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Electrochemical Cross-Dehydrogenative Coupling between Phenols and β-Dicarbonyl Compounds: Facile Construction of Benzofurans

Yandong Wang,[a] Bailin Tian, [b] Mengning Ding,[b] and Zhuangzhi Shi[a]*

Dedication ((optional))

Abstract: Preparative electrochemical synthesis is an ideal method for establishing green, sustainable processes. The major benefits of electro-organic strategy over conventional chemical synthesis are the avoidance of reagent waste and the mild reaction conditions. Here, an intermolecular cross-dehydrogenative coupling (CDC) between phenols and β-dicarbonyl compounds to build various benzofurans under undivided electrolytic conditions has been developed. Neither transition metals nor external chemical oxidants are required to facilitate the dehydrogenation and dehydration processes. The key factor in the success was the use of $^{n}Bu_4NBF_4$ as the electrolyte and hexafluoroisopropanol (HFIP) as the solvent, which play key roles in the cyclocondensation step. This electrolysis is scalable and can be used as a key step in drug synthesis. On the basis of the several experimental results, the mechanism, particularly of the remarkable anodic oxidation and cyclization process, was illustrated.

Introduction

The diversity of benzofuran scaffolds found in natural products and synthetic compounds, as well as their biological and pharmaceutical relevance, have stimulated research into the development of new synthetic strategies for the construction of readily functionalized benzofuran ring systems (Figure 1a).[1] Although numerous procedures have been established for this purpose,[2] transition-metal-catalyzed cyclization reactions are the most common in such target or diversity-oriented syntheses.[3] Of particular interest is the iron-catalyzed cascade CDC[4] and cyclization between phenols and *β*-dicarbonyl compounds. However, these methods require using stoichiometric amounts of peroxides, which can be explosive and environmentally unfriendly.[5] Undoubtedly, the development of a safe and low-cost strategy enabling the efficient synthesis of benzofurans under transition-metal and chemical oxidant-free conditions is in high demand.

Electrochemical synthesis[6] is a green and sustainable method for organic synthesis, which usually does not use metal catalysts or chemical oxidants.[7] Based on this chemistry, electrochemical cross-dehydrogenative coupling (CDC) and cyclization has been an efficient method for the construction of cyclic compounds.[8] Such a process typically proceeds in an intramolecular manner.[9] Recently, the intermolecular anodic C-H oxidation and functionalization of arenes,[10] especially treatment of phenols for phenol–arene,[11] phenol–phenol[12] and phenol–thiophene[13] cross-couplings has been developed successively (Fig. 1b). Inspired by these precedent results, we wondered whether β-dicarbonyl compounds could be employed as sp^3 carbon coupling partners with phenols. We serendipitously found that benzofurans could be formed directly without addition of any Lewis acid for dehydration. Here, we report a robust electrochemical synthesis of benzofurans from phenols and β-dicarbonyl compounds through cascade intermolecular dehydrogenative C(sp^2)-C(sp^3) coupling and cyclization (Fig. 1c). Notably, the electrolyte $^{n}Bu_4NBF_4$ and the solvent HFIP were first found to be crucial for the dehydrative step. The electrooxidation of phenols with β-dicarbonyl compounds showed excellent chemoselectivity, without formation of any homocoupling byproducts. Mechanistic experiments and cyclic voltammetry (CV) investigations were conducted to demonstrate an unusual pathway for this transformation. Such a strategy for benzofuran synthesis has exciting possibilities because of its superior practicality, scalability, safety, and environmental friendliness.

