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Low-Voltage-Driven Electrochemical Aerobic Oxygenation with Flavin Catalysis: Chemoselective Green Synthesis of Sulfoxides from Sulfides

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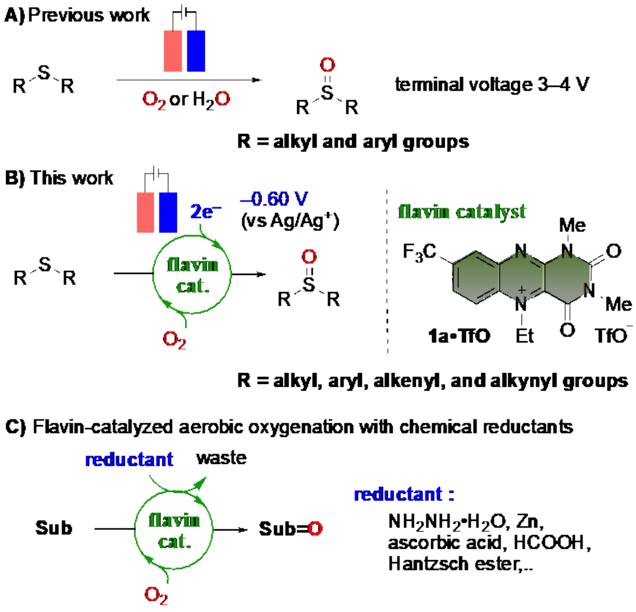
Abstract: The chemoselective electrochemical oxygenation of sulfides to sulfoxides is performed using a biomimetic flavin catalyst that enables the efficient activation of molecular oxygen under a low cathode potential. Diverse functional groups, including alcohols, ketones, aldehydes, cyclopropane, carboxylic acids, pyridine, alkenes, and alkynes, are well tolerated under mild low-voltage electrolytic conditions.

Keywords: Organocatalysis; Oxygenation; Electrochemistry; Flavin; Sulfide

Organosulfur compounds are privileged functional molecules widely found in numerous pharmaceuticals,[1] natural products,[2] and polymeric functional materials.[3] In particular, sulfoxides act as ligands for transition-metal catalysis[4] and synthetic intermediates for various bond-forming reactions[5] and rearrangements.[6] Sulfide oxygenation is the simplest and most popular method for the synthesis of sulfoxides; however, it is often limited by problems related to the use of stoichiometric amounts of oxidants, which are characterized by high volatility and cost, excessive waste generation, and poor chemoselectivity.[7]

Electrochemical synthesis is generally considered an alternative green methodology for traditional synthesis techniques, which require the use of harmful external oxidants and reductants.[8] Several electrochemical methods in which molecular oxygen (O_2) and water are employed as eco-friendly oxygen sources for the green synthesis of sulfoxides from sulfides have recently been developed (Scheme 1A).[9] For instance, in 2017, Noël and co-workers reported the selective electrochemical oxygenation of sulfides using water at a terminal voltage of 2.5–4.0 V.[9a] Very recently, Jiao and co-workers demonstrated a novel strategy for the aerobic oxygenation of sulfides by using a Ni(II) catalyst for O_2 activation with the help of electricity.[9b] These electrochemical sulfoxidation reactions do not utilize toxic and harmful reagents and are atom economical; thus, they are attractive approaches from the viewpoint of green and sustainable chemistry.[9] However, the electrochemical process of these reactions requires an applied voltage of approximately 3–4 V for direct O_2 or water activation.[9a,c] This necessity presents difficulties in promoting the chemoselective oxygenation of sulfides in the presence of reactive functional moieties such as unsaturated hydrocarbons, which are generally unstable in radical and oxidative reaction conditions.

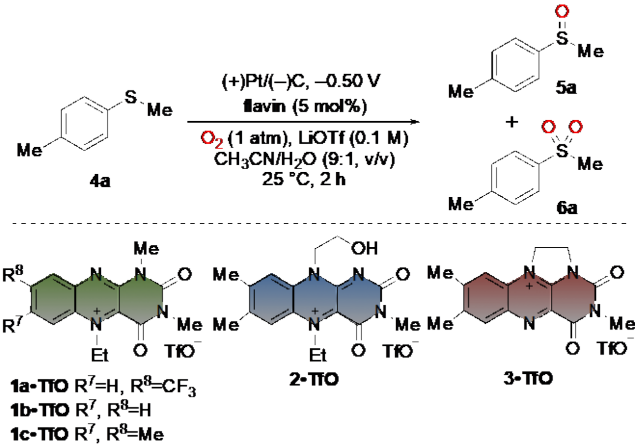


Scheme 1. (A) Previous and (B) present electrochemical methods for the oxygenation of sulfides. (C) Conventional flavin-catalyzed aerobic oxygenation using chemical reductants.

