CHEMISTRY
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Authors: Jian-Jun Dai, Xiang-Zhang Tao, Jie Zhou, Jun Xu, and Hua-Jian Xu

To be cited as: *Chem. Eur. J.* 10.1002/chem.201801108

Link to VoR: http://dx.doi.org/10.1002/chem.201801108

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Electrochemical C–O Bond Formation: A Facile Access to Aromatic Lactones

Xiang-Zhang Tao,[a] Jian-Jun Dai,*[a] Jie Zhou,[a] Jun Xu,[a] and Hua-Jian Xu*[a]

Abstract: An efficient and robust methodology based on electrochemical techniques for the direct synthesis of aromatic lactones *via* dehydrogenative C–O cyclization is described. This new and useful electrochemical reaction can tolerate a variety of functional groups, and is scalable to 100 grams under mild conditions. Remarkably, heterocycle-containing substrates can be employed, thus expanding the scope of radical C–O cyclization reaction.

Aromatic lactones are an important class of compounds, which exhibit a key structure in a variety of natural products, pharmaceutical agents and functional materials (Figure 1).[1]

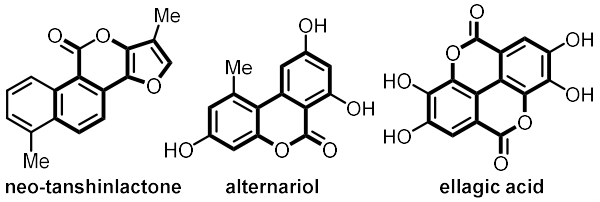
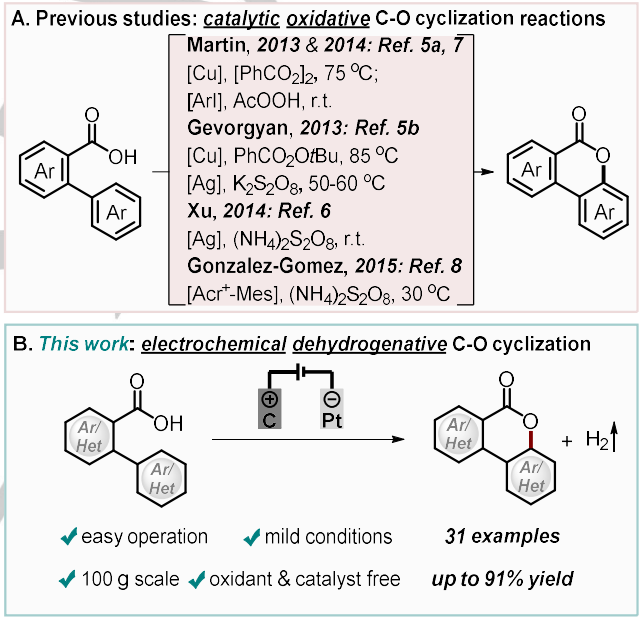


Figure 1. Selected bioactive compounds containing aromatic lactones motif.

Significant achievements have been made by using the C–H activation strategy for the synthesis of aromatic lactones.[2–4] Among these synthetic protocols, radical C–H functionalization/C–O cyclization of 2-arylbenzoic acids emerged as attractive and efficient methods, providing powerful tool for the preparation of such molecules (Scheme 1A). These processes are generally conducted using transition metals catalysts including Cu,[5] Ag[6], aryl iodine[7] catalyst and photocatalyst[8] in the presence of peroxides or persulfates as oxidants. However, *a common feature of these methods is the requirement of stoichiometric chemical oxidants* (e.g., $[PhCO_2]_2$, AcOOH, $PhCO_2OtBu$, $K_2S_2O_8$, $(NH_4)_2S_2O_8$) that led to distinct waste generation. Consequently, the development of sustainable synthesis of aromatic lactones is still highly desirable.

Electro-organic synthesis has emerged as an environmentally friendly and powerful synthetic tool for numerous useful transformations.[9–10] In this context, we reasoned that the electrochemical oxidation of 2-(hetero)arylbenzoic acids *via* dehydrogenative C–O cyclization[11–12] would provide facile and clean formation of aromatic lactones (Scheme 1B). This electrochemical process is synthetically complementary to both transition-metal-catalyzed and photoredox-mediated approaches. In particular, neither transition-metal catalysts nor added oxidants were used in the present study, thereby making this method an atom economically protocol. Additionally, this reaction can be conducted on 100 grams scale with mild conditions and easy operations. Moreover, this reaction also provides a new example for the construction of oxygen-containing heterocycles by applying electrochemical techniques.[13]



Scheme 1. Approaches to biaryl lactones via C–O cyclization.

