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Radical α-addition involved electrooxidative [3 + 2] annulation of phenols and electron-deficient alkenes†

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An electrooxidative [3 + 2] annulation of phenols and electron-deficient alkenes for the synthesis of C3-functionalized 2-aryl-2,3-dihydrobenzofuran derivatives was achieved. The ring construction starts by a unique α-addition of carbon radicals derived from anodic oxidation of phenols to electron-deficient alkenes. The subsequent anodic oxidation of the resulting alkyl radical intermediates followed by trapping with the phenolic hydroxy group assembles the 2,3-dihydrobenzofuran core. Such a pathway enables the installation of various electrophilic functionalities including alkoxycarbonyl, alkylaminocarbonyl, trifluoromethyl, and cyano groups at the C-3 of the 2,3-dihydrobenzofuran framework, which is unattainable by other intermolecular reactions. The application of this method for a rapid synthesis of a bioactive natural product is demonstrated.

Introduction

2,3-Dihydrobenzofurans constitute the core skeletons of a number of natural products and bioactive molecules.[1] In particular, 2-aryl-2,3-dihydrobenzofuran-3-carboxylic acid derivatives have shown important biological and medicinal applications (Fig. 1a).[2] Therefore, the development of methods for practical and environmentally friendly synthesis is of great significance. So far, methods to assemble such a 2-aryl-3-carboxyl-2,3-dihydrobenzofuran framework have been mainly limited to intramolecular annulation reactions (Fig. 1b),[3] including carbene C–H insertion reactions of alkylated phenols,[4] radical Witkop photocyclization/elimination/addition cascades,[5] alkylation *via* C–H bond activation,[6] oxidative [3 + 2] cyclization,[7] and hydrogenation of benzofurans.[8] Notably, many approaches suffered from multiple-step synthesis of pre-functionalized starting materials, limited substrate scope, and the use of precious transition metal catalysts or stoichiometric amounts of strong oxidants. To achieve green and more step- and atom-economical synthesis, the exploration of new protocols based on intermolecular reactions of readily accessible starting materials is highly desirable.[9]

Oxidative [3 + 2] annulation of easily available phenols and alkenes presents an appealing strategy to assemble the 2,3-dihydrobenzofuran framework.[10] For example, the pioneering work by Swenton[11] and Chiba[12] demonstrated successful anodic cycloaddition reactions. However, most reported reactions rely on the use of electron-rich alkenes as electron donor components that can either trap electron-demanding intermediates[10a–d,11,12] or serve as reductive partners to promote oxidative transformations.[10e–g] In contrast, alkenes bearing electron-withdrawing groups have rarely been used as viable substrates most likely due to the unmatched electronic nature. Considering that a wide variety of electron-poor alkenes are readily accessible, the success of reliable annulation methods

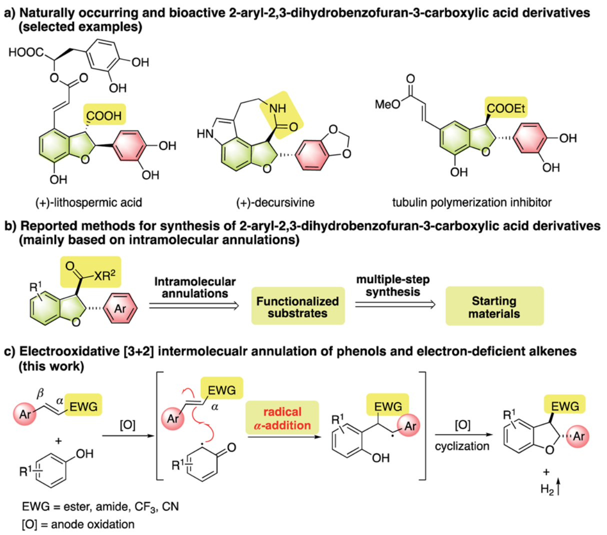

Fig. 1 Synthesis of 2-aryl-2,3-dihydrobenzofuran-3-carboxylic acid derivatives and analogous.

