Manganese-Catalyzed Electrochemical Deconstructive Chlorination of Cycloalkanols via Alkoxy Radicals

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Supporting Information Placeholder

ABSTRACT: A manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols has been developed. This electrochemical method provides access to alkoxy radicals from alcohols and exhibits a broad substrate scope, with various cyclopropanols and cyclobutanols converted into synthetically useful β- and γ-chlorinated ketones (40 examples). Furthermore, the combination of recirculating flow electrochemistry and continuous inline purification was employed to access products on gram scale.

Alkoxy radicals are highly transient species that exhibit diverse reactivity, including hydrogen atom transfer,‡ addition to π-systems and β-scission processes (Scheme 1A).‡ The generation of alkoxy radicals directly from aliphatic alcohols is challenging, partly due to the high dissociation energy of RO–H bonds (~105 kcal/mol). Hazelwood and coworkers developed recyclable catalytic approaches for alkoxy radical generation employing various radical precursors including peroxides, N-alkoxyphthalimides, N-alkoxybenzimidazoles, N-alkoxytriazoliums, and unprotected alcohols. Despite these important advances, many existing approaches require the use of pre-functionalized substrates, (super)stoichiometric reagents (generating waste/by-products) and/or precious metal (photo)catalysts.

Organic electrochemistry represents one of the cleanest possible chemical processing technologies, which has recently undergone a renaissance due partly to the increasing availability of standardized batch and flow electrochemical reactors. By careful tuning of electrochemical parameters, specific single electron transfer processes can be targeted, accessing powerful radical intermediates. Despite these characteristics, the development of an electrochemical method for the generation of alkoxy radicals from alcohols remains an unsolved problem. To this end, herein we report the manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols via alkoxy radical intermediates, accessing synthetically useful β- and γ-chlorinated ketones (Scheme 1C). Furthermore, by employing microreactor technology and recirculating flow, the electrochemical method can be performed on gram scale, with continuous inline purification incorporated.

To commence our studies, 1-phenylcyclobutan-1-ol 1 was selected as the model substrate (Table 1). After extensive optimization, it was found that an electrochemical system composed of MnCl2·4H2O (10 mol %) as catalyst, MgCl2 (5 equiv.) as chloride source and LiClO4 as supporting electrolyte in MeCN/AcOH (7:1, [I] = 0.05 M) using galvanostatic conditions (i = 10 mA, j_total = 7.8 mA/cm2, Q = 3.73 F/mol) and graphite electrodes at 25 °C for 3 h under N2 enabled the deconstructive chlorination of 1, giving γ-chlorinated ketone 2 in 82% NMR yield (entry 1). No conversion occurs in the absence of electricity or the manganese catalyst (entries 2 and 3). Employing a constant cell potential (E_cell = 2.4 V) or variation of the current (i = 12.5 mA or 7.5 mA) lowered the NMR yield of 2 (entries 4-6). Employing TBAPF6 as electrolyte (entry 7) or substituting the graphite cathode for Pt foil or Ni plate (entries 8 and 9) each had a negligible impact on conversion. However, upon evaluating alternative Mn(II) salts (entries 10 and 11), it was found that

Scheme 1. Context and Outline of Electrochemical Strategy

A) Bond dissociation energy (RO–H) and alkoxy radical reactivity

B) Generation of alkoxy radicals

C) Mn-catalyzed electrochemical deconstructive chlorination (this work)
Table 1. Optimization of Electrochemical Process

| entry | variation from “standard” conditions | yield (%) |
|-------|-----------------------------------|-----------|
| 1     | none                              | 82        |
| 2     | no electricity                    | < 2       |
| 3     | no MnCl₂, 4H₂O                    | < 2       |
| 4     | Eₐsc = 2.4 V                       | 66        |
| 5     | i = 12.5 mA, Jₐsc = 9.8 mA/cm²    | 74        |
| 6     | i = 7.5 mA, Jₐsc = 5.9 mA/cm²     | 80        |
| 7     | TBAPF₆ instead of LiClO₄          | 82        |
| 8     | Pt foil cathode instead of graphite | 82       |
| 9     | Ni plate cathode instead of graphite | 75      |
| 10    | Mn(OAc)₂, 4H₂O instead of MnCl₂, 4H₂O | 82    |
| 11    | Mn(OTf)$_₂$ instead of MnCl₂, 4H₂O | 97 (78)  |

