Green Chemistry

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1. This study introduces a green electrochemical method for synthesizing adipic acid (AA) from biomass-derived 2-methoxycyclohexanone (MCH). Using molecular oxygen (O_2) and water as oxidants, this flavin-catalyzed process operates under mild, metal-free conditions, offering an environmentally friendly alternative to conventional petrochemical synthesis.

2. The method achieves high atom and electron economy, producing only water as a byproduct while avoiding the use of hazardous oxidants or metals. Under optimized conditions, it delivered a sustainable 76% yield of AA, demonstrating both efficiency and practicality.

3. Future work could focus on improving catalyst recyclability, scaling up for industrial applications, and exploring alternative feedstocks to expand the method's applicability and further enhance its environmental and economic impact.

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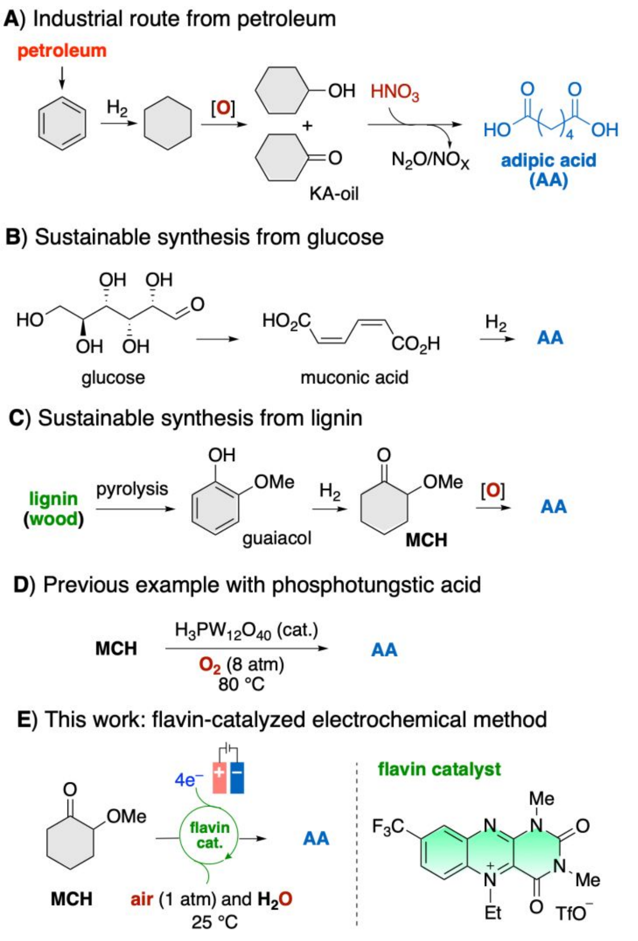
Here, we present an efficient electrochemical synthesis of adipic acid (AA) from 2-methoxycyclohexanone (MCH), which is derived from lignin, a major component of woody biomass. The tandem Bayer–Villiger reaction and oxygenation of MCH are promoted to produce AA using a metal-free flavin catalyst under mild, low-voltage electrolytic conditions. By the biomimetic flavin catalysis, the entire process is conducted using ambient air (1 atm) and water, which are readily available and sustainable resources. It offers a renewable alternative to petroleum-based AA synthesis, advancing green electrochemical biomass conversion methods.

Adipic acid (**AA**) is a critical commodity chemical, with annual production exceeding 3 million tons, primarily for use in polymers such as Nylon-6,6.[1] Currently, **AA** is synthesized in the chemical industry from petroleum-derived benzene (Scheme 1A). In this process, KA-oil, a mixture of cyclohexanol and cyclohexanone, is first obtained by hydrogenating benzene, followed by the oxygenation of cyclohexane. The conversion of KA-oil to **AA** relies on oxygenation using nitric acid, but this traditional process presents major sustainability concerns: (i) it depends on fossil-based resources, (ii) it has a low conversion efficiency (4–8%) for cyclohexanone oxygenation, and (iii) it releases N_2O, which is a potent greenhouse gas with a global warming potential approximately 300 times that of CO_2.[2] As a result, there is an increasing demand for a greener, more sustainable method of **AA** production that utilizes renewable resources.[3] For example, the microbial conversion of glucose into *cis*,*cis*-muconic acid, followed by its catalytic hydrogenation, has emerged as a promising renewable route to **AA** (Scheme 1B).[3a,b]



Scheme 1. Synthetic routes to adipic acid (**AA**): (A) Industrial process from petroleum. (B) Sustainable **AA** synthesis from glucose and (C) sustainable **AA** synthesis from lignin via MCH. Sustainable **AA** production from 2-methoxycyclohexanone (**MCH**) using (D) tungstic acid-catalyzed aerobic oxygenation and (E) flavin-catalyzed electrochemical aerobic oxidation.