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would enable economical and diverse synthesis of structurally elaborate products. More importantly, many electrophilic motifs, such as carbonyl groups, could be easily converted to various functionalities, which would enrich 2,3-dihydrobenzofuran libraries for further biological and medicinal applications. To this end, developing conceptually distinct pathways is of great significance. Herein, we report an unprecedented electrooxidative [3 + 2] annulation between phenols and electron-deficient alkenes towards the synthesis of structurally novel C3-functionalized 2-aryl-2,3-dihydrobenzofuran derivatives (Fig. 1c). In this process, the key step is a radical α-addition of carbon radicals derived from single-electron oxidation of phenols to electron-poor alkenes.

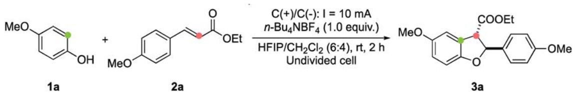
In radical addition reactions, a radical species usually prefers to undergo β-addition to electron-deficient alkenes owing to the strong inductive effect of the electron-withdrawing group or the external Lewis acid activation.[13] For substrates bearing a β-radical stabilizing group, such as an aryl functionality, α-addition is possible to be the main pathway,[14] in particular for the case where the ensuing step is driven by an energetically highly favorable process.[15] Very recently, our group disclosed an interesting radical α-addition of NHC–boryl radicals to electron-poor alkenes.[16] Mechanistic studies revealed that such α-addition was actually kinetically and thermodynamically feasible, especially for β-aryl substituted ones. Stimulated by this finding, we posited a radical α-addition involved oxidative annulation of phenols and electron-deficient alkenes. Meanwhile, as a green and oxidant-free synthetic tool,[17] an electrochemical reaction was considered as the preferred choice to promote this assumed process. As depicted in Fig. 1c, single-electron oxidation of phenols on the anode could easily take place,[18] and the resulting carbon radicals were expected to undergo α-addition to electron-deficient alkenes. The subsequent single-electron oxidation of the resulting radical intermediates followed by cyclization would provide a 2,3-dihydrobenzofuran framework. At the same time, hydrogen gas would be released as the sole byproduct by the reduction of protons at the cathode.

Results and discussion

We commenced our study by investigating the reaction of 4-methoxyphenol (**1a**) and cinnamate **2a** in an undivided cell equipped with two electrodes. To our delight, the proposed annulation product **3aa** was isolated in 82% yield using *n*-Bu_4NBF_4 as the electrolyte and 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP)/CH_2Cl_2 as co-solvents at 10 mA constant current for 2 h (Table 1, entry 1). The solvent effect was examined. It was found that a comparable yield was obtained when HFIP was used as the sole solvent (entry 2), while the employment of CF_3CH_2OH/CH_2Cl_2 (6 : 4) led to a decreased yield (entry 3). Moreover, replacing HFIP with $(CH_3)_3CHOH$ resulted in a dramatic decrease in the reaction efficiency (entry 4). Using *n*-Bu_4NPF_4 as the electrolyte instead of *n*-Bu_4NBF_4 led to a lower yield (entry 5). As for the electrode material used, replacing the graphite rod cathode with a platinum plate one could also give high product yield (entry 6). Importantly, the reaction could be carried out under atmospheric conditions while maintaining a good efficiency (entry 7). The control experiment showed that no reaction occurred without electric current (entry 8), verifying the electron transfer mechanism of this process.

