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Seminormal-BrCH₂CH₂OH-mediated electrochemical epoxidation of unactivated olefins†

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An electrochemical epoxidation of unactivated olefins using water as the source of oxygen atoms has been developed. The epoxidation reaction employs seminormal-BrCH₂CH₂OH as the mediator, which shows good functional group compatibility, and can easily be performed on the gram scale. A wide range of unactivated olefins could be tolerated to give the functionalized epoxides with satisfactory results at room temperature.

Introduction

Epoxides fulfill a plethora of important roles in the fields of synthetic chemistry, pharmaceutical science and materials science.¹ Olefins are some of the most common organic molecules and are widely used in organic synthesis because of their abundant source, easy availability and diverse reactivity.² The direct epoxidation of olefins provides an efficient method for rapidly increasing the complexity of molecules to obtain epoxides.³ In this regard, olefin epoxidation has been extensively explored using stoichiometric oxidants⁴ such as O₂, H₂O₂, *m*-CPBA, *etc.* However, these reported methods are frequently limited by their drawbacks such as severe conditions, low efficiency, poor atom economy and huge amounts of waste. Therefore, the development of oxidant-free olefin epoxidation methods is highly desirable.

As a green synthetic technology, organic electrochemistry⁵ uses electrons as reagents and avoids the addition of redox reagents, which has attracted more and more attention.⁶ The electrochemical epoxidation of olefins has been performed by direct electrolysis or indirect electrolysis. Direct electrochemical epoxidation of olefins could be achieved at high current density (Scheme 1a).⁷ Metal [*e.g.* Mn and Fe]⁸ and iminium salt-catalyzed⁹ routes for the epoxidation of styrenes

or cyclic alkenes have been reported in recent years. Halides are cheap and readily available activated reagents to achieve electrochemical transformations.¹⁰ Halides (*e.g.* NaCl, KCl, NaBr, *n*-Bu₄NBr and *n*-Bu₄NI) facilitated electrochemical epoxidation of alkenes and demonstrated good efficiency and universality with water as the source of oxygen atoms, but excess halides or activated olefins are often necessary for these transformations (Scheme 1b).¹¹ For example, in 2020, the chloride-mediated electrosynthesis of ethylene and propylene oxides with high selectivity and efficiency at high current density was reported by Sargent.¹² In 2022, Zai described a NaBr- and oxygen redox species-mediated selective electrochemical epoxidation of styrenes using a CoS₂/CoS modified graphite felt as

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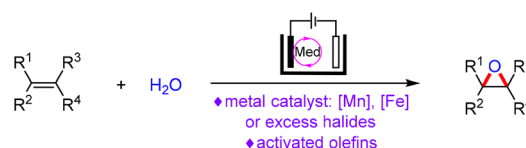
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Previous work:

(a) Direct electrochemical epoxidation of olefins

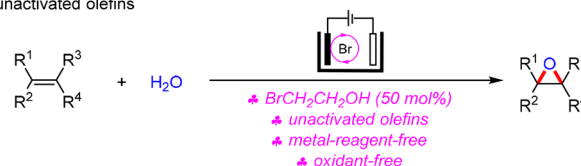


(b) Indirect electrochemical epoxidation of olefins



This work:

(c) Seminormal-BrCH₂CH₂OH-mediated electrochemical epoxidation of unactivated olefins



Scheme 1 Electrochemical epoxidation of olefins.

the anode.¹³ While we were preparing the article, Qiu and co-workers reported a metal-free electrochemical dihydroxylation and epoxidation of unactivated alkenes using Et₄Ni (2 equiv.) and NH₄I (2 equiv.) at 50 mA and 50 °C for 12 h.¹⁴

Although much progress has been made in this field, a mild and efficient approach for the electrochemical epoxidation of unactivated olefins is still worth exploring.¹⁵ Recently, our group found that BrCH₂CH₂OH is an effective brominating reagent to achieve the bromination of arenes and alkenes.¹⁶ Inspired by the above progress and our interest in electrochemistry,¹⁷ we herein developed a facile and versatile electrochemical approach for the epoxidation of unactivated olefins with seminormal-BrCH₂CH₂OH as the mediator and water as the source of oxygen atoms (Scheme 1c). This reaction provides a general route for the electrosynthesis of unactivated epoxides with good selectivity and efficiency under metal reagent-free and oxidant-free conditions, and is also highly complementary to previously reported methods.