Herein, we propose a novel low-voltage-driven electrochemical process to realize highly chemoselective oxygenation under transition-metal-free conditions using a cationic flavin catalyst and O_2 (air), which is widely recognized as an atom-economical, sustainable, cost-effective, and minimally polluting oxidant.[10] In this system, we used a mono-oxygenase-mimicking flavin organocatalyst that can mildly activate O_2 via an electron supply with a controlled low cathode potential of −0.60 V (vs Ag/Ag$^+$); such a system avoids direct O_2 or water activation at relatively high potentials, which results in undesirable side reactions (Scheme 1B). We successfully applied this system to achieve environmentally friendly aerobic sulfoxidation, in which sulfides bearing alkene and alkyne functionalities were chemoselectively converted to the corresponding sulfoxides without substantial side reactions. Cationic flavins mimicking the function of flavin monooxygenase[11] have received increased attention as unique biomimetic organocatalysts for various oxygenation reactions using O_2, in which the catalytically generated hydroperoxy flavins act as the oxidatively active species.[12-14] Although flavin-oxygenation reactions generally show high chemoselectivity, such aerobic processes consistently require a stoichiometric amount of chemical reductants, such as hydrazine,[12a,e] zinc,[12b] ascorbic acid,[12d] formic acid,[12f] and Hantzsch ester[12c] (Scheme 1C). A different approach that has been developed is aerobic sulfide photooxygenation, in which neutral flavins catalyze the formation of the oxidatively active species, singlet oxygen.[15] However, an electrochemical method for flavin-catalyzed sulfoxidation has never been adopted despite the expected high chemoselectivity of this aerobic process.

We initially elucidated the effect of various cationic flavins (**1**–**3**) on the electrochemical oxygenation of **4a**, which was carried out under O_2 (1 atm, balloon) at 25 °C for 2 h in CH_3CN/H_2O solution (9:1, v/v) containing LiOTf as the electrolyte (Table 1). Electrolysis was conducted at a constant potential (−0.50 V vs Ag/Ag$^+$) in an undivided cell consisting of a graphite carbon working electrode, a Pt counter electrode, and Ag/Ag$^+$ reference electrodes. Cationic flavins are known to undergo two-electron reduction.[16] The redox potentials of the flavin catalysts, E_1 and E_2, which were determined by cyclic voltammetry (CV) in a solution of CH_3CN (1.0 mM), are also shown in Table 1. Among the three riboflavin-derived cationic flavin catalysts used in our studies, viz. 5-ethyl alloxazinium **1c•TfO**, 5-ethyl isoalloxazinium **2•TfO**, and 1,10-bridged alloxazinium **3•TfO**,[16c] **1c•TfO** showed the highest yield of the corresponding sulfoxide **5a** (entries 3–5). To investigate the substituent effects of R^7 and R^8, we synthesized more electron-deficient 5-ethyl alloxaziniums, i.e. 8-trifluoromethyl-substituted **1a•TfO** and 7,8-unsubstituted **1b•TfO**, with redox potentials that were more positive relative to those of 7,8-dimethyl substituted **1c•TfO**. The most electron-deficient alloxazinium, **1a•TfO**, afforded higher yields than **1b•TfO** or **1c•TfO**, which clearly indicates that flavin redox catalysis plays a crucial role in the present electrochemical sulfoxidation system (entries 1–3). In sharp contrast to the 72% yield afforded by **1a•TfO**, the yield of the reaction conducted without the flavin catalyst was extremely low (4% yield, entry 6). This finding supports the notion that **1a•TfO** efficiently catalyzes the oxygenation of **4a** by electron transfer from the electrode. This reaction is the first example of flavin-catalyzed electrochemical aerobic oxygenation.