Using the optimized reaction conditions, the scope of electron-deficient alkenes in this electrooxidative [3 + 2] annulation was first evaluated (Table 2). A broad range of β-aryl-α,β-unsaturated esters could be converted to cyclized products in good yields (**3b–3f**). A gram scale synthesis of **3b** was achieved in 66% yield, demonstrating the practicability of this electrochemical protocol. Notably, a free-phenol containing substrate **2g** was also a viable substrate, furnishing the desired annulation product **3g** in 65% yield without the detection of any dimerization product of **2g**.[19] Moreover, no further oxidation of this phenol product to engage in a second cyclization was observed. This protocol was also applicable for the construction of alkylamino-substituted products (**3h** and **3i**). However, the reaction of **2j–2l**, where the aryl ring bears less electron-donating groups, led to decreased yields (for **3j–3l**) most likely due to the inferior efficiency for the second single-electron oxidation to generate

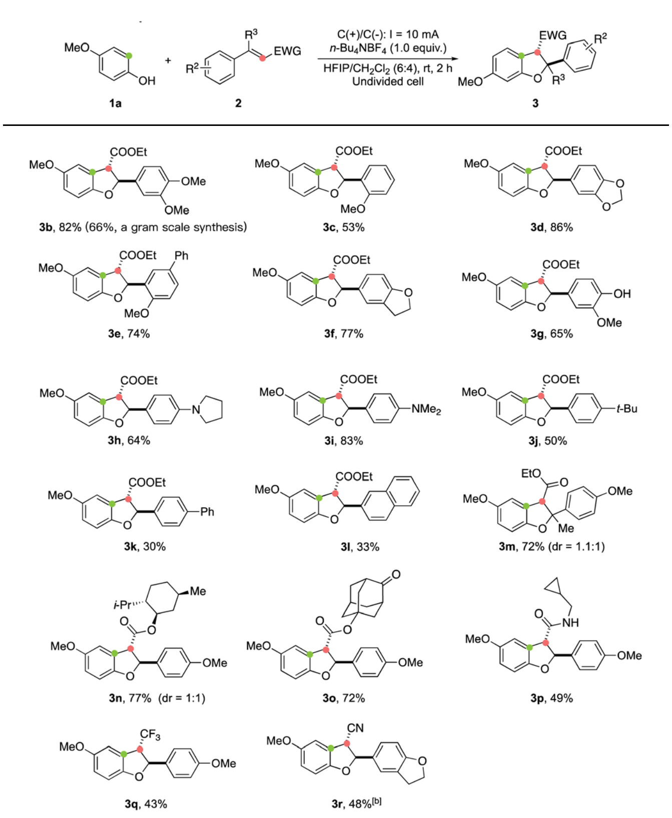
Table 1 Effects of reaction parameters[a]



Entry	Variation from the standard conditions	**3aa** yield[b]
1	None	83% (82%)[c]
2	HFIP instead of HFIP/CH_2Cl_2 (6 : 4)	76%
3	CF_3CH_2OH instead of HFIP	65%
4	$(CH_3)_2CHOH$ instead of HFIP	9%
5	*n*-Bu_4NPF_6 instead of *n*-Bu_4NBF_4	58%
6	Platinum plate cathode instead of graphite rod cathode	88%[c]
7	Under air	80%[c]
8	No electric current	NR

[a] Reaction conditions: graphite rod anode, graphite rod cathode, constant current = 10 mA. **2a** (0.3–0.4 mmol), **1a** (1.5 equiv.), *n*-Bu_4NBF_4 (1.0 equiv.), solvent (10 mL), rt, 2 h, under N_2. [b] NMR yields using 1,1,2,2-tetrachloroethane as the internal standard. [c] Isolated yield.

