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Electrochemical oxidative dearomatization of electron-deficient phenols using Br^+/Br^- catalysis[†]

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An electrochemical method for the oxidative dearomatization of electron-deficient phenols by employing tetrabutylammonium bromide as a mediator under aqueous biphasic conditions is reported. This approach represents a safer alternative to the use of stoichiometric chemical oxidants and enables oxidative dearomative spirolactonization and spiroetherification reactions. Compared to previous approaches based on direct electrolysis, this strategy expands the substrate scope to electron-deficient phenols. Cyclic-voltammetry analysis suggests that the bromide ions might be oxidized to Br_2 or Br_3^- ions that are in equilibrium with the catalytically active hypobromite under aqueous conditions.

The dearomatization of arenols represents a powerful strategy for the synthesis of three-dimensional complex molecules.¹ Halogens, especially iodine-based oxidants or catalysts, have emerged as desirable reagents to accomplish such oxidative transformations without relying on toxic or expensive transition metals.² We have previously developed a quaternary ammonium hypoidite catalysis^{2c,3} for the oxidative dearomative spirocyclization of arenols using hydrogen peroxide or oxone as a stoichiometric chemical oxidant (Scheme 1a).⁴ However, the scope of these reactions is restricted to electron-rich arenols that bear electron-donating groups (EDGs). To address this limitation, we have recently developed a catalytic approach using ammonium hypobromite,⁵ which offers a higher oxidation potential than hypoidite, thereby expanding the scope to include phenols substituted with electron-withdrawing groups (EWGs) (Scheme 1b).⁶

Despite these advances, the development of safer oxidation methods that minimize the risks associated with high-energy and potentially hazardous chemical oxidants remains a pressing challenge. In this context, electrochemical approaches have garnered attention as inherently safer alternatives.^{7,8} For instance, Kalek and colleagues have recently reported an anodic oxidative

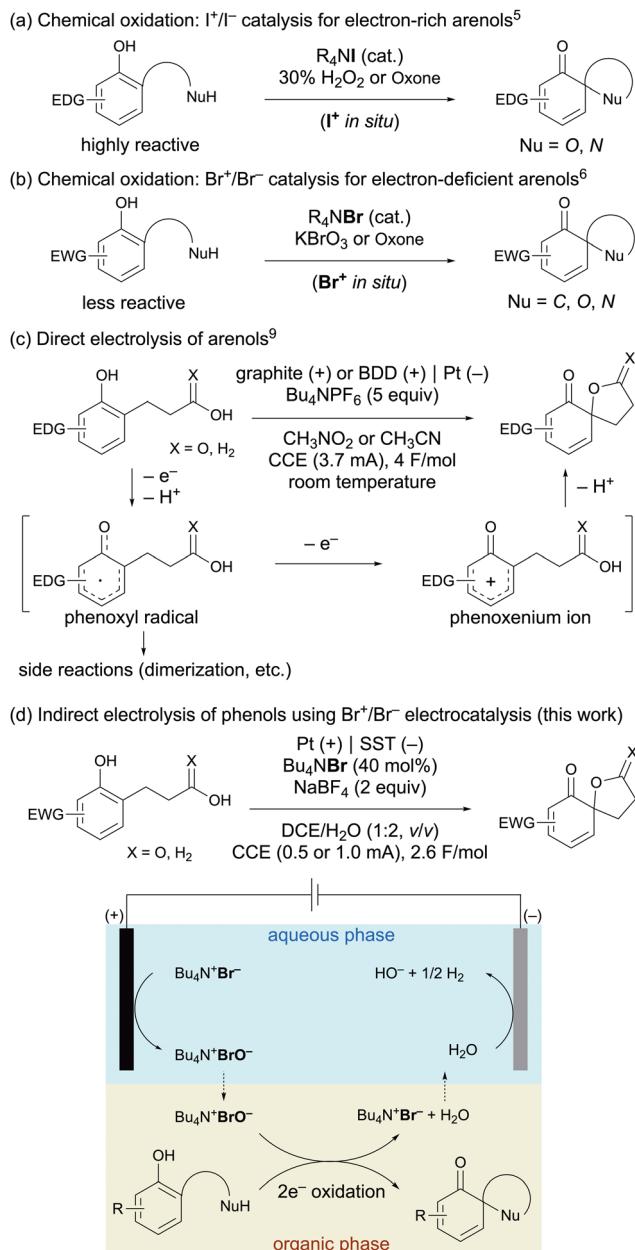
dearomative spirolactonization and spiroetherification of arenols tethered to a carboxylic acid or alcohol as an internal nucleophile, respectively, which generates hydrogen as the sole side product (Scheme 1c).⁹ This method involves the direct electrolysis without a mediator under nonaqueous conditions, and the phenols are oxidized directly at the anode through a single-electron-transfer (SET) mechanism coupled with a proton transfer.⁸ In this process, a phenoxy radical is initially generated, subsequently oxidized to a phenoxenium ion, and then trapped by an internal nucleophile, leading to the desired product. However, the phenoxy radical intermediate is prone to side reactions, such as dimerization,^{8,9b} especially when the second oxidation step is slow. This limitation in chemoselectivity potentially restricts the direct electrolysis method to highly reactive, electron-rich arenols, such as 1- or 2-naphthols or phenols with electron-donating groups (EDGs).⁹