Results and Discussion

To begin our studies, we chose 4-methoxyphenol (**1a**) and dibenzoylmethane (**2a**) as the model substrates (Table 1). The electrochemical oxidation of **1a** (0.60 mmol) and **2a** (1.20 mmol) was carried out in a 0.06 M solution of $^{n}Bu_4NBF_4$ as the electrolyte using DCM/HFIP (1/1) as cosolvents in an undivided cell equipped with platinum plates as the anode and cathode under a 2.5 V potential for 10 hours, and the desired product **3aa** was generated in an 83% yield (Table 1, entry 1). No products of oxidation of the enol tautomer of dibenzoylacetone (**2a**) and of the benzofurans **3aa** were detected. This is because the onset potential of oxidation the enol of **2a** and of **3aa** is about 0.4 V and 0.3 V higher respectively than that of phenol **1a** (Table S1, entries 5 and 8). The current efficiency of this reaction, determined by a constant-current electrolysis at a

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Supporting information and the ORCID identification number(s) for the author(s) for this article can be found under ((Please delete this text if not appropriate))

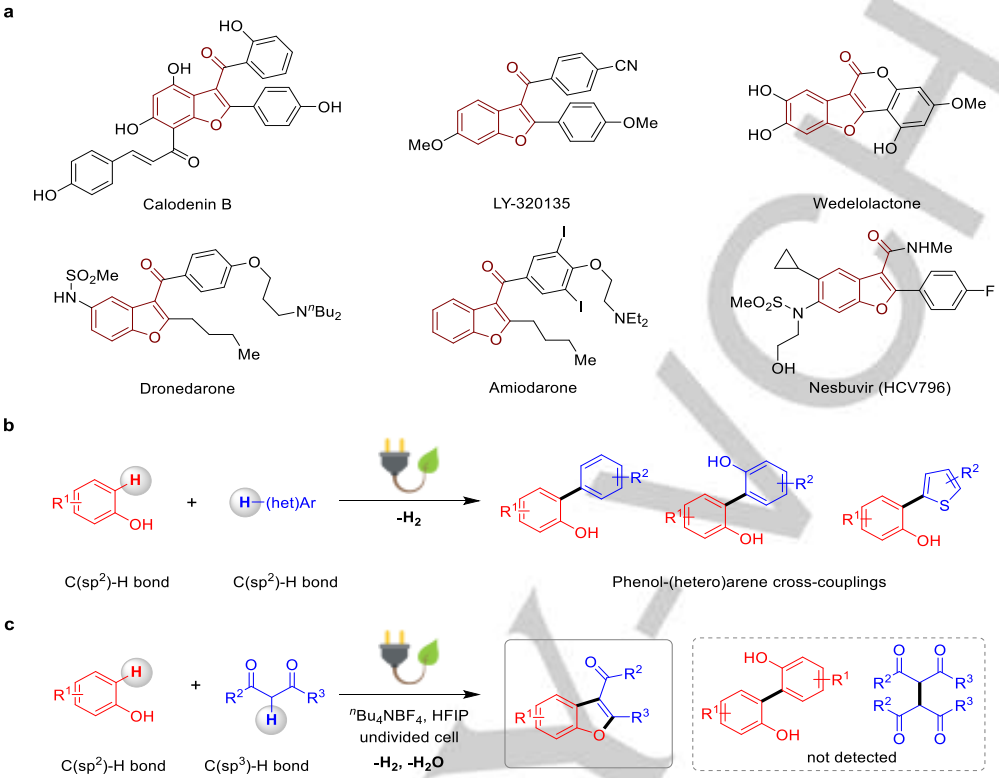
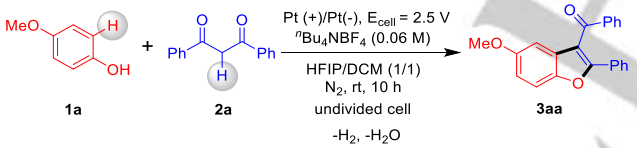


Fig. 1 Construction of benzofurans by electrochemical CDC strategy. (a) Examples of bioactive compounds containing a benzofuran scaffold. (b) Electrochemical C-H (hetero)arylation of phenols. (c) Electrochemical intermolecular cyclization of phenols and β-dicarbonyl compounds to construct benzofurans.

Table 1 Reaction optimization.