At the beginning, we screened the reaction conditions for the electrochemical epoxidation of alkene **1**. The reaction was carried out at 3 mA for 6 h in an undivided cell with reticulated vitreous carbon (RVC) as the anode and a platinum sheet as the cathode (Table 1). (3,3-Dimethyloxiran-2-yl)methyl benzoate (**2**) was isolated in 83% yield under the standard conditions using BrCH₂CH₂OH (50 mol%) as the mediator, *n*-Bu₄NBF₄ as an electrolyte and K₃PO₄ as a base in MeCN/H₂O (6 : 1) at room temperature (Table 1, entry 1). Inorganic bromides such as NaBr (Table 1, entry 2) and KBr (Table 1, entry 3) were tested and lower yields were observed. The yield of **2**

slightly increased to 85% when employing 1 equivalent of BrCH₂CH₂OH (Table 1, entry 4). Upon decreasing the equivalent of BrCH₂CH₂OH to 0.2, the formation of **2** was suppressed (Table 1, entry 5). The product **2** was not obtained in the absence of BrCH₂CH₂OH (Table 1, entry 6). Bromide-catalyzed epoxidation was still not achieved although great efforts were made. After removing K₃PO₄ or *n*-Bu₄NBF₄, 26% and 36% yields of **2** were generated (Table 1, entries 7 and 8). The reaction solvents were then investigated by adjusting the ratio of MeCN and H₂O in mixed solvents. When MeCN/H₂O (13 : 1) or MeCN/H₂O (5 : 2) was used, electrochemical epoxidation occurred with low efficiency (Table 1, entries 9 and 10). Trace amounts of the product **2** were detected when applying MeCN as the reaction solvent (Table 1, entry 11). No product was formed in the absence of electricity (Table 1, entry 12).

After the reaction conditions were determined, the substrate scope for the electrochemical epoxidation was explored (Scheme 2). We found that this method could be compatible with a variety of ester-linked olefins containing common functional groups such as H (**2**, 83% yield), F (**3**, 71% yield), Br (**4**, 85% yield) and Ph (**5**, 63% yield) at the *ortho*-position of the aromatic rings. Substrates with a *para*-substituent including OMe (**6**, 57% yield), CF₃ (**7**, 69% yield) and NO₂ (**8**, 64% yield) groups were applicable for the electrochemical epoxidation. (3,3-Dimethyloxiran-2-yl)methyl 2,4,6-trimethylbenzoate (**9**) was obtained in 54% yield under electrochemical epoxidation conditions. Substrates attached with naphthalene or pyridine were tolerated to give epoxides **10** and **11** in 56% and 72% yields, respectively. The electrochemical epoxidation could selectively occur in an electron-rich alkenyl moiety rather than an alkynyl or alkenyl moiety connected to a carbonyl group, producing **12** and **13** with acceptable efficiency. The ibuprofen derivative **14** containing an epoxy group was formed in 57% yield under the standard conditions. Epoxide **15** containing an amino acid fragment could also be quickly prepared. Furthermore, different types of olefin structures were investigated. The corresponding epoxy products were prepared in satisfactory yields by electrochemical epoxidation of 1,1-disubstituted alkenes (**16** and **17** in 74% and 72% yields, respectively), 1,2-disubstituted alkenes (**18** and **19**, 52 and 54% yields, respectively) and monosubstituted alkenes (**20–23**, 48–63% yields).