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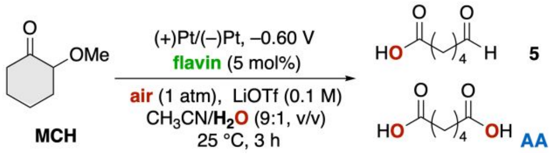
Lignin, a major component of woody biomass, remains underutilized compared with cellulose and hemicellulose. This has driven the demand for innovative processes to convert lignin into value-added products.[4] The pyrolysis of soft wood lignin produces guaiacol as the main product, making it a promising natural organic resource (Scheme 1C).[5] Guaiacol can be selectively converted to 2-methoxycyclohexanone (**MCH**) in good yields through catalytic hydrogenation; for example, a 98% yield was reported using a heterogeneous Pd catalyst.[6] If a green and selective oxidation process for converting **MCH** to **AA** is developed, it could serve as an appealing renewable approach for **AA** production. In 2020, Nakagawa, Tomishige and coworkers presented an example of the catalytic aerobic oxidation of **MCH** using phosphotungstic acid ($H_3PW_{12}O_{40}$) as a catalyst, introducing a novel route for sustainable **AA** production (Scheme 1D).[7] Molecular oxygen (O_2) is an attractive oxygen atom source because of its sustainability, safety, atom economy, cost-effectiveness, and minimal environmental impact.[8] However, this system has limitations, including the need for high-pressure O_2 (8 atm), elevated temperatures (80 °C), and an extended reaction time of 5 days. Therefore, an alternative environment-friendly and sustainable approach is needed.

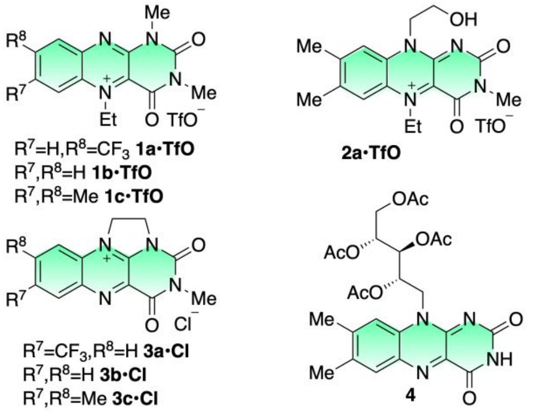
Recently, electrochemical synthesis has emerged as a green alternative to traditional synthetic methods, as it offers a mild and selective approach to both oxidative and reductive transformations.[9] Moreover, using electrons as redox agents eliminates the need for harsh and often toxic chemical oxidants and reductants, thereby improving atom economy and reducing chemical waste. In this study, we present a novel green method for **AA** synthesis via the biomimetic organocatalyzed electrochemical oxygenation of **MCH** at 25 °C, using ambient air (1 atm) and water as oxygen sources (Scheme 1E). The cationic flavin-based organocatalyst, which was designed to mimic the enzymatic function of flavin-containing monooxygenases,[10] activates O_2 mildly by supplying electrons at a controlled low cathode potential (–0.6 V versus Ag/Ag$^+$), thereby facilitating the chemoselective aerobic Baeyer–Villiger reaction of **MCH** and its subsequent oxygenation to **AA**. Electrochemical oxidation, particularly with ambient air and water, offers a green approach because it avoids the use of toxic reagents and promotes atomic economy. Recently, we developed low-voltage-driven electrochemical aerobic oxygenation of sulfides mediated by a flavin catalyst.[11] This process operates under mild conditions without high voltages or reactive radical intermediates, which could lead to undesirable side reactions. This electrochemical system enabled the chemoselective oxygenation of sulfides containing alkene and alkyne groups, which are typically vulnerable to oxidation and degradation. In this study, we anticipate that this flavin-catalyzed, mild electrochemical method will be suitable for the sustainable synthesis of **AA** via the tandem aerobic oxygenation of **MCH**.