*Reactions performed with 0.3 mmol of cyclobutan-1 using the ElectraSyn 2.0 batch electrochemical reactor. [*] = 0.05 M. *Yield after 3 h as determined by $^1$H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. *1 hour 36 minutes reaction time.

97% conversion was obtained using Mn(OTf)$_₂$ as catalyst, which was adopted for further optimization. Employing LiCl or NaCl as the chloride source was detrimental to conversion, presumably due to decreased solubility in MeCN/AcOH (entries 12 and 13). Gratifyingly, the quantities of MgCl₂ and Mn(OTf)$_₂$ could be lowered to 2 equivalents and 5 mol %, respectively, without significant reduction in conversion (entries 14 and 15). A Faradaic efficiency of 67% was obtained when 2 F/mol of charge was passed (entry 16), which indicated that most of the electricity passing through the cell is utilized productively.

The full scope of the electrochemical process was explored starting with the deconstructive chlorination of cyclobutane to form γ-functionalized ketones (Scheme 2A). From the outset, it was found that 1-arylcylobutan-1-1-ols containing aromatic systems with electron-releasing groups at the 2- or 4-positions (e.g. 4-/Bu) or extended π systems (e.g. 4-Ph) undergo decompositional decomposition using the optimized reaction conditions (Table 1, entry 11). This instability was attributed to ionization of the C–OH bond in the presence of Brensted and/or Lewis acids, forming stabilized carbocations that are unproductive for the desired transformation. In such cases, this issue was addressed by employing syringe pump addition of the substrate over 2 h and using TBAOAc as the supporting electrolyte. With a choice of two suitable reaction conditions in hand, a variety of 1-arylcylobutan-1-1-ols were converted to the corresponding γ-chlorinated ketone products in good to excellent isolated yields (products 2–20). Within the aryl unit, various alkyl and aryl substitution was tolerated at the 4-, 3- and 2- positions in addition to halides and electron-withdrawing substituents (e.g. 4-CF₃). The electrochemical method exhibits good functional group tolerance as demonstrated by the presence of aldehyde, carboxylic acid, methyl ester, primary amide, nitrile, benzyl primary alcohol and silyl ether functionalities present within products 14-20. A selection of 1-alkylcylobutan-1-1-ols were also converted into the corresponding γ-chlorinated ketones in good isolated yields (products 21-26). Benzo fused cyclobutan-1-1-ols participated in deconstructive chlorination, giving benzyl chloride products 27-31, including the formation of 7-, 8-, 9- and 10-membered rings. This strategy was also applied to the formation of disubstituted cycloheptane 32 in 77% isolated yield. Additional substitution at the 2- and 3-positions of the cyclobutanol was tolerated, accessing γ-chlorinated ketones 33-35 in high yields. We also investigated the deconstructive chlorination of cyclopropanols (Scheme 2B). Gratifyingly, it was found that a representative selection of 1-arylcyclopropan-1-ols and 1-alkylycyclopropan-1-ols could be readily converted to the corresponding β-chlorinated ketones in good yields (36-39). Additional substitution is tolerated within the cyclopropanol, giving secondary radical derived product 40 as the major regioisomer. Furthermore, bicyclo[4.1.0]heptan-1-1-ol was converted to 3-chlorocycloheptan-1-one 41 in 48% isolated yield. At the current stage of development, the electrochemical method does not tolerate larger ring sizes with reduced ring strain. For example, despite assessing various reaction conditions, 1-phenylcyclopentan-1-ol underwent decomposition, whereas 1-phenylcyclobutan-1-ol was unreactive.