Subsequently, the electrochemical epoxidation of substrates bearing amides and sulfonamides was examined. However, epoxide **24** was only obtained in a yield of 36% under standard conditions. By increasing the amounts of BrCH₂CH₂OH to 2 equivalents, the yield of **24** was improved to 92%. A series of amide-containing epoxides (**24** and **25**, 92% and 58% yields, respectively) and sulfonamide-containing epoxides (**26–29**, 31–60% yields) were synthesized in moderate to good yields, in which the active NH group could be well compatible. Additionally, the electrochemical epoxidation of styrenes, cycloolefins, and α,β-unsaturated ketones was tested, and the production of the corresponding epoxides was either inefficient or entirely unsuccessful. Detailed information on the unsuccessful substrates is provided in the ESI.†

Table 1 Optimization of the reaction conditions^a



Entry	Variation from the standard conditions	Yield ^b (%)
1	None	83 ^c
2	NaBr (0.5 equiv.)	61
3	KBr (0.5 equiv.)	60
4	BrCH ₂ CH ₂ OH (1 equiv.)	85
5	BrCH ₂ CH ₂ OH (0.2 equiv.)	60
6	No BrCH ₂ CH ₂ OH	0
7	No K ₃ PO ₄	26
8	No <i>n</i> Bu ₄ NBF ₄	36
9	MeCN/H ₂ O (13 : 1) as solvent	57
10	MeCN/H ₂ O (5 : 2) as solvent	63
11	MeCN as solvent	Trace
12	No electricity	0

^a Reaction conditions: RVC anode, Pt cathode, undivided cell, **1** (0.2 mmol), BrCH₂CH₂OH (50 mol%), K₃PO₄ (0.24 mmol), *n*Bu₄NBF₄ (0.1 mmol), MeCN (6 mL), H₂O (1 mL), rt, 3 mA, 6 h (3.3 F mol⁻¹).

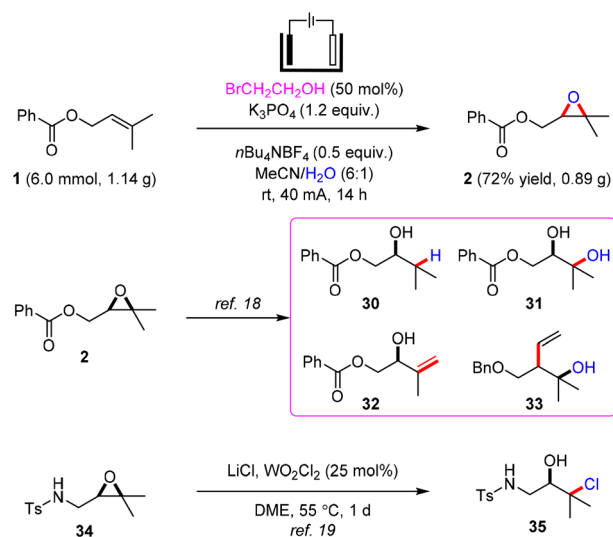
^b Yield was determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

^c Isolated yield.



Scheme 2 Scope of the electrochemical epoxidation [reaction conditions: RVC anode, Pt cathode, undivided cell, alkene (0.2 mmol), BrCH₂CH₂OH (50 mol%), K₃PO₄ (0.24 mmol), nBu₄NBF₄ (0.1 mmol), MeCN (6 mL), H₂O (1 mL), rt, 3 mA, 6 h (3.3 F mol⁻¹); isolated yields of the products]. ^a BrCH₂CH₂OH (2 equiv.) was used.