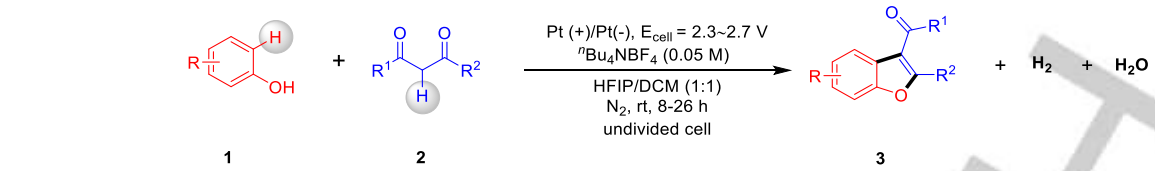


Entry	Variation from the standard conditions	Yield of **3aa** (%)[b]
1	none	83
2	without HFIP	0
3	without DCM	78
4	Using $^{n}Bu_4NPF_6$ instead of $^{n}Bu_4NBF_4$	80
5	Using C(+)/Pt(-)	79
6	2.0 V instead of 2.5 V	59
7	**1a**/**2a** = 1/1	68
8	**1a**/**2a** = 2/1	63
9	under air	81
10	without electric current, under air	0

[a]Reaction conditions: platinum plate anode and cathode (1.0 cm×1.0 cm×0.1 mm) with an oven-dried undivided cell, constant potential = 2.5 V, **1a** (0.60 mmol), **2a** (1.20 mmol), $^{n}Bu_4NBF_4$ (0.60 mmol), HFIP/DCM (1/1, 10 mL), 10 hours, room temperature, under N_2. [b]Isolated yield

current density of 4 mA cm^{-2}, was very good, 65% for an 81% yield of **3aa**. The reaction failed in the absence of HFIP (entry 2), and a 78% yield was observed using pure HFIP as the solvent (entry 3). Other supporting electrolytes such as $^{n}Bu_4NPF_6$ (entry 4) and other electrodes such as a graphite rod cathode (entry 5) were also effective for this transformation, although with slightly lower yields. Under the current reaction conditions, lowering the potential to 2.0 V decreased the yield to 59% (entry 6). In addition, changing the ratio of substrates **1a** and **2a** decreased the yield (entries 7-8). Under an air atmosphere, the reaction maintained a good reactivity (entry 9). Finally, a control experiment confirmed that the transformation did not occur without electricity (entry 10).

Scope of the methodology. With the optimized reaction conditions in hand, we examined the substrate scope (Fig. 2). The reactions of β-diketone **2a** with a broad range of phenols were first examined. Commercially available phenols bearing ^{n}BuO (**1b**), PhO (**1c**), and allyloxy (**1d**) substituents at the C4-position underwent facile cross-coupling and cyclization, affording the corresponding products **3ba-3da** in 75-86% yields. Substrate **1e** containing a dihydrobenzofuran motif led to product **3ea** in an 82% yield, without any overoxidation byproduct. In addition to ether substituents, para-substituted phenols with aryl substituents such as **1f**-**1g** were also