In order to demonstrate scalability, the batch process was translated to a flow electrochemical setup. Employing the commercially available Ammonite8 flow reactor, a variety of reaction parameters were evaluated including electrolyte loading, temperature, solvent ratio, residence time, charge and mixing efficiency (Scheme 2C). However, using MnCl₂, 4H₂O (10 mol %) as catalyst, the conversion to 2 could not be increased beyond 20% using single-pass flow electrochemistry. The yield was increased by applying the optimized reaction parameters to a recirculating flow electrochemical setup, which provided access to 2 in 84% isolated yield (Scheme 2D). Advantageously, due to the decreased distance between the electrodes in flow, a supporting electrolyte was not required. Furthermore, by employing a 6-port 2-position switching valve, the flow could be redirected from recirculation to continuous inline purification (Scheme 2E). Once the electrochemical reaction was complete, the valve was switched from position 1 to position 2 to redirect the flow into the path of work-up solvents. The flow was passed through a mixing unit before entering a liquid/liquid phase separator containing a hydrophobic membrane that allowed separation of the organic layer, which was subsequently dried over MgSO₄, filtered and concentrated in vacuo to provide 1.2 g of product. This flow setup, which combines recirculating flow electrochemistry and continuous inline purification for the first time, enabled the electrochemical process to be performed on gram scale.

Cyclic voltammetry was employed in order to gain mechanistic insight into the electrochemical process. In accordance with the literature, the combination of Mn(OTf)$_₂$ and MgCl₂ produced a new quasi-reversible redox event at 0.8 V vs Fe/Fe$^+$, which provided evidence for the formation of a Mn(II)X₂Cl species from [Mn(II)X₂Cl]$.^1^$ Furthermore, a small increase in current was observed upon addition of 1-phenylcylobutan-1-1-ol 1, which suggested that Mn(III)X₂Cl is consumed by 1. When methyl ether cyclobutane 42 was employed as the substrate using the standard electrochemical reaction conditions, no γ-chlorinated ketone 2 was observed, with 82% starting material recovered (Scheme 3A). This indicated that the proposed
Scheme 2. Substrate Scope — Batch and Flow Electrochemistry

A) \(\gamma\)-chlorinated ketones

| Substrate | Product | Yield |
|-----------|---------|-------|
| ![Image](https://example.com/image1.png) | ![Image](https://example.com/image2.png) | 2. R = H, 78% |
| | | 3. R = 4-t-Bu, 80% |
| | | 4. R = 4-Me, 76% |
| | | 5. R = 3-Me, 44% |
| | | 6. R = 2-Me, 43% |
| | ![Image](https://example.com/image3.png) | 7. R = 4-Ph, 41% |
| | | 8. R = 4-I, 62% |
| | | 9. R = 4-Br, 73% |
| | | 10. R = 4-Cl, 90% |
| | | 11. R = 4-F, 84% |
| | ![Image](https://example.com/image4.png) | 12. R = 4-CF<sub>3</sub>, 67% |
| | | 13. R = 4-OCF<sub>3</sub>, 61% |
| | | 14. R = 4-CHO, 35% |
| | | 15. R = 4-CO<sub>2</sub>H<sub>3</sub>, 47% |
| | | 16. R = 4-CO<sub>2</sub>Me, 57% |
| ![Image](https://example.com/image5.png) | ![Image](https://example.com/image6.png) | 17. R = 4-C(O)(OMe)<sub>2</sub>, 61% |
| ![Image](https://example.com/image7.png) | ![Image](https://example.com/image8.png) | 18. R = 4-CN, 40% |
| ![Image](https://example.com/image9.png) | ![Image](https://example.com/image10.png) | 19. R = 4-CH=OH, 58% |
| ![Image](https://example.com/image11.png) | ![Image](https://example.com/image12.png) | 20. R = 4-CH<sub>2</sub>OTBS, 47% |