Our work started with the electrochemical C–O cyclization of 2-phenylbenzoic acid (**1a**) with graphite and platinum as anode and cathode, respectively. It was found that the desired product **2a** was obtained in 91% yield with 6 mA (4.0 mA cm^{-2}) constant current in an undivided cell at room temperature (r.t.) for 5 hours (Table 1, entry 1). Using other supporting electrolytes and/or solvents can also cause the reaction with lower yields (See Table S1 for more details). In addition, either increasing or decreasing the constant current led to inferior yields (Table 1, entries 2 and 3). As expected, the nature of the electrode materials are usually important to the electrochemical reactions.[14] Indeed, only 12% and 16% yields were observed when graphite was replaced by platinum or glass carbon as the anode (Table 1, entries 4 and 5). Finally, a control experiment showed that no product was obtained in the absence of electric current (Table 1, entry 6).

[a] X.-Z. Tao, Prof. Dr. J.-J. Dai, J. Zhou, Prof. Dr. J. Xu, Prof. Dr. H.-J. Xu
School of Biological and Medical Engineering
Anhui Province Key Laboratory of Advance Catalytic Materials and Reaction Engineering
Hefei University of Technology
Hefei, 230009 (China)
E-mail: daijj@hfut.edu.cn
hjxu@hfut.edu.cn

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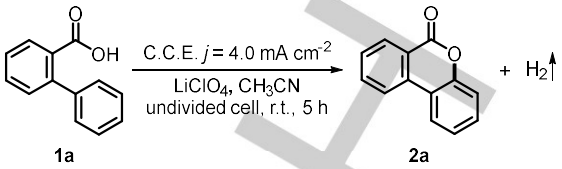
Having identified optimal reaction conditions, we sought to evaluate the scope of the electrochemical C–O cyclization reaction with respect to 2-arylbenzoic acids (**1b**–**s**).[15] As shown in Scheme 2A, the present electrochemical C–O cyclization methodology displayed good functional-group tolerance and proved to be an efficient route for the preparation of biaryl lactones in good to excellent yields (57–93%) under very mild conditions. As to the electronic effect of the substituents, a range of electron-rich groups, such as methyl (**2b**, **2l** and **2q**), methoxy (**2t**), dioxole (**2r**), and electron-withdrawing groups, such as cyanide (**2h**), nitro (**2i** and **2o**), fluoro (**2d**, **2m** and **2p**), trifluoromethyl (**2c**), ketone (**2j**) and trifluoromethoxy (**2k**) are well tolerated. Importantly, synthetically valuable halide groups, including chloride (**2e** and **2s**), and bromide (**2f**) were also well compatible with the reaction, providing easy handles for further transformations using the popular cross-coupling reactions.[16] Furthermore, unprotected hydroxyl group (**2g**) was well tolerated, which is an outcome that considerably highlights the synthetic utility of the present protocol. Finally, *meta* substituted substrates also cyclized in good yields and with regioselectivities (**2r** and **2s**).