Table 2 Scope of electron-deficient alkenes[a]

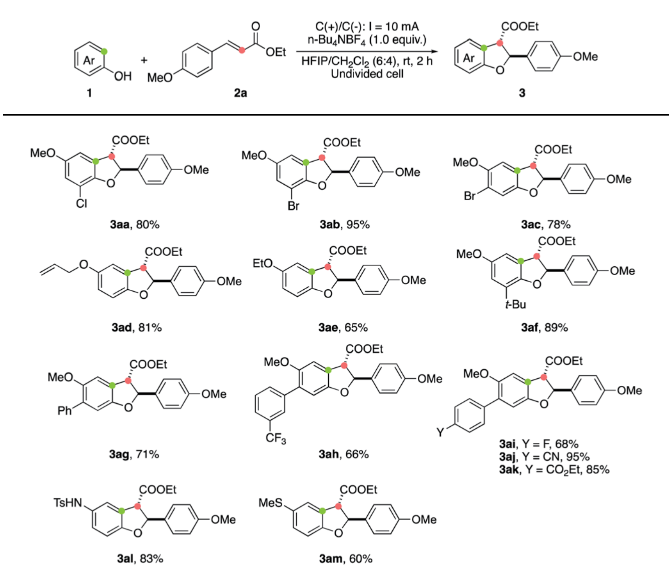


[a] Standard reaction conditions: graphite rod anode, graphite rod cathode, constant current = 10 mA. **2** (0.3–0.4 mmol), **1a** (1.5 equiv.), n-Bu_4NBF_4 (1.0 equiv.), HFIP/CH_2Cl_2 (6 : 4, 10 mL), rt, 2 h, under N_2. [b] The reaction was conducted with a constant cell potential of +2.5 V in HFIP/CH_2Cl_2 (7 : 3, 10 mL) for 10 h at rt.

carbon cation intermediates. Remarkably, the presence of an additional methyl group at the β-carbon of **2** (R^3 = Me) did not retard the annulation, forming product **3m** containing a tetra-substituted carbon center[20] in 72% yield, albeit with low diastereoselectivity. This annulation method also allowed for the incorporation of alcohol-containing functional molecules, such as menthol (**3n**) and 5-hydroxy-2-adamantanone (**3o**), onto the 2,3-dihydrobenzofuran framework. Importantly, other electron-withdrawing groups, such as alkylaminocarbonyl (**3p**), trifluoromethyl (**3q**), and cyano (**3r**) moieties, could also be installed at the C-3 position from annulation reactions of the corresponding electron-deficient alkenes.

Next, we turned our attention to study the applicability of phenol components in this annulation reaction. The reactions between a variety of substituted phenols **1** and cinnamate **2a** worked well, delivering the corresponding annulated products **3** in moderate to good yields (Table 3). Various functional groups, including chloride (**3aa**), bromide (**3ab**, **3ac**), simple alkene (**3ad**), alkoxyl (**3ae**), and alkyl (**3af**) could be tolerated. The 2,3-*trans* stereochemistry of **3ac** was confirmed by X-ray crystallographic analysis.[21] A range of 6-aryl-substituted products bearing CF_3, F, CN, and CO_2Et motifs (**3ag–3ak**) were accessed in good yields. Furthermore, TsNH- and MeS-substituted phenols were capable of participating in this electrooxidative annulation, providing cyclized products **3al** and **3am** in synthetically useful yields.

Table 3 Scope of phenols[a]



[a] Standard reaction conditions: graphite rod anode, graphite rod cathode, constant current = 10 mA. **2a** (0.3–0.4 mmol), **1** (1.5 equiv.), n-Bu_4NBF_4 (1.0 equiv.), HFIP/CH_2Cl_2 (6 : 4, 10 mL), rt, 2 h, under N_2.

The synthetic utility of this electrooxidative [3 + 2] annulation protocol was demonstrated by a rapid synthesis of 3′,4-di-*O*-methylcedrusin (**4**), which is a natural product[22] with a broad spectrum of bioactivity.[2a,23] As depicted in Fig. 2, the annulation of **1n** and **2b** took place smoothly under the standard reaction conditions, affording **3bn** in 42% yield. The following reduction of two ester groups with $LiAlH_4$ provided product **4** directly in 76% yield. It should be noted that a commonly used method to assemble **4** relies on a four-step synthesis,[24] including an oxidative annulation using stoichiometric amounts of oxidants to construct the 2,3-dihydrobenzofuran skeleton. The present two-step procedure offers a more straightforward and oxidant-free route, thereby enjoying more advantages in economical and green synthesis.