Meanwhile, recent studies have highlighted the potential of anodic oxidations employing halides as mediators (*i.e.*, indirect electrolysis), particularly for enhancing substrate compatibility and chemoselectivity.¹⁰ Notably, several advancements have been made in catalytic halide mediators for various transformations.¹⁰ However, to the best of our knowledge, no examples of halide-mediated electrooxidative dearomative transformations have been reported so far. Inspired by these halide-mediated anodic oxidation reactions, we sought to integrate anodic oxidation into our hypobromite catalysis,⁶ allowing us to leverage the advantages of indirect electrolysis in dearomatization reactions as a safer alternative to stoichiometric chemical oxidants (Scheme 1d). This approach differs fundamentally from Kalek's method; rather than the phenols being directly oxidized at the anode, preferential oxidation of bromide to Br^+ species (*i.e.*, $\text{Bu}_4\text{N}^+\text{BrO}^-$) would occur. These active Br^+ species would subsequently oxidize the phenol substrate through a two-electron transfer process,⁶ thus bypassing the formation of radical intermediates. We envisioned that this mechanism would suppress undesired side reactions, thereby improving the chemoselectivity and potentially broadening the substrate compatibility of this transformation. We focused specifically on the oxidative dearomative spirolactonization and spiroetherification (C–O coupling) of phenols substituted with

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EWGs in order to expand the substrate scope beyond the electron-rich arenols commonly employed in previous direct electrolysis methods.⁹

To further minimize the direct oxidation of phenols at the anode, especially under catalytic conditions, we designed a biphasic organic solvent/water system for hypobromite electrocatalysis in which the electrodes are located in the aqueous phase (Scheme 1d).¹¹ This setup physically separates the phenol substrate from the electrodes, thus reducing the likelihood of its direct electrolysis. Moreover, this biphasic electrolysis system allows for the use of inexpensive inorganic salts as electrolytes in the aqueous phase, eliminating the need for the more costly ammonium salts (e.g., $\text{Bu}_4\text{N}^+\text{PF}_6^-$) that are typically used, thereby enhancing the practicality of the method.