Table 1. Redox potentials of flavin catalysts and their effect on the electrochemical oxidation of **4a**.[a]



1a•TfO R^7=H, R^8=CF_3
1b•TfO R^7, R^8=H
1c•TfO R^7, R^8=Me

Entry	Flavin	E_1 [V vs Fc/Fc$^+$][b]	E_2 [V vs Fc/Fc$^+$][b]	Conv. [%][c]	Yield of 5a [%][c]	Yield of 6a [%][c]
1	**1a•TfO**	–0.168	–0.986	100	72	0
2	**1b•TfO**	–0.326	–1.13	57	30	0
3	**1c•TfO**	–0.425[d]	–1.19[d]	65	28	0
4	**2•TfO**	–0.136[d]	–0.764[d]	32	7	0
5	**3•TfO**	–0.654[d]	–1.65[d]	28	17	0
6	–	–	–	21	4	0

[a] Conditions: **4a** (0.1 M), flavin (5mol%), LiOTf (0.1 M), and CH_3CN/H_2O (9:1, v/v) in an undivided cell under constant-voltage electrolysis (–0.50 V vs Ag/Ag$^+$) with O_2 (1 atm) at 25 °C for 2 h. [b] The electrochemical potentials (E_1 and E_2) of each flavin were determined by the relationship $E = (E^p{}_c + E^p{}_a)/2$ relative to Fc/Fc$^+$. [c] The conversion rate and yield were determined by gas chromatography using biphenyl as an internal standard. [d] From ref. 16c.

Further optimization of the electrodes (entries 1 and 8–10, Table S1), reduction potential (entries 1 and 11–13), and electrolyte (entries 1 and 14–17) revealed that sulfoxidation could proceed to afford the corresponding products in 98% yield at −0.60 V (vs Ag/Ag$^+$) using KCl as the electrolyte (entry 1, Table 2). The reaction conducted without electricity or O_2 did not occur (entries 2 and 3). The yield of **5a** decreased with the decrease in water content in CH_3CN and reached 6% in dry CH_3CN (entries 4–6). Water is necessary for the proposed reaction system because it functions as a proton donor.

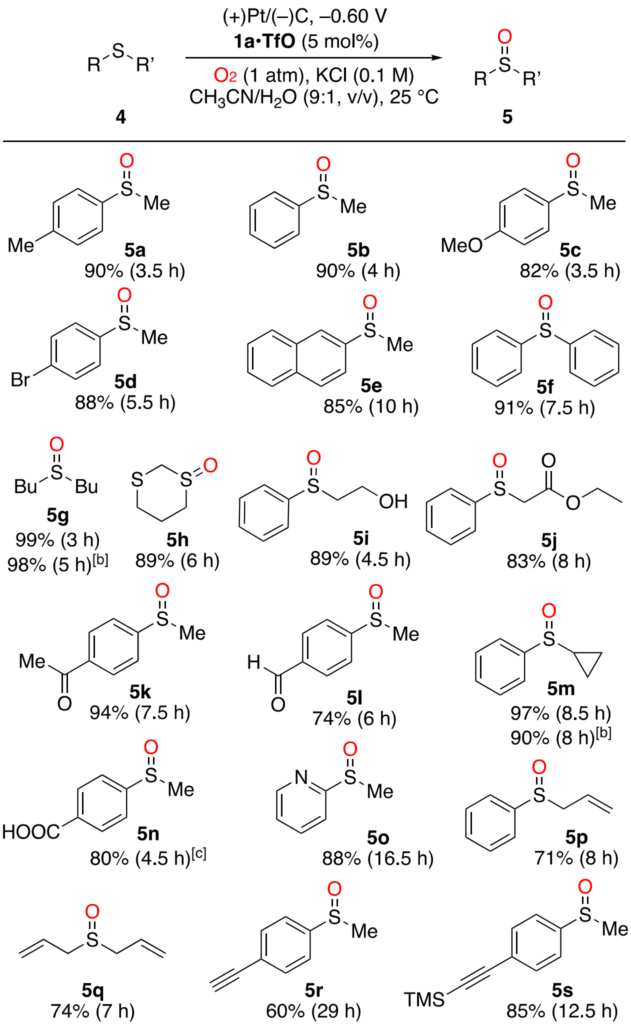
Table 2. Optimization of the reaction conditions.[a]

$$\textbf{4a} \xrightarrow[\text{O}_2\text{ (1 atm), KCl (0.1 M)} \atop \text{solvent, 25 °C, 2 h}]{\text{(+)Pt/(–)C, –0.50 or –0.60 V} \atop \textbf{1a•TfO}\text{ (5 mol\%)}} \textbf{5a}$$

Entry	Voltage [V]	Solvent	Conv. [%][b]	Yield of **5a** [%][b]
1	–0.60	CH_3CN/H_2O (9:1)	98	98
2	none	CH_3CN/H_2O (9:1)	0	0
3[c]	–0.60	CH_3CN/H_2O (9:1)	16	5
4[d]	–0.50	CH_3CN/H_2O (9:1)	100	72
5[d]	–0.50	CH_3CN/H_2O (49:1)	100	47
6[d]	–0.50	dry CH_3CN	40	6