To test the reaction mechanism of this oxidative annulation, several mechanistic studies have been performed. As illustrated

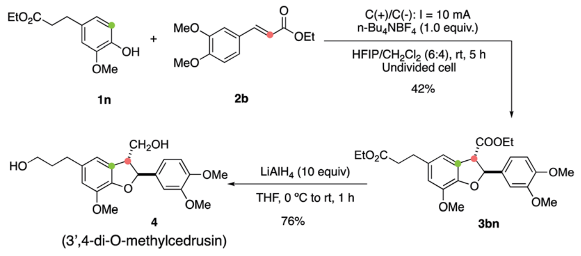


Fig. 2 Synthesis of 3′,4-di-*O*-methylcedrusin.

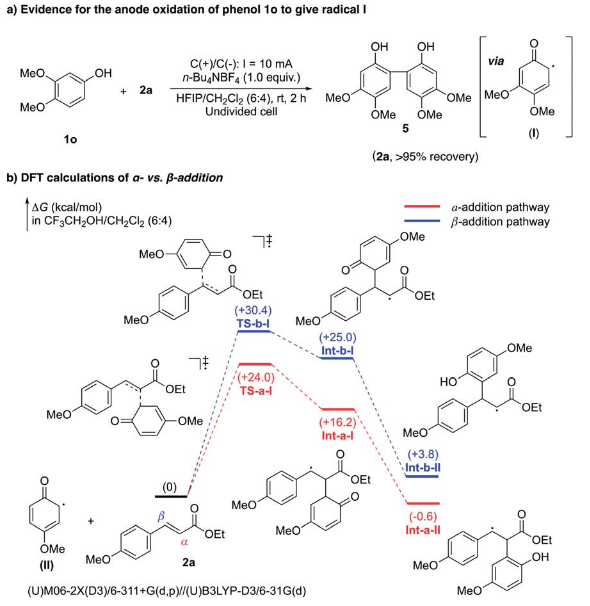


Fig. 3 Mechanistic studies.

in Fig. 3a, when **1o** was subjected to the standard annulation reaction condition, its dimerization product **5** was isolated in 87% yield. This suggests that radical **I** should be generated by anodic oxidation, while its addition to electron rich **1o** would proceed much faster than its addition to **2a**,[25] thereby affording dimer **5** without the detection of the cyclization product. DFT calculations were then carried out to gain deeper insights into the specific α-regioselectivity of the radical addition step (Fig. 3b).[26] The addition of radical **II** to the α-position of **2a** requires a much lower activation free energy than addition to the β-position (**TS-a-I** +24.0 kcal mol^{-1} *versus* **TS-b-I** +30.4 kcal mol^{-1}). Besides, the resulting **Int-a-II** (−0.6 kcal mol^{-1}) is more stable than **Int-b-II** (+3.8). Furthermore, the subsequent single-electron oxidation of **Int-a-II** to a carbon cation should be an energetically favorable process, owing to the strong stabilization from the adjacent *para*-methoxyphenyl group. As a result, the α-addition pathway is thermodynamically and kinetically more favored than the β-addition pathway, thereby ensuring exclusive radical α-regioselectivity.

Conclusions

In summary, we have developed a practical and green electrooxidative [3 + 2] annulation of phenols and electron-deficient alkenes. This protocol enables the construction of C3-functionalized 2,3-dihydrobenzofuran derivatives from simple starting materials. These products are difficult to access using the reported oxidative annulation methods. The key to success lies in a kinetically and thermodynamically favorable regioselective α-addition of carbon radicals to electron-deficient alkenes. Such specific α-regioselectivity as well as the electrooxidative annulation method may inspire the design of new radical approaches for further synthetic applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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