Regioselective Electrochemical Cyclobutanol Ring Expansion to 1-Tetralones

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A mild electrochemical method for the regioselective preparation of 1-tetralones under environmentally friendly conditions from readily available cyclobutanols was developed. A series of aromatic- and heteroaromatic-fused 1-tetralones was accessed through ring expansion of the functionalized cyclobutanols via electrochemical generation of alkoxy radicals and intramolecular cyclization.

The use of electricity as a driving force for non-spontaneous organic reactions has its roots in the early 19th century with Kolbe’s seminal work on the electrolysis of aliphatic carboxylic acids. [2] Although a plethora of synthetic transformations have since been developed, [3–7] including numerous applications in industry, the potential of preparative organic electrochemistry remains underutilized. However, with the advent of easily accessible standardized electrochemical set-ups and the growing interest toward greener, safer, and more cost-efficient processes, [11] this discipline has recently experienced a renaissance. [12,13] Indeed, the need for toxic and expensive reagents or harsh reaction conditions can be significantly diminished when an electric current is used; in particular when this is provided by renewable sources. Examples of recently developed electrochemical protocols include the mild synthesis of orthoesters, [13] allylic oxidation of alkenes, [14] the synthesis of 2-pyrrolidinones, [15] or the fluorination of sp3-carbon centres. [16]

In line with the synthetic community’s progression toward milder synthetic techniques, the functionalization of the cyclobutanol ring under electrochemical conditions has gained particular attention (Scheme 1). [17–22] The relief of ring strain (strain energy of 26.3 kcal mol−1) [23] and the formation of a strong carbonyl bond (179 kcal mol−1 vs 92 kcal mol−1 for C–O bonds) [22] as thermodynamic driving forces enabled the cyclobutanol ring to be established as a versatile precursor to a range of value-added cores with functional handles and increased molecular complexity. [24–27] For example, in 1996 Nikishin and co-workers reported the manganese(III)-mediated electrooxidative ring-opening to linear ketones. [28] In the same publication they showed that γ-chlorinated linear butanones were formed as the major product when a chloride salt was added to the electrochemical manganese(III)-catalyzed cyclobutanol ring-opening reaction; [28] this work was repeated by Morrill in 2019. [21] The groups of Zhang and Kim, on the other hand, were particularly productive in the area of tandem functionalization/semi-pinacol rearrangements and pioneered the electrochemical synthesis of a variety of β-functionalized cyclopentanones from vinyl-substituted cyclobutanols. [17–20,22]

Although protocols for the ring expansion of cyclobutanols to tetralones under traditional synthetic methods (e.g. [Ag],[29] [Rh],[30] [Pd],[31,32] [Ce],[33] N-bromosuccinimide,[34–36]) were previously disclosed, a two-carbon ring homologation to tetralones under mild and ecological electrochemical techniques has not yet been accomplished (Scheme 1).

This is perhaps surprising given the widespread occurrence of the 1-tetralone motif in biologically active natural and synthetic compounds. Levobunolol, for example, is a widely marketed beta-blocker, whereas naturally occurring 6-hydroxyysgol and myrhyfne show promising antitumor- [27] and anti-inflammatory activity, [38] respectively (Figure 1). Despite their evident importance, conventional protocols to access 1-tetralones from cyclobutanols pose several significant drawbacks. Specifically, they usually rely on (i) superstoichiometric quantities of co-oxidant together with a transition-metal catalyst, [29,32] (ii) long reaction durations, [29] and (iii) superstoichiometric quantities of co-oxidant...
of transition-metals,\textsuperscript{[33]} or (iv) very careful substrate design to avoid undesired β-carbon elimination processes.\textsuperscript{[26,32]} To overcome these limitations, we sought to employ electrosynthesis as a tool to effect this transformation in a regioselective, functional group-tolerant and cost-efficient fashion. Herein, we report our findings on the implementation of these ideas.