Initially, we explored the effects of various flavin catalysts, including 5-ethylalloxazinium **1**, 5-ethylisoalloxazinium **2**, 1,10-ethylene-bridged alloxazinium **3**, and neutral tetraacetyl riboflavin (**4**), because of the significant impact of the flavin structure on both redox and catalytic activities (Table 1). Table 1 presents the redox potentials of the first single-electron reduction (E_1) which was determined by cyclic voltammetry in a CH_3CN solution, for these flavin catalysts (1.0 mM),[11-12] enabling a comparison of their catalytic and redox activities. Aerobic electrochemical oxygenation of **MCH** was conducted in air (1 atm, balloon) at 25 °C for 3 h in a CH_3CN/H_2O solution (9:1, v/v) containing LiOTf as the electrolyte. The electrolysis was maintained at a constant potential (–0.60 V versus Ag/Ag$^+$) in an undivided cell with Pt working, Pt counter, and Ag/Ag$^+$ reference electrodes. The oxygenation of **MCH**, catalyzed by alloxaziniums **1a–c**, yielded **AA** and its precursor, 6-oxohexanoic acid (**5**), in a combined yield of up to 17% (entries 1–3, Table 1). We observed a linear correlation between the redox potential and catalytic activity. The highest yield was achieved with 8-trifluoromethyl isoalloxazinium **1a**, as opposed to the more electron-rich 7,8-non-substituted **1b** and 7,8-dimethyl **1c**. In contrast, the catalytic activities of isoalloxazinium **2**, ethylene-bridged alloxazinium **3**, and a neutral flavin **4** were low (entries 4–8). Notably, in the absence of a flavin catalyst, the formation of **AA** and **5** was negligible (entry 9).

Table 1 Catalytic activity of flavins for the electrochemical oxidation of **MCH**[a]



Entry	Flavin	E_1 [V vs Fc/Fc$^+$][b]	Conv. (%)	Total yield of **5** and **AA** (%)[c]
1	**1a•TfO**	–0.168	65	17
2	**1b•TfO**	–0.326	53	14
3	**1c•TfO**	–0.425	50	11
4	**2a•TfO**	–0.136	55	<5
5	**3a•Cl**	–0.426	43	<5
6	**3b•Cl**	–0.564	46	<5
7	**3c•Cl**	–0.650	65	<5
8	**4**	–1.18	44	<5
9	–	–	48	<5



R^7=H,R^8=CF$_3$ **1a·TfO**
R^7,R^8=H **1b·TfO**
R^7,R^8=Me **1c·TfO**

2a·TfO

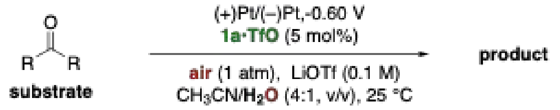
R^7=CF$_3$,R^8=H **3a·Cl**
R^7,R^8=H **3b·Cl**
R^7,R^8=Me **3c·Cl**

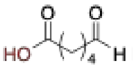
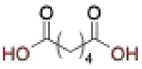
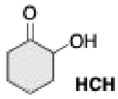
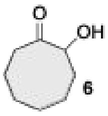
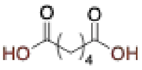
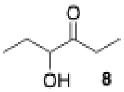
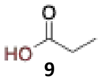
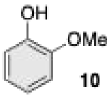
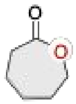
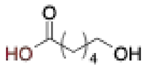
4

[a] Conditions: **MCH** (0.5 mmol, 0.1 M), flavin (5 mol%), LiOTf (0.1 M), and CH_3CN/H_2O (9:1, v/v) were placed in an undivided cell. Electrolysis was performed under a constant voltage (–0.60 V versus Ag/Ag$^+$) with air bubbling (1.2 mL/min via peristaltic pump) at 25 °C for 3 h. The conversion and yield were determined by GC, using biphenyl as an internal standard. [b] Data from Refs. 11 and 12. [c] Detected as the corresponding methyl ester after esterification with $TMSCHN_2$.

The electrodes, electrolytes, solvents, and other reaction conditions were further optimized (Table S1). As a result, the electrochemical aerobic oxidation of **MCH** was successfully performed, yielding **AA** in 76% and **5** in 12% when **1a•TfO** (5 mol%) was used in CH_3CN/H_2O (4:1, v/v) containing LiOTf (0.1 M) under constant potential electrolysis (–0.60 V versus Ag/Ag^+) with air bubbling at 25 °C (Table 2). Notably, the reaction proceeded efficiently in atmospheric air at a mild temperature of 25 °C, achieving a total yield of **AA** and **5** up to 88%. In this reaction, the terminal voltage was kept at a low level of 3.1 V. The formation of **5** suggested that the Baeyer–Villiger reaction of **MCH** occurred, producing oxygen-inserted **5**, which then underwent further oxygenation to form **AA**. Similarly, 2-hydroxycyclohexanone (**HCH**), also derived from lignin,[13] was efficiently converted to **AA** and **5** in yields of 85% and 5%, respectively. This electrochemical method was applicable to similar cyclic and linear alpha-hydroxyketones. A 2-hydroxycyclooctanone (**6**) with an eight-membered ring was also converted to the corresponding suberic acid (**7**) in 80% yield. Using a linear 4-hydroxyhexan-3-one (**8**) as the substrate, two equivalents of propanoic acid (**9**) was obtained in 88% yield, which is formed via the Baeyer–Villiger reaction of **8** and the oxygenation of propanal obtained by the hydrolysis of the Baeyer–Villiger product. In contrast, guaiacol (**10**), which did not undergo oxygenation, did not yield any detectable **AA** under these conditions.