B) \(\beta\)-chlorinated ketones

| Substrate | Product | Yield |
|-----------|---------|-------|
| ![Image](https://example.com/image13.png) | ![Image](https://example.com/image14.png) | 21. R = Et, 57% |
| | | 22. R = n-Bu, 60% |
| | | 23. R = n-Hex, 47% |
| | | 24. R = o-Hex, 42% |
| | | 25. R = Bn, 68% |
| | | 26. R = CH<sub>2</sub>Bn, 65% |
| | ![Image](https://example.com/image15.png) | 27. 30% |
| | | ![Image](https://example.com/image16.png) |
| ![Image](https://example.com/image17.png) | ![Image](https://example.com/image18.png) | 28. n = 1, 54% |
| ![Image](https://example.com/image19.png) | ![Image](https://example.com/image20.png) | 29. n = 2, 42% |
| ![Image](https://example.com/image21.png) | ![Image](https://example.com/image22.png) | 30. n = 3, 53% |
| ![Image](https://example.com/image23.png) | ![Image](https://example.com/image24.png) | 31. n = 4, 51% |

C) Parameter assessment - single-pass flow electrochemistry

- MnCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %)
- MgCl<sub>2</sub> (5 equiv.)
- LiClO<sub>4</sub> (mol %) in MeCN:AcOH
- MnCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %)
- MgCl<sub>2</sub> (5 equiv.)
- LiClO<sub>4</sub> (mol %) in MeCN:AcOH

- C<sub>(+)</sub> (1) C<sub>(-)</sub>

- 1 mL
- 20% conversion
- electrolyte loading
- solvent ratio
- charge (Q)
- temperature
- residence time
- mixing efficiency (k, calc.)

D) Yield optimization - recirculating flow electrochemistry

- fixed parameters:
  - 2.5 mL/min, 25°C
  - 400 mA
  - MnCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %)
  - MgCl<sub>2</sub> (5 equiv.)
  - LiClO<sub>4</sub> (mol %)

- MnCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %)
- MgCl<sub>2</sub> (5 equiv.)
- LiClO<sub>4</sub> (mol %)

- C<sub>(+)</sub> (1) C<sub>(-)</sub>

- 1 mL
- 84% Cl

E) Inline purification - recirculating flow electrochemistry + liquid/liquid extraction module

fixed parameters:
- 2.5 mL/min, 25°C
- MnCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %)
- MgCl<sub>2</sub> (5 equiv.)
- LiClO<sub>4</sub> (mol %)
- MeCN:AcOH (7:1)

- k = 1.13 x 10<sup>2</sup>

Reactions performed with 0.3 mmol of cycloalkanol using the ElectraSyn 2.0 batch electrochemical reactor with isolated yields after chromatographic purification quoted unless stated otherwise. Cycloalkanol was added over 2 h via syringe pump, TBAOAc (0.1 M) as electrolyte; TBAOAc (0.1 M) as electrolyte; yield as determined by 1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard; 6 h
In conclusion, we have developed a first electrochemical method for alkyl radical generation from alcohols and utilized this for the manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols. The method is applicable across various cyclopropanols and cyclobutanols, accessing a broad range of synthetically useful \( \beta \)- and \( \gamma \)-chlorinated ketones (40 examples). Furthermore, the combination of recirculating flow electrochemistry and continuous inline purification was employed to access products on gram scale. Ongoing studies are focused on further applications of earth-abundant transition metals in synthetic organic electrochemistry and these results will be reported in due course.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXX. Optimization data, experimental procedures, characterization of new compounds and spectral data (PDF)

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BDWA and MDH contributed equally to this work.

NOTES

The authors declare no competing financial interest.

Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/XXXX (accessed XXXX).

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