To commence our studies, we drew inspiration from the electrochemical cyclobutanol ring-opening first reported by Nikishin.\textsuperscript{[28]} Their group showed that through the heterogenous electrochemical formation and regeneration of manganese(III)-catalysts, alkoxy radicals can be generated from hydroxyl groups through a homogenous single electron transfer (indirect electrolysis). This alkoxy radical would easily undergo a β-scission process and lead to the formation of a new carbonyl and carbon-centred radical. The newly generated radical can then be trapped to furnish diversified γ-functionalized butanones.\textsuperscript{[28]} We hypothesized that in the absence of an external radical scavenger, these conditions might be amenable to induce intramolecular ring closure. To this end, we treated cyclobutanol 1\textsuperscript{a} with Mn(OTf)\textsubscript{2} at a current density of 10 mA.cm\textsuperscript{-2}, using carbon electrodes and lithium perchlorate/acetonitrile as the supporting electrolyte/solvent system (Table 1, entry 1).\textsuperscript{[28,39,40]} To our delight, the starting material was completely consumed within three hours (10 F.mol\textsuperscript{-1}) and the desired 1-tetralone 2\textsuperscript{a} was formed in 32% yield. The remaining mass balance was found to consist of nonpolar alkene-containing side products and unidentifiable polymeric materials, which were easily separated from the desired tetralone product through flash column chromatography. Variation of the catalyst loading (Table 1, entries 2–3) had a detrimental effect on the yield and other solvent systems, like CH\textsubscript{2}Cl\textsubscript{2} or HFIP (Table 1, entries 6–7). Similarly, conducting the reaction in other solvent mixtures, such as ethyl acetate/acetonic acid or acetonitrile/water, failed to yield the desired product (Table 1, entries 8–10), whereas a decrease in yield was observed when acetonitrile/HFIP or acetonitrile/acetonic acid systems were used (Table 1, entries 11–12). Consequently, acetonitrile was established as the optimal solvent for this transformation, since it favors the stabilization of transient cationic intermediates\textsuperscript{[25]} and offers a large electrochemical window.\textsuperscript{[41]} After studying the impact of a different supporting electrolyte on the outcome of the reaction (Table 1, entries 13–14), [Li][ClO\textsubscript{4}] was found to be the most suitable electrolyte for our transformation. A significant decrease in yield was observed when using [nBu\textsubscript{4}N][PF\textsubscript{6}], possibly due to the formation of a more hydrophobic electrical double-layer. Upon investigating other reaction parameters (Table 1, entries 15–19), such as temperature or current density, we found that a current density of 10 mA.cm\textsuperscript{-2}, an open atmosphere, and a reaction temperature between 0–25°C were essential for the desired outcome of this reaction.

In line with our aim to develop mild and sustainable conditions for this expansion, we turned our attention to the possibility of direct anodic oxidation in the absence of a metal catalyst. To this end, we performed cyclic voltammetry studies on alcohol 1\textsuperscript{a} in the presence and absence of a manganese catalyst (see Supporting Information). The first oxidation wave of 1\textsuperscript{a} was shown to be chemically irreversible, indicating a rapid subsequent chemical reaction triggered by the electron transfer. Unsurprisingly, in presence of the manganese catalyst, the first oxidation potential significantly decreased (E\textsubscript{pa} = 1.2 V vs Fc\textsuperscript{+}/Fc\textsuperscript{−}), in comparison to the oxidation potential observed for 1\textsuperscript{a} in absence of a catalyst (E\textsubscript{pa} = 1.4 V vs Fc\textsuperscript{+}/Fc\textsuperscript{−}). The new lower oxidation potential could be attributed to the complex
formed in situ between the manganese catalyst and the cyclobutanol 1a, as the catalyst itself did not exhibit an oxidation wave in the cyclic voltammetry studies (see Supporting Information). When alcohol 1a was treated with the conditions described in Table 1 (entry 20) in absence of the manganese catalyst, the desired ketone was formed in 11% yield.