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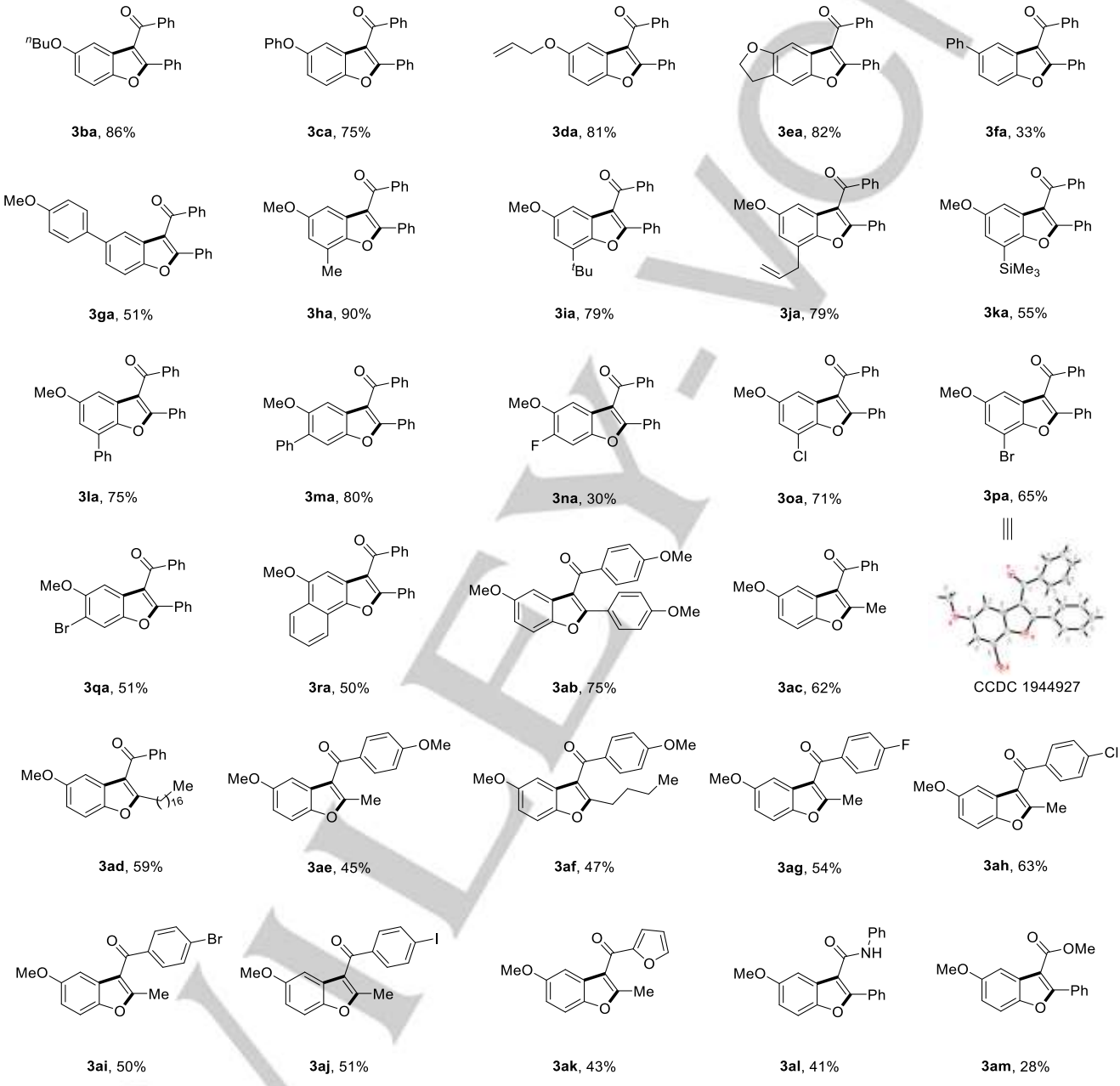

Fig. 2 Substrate scope for the construction of benzofurans 3 between phenols 1 and β-dicarbonyl compounds 2. Reaction conditions: platinum plate anode and cathode (1.0 cm×1.0 cm×0.1 mm) with an oven-dried undivided cell, constant potential = 2.3~2.7 V, **1** (0.60 mmol), **2** (1.20 mmol), $^{n}Bu_4NBF_4$ (0.60 mmol), HFIP/DCM (1/1, 10 mL), 8~26 hours; room temperature, under N_2; Isolated yields. See supporting information for experimental details.

compatible. Phenols bearing Me (**1h**), ^{t}Bu (**1i**), allyl (**1j**), ^{t}Bu (**1i**), $SiMe_3$ (**1k**), Ph (**1l-1m**), F (**1n**), Cl (**1o**) and Br (**1p-1q**) groups at the C2 or C3 position gave the corresponding benzofurans in 30-90% yields. Among them, the structure of **3pa** was further confirmed by X-ray analysis. Naphthol **1r** underwent facile cross-coupling, affording the product **3ra** in modest yield. Next, various β-diketones (**2b-2k**) with a wide range of substituents were also employed for cyclization with phenol **1a**. Among them, excellent

regioselectivity was obtained with nonsymmetric benzoyl acetones **2c-2j** with different substituents, as well as furan-based substrate **1k**. Notably, this strategy was not limited to β-diketones; β-keto amide **2l** and β-keto ester **2m** were also tolerable, providing the desired products in 41% and 28% yields.