Table 2. Flavin-catalyzed electrochemical aerobic oxidation of ketones [a]



Substrate	Time (h)	Conversion (%)	Product		Equiv. of e⁻ (F/mol)
 **MCH**	5.5	>99	 **5** 12%[b]	 **AA** 76%[c]	5.54
 **HCH**	8	>99	**5** 5%[b]	**AA** 85%[c]	5.87
 **6**	12	>99	 **7** 80%[c]		4.88
 **8**	11	>99	 **9** 88%		6.15
 **10**	5.5	>99	**5** none[b]	**AA** none[b]	16.3
 **11**	6.5	22	 **12** trace	 **13** trace[b]	2.49

[a] Conditions: Substrate (0.5 mmol, 0.1 M), **1a•TfO** (5 mol%), LiOTf (0.1 M), and CH_3CN/H_2O (4:1, v/v) were placed in an undivided cell under constant-voltage electrolysis (–0.60 V versus Ag/Ag^+) with air bubbling via a peristaltic pump (1.2 mL/min) at 25 °C. Conversion and yield were determined by GC using biphenyl as an internal standard. [b] Detected as the corresponding methyl ester after esterification with $TMSCHN_2$. [c] Isolated yield.

Based on the experimental results and literature, we proposed the reaction mechanism shown in Scheme 2. The flavin-catalyzed aerobic Baeyer–Villiger reaction of **MCH** initially produced lactone **14a** by supplying electrons under low-voltage electric conditions (Scheme 2A). This process was supported by the formation of the Baeyer–Villiger reaction product **14b** (**14b**+Na^+, m/z = 153.0516), as confirmed by electrospray ionization mass spectrometry of the reaction mixture of **HCH** obtained after 2 h of stirring (Scheme 3A and Fig. S1). Subsequent ring cleavage via hydrolysis of **14a** and elimination of methanol to give **5** with an aldehyde moiety (Scheme 2A). The aliphatic aldehyde was further converted to carboxylic acid through aerobic oxygenation under the current reaction conditions. Indeed, under the standard conditions, **1a•TfO** facilitated the conversion of hexanal (**15**) to the corresponding hexanoic acid (**16**) (Scheme 3B). Although the oxygenation of **15** also occurred in the absence of **1a•TfO**, the yield and selectivity were relatively low. These results indicated that flavin catalysis effectively promoted both the Baeyer–Villiger reaction of **MCH** and aerobic oxygenation of aldehyde **5**, thereby producing the desired **AA** through the tandem aerobic Baeyer–Villiger reaction and oxygenation. In this system, the flavin catalyst **Fl** was reduced to yield the flavin radical $\mathbf{Fl_{rad}}$ by accepting an electron from the cathode at potential of –0.6 V (Scheme 2B).[14] The formation of $\mathbf{Fl_{rad}}$ was confirmed by the electron spin resonance (ESR) analysis of the reaction mixture obtained after **1a•TfO** underwent electrolysis for 10 min, showing a characteristic radical signal of the flavin molecule with a g-value of 2.00104 (Fig. 1A).[14] Stabilized by the π-conjugated system, $\mathbf{Fl_{rad}}$ did not undergo side reactions.[11] Through disproportionation, two $\mathbf{Fl_{red}}$ molecules were partially converted to **Fl** and reduced flavin **FlH**, which activated O_2 to form the oxidatively active 4a–hydroperoxyflavin **FlOOH**.[16] **FlOOH** attacked the carbonyl functionality, enabling the Baeyer–Villiger reaction of **MCH** and oxygenation of **5** to produce oxygenated products **14a** and **AA**, respectively. The generated **FlOH** was converted back to the initial **Fl** through dehydration, completing the catalytic cycle. To facilitate the aerobic oxygenation of the substrate (Sub), the flavin catalyst required two electrons and one O_2 molecule to produce an oxygenated product (Sub=O) and water. Electricity of 5.54 and 5.87 F/mol was consumed in the reaction of **MCH** and **HCH**, respectively, both of which underwent two-step oxygenation (Table 2). Given that the theoretical requirement for this two-step transformation is 4 F/mol, these results indicate relatively high electron efficiency and selectivity in this electrochemical process.

