%
6	 **1f**	 **6f**: 73%

[a] Unless otherwise noted, the reaction was carried out with **1h** (0.3 mmol), **2a** (0.3 mmol), **1** (0.5 mmol), 2-chloroquinone (0.4 mmol), HOTf (0.03 mmol), MeCN (2 mL), at RT for 0.5 h. Yields shown are of isolated products. PMP = *para*-methoxyphenyl.

olefins for tetrahydrobenzodifurans synthesis. A synergetic oxidative/[3+2] cyclization mechanism was proposed based on the experimental results. A variety of substituents were found to be tolerated, including halogen groups. An asymmetric tetrahydrobenzodifuran could also be synthesized from two different olefins in one pot. Further mechanistic and substrate-scope studies are currently underway.

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