Synthetic Applications. The drug Dronedarone was developed by Sanofi Pharm for the treatment of atrial fibrillation and atrial flutter.[14] The original route was patented by Gubin et al., based on the construction of a functionalized benzofuran **6** (Fig. 3).[15] To demonstrate the applicability of our methodology, we provided an alternative route to obtain the intermediate **6**. The reaction of phenol **1d** was scalable to 6.0 mmol with β-diketone **2g**, giving **4** in 52% yield on a gram-scale. One-pot deprotection followed by a reaction with Tf_2O afforded compound **5** in 74% yield. It was then subjected to nitration[16] to provide the desired product **6** in good yield.

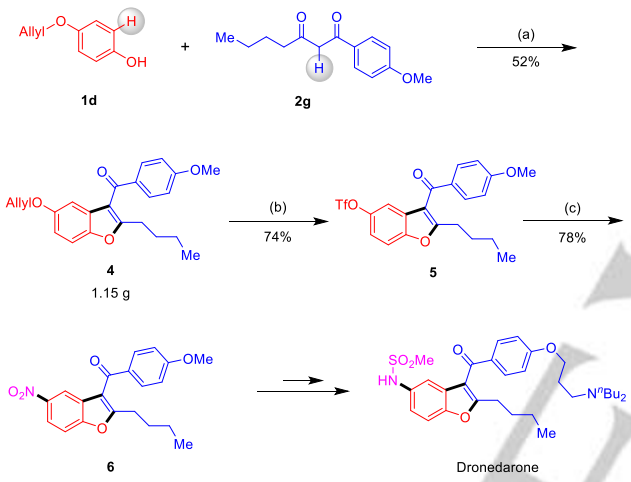

Fig. 3 Synthesis of compound 6 as a key intermediate for Dronedarone. (a) platinum plate anode and cathode (1.0 cm×1.0 cm×0.1 mm) with an oven-dried undivided cell, constant potential = 2.7 V, **1d** (6.0 mmol), **2g** (10.0 mmol), $^nBu_4NBF_4$ (3.0 mmol), HFIP/DCM (1/1, 50 mL), room temperature, under N_2. (b) 1 mol% $Pd(PPh_3)_4$, 1.0 equiv of **4**, 3.0 equiv of K_2CO_3, MeOH, 10 h; then Tf_2O, pyridine, 0 °C to room temperature, 10 h. (c) 0.5 mol% $Pd_2(dba)_3$, 1.2 mol% ^{t}BuBrettPhos, 5.0 mol% tris(3,5-dioxaheptyl)amine, 1.0 equiv of **5**, 2.0 equiv of $NaNO_2$, ^{t}BuOH, 130°C, 24 h, under Ar.

Mechanistic Studies. Several experiments were conducted to elucidate the reaction mechanism (Scheme 2). We first investigated the reaction of **1a** and **2a** under reported Fe-catalyzed systems using $(^tBuO)_2$ as the oxidant.[5] Low yields of the desired product **3aa** were observed, demonstrating the unique reactivity of this electrochemical chemistry (Fig. 4a). Under standard conditions, a radical clock experiment was performed on an olefin-containing substrate **7**, only yielding the normal cyclization product **8** in a 52% yield. This result can exclude the free radical generated at the acidic α methylene group of β-diketones during the reaction (Fig. 4b). The oxidative [3+2] cycloaddition of phenols and alkenes via a phenoxonium cation intermediate has been reported under photo[17] or electrochemical[18] conditions. Substrates **1a** and **9** used in Yoon's conditions[17] could also undergo annulation to form product **10** in a 46% yield in our reaction conditions (Fig. 4c). Using a nonsymmetric β-diketone **11** with 4-^{t}BuBz and 4-OMeBz as a substrate, we got products **12** and **13** in 52% and 20% yields, respectively, indicating that the less electron-rich benzoyl carbonyl is the most reactive towards the intramolecular addition of the phenol hydroxyl followed by dehydration (Fig. 4d). The known compound **14** was proven to undergo intramolecular condensation to form benzofuran **15** in the presence of an iron salt.[5a] In our catalyst-free conditions, such a cyclization could occur by the combination of HFIP and $^nBu_4NBF_4$ (Fig. 4e).