Following these initial metal-free electrolysis studies, we found that an increase of the electron flow to 25 F.mol⁻¹ enabled the desired ring expansion of 1a to 2a in 36% yield through direct electrochemical oxidation in the absence of any metal catalyst (Table 1, entry 21). Despite the relatively low mass recovery, we were delighted to find that the yield of 2a compared favorably with that obtained for the identical transformation under traditional metal-catalyzed conditions.²⁻³⁶ Finally, we discovered that graphite electrodes offer superior performance in comparison to a Pt/Ni electrode system, potentially due to improved substrate adsorption (Table 1, entry 12). As a consequence of this improved adsorption, inversion of electrode polarity every 30 seconds was also required to minimize electrode fouling (Table 1, entry 23).

With suitable metal-free ring expansion conditions in hand (Table 1, entry 21), we sought to define the substrate scope using a variety of differently substituted cyclobutanols. These were readily synthesized through lithiation of the (hetero-) aromatics with n-butyllithium, followed by an addition to cyclobutanone (see Supporting Information). Based on the oxidation potential obtained from cyclic voltammetry studies for 1-phenylcyclobutan-1-ol 1b (E° = 1.5 V vs Fc⁺/Fc), we anticipated that our direct electrochemical ring expansion should also be compatible with a range of aromatic-substituted cyclobutanols. As shown in Scheme 2, our initial explorations into the scope subsequently focused on a range of aromatic-substituted cyclobutanols. To this extent, we were pleased to find that 1-phenylcyclobutan-1-ol 1b successfully underwent the ring expansion under our direct electrolysis conditions to 1-tetralone 2b in 28% yield. Following this result, we directed our studies toward investigating various electronic effects on the aromatic ring on the outcome of the reaction. Gratifyingly, when weakly activated naphthalene-derivative 1c was treated under our standard conditions, the desired tetralone 2c was produced in 36%, without the requirement for further purification. Equally, when the same ring expansion was scaled-up to a 1 mmol scale, to our delight, the desired product was formed in 69% yield, further proving the suitability of our method to environmentally friendly larger-scale syntheses. Strong resonance donors such as methoxy groups were also well-tolerated in the para- and meta-positions (2d and 2e). Tetralone 2e, however, was isolated as an inseparable equimolar mixture of regioisomers, resulting from unselective cyclization on the electronically activated ortho- and para-positions (with respect to the methoxy group). Similarly, weakly activating para-phenyl-substituted and para-fluorinated analogues 1f and 1g underwent the desired ring expansion in 30% and 68% yield, respectively. Next, we turned our attention to the scope of aromatic rings containing weakly deactivating substituents, such as para-bromo 1h and para-iodo groups 1i. Our investigations revealed that these para-halogenated aryl groups were also able to undergo a ring-expansion to form the tetralones 2h and 2i without concomitant electrochemical cathodic reduction of the aryl-halide bond.

At last, we defined the limitations of the direct anodically driven ring expansion reaction. Unsurprisingly, electron-deficient ortho-fluorinated and para-trifluoromethoxylated analogues 1j and 1k did not ring-expand under direct anodic oxidation conditions. We attribute this to the higher oxidation potential of electron-deficient aromatics due to the deepening HOMO. In the presence of 10 mol% of Mn(OTf)₃, however, the ring expansion was catalyzed successfully to obtain tetralones 2j and 2k in 13% and 20% yield, respectively. We hypothesize that in these cases the successful conversion hinges on the formation of a manganese-cyclobutanol complex.

Scheme 2. Scope of the regioselective electrochemical ring expansion of cyclobutanols to 1-tetralones; [a] Obtained as a 1 : 1 mixture of the ortho-cyclized and para-cyclized regioisomers (with respect to the methoxy group). [b] Reaction performed in presence of 0.1 eq of Mn(OTf)₃. 
with a lower oxidation potential. Additionally, more challenging heteroaromatic substrates, such as the benzothiophene analogue 11, N-tosylated indole-analogue 1m, fused cyclobutanol 1n, and the phenyl-substituted benzothiophene-analogue 1o failed to reliably ring-expand under the direct anodic oxidation conditions and only trace quantities of the desired products were isolated in each case. We found that the efficient ring expansion of these substrates could again be effected by the introduction of a manganese(II)-catalyst (10 mol%). Under indirect electrolysis conditions, the desired ring expansion to 21, 2m, 2n, and 2o was effected in 53%, 32%, 30%, and 36%, respectively. It is important to note that the β,γ-fused product 2n was produced as the sole regioisomer and the isomeric α,β-fused product was not observed. We attribute this observation to the higher stability of the transient secondary radical in comparison to a primary radical.