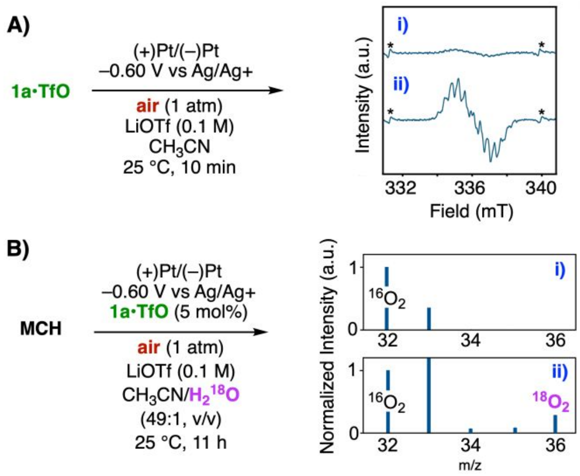
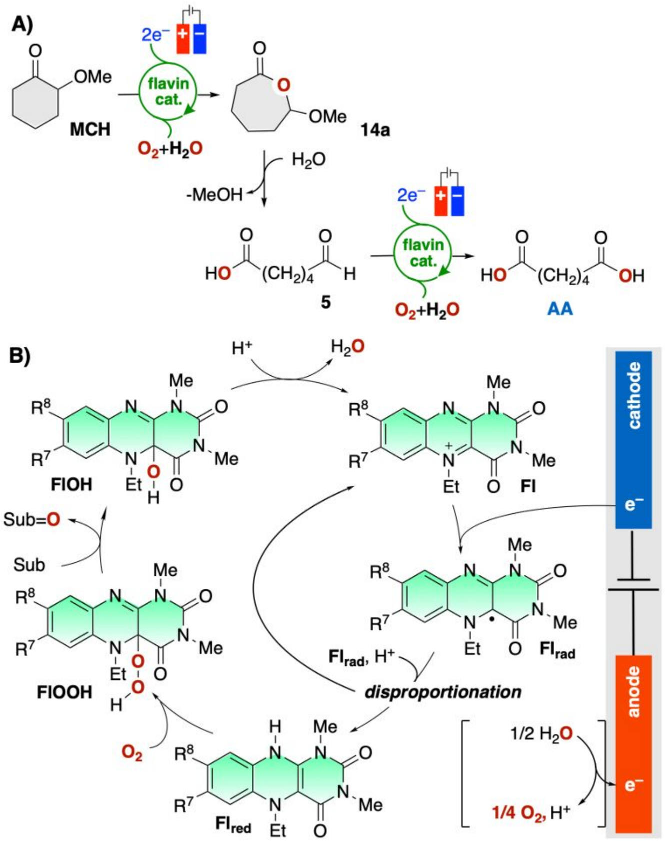


Fig. 1 (A) Electron spin resonance measurements of a **Fl$_{rad}$** solution in CH_3CN (5 mM): (i) before and (ii) after electrolysis (g=2.00104). Asterisks indicate signals from the standard marker Mn^{2+}/MgO. (B) Mass spectra of (i) air and (ii) gas generated at the anode during the electrolysis of **MCH** for 11 h in $CH_3CN/H_2{}^{18}O$ (49:1, v/v).