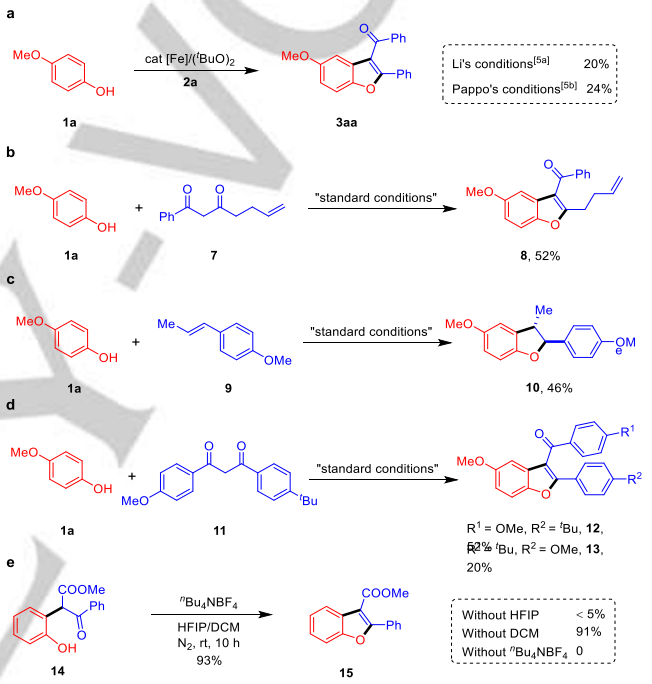

Fig. 4 Mechanistic experiments. (a) Comparing Fe-catalyzed and electrochemical system. (b) Radical clock experiment. (c) Oxidative [3+2] cycloaddition of phenol **1a** and olefin **9**. (d) The selectivity of nonsymmetrical β-diketone **11**. (e) Investigation of the dehydration step.

To further obtain mechanistic insights into the cationic oxidation pathway, cyclic voltammetry (CV) investigations were systematically conducted on the reaction of phenol **1a** and β-diketone **2a**, as well as various combinations of the substrates (Fig. 5). Both phenol **1a** and the enol of β-diketone **2a** show electrochemical reactivity at relatively high oxidative potentials, with onsets of ~1.2 V and ~1.6 V vs Ag/AgCl, respectively (Table S1, entries 1 and 5). The mixture of **1a** and **2a** shows an increased anodic current, consistent with the occurrence of an electroorganic reaction that involves both reactants. The addition of HFIP to the system further enhances the anodic current with an unaltered onset potential (relative to that of **1a**). This result clearly reveals the unique role of HFIP to facilitate the coupling reaction[19] and supports our assumption that the overall reaction began with the oxidation of phenols.

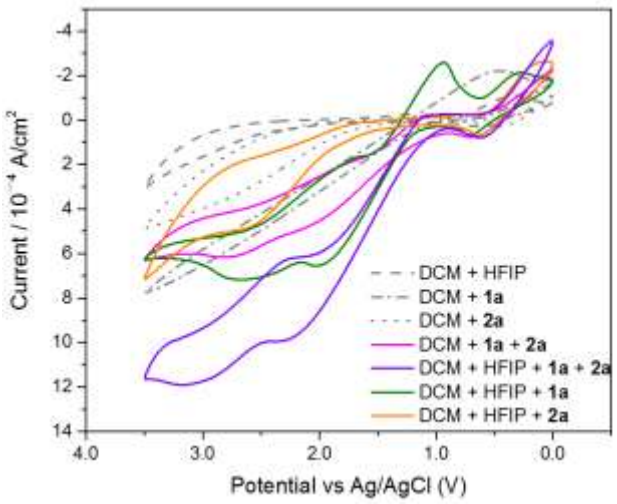

Fig. 5 CV investigations of reaction mixtures. CV characteristics of reaction background (solvent and additives), phenol **1a** in DCM, β-diketone **2a** in DCM, mixture of **1a** and **2a** in DCM, mixture of **1a** and **2a** in DCM and HFIP (best mimicking the reaction conditions), **1a** in DCM and HFIP, and **2a** in DCM and HFIP.