In order to conclude our study, we sought to investigate the mechanism for the direct anodic oxidative ring expansion (Scheme 3A). To this end, we found the role of the hydroxyl group in the underlying mechanism of particular interest. When the ether 3 was treated under our standard electrochemical ring expansion conditions in the absence of a catalyst, only trace conversion (<5% yield) to the desired ketone 2b was observed, with most of the starting material recovered. This indicated that the initiation of the reaction involves a single-electron oxidation of the alcohol moiety. On this basis, and in accordance with the literature, a plausible reaction mechanism for the direct electrochemical ring expansion is presented in Scheme 3B. We postulated that anodic single-electron oxidation would unveil the alkoxy radical cation A, as the hydroxyl group was found to be essential for the success of this reaction. The feasibility of direct electrochemical oxidation of benzylic alcohols was previously investigated. It is known that the most likely fate of carbinols such as A is a concerted β-scission of the C(sp²)–C(sp³) single bond which, in the absence of external scavengers, leads to an intramolecular addition to the aromatic system to form the six-membered ring B. This process is thermodynamically driven by the formation of a carbonyl group and a highly stabilized captodative radical B, as well as the release of ring strain from the four-membered ring. Finally, aromaticity can be restored through anodic overoxidation of the radical to the carboxylation, followed by an elimination. Concomitant proton reduction at the cathode would generate hydrogen gas. Substrates that require the addition of stoichiometric quantities of Mn(OTf)₃ for successful ring expansion will proceed through indirect electrochemical oxidation. Instead of direct anodic oxidation of the alcohol, the addition of Mn(OTf)₃ leads to the formation of a Mn(III)-alkoxide complex with a lower oxidation potential, which was observed in our cyclic voltammetry studies. This complex can be anodically oxidised to a Mn(III)-alkoxide species which can undergo an inner sphere electron transfer to form the alkoxide radical A and regenerate the Mn(II) catalyst.

In summary, the first electrochemical synthesis of 1-tetralones from cyclobutanols is reported. This provides the community with a rapid, mild, and functional-group tolerant procedure to access functionalized heteroaromatic and aromatic 1-tetralones. The effect of different substituents on the cyclobutanol as well as on the aromatic/heteroaromatic core was also evaluated. Based on our studies, we found that most substrates containing electron-donating groups and mildly electron-withdrawing substituents could ring-expand under direct anodic expansion conditions. Substrates with strongly electron-withdrawing substituents exhibited elevated oxidation potentials and required the addition of a manganese catalyst for successful ring expansion to occur.

**Acknowledgements**

The authors gratefully acknowledge an EPSRC Imperial College President’s Scholarship (to P.N.) and additional funding from Dr. Isabel Bader and her late husband Dr. Alfred Bader (to P.J.P.), Oxana Bennett (to P.J.P.), the University of Greenwich Vice Chancellor’s Ph.D. Scholarship (to A.P.), the Engineering and Physical Sciences Research Council (Grant EP/S017097/1 to K.L.) and IKA for their material support (to K.L.). The authors thank Dr.
Lewis Allen for proofreading this article and Dr. Matthew Leech for help with cyclic voltammetry studies. The authors also wish to thank Pete Haycock and Dr. Lisa Haigh for NMR and mass spectrometric analysis at Imperial College London, Dr. Iain Goodall, and Victoria Elmes for mass spectrometric and NMR analysis at the University of Greenwich, respectively. The authors dedicate this work to the late Horst Natho.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cyclobutanols · Electro catalysis · Ring expansion · Synthetic methods · Tetralones


Manuscript received: November 24, 2020
Revised manuscript received: December 13, 2020
Accepted manuscript online: December 16, 2020