[a] Conditions: **4a** (0.1 M), **1a•TfO** (5 mol%), KCl (0.1 M), and solvent in an undivided cell under constant-voltage electrolysis (–0.50 or –0.60 V vs Ag/Ag$^+$) with O_2 (1 atm) at 25 °C for 2 h. [b] The conversion rate and yield were determined by gas chromatography using biphenyl as an internal standard. [c] Under N_2 (1 atm). [d] LiOTf was used as the electrolyte.

Table 3. Substrate scope for the electrochemical flavin-catalyzed oxidation of sulfides.[a]

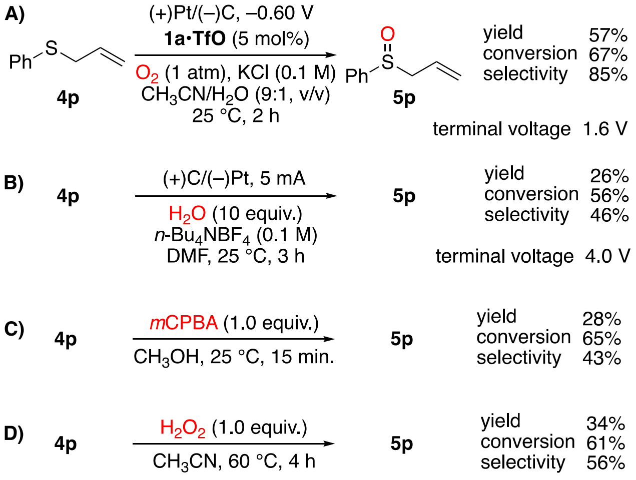


[a] Conditions: **4** (0.1 M), **1a•TfO** (5 mol%), KCl (0.1 M), and CH_3CN/H_2O (9:1, v/v) under constant-voltage electrolysis (–0.60 V vs Ag/Ag$^+$) with O_2 (1 atm) at 25 °C. [b] Under air (1 atm). The yield was determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated as the corresponding methyl ester after esterification with trimethylsilyldiazomethane.

With the optimized conditions in hand, we explored the substrate scope of the present electrochemical sulfoxidation reaction (Table 3). A series of aryl and alkyl sulfides could be converted to the corresponding sulfoxides **5a**–**5g** in 82–99% yields. The selective monooxygenation of dithiane afforded monosulfoxide **5h** in 89% yield without over-oxidation to the di-sulfoxide and sulfone, thereby revealing the selective oxidizing ability of the flavin catalyst.

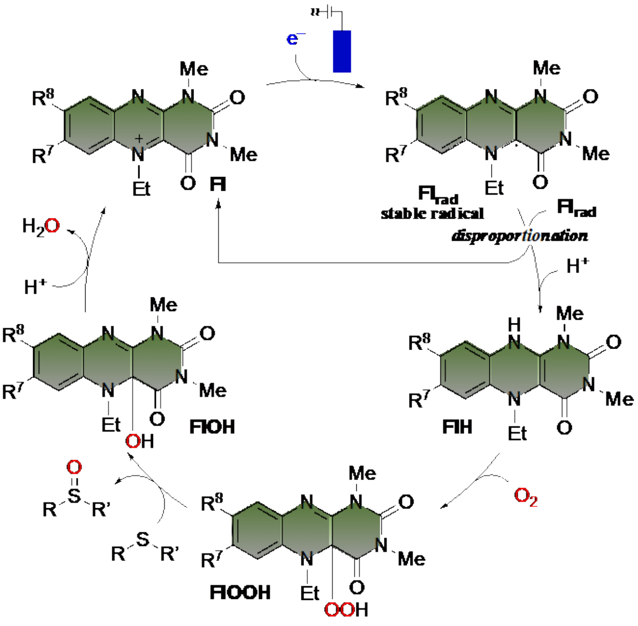
Alcohol- (**5i**) and ester-bearing (**5j**) sulfoxides were also selectively obtained in 89% and 83% yields, respectively. Although ketones and aldehydes are often converted to the corresponding carboxylic acid, ester, or phenol by the incorporation of oxygen atoms under oxidative conditions, our system promoted selective sulfoxidation to give **5k** and **5l** in 94% and 74% yields, respectively. A cyclopropyl unit was also tolerated (**5m**) without ring cleavage under the present electrochemical reaction conditions. The carboxyl-bearing sulfoxide **5n** was successfully obtained in 80% yield. Furthermore, the pyridyl-substituted sulfide was selectively converted to the corresponding sulfoxide **5o** in 88% yield without the *N*-oxidation of pyridine. These results indicate that acidic and basic functionalities do not interfere with the present sulfoxidation. To our delight, the alkene moiety was also tolerated under the present electrolytic conditions, and the reaction gave the corresponding sulfoxides **5p** and **5q** in 71% and 74% yields, respectively. While the yield of the acetylene-bearing sulfoxide **5r** slightly decreased to 60%, the TMS-protected acetylene was well tolerated and the corresponding sulfoxide **5s** was obtained in 85% yield. Notably, the production of **5g** and **5m** (Table 3) demonstrated that air (1 atm, balloon) could be used instead of pure O_2 as the oxidant.