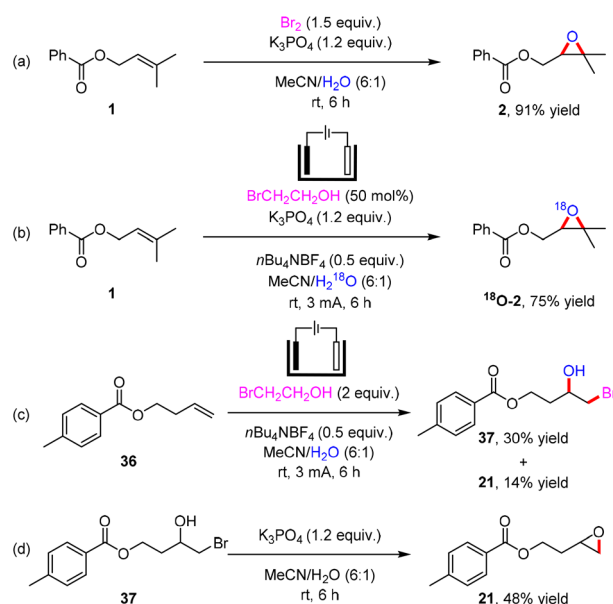
To further highlight the availability of electrochemical epoxidation, the gram-scale electrolysis of **1** was conducted on a 6 mmol scale at a constant current of 40 mA and room temperature for 14 h (Scheme 3). 0.89 g of epoxy product **2** was



Scheme 3 Gram-scale electrolysis and reported transformations.

obtained in 72% yield under simple electrolysis conditions. The epoxy product **2** could undergo diverse transformations into highly functionalized complex structures **30–33** via a ring-opening reaction according to the reported methods.¹⁸ The regioselective chlorination of 2,3-epoxy sulfonamide **34** was achieved by the Yamamoto group, which then gets converted into chloroaminoalcohol **35**.¹⁹

To clarify the reaction process, control experiments were performed (Scheme 5). 91% yield of **2** was formed with Br₂ as the activated reagent without electricity (Scheme 4a), showing that the success of the reaction probably depends on the generation of Br₂ *in situ*. ¹⁸O-**2** was primarily obtained in 75% yield when using H₂¹⁸O instead of H₂O (Scheme 4b), indicating that



Scheme 4 Control experiments.



Scheme 5 Proposed mechanism.

the oxygen atom in the epoxy group of the product comes from water. Moreover, the bromohydroxylation product 37 was afforded in 30% yield by electrolyzing 36 without K_3PO_4 and epoxy product 21 was detected in 14% yield (Scheme 4c), supporting that the epoxidation involves a bromohydroxylation process. In addition, the epoxidation product 21 could be obtained from 37 in 48% yield with K_3PO_4 in a solution of MeCN/ H_2O . The addition of K_3PO_4 could facilitate the conversion of the bromohydroxylation intermediate to the epoxidation product.

Based on the above-mentioned findings, cyclic voltammograms (Fig. S3–S5, in the ESI†) and previous research studies,^{11,14,16} a possible mechanism for the electrochemical epoxidation is proposed (Scheme 5). At first, Br^- is produced by the cathodic reduction and nucleophilic cyclization of $BrCH_2CH_2OH$ through ethylene oxide and H_2 evolution, and then is oxidized at the anode to form Br_2 *in situ*. Subsequently, alkenes 38 react with Br_2 *via* electrophilic addition to generate bromonium ions 39, which are trapped by water to give bromohydroxylation intermediates 40.²⁰ Finally, the K_3PO_4 -facilitated intramolecular epoxidation of 40 yields the target products 41 with the release of Br^- and K_2HPO_4 . The anodic oxidation of Br^- preferentially occurred due to the oxidation potential of Br^- ($E_{p/2} = 0.77$ V *vs.* Ag/AgCl) being obviously lower than that of substrate 1 ($E_{p/2} = 2.10$ V *vs.* Ag/AgCl) and substrate 2 ($E_{p/2} \geq 2.17$ V *vs.* Ag/AgCl), supporting our proposed mechanism shown in Scheme 5. The low concentration of Br^- is anodized to regenerate Br_2 to allow the reaction to proceed smoothly under seminormal bromine source conditions and effectively avoid the dibromination of olefins.²¹

Conclusions

In conclusion, we have developed an electrochemical epoxidation of unactivated olefins with seminormal- $BrCH_2CH_2OH$

as the mediator and water as the oxygen atom source. The method is performed at room temperature in a simple undivided cell and shows good functional group tolerance. A series of functionalized epoxides are obtained in moderate to good yields without the need for metal reagents and oxidants. Further efforts on halogen-catalyzed electrochemical epoxidation of unactivated olefins are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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