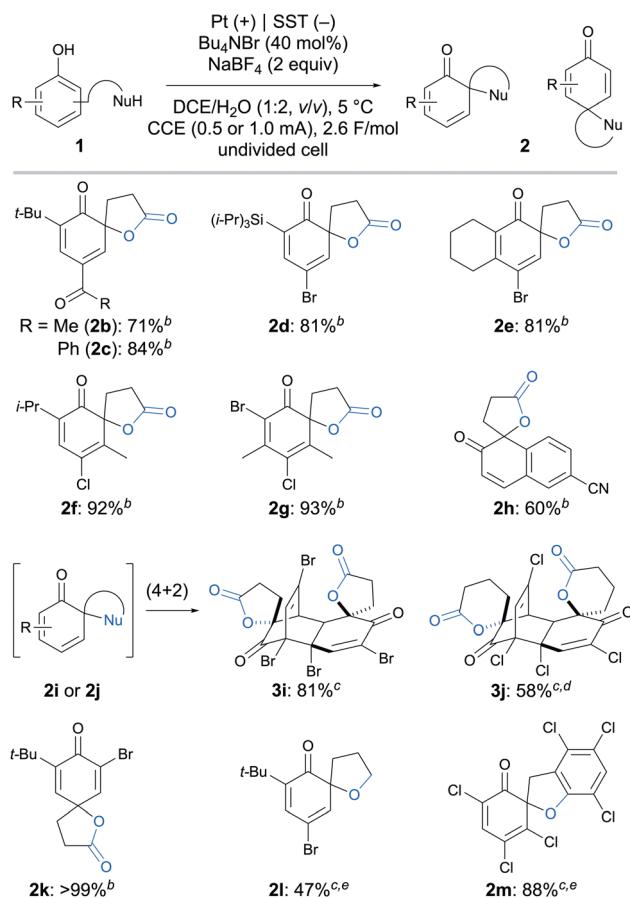
Table 1 Optimization of the reaction conditions^a

Entry	Solvent	x (mol%)	T (°C)	1a, Conv. ^b (%)		2a, Yield ^b (%)
				1a, Conv. ^b (%)	2a, Yield ^b (%)	
1	DCE	20	25	84	72	
2 ^c	DCE	20	25	73	60	
3	DCE	20	5	78	71	
4	DCE	40	5	95	92	
5	CH_2Cl_2	40	5	83	78	
6	$\text{C}_6\text{F}_5\text{CF}_3$	40	5	88	83	
7	CH_3NO_2	40	5	18	5	
8 ^d	DCE	40	5	94	92 ^e	
9 ^f	DCE	40	5	>99	99 ^e	
10	DCE	0 ^g	25	12 ^h	<5	

^a Unless otherwise noted, the reactions were carried out using **1a** (0.2 mmol), Bu_4NBr (40 or 20 mol%), and NaBF_4 (2.0 equiv.) under constant-current electrolysis using a Pt anode (10 mm \times 10 mm \times 0.2 mm) and an SST cathode (10 mm \times 10 mm \times 0.15 mm). The distance between electrodes was 10 mm. ^b Determined by ^1H NMR analysis of the crude product using methyl 3,5-dibromobenzoate as an internal standard. ^c NaHSO_4 (2.0 equiv.) was used as an additive. ^d CCE (1.0 mA); reaction time: 13.9 h. ^e Isolated yield. ^f **1a** (1.0 mmol), NaBF_4 (0.8 equiv.) under CCE (1.5 mA) using a Pt anode (10 mm \times 15 mm \times 0.2 mm) and an SST cathode (10 mm \times 15 mm \times 0.15 mm), 46.5 h. ^g Bu_4NPF_6 (20 mol%) was used instead of Bu_4NBr . ^h 6-Bromo-8-(*tert*-butyl)chroman-2-one generated by intramolecular dehydration of **1a** was obtained in 9% as the main side product.