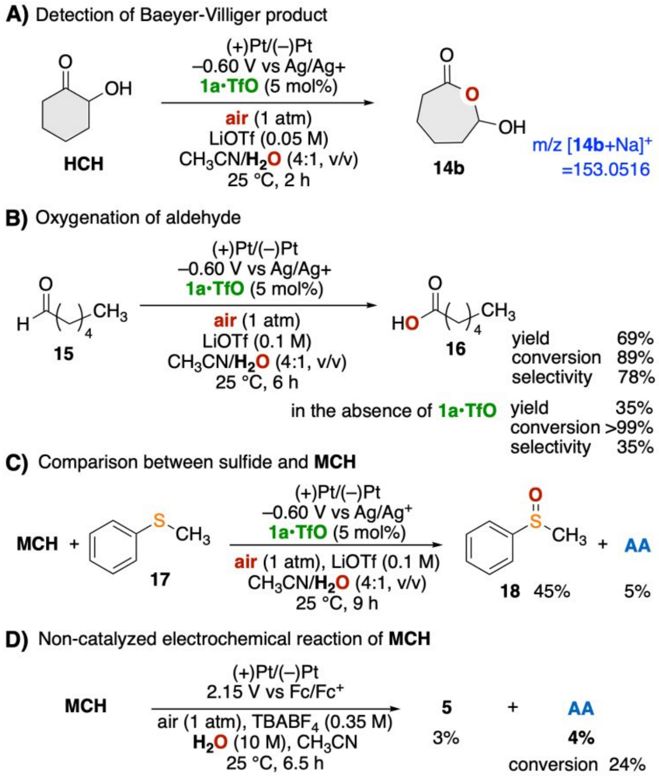


Scheme 2. Proposed mechanism for the (A) aerobic oxidative formation of **AA** and (B) catalytic cycle of flavin.

The peroxy anion **FlOO$^-$** was identified as the active oxidative species in the enzymatic Baeyer–Villiger reaction catalyzed by Baeyer–Villiger monooxygenase.[17] To confirm the active oxidative species in the present electrochemical system, we conducted the reaction of **MCH** in the presence of sulfide **17**, which is highly reactive toward electrophilic oxygenation by peroxy species such as the hydroperoxy flavin **FlOOH** but less reactive to nucleophilic peroxy anions such as **FlOO$^-$** (Scheme 3C).[17,18] Sulfoxidation occurred preferentially over the reaction of **MCH**, which is consistent with the involvement of hydroperoxyflavin **FlOOH** as the active oxidative species in this electrochemical system. In a previous study, experiments using ^{18}O-isotope-labeled water indicated that both O_2 and water served as oxygen sources in electrochemical flavin-catalyzed oxygenation.[11] Although it was challenging to completely exclude the possibility that water partially acted as a direct oxygen source, the electrolysis of water likely occurred at the anode, generating H^+ and O_2 as proton and oxygen sources, respectively. When **MCH** was reacted, gas evolution from the anode was observed, and the pH of the reaction mixture after 6.5 h was 2.1. Under acidic conditions, **FlOOH** acted as the active oxidative species rather than **FlOO$^-$**. To analyze the gas generated at the anode, we conducted a mass spectrometry analysis of the gas when the reaction of **MCH** was conducted in the presence of ^{18}O-isotope-labeled water (11 equivalents of **MCH**, Fig. 1B). Mass analysis of the gas in the bubbles attached to the anode revealed the formation of $^{18}O_2$ (m/z = 36) despite the absence of any detectable amount of $^{18}O_2$ in the ambient air used for bubbling. Quantitative analysis of $^{18}O_2$ was challenging because of the presence of $H_2{}^{16}O$ from the bubbled air ($^{16}O_2$), which was involved in the flavin-catalyzed cycle, as well as the exchange between the $H_2{}^{18}O$ and ^{16}O atoms of **5** and **AA**. Nevertheless, this outcome corroborated the hypothesis that water underwent anodic electrolysis.

Since the cationic flavin catalyst is known to function as an organocatalyst for the electrochemical water oxidation to produce O_2,[19] **1a•TfO** might catalyze the electrolysis of water at anode in the present system, in addition to facilitating the oxygenation at cathode. Indeed, when using a divided cell and omitting the flavin catalyst from the anodic compartment, the yield of **AA** dropped to less than 1% and no oxygen evolution was detected. This difference indicates that the presence of the flavin catalyst in the anodic chamber is essential for efficient product formation in the present condition. Furthermore, when **1a·TfO** was added to both the cathode and anode chambers of the divided cell, the yield remained similarly low, suggesting that chemical species and/or intermediates generated from **1a·TfO** at each electrode may need to interact for the reaction to proceed. Since similar flavin-catalyzed electrochemical reactions have been shown to promote oxygenation of sulfides,[11] it is unlikely that the observed phenomenon is due to interference from intermediates derived from the present substrate (**MCH**). We proposed the reaction mechanism shown in Scheme 2B based on previously reported redox behavior of flavin catalysts and known mechanisms of aerobic oxidation. However, the actual reaction pathway may involve more complex processes, particularly on the anodic side, where the reactions appear to be intricate and not yet fully understood. Although elucidating the detailed mechanism remains a considerable challenge, this intriguing phenomenon warrants further investigation in future studies.