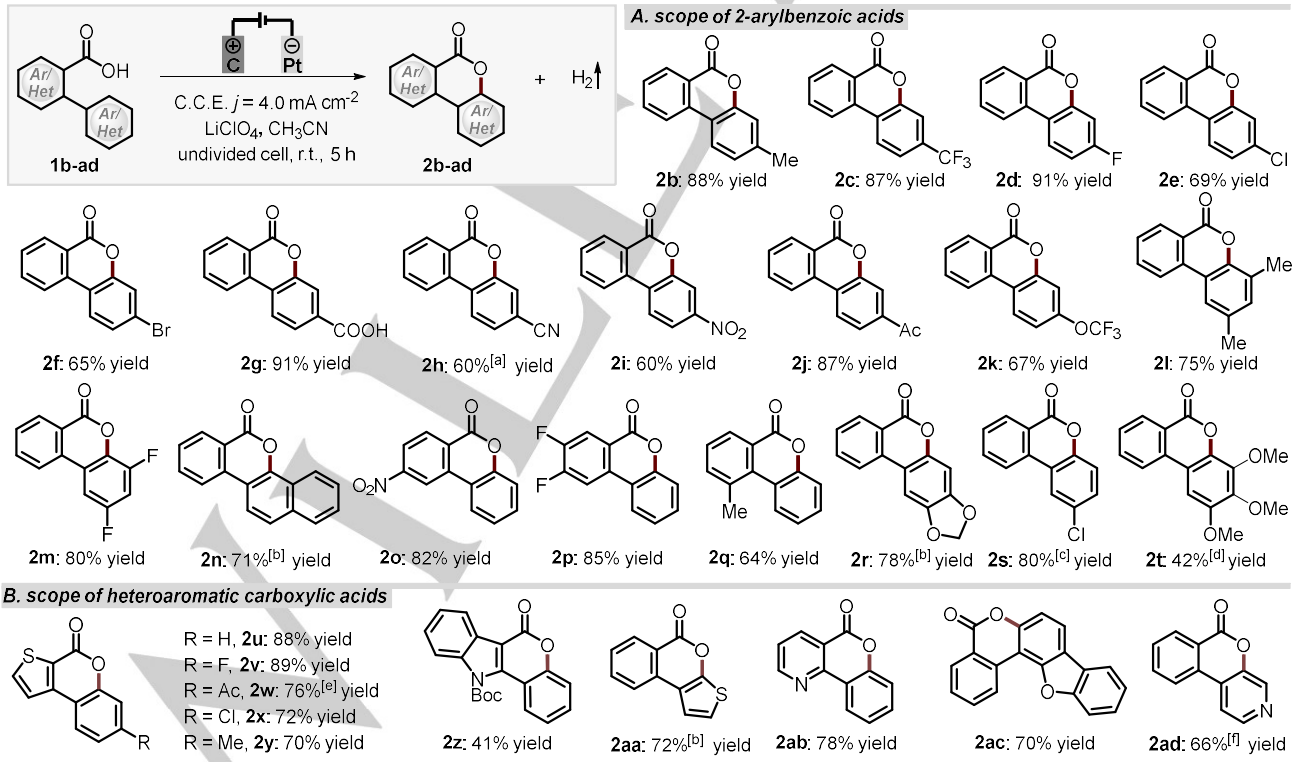
Heteroaromatic compounds are of particular importance and highly interest for pharmaceutical applications. Accordingly, we were interested to test whether the electrochemical C–O cyclization reaction could be used in the synthesis of heterocycle-containing lactones (Scheme 2B). Pleasingly, the

Table 1. Optimization of the reaction conditions.[a]



Entry	Variation from the standard conditions	Yield [%][b]
1	**None**	**91 (90)**
2	8.0 mA cm^{-2} instead of 4.0 mA cm^{-2}, 2.5 h	71
3	2.0 mA cm^{-2} instead of 4.0 mA cm^{-2}, 10 h	80
4	Platinum instead of graphite as anode	12
5	Glass carbon instead of graphite as anode	16
6	No electric current	0

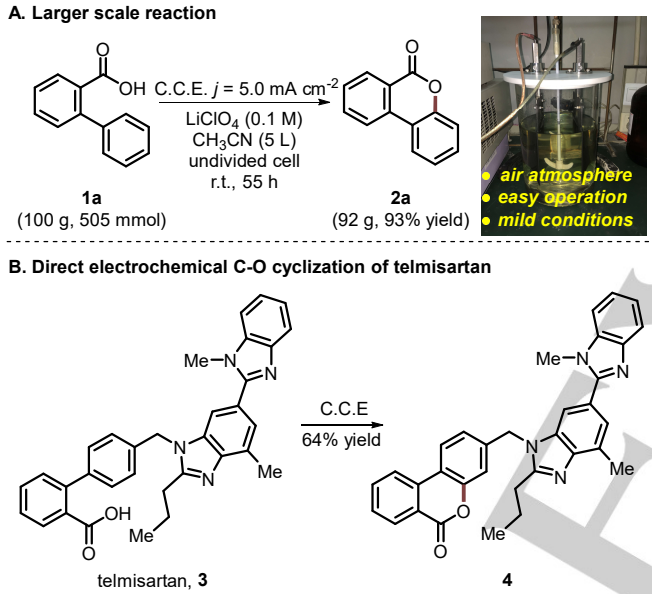
[a] Standard conditions: graphite plate anode: (10 mm × 15 mm), platinum plate cathode: (10 mm × 10 mm), constant current: 6.0 mA (j_{anode} = 4.0 mA cm^{-2}), supporting electrolyte: 0.1 M $LiClO_4$, **1a** (0.5 mmol), CH_3CN (10 mL), air, r.t., 5 h, undivided cell. The cell voltage was 2–8 V. [b] GC yield. [c] Isolated yield was shown in the parentheses. C.C.E. = Constant current electrolysis.