Next, systematic CV studies of phenols and β-diketones with different electron densities provide further mechanistic clues. As shown in the CVs of Fig. 6a, the onset of the oxidation potential of **1a** and **1f** (~1.2 V vs Ag/AgCl) is lower than that of **1s** (~2.0 V). Therefore, the oxidation of phenols **1a** and **1f** should be much faster than that of the enols of **2a** and **2f**. As a result, benzofurans **3aa**, **3ca**, and **3fa** were formed. This is the case, in Fig. 2, for the phenols **3b-r** electro-oxidized in the presence of diketone **2a** and for phenol **1a** electro-oxidized in the presence of diketones **2b-m**. In the case of phenol **1s** and diketone **2a**, the oxidation of the enol of diketone **2a** should be easier than that of phenol **1a** ($\Delta E_{onset(\mathbf{2a}\text{-}\mathbf{1a})}$ ~-0.8 V), and, as a result, no benzofuran was obtained. Similarly, due to the presence of the strongly electron-attracting CF_3 group, the enol of diketone **2n** is probably as easily oxidized as phenol **1a** (close onsets of their oxidation potential as shown in Figs 6a and 6b). Since there was a 100% mole excess of diketone, the oxidation of the enol of **2n** was faster enough to prevent the formation of the benzofuran. These results demonstrate the utility of CV in rationalizing the formation of benzofurans by oxidizing phenols in the presence of β-diketones: the phenol must be more easily oxidized that the enol of the diketone.

Based on the above experimental results, a mechanism has been proposed in Fig. 7. A successive single-electron-transfer oxidation of phenol **1** by anodic oxidation (*via* **A**) generates a phenoxonium cation **B**.[18] This cation species can isomerize to a highly reactive oxonium ion as a Michael receptor,[20] which then reacts with nucleophilic β-dicarbonyl compounds **2** to afford intermediate **D** with excellent site-selectivity. Then, the tautomerization of **D** would provide phenol **E**. Finally, the cooperation between HFIP and $^{n}Bu_4NBF_4$ triggers intramolecular condensation to generate the benzofurans **3**. The formed protons or HFIP could be reduced at the Pt cathode to generate hydrogen gas.