In a single step of the oxygen-atom transfer process to the substrate, it is proposed that 1 equivalent of water undergoes electrolysis via a two-electron transfer, producing 0.5 equivalents of O_2 and 1 equivalent of the oxidized product (Sub=O, Scheme 2B). Therefore, it was estimated that approximately half of the oxygen atoms incorporated into **MCH** were derived from water. This finding was corroborated by the observation that approximately half of the oxygen inserted during the previously-reported sulfoxidation in the presence of $H_2{}^{18}O$ was ^{18}O.[11] The current conditions allowed the tandem Baeyer–Villiger reaction and oxygenation to proceed via the consumption of O_2 and water, thereby enabling the green synthesis of **AA** from **MCH**.



Scheme 3. Control experiments: (A) Detection of the Baeyer–Villiger product **10b** in the reaction mixture of **HCH**, (B) the oxygenation of aldehyde **15**, (C) comparison of reactivity between sulfide and **MCH**, and (D) direct electrochemical reaction of **MCH** without the flavin catalyst.

Flavin compounds are known to catalyze the aerobic Baeyer–Villiger reaction using additional reductants, such as zinc dust and NADH.[18,20] The regulated oxidizing power of flavin catalysts enables selective oxygenation,[21] which has typically restricted the substrate scope to relatively reactive ketones, such as strained cyclobutanones.[18,20] Indeed, the current system hardly achieved the Baeyer–Villiger reaction of less-strained cyclohexanones lacking methoxy and hydroxy substituents (**12**, Table 2). However, the electron-donating 2-methoxy and hydroxy groups on **MCH** and **HCH**, respectively, facilitated carbon migration in the transition state, known as the "Criegee intermediate," required for the rearrangement.[22] As a result, the flavin-catalyzed reaction selectively inserted an oxygen atom into the C^1–C^2 bond between the carbonyl- and 2-methoxy-substituted carbons of **MCH** rather than into the C^1–C^6 bond. Recently, electrochemical methods for Baeyer–Villiger-type reactions using pure O_2[23], water[24], and H_2O_2[25] as the oxygen source have emerged as promising alternatives to conventional methods employing peracids. For example, Hu and co-workers demonstrated aerobic Baeyer-Villiger oxidation using activated carbon electrodes in ionic liquid.[23] When fluorinated tin oxide[24a], iron oxide,[24b] and CeO_2@PbO_2@Ti electrode[24c] were employed as an anode, electrochemical Baeyer–Villiger reaction took place using water as the oxygen source. Manthiram and colleagues also demonstrated the appealing electrochemical lactonization of ketones, such as cyclohexanone, using water.[26] However, the direct electrochemical conditions without flavin catalysts were unsuitable for **AA** synthesis from **MCH** (Scheme 3D). Therefore, flavin catalysis played a crucial role in **AA** synthesis. To the best of our knowledge, this is the first electrochemical method for the Baeyer–Villiger reaction that uses both atmospheric air and water as the oxygen source, and offers significant environmental and economic advantages. By directly utilizing electrical energy, the present electrochemical method represents a preliminary example contributing to greener synthetic strategies. To ensure that this approach offers a truly sustainable alternative to conventional chemical methods, future efforts should focus on developing work-up procedures that allow for the recovery and reuse of the electrolyte, solvent, and catalyst[27]. Although the platinum electrodes used in this system are expensive, they offer the advantage of being reusable.

Conclusions

We successfully achieved an efficient electrochemical synthesis of **AA** from sustainable **MCH** using ambient air and water. This flavin-catalyzed process effectively activated O_2 and enabled selective tandem oxygenation, specifically the aerobic Baeyer–Villiger reaction of **MCH** and subsequent aerobic oxidation of the in-situ-generated aldehyde, all under mild, metal-free, and low-voltage electrolytic conditions. This approach has the potential to not only facilitate the sustainable synthesis of **AA** but also to pave the way for developing green electrochemical methods for multi-step oxidative transformations of biomass-derived α-hydroxy ketones using atmospheric air and water, which are simple, highly accessible sustainable resources. This study demonstrates the potential of renewable resources to reduce the dependency on petrochemical sources.

Author contributions

H. I. conceived and directed the study. M. M., T. M., and H. M. performed the experiments and characterization. A. D. performed the GC-MS analysis using ^{18}O-isotope-labeled water. M. M. and H. I. wrote the manuscript. All the authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 K. C. Hwang, A. Sagadevan, *Science*, 2014, **346**, 1495-1498.

2 (a) J. Iglesias, I. Martínez-Salazar, P. Maireles-Torres, D. Martin Alonso, R. Mariscal, M. López Granados, *Chem. Soc. Rev.*, 2020, **49**, 5704-5771; (b) M. Lang, H. Li, *ChemSusChem*, 2022, **15**, DOI: 10.1002/cssc.202101531.