We then compared the chemoselectivities of the present and previously reported systems for the oxygenation of the alkenyl-bearing sulfide **4p** (Scheme 2). The present flavin-catalyzed electrochemical system with a constant potential (−0.60 V) selectively promoted the oxygenation of the sulfide moiety, and its selectivity after 2 h of reaction reached 85% (Scheme 2A). In this case, the terminal voltage was 1.6 V. The green non-catalyzed electrochemical oxygenation of sulfides using water as the oxygen source has recently been reported; in this process, the synthesis of sulfoxides or sulfones can be switched by changing the applied voltage or current.[9a, d] However, the non-catalyzed system could not achieve the chemoselective oxygenation of **4p** because of the side reaction of the alkene moiety, which is likely due to its relatively higher terminal voltage (4.0 V) in comparison with that in the flavin-catalyzed system (1.6 V; Scheme 2B). The conventional method with stoichiometric amounts of oxidants, such as *m*-chloroperbenzoic acid and H_2O_2, showed modest selectivities of 43% and 56%, respectively (Scheme 2C and D). These results reveal the unique chemoselectivity of the flavin-catalyzed electrochemical oxygenation reaction.



Scheme 2. Control experiments.

Based on the experimental results and relevant literature, a possible mechanism was proposed (Scheme 3). As shown by the results of the CV analysis, the cationic flavin catalyst **Fl** receives one electron from the cathode at the cathode potential of −0.60 V to give the flavin radical intermediate $\mathbf{Fl_{rad}}$.[16] Because of its π-conjugated system, $\mathbf{Fl_{rad}}$ is a stable radical and unreactive towards diverse functionalities. The disproportionation of two $\mathbf{Fl_{rad}}$ molecules is known to occur to form **Fl** and the reduced flavin **FlH** that received two electrons.[17a] Thus, the obtained **FlH** can react with O_2 to give 4a-hydroperoxy flavin **FlOOH**, which possesses a well-regulated oxidative activity and enables the chemoselective oxygenation of sulfides.[17,18] Sulfoxidation with **FlOOH** forms the corresponding hydroxy flavin **FlOH**, which affords the initial **Fl** and water.[11a] In the reaction described in Table 3, when **5a** and **5h** were obtained in 90% and 89% yields, 1.7 and 1.9 F/mol, respectively, of electricity were passed. This amount of electricity supports the proposed reaction mechanism requiring two electrons for the aerobic oxygenation of one sulfide. This finding also reveals that minimal electricity is consumed by side reactions. The rate-determining step is assumed to be either the electrochemical reduction of **Fl** to **FlH** or the sulfoxidation of **FlOOH** and sulfide, as supported by the fact that electron-deficient **1a** shows better catalytic activity than the relatively electron-rich **1b** and **1c** (entries 1–3, Table 1). Previously reported flavin-catalyzed aerobic oxygenation processes consistently require chemical reductants (Scheme 1C).[12] In the present electrochemical system, however, the flavin catalyst receives electrons directly from the cathode under a well-controlled minimal potential, thereby eliminating the need for chemical reductants, which cause low atom efficiency and poor chemoselectivity.



Scheme 3. Possible mechanism.

By combining an electrochemical method and organocatalysis for O_2 activation, we successfully achieved a novel green electrochemical oxygenation process for the chemoselective synthesis of sulfoxides from sulfides bearing diverse functionalities. Sulfoxidation proceeded under mild and metal-free conditions at low voltages via the consumption of O_2 (air). This approach provides a variety of oxygenation and oxidative transformations using O_2.

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