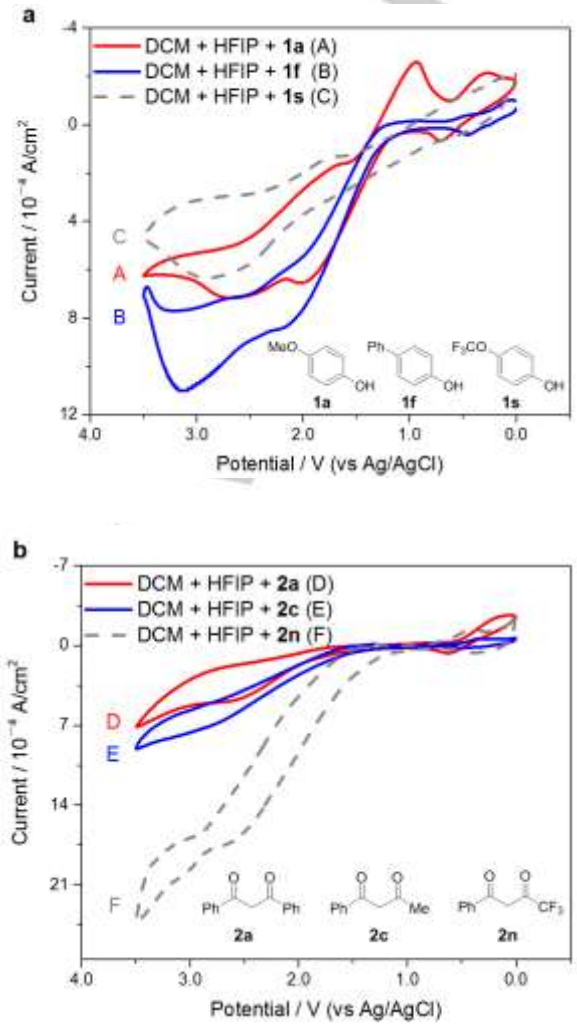

Fig. 6 CV characteristics of different phenols and β-diketones. (a) CV characteristics of phenols **1a**, **1f** and **1s** (non-reactive). (b) CV characteristics of diketones **2a**, **2c**, and **2n** (non-reactive). Different conditions in (a) and (b) were labeled A-F for better visualization.

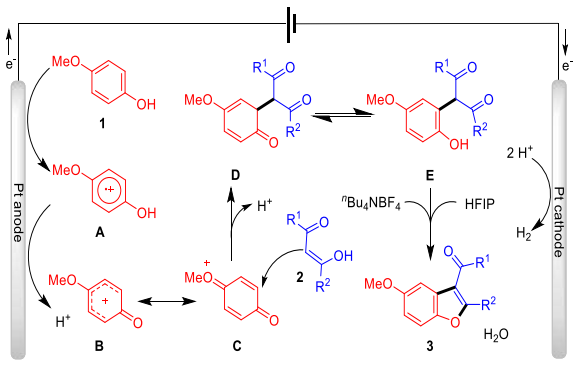

Fig. 7 Proposed mechanism.

Conclusions

In summary, we have developed an efficient electrochemical system that can undergo a CDC reaction and condensation between phenols and β-dicarbonyl compounds to produce a series of benzofurans. This strategy avoids the use of transition metals and external chemical oxidants and provides a simple and atom-economical way to synthesize benzofurans. Due to these advantages, this reaction should be of high synthetic value.

Experimental Section

General procedures for synthesis of 3aa. A solution of phenol **1a** (0.6 mmol), β-diketone **2a** (1.2 mmol) and $^{n}Bu_4NBF_4$ (0.6 mmol) in HFIP/DCM = 1/1 (10.0 mL) was stirred at room temperature under N_2 atmosphere in an oven-dried undivided cell which was equipped with platinum plate electrodes (1.0 cm×1.0 cm×0.1 mm) as both the anode and cathode. A balloon filled with N_2 atmosphere was connected to the electrolytic cell. The reaction mixture was stirred and electrolyzed at a constant potential of 2.5 V for 10 hours. The reaction was monitored by thin layer chromatography(TLC), visualized by fluorescence quenching under UV light. After the reaction was completed, the product **3aa** (162.9 mg, 83% yield) was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 100:1 (v/v)).

CV Experiments. Cyclic voltammetry was performed with a potentiostat (Corrtest CS3104) in a three-electrode cell at synthetic conditions. Platinum plates were used as working and counter electrodes and a leak-free Ag/AgCl (Harvard Apparatus LF-2) was used as reference electrode. The ranging of scan was 0V to 3.5V with a 0.1 V/s scan rate.

Data availability. The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information Files.

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Keywords: Electrochemistry ·phenols ·β-diketones ·CDC ·benzofurans

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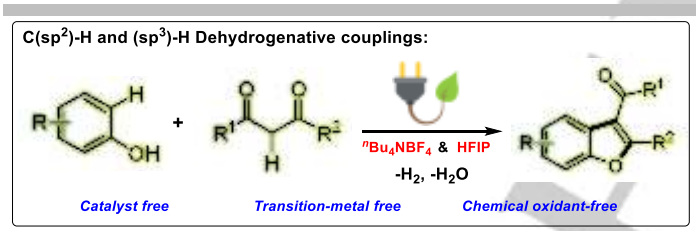

Electrifying: A mild electrochemical system was developed for the preparation of benzofurans via cross-dehydrogenative coupling between phenols and β-dicarbonyl compounds. This method has good functional group compatibility and can serve as a powerful synthetic tool with high synthetic value.

Yandong Wang,[a] *Bailin Tian,* [b] *Mengning Ding,*[b] *and Zhuangzhi Shi*[a]*

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