We commenced our investigation by examining the electro-oxidative spirolactonization of 4-bromo-substituted phenol **1a** as a model substrate using a catalytic amount of tetrabutylammonium bromide as a mediator (Table 1). Platinum and stainless steel (SST) were chosen as the anode and cathode materials, respectively, and the electrolysis was conducted in an undivided cell using the inexpensive inorganic electrolyte sodium tetrafluoroborate (for details, see Table S1, ESI†). To meet the specific requirements of our system, we employed a dichloroethane (DCE)/water biphasic solvent, in which the denser organic layer remains beneath the aqueous phase (Scheme 1d). This arrangement is essential to ensure that electrolysis occurs in the upper aqueous layer containing the electrolyte and electrodes to generate Br^+ species. These catalytically active species then migrate into the organic layer to facilitate the desired reaction.

Electrolysis was conducted at a constant current of 0.5 mA at room temperature until a total charge of 2.6 F mol^{-1} had been passed, which afforded the desired spirolactone **2a** in 72% yield (entry 1). Drawing on our previous studies, which showed that acidic conditions could accelerate hypohalite catalysis,^{4,6} we tested the use of NaHSO_4 as an acidic additive (entry 2). However, the yield of **2a** decreased in that case, likely due to the accelerated generation⁶ and subsequent escape of Br_2 from the reaction mixture, as evidenced by the presence of brown droplets on the rubber septum and electrodes. To improve mass balance, we lowered the reaction temperature to 5 °C (entry 3). Furthermore, a higher loading of Bu_4NBr (40 mol%) was found to significantly improve the yield of **2a** to 92% (entry 4).



Scheme 2 Substrate scope. ^a **1** (0.2 mmol), Bu₄NBr (40 mol%), and NaBF₄ (2.0 equiv.) under constant-current electrolysis using a Pt anode (10 mm × 10 mm × 0.2 mm) and SST cathode (10 mm × 10 mm × 0.15 mm) at 5 °C. The distance between electrodes was 10 mm. ^b CCE (1.0 mA). ^c CCE (0.5 mA). ^d After the electrolysis was completed, the reaction mixture was further stirred at 25 °C for 14 h to complete the (4+2) cyclodimerization. ^e The reaction was performed at 25 °C.

Alternative denser-than-water solvents, such as dichloromethane, trifluorotoluene, and nitromethane, were also examined; however, neither improved the yield (entries 5–7). Finally, the reaction time was reduced by half by increasing the current from 0.5 to 1.0 mA without compromising the yield of **2a**, effectively suppressing the competitive oxidation of water (entry 8). Additionally, we have successfully scaled up the reaction to a 1 mmol scale (entry 9). Notably, when Bu₄NPF₆ was used instead of Bu₄NBr, only trace amounts of product were observed, underscoring the crucial role of bromide as a mediator under the biphasic electrolysis conditions (entry 10).

Then, several electron-deficient phenols bearing EWGs were examined under the optimal conditions (Scheme 2). The chemoselective oxidative dearomatization of 4-acetylphenol derivative **1b** afforded the desired product (**2b**) in 71% yield; no side product corresponding to carbonyl α -bromination was observed.¹² In addition, substrates containing silyl (**1d**) or additional benzylic methylene (**1e–g**) groups, which are potentially sensitive to Br⁺ or Br[•] species,¹³ were well-tolerated under the reaction conditions, providing the corresponding cyclohexadienone spirolactones in good

yield. Moreover, in addition to halogens (**1a**, **1d–g**, and **1i–m**) and acyl (**1b** and **1c**) groups, a cyano group (**1h**) was also tolerated as an electron-withdrawing group in this Br⁺ electrocatalysis. The dearomatic 5- or 6-membered spirolactonization of dihalo-substituted phenol derivatives **1i** and **1j** gave the corresponding (4+2)-cyclodimers (**3i** and **3j**) as single diastereomers *via* the *in situ* generation of the less-hindered and unstable cyclohexadienones **2**.^{4,6,14} Dearomatic spirolactonization at the *para*-position was also achieved, *i.e.*, **2k** was obtained quantitatively from the oxidation of **1k**. In addition to spirolactonization, spiroetherification reactions were also performed. Using alcohol and phenol as the internal nucleophiles, the corresponding spiroethers (**2l** and **2m**) were obtained in moderate-to-high yield.