Scheme 2. Substrate scope. Unless otherwise noted, the reaction conditions are the same as in Table 1, isolated yield was reported for each reaction. C.C.E. = Constant current electrolysis. [a] The reaction time was 24 h. [b] The product was obtained as a single regioisomer. [c] Isolated as a regioisomeric mixture (6:1). [d] The reaction time was 10 h. [e] nBu_4NBF_4 was used as the supporting electrolyte. [f] *I* = 10 mA (j_{anode} = 6.67 mA cm^{-2}), CH_3CN/CH_3OH (1:1, 10 mL) as the solvent, the reaction time was 12 h.

desired C–O cyclization products of thiophene (**2u**–**y**, **2aa**), indole (**2z**), and dibenzofuran (**2ac**) derivatives were successfully achieved under constant current electrolysis. It is particularly noteworthy that this protocol tolerates pyridine containing substrates (**2ab** and **2ad**), which were not effectively transformed under previous reported radical C–O cyclization conditions.[5–6]

In order to demonstrate the practicality of the electrochemical C–O cyclization reaction in preparative organic synthesis, a larger scale reaction was conducted. As depicted in Scheme 3A, the reaction of **1a** was conducted on 100 g (505 mmol) scale, and the desired product **2a** was smoothly furnished in 93% yield (92 g) after 55 h constant current electrolysis. It was worth mentioning that all reaction steps were operated in air atmosphere.[17]



Scheme 3. Synthetic applicability. A. Larger scale reaction: **1a** (100 g, 505 mmol), $LiClO_4$ (53.2 g, 500 mmol), CH_3CN (5 L), graphite anode (20 cm × 15 cm) and graphite cathode (20 cm × 15 cm), at a constant current of 1 A (j_{anode}= 5.0 mA cm^{-2}, effective electrode area was 200 cm^2) for 55 h in an undivided cell at room temperature. B. Direct electrochemical C–O cyclization of telmisartan: **3** (0.2 mmol), $LiClO_4$ (1.0 mmol), $CH_3CN/CHCl_3$ (4:1, 10 mL) as the solvent, graphite anode and platinum cathode, at a constant current of 6 mA (j_{anode}= 4.0 mA cm^{-2}) for 5 h in an undivided cell at room temperature.

Also in connection to the synthetic utility, we next test the direct electrochemical C–O cyclization of telmisartan **3**, an angiotensin II receptor antagonist used in the treatment of hypertension (Scheme 3B). By applying the electrochemical C–H functionalization/C–O cyclization reaction, telmisartan analogue **4** was isolated in 64% yield.[18]

In conclusion, an efficient electrochemical method for the C–O cyclization of 2-(hetero)arylbenzoic acids is accomplished. The reaction is operationally simple and scalable under ambient conditions, presents a broad substrate scope. Importantly, a range of valuable heterocycle-containing substrates are obtained in good yields, thus highlighting the complementary to previous reported methods. In addition, we have demonstrated the direct electrochemically C–O cyclization of drug molecule telmisartan. We expect that this method can be used for the synthesis of valuable biologically active molecules. Further studies on electrochemically-based radical reactions are ongoing in our laboratory.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 21402036, 21472033, 21502038) and the Fundamental Research Funds for the Central Universities for financial support.

Keywords: electrochemistry • dehydrogenative • heterocycles• cyclization • lactones

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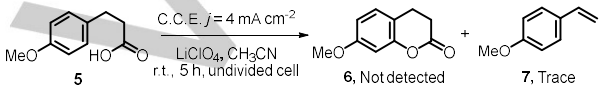
[15] Notably, under optimal conditions, aliphatic acids such as 3-(4-methoxyphenyl)propanoic acid (**5**) failed to yield the desired C–O cyclization product **6**, and decarboxylation of acid into olefin **7** was observed by GC-MS analysis.



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[17] For more details, please see the Supporting Information.

[18] We also tested the C–O cyclization of telmisartan **3** under Cu- and Ag-catalyzed conditions, respectively (Ref. [5a] and [6]). However, no desired product was obtained. This result highlights the synthetic applicability of current electrochemical protocol.

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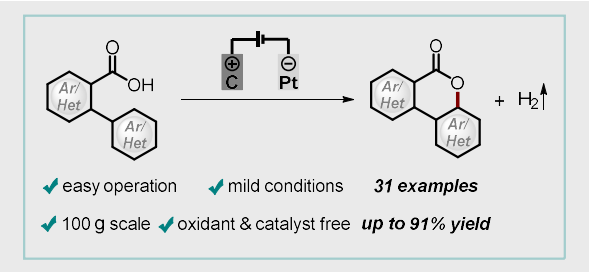

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Electrochemical C–O Bond Formation: A Facile Access to Aromatic Lactones

An electrochemical method was developed for the facile synthesis of aromatic lactones. These mild, scalable, and atom economically reactions feature good yields, broad substrate scope (31 examples), and good functional-group tolerance.