To elucidate the reaction mechanism, cyclic-voltammetry (CV) measurements were performed under anhydrous and aqueous conditions using CH₃CN and CH₃CN/H₂O (9:1, v/v) as the solvent, respectively, and Bu₄NPF₆ (0.1 M) as the electrolyte (Fig. 1). The CV curve for Bu₄NBr in CH₃CN showed two distinct oxidation peaks at 0.40 V and 0.71 V *vs.* Ag/Ag⁺ (Fig. 1a, curve i), which corresponded to the 3Br[–] → Br₃[–] and 2Br₃[–] → 3Br₂ oxidation processes, respectively, in agreement with previous reports.¹⁵ In comparison, **1a** showed a higher oxidation potential of 1.21 V *vs.* Ag/Ag⁺ (Fig. 1a, curve ii), indicating that Br[–] oxidation remained more favorable. When Bu₄NBr and **1a** were combined, the resulting CV curve displayed two peaks resembling those of Bu₄NBr (Fig. 1b, curve iii). Notably, the absence of an increase in the oxidation current suggests that the direct involvement of Br[•], Br₃[–], or Br₂ in the oxidation of **1a** would be unlikely.

In contrast, an obvious catalytic current was observed in the CV curve of Bu₄NBr in the presence of **1a**, indicating that Bu₄NBr acted as a redox mediator (Fig. 1b, curve vi). These findings align with our previous study⁶ and strongly support the proposed mechanism (Scheme 1d), in which electrochemically generated bromine-based intermediates, such as Br₂ or Br₃[–], are in equilibrium with hypobromite (BrO[–]) or hypobromous acid (BrOH) under aqueous conditions.^{15a,16} These active species would then migrate into the organic phase, facilitating the oxidative dearomatization of **1a** *via* a two-electron oxidation

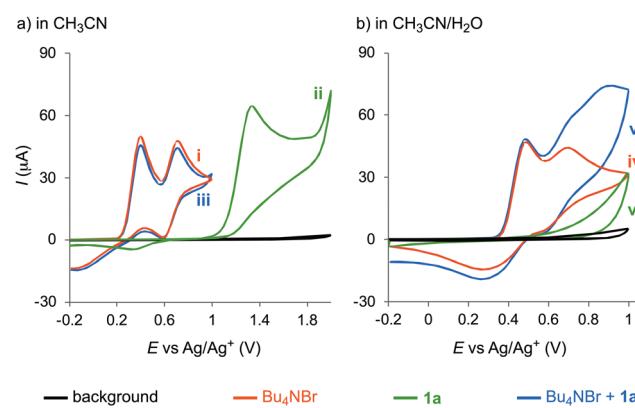


Fig. 1 Cyclic voltammetry measurements under non-aqueous (a) and aqueous conditions (b) at room temperature at a scan rate of 100 mV s^{–1}.

process⁶ to yield the desired product. Taken together, these findings emphasize the role of hypobromite as a catalytically active species and highlight the importance of aqueous conditions in modulating both the reactivity and selectivity of bromine-based catalysis under biphasic electrochemical conditions (for further discussion, see Schemes S1–S3, ESI†).

In summary, we have developed an electrochemical approach for the oxidative dearomatization of electron-deficient phenols using tetrabutylammonium bromide as a catalytic mediator under aqueous biphasic conditions. This method offers greater safety by eliminating the use of stoichiometric chemical oxidants while maintaining the efficiency of our previously reported hypobromite catalysis.⁶ Compared to direct electrolysis methods, this approach expands the substrate scope to include electron-deficient phenols, enabling oxidative dearomatic spirolactonization and spiroetherification reactions. Mechanistic studies using cyclic voltammetry suggested that bromide ions are oxidized at the anode to form bromine-based intermediates that are in equilibrium with hypobromite species, which ultimately mediate the oxidative dearomatization reaction.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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