3 (a) K. M. Draths and J. W. Frost, *J. Am. Chem. Soc.*, 1994, **116**, 399-400; (b) W. Niu, K. M. Draths and J. W. Frost, *Biotechnol. Progr.*, 2002, **18**, 201-211; (c) D. R. Vardon, M. A. Franden, C. W. Johnson, E. M. Karp, M. T. Guarnieri, J. G. Linger, M. J. Salm, T. J. Strathmann and G. T. Beckham, *Energy Environ. Sci.*, 2015, **8**, 617-628; (d) W. P. Deng, L. F. Yan, B. J. Wang, Q. H. Zhang, H. Y. Song, S. S. Wang, Q. H. Zhang, Y. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 4712-4719.

4 (a) A. J. Ragauskas, G. T. Beckham, M. J. Biddy, R. Chandra, F. Chen, M. F. Davis, B. H. Davison, R. A. Dixon, P. Gilna, M. Keller, P. Langan, A. K. Naskar, J. N. Saddler, T. J. Tschaplinski, G. A. Tuskan, C. E. Wyman, *Science*, 2014, **344**, 709-720; (b) C. Z. Li, X. C. Zhao, A. Q. Wang, G. W. Huber, T. Zhang, *Chem. Rev.*, 2015, **115**, 11559-11624; (c) R. Rinaldi, R. Jastrzebski, M. T. Clough, J. Ralph, M. Kennema, P. C. A. Bruijnincx, B. M. Weckhuysen, *Angew. Chem., Int. Ed.*, 2016, **55**, 8164-8215.

5 (a) M. Saidi, F. Samimi, D. Karimipourfard, T. Nimmanwudipong, B. C. Gates, M. R. Rahimpour, *Energy Environ. Sci.*, 2014, **7**, 103-129; (b) A. Kumar, Anushree, J. Kumar, T. Bhaskar, *J. Energy Inst.*, 2020, **93**, 235-271.

6 G. Y. Xu, J. H. Guo, Y. Zhang, Y. Fu, J. Z. Chen, L. L. Ma, Q. X. Guo, *ChemCatChem*, 2015, **7**, 2485-2492.

7 K. Hatakeyama, Y. Nakagawa, M. Tamura, K. Tomishige, *Green Chem.*, 2020, **22**, 4962-4974.

8 (a) C. L. Hill, *Nature*, 1999, **401**, 436-437; (b) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.*, 2012, **45**, 851-863; (c) K. P. Bryliakov, *Chem. Rev.*, 2017, **117**, 11406-11459; d) N. Jiao, S. S. Stahl, Green Oxidation in Organic Synthesis, John Wiley & Sons, Hoboken, 2019.

9 (a) R. Francke and R. D. Little, *Chem. Soc. Rev.*, 2014, **43**, 2492-2521; (b) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230-13319; (c) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2018, **57**, 5594-5619; (d) C. Schotten, T. P. Nicholls, R. A. Bourne, N. Kapur, B. N. Nguyen and C. E. Willans, *Green Chem.*, 2020, **22**, 3358-3375; (e) C. B. Liu, F. P. Chen, B. H. Zhao, Y. M. Wu and B. Zhang, *Nature Rev. Chem.*, 2024, **8**, 277-293.

10 (a) S.-I. Murahashi, T. Oda, Y. Masui, *J. Am. Chem. Soc.*, 1989, **111**, 5002-5003; (b) Y. Imada, H. Iida, S. Ono, S. I. Murahashi, *J. Am. Chem. Soc.*, 2003, **125**, 2868-2869; (c) H. Iida, Y. Imada, S.-I. Murahashi, *Org. Biomol. Chem.*, 2015, **13**, 7599–7613; (d) R. Cibulka, M. W. Fraaije, Flavin-Based Catalysis, Wiley-VCH, Weinheim, 2021.

11 T. Mizushima, M. Oka, Y. Imada, H. Iida, *Adv. Synth. Catal.*, 2022, **364**, 2443-2448.

12 H. Miyake, H. Iida, *Adv. Synth. Catal.*, 2024, **366**, 402-407.

13 (a) C. Zhao, J. He, A. A. Lemonidou, X. Li, J. A. Lercher, *J. Catal.*, 2011, **280**, 8-16; (b) H. Wang, J. Male, Y. Wang, *ACS Catal.*, 2013, **3**, 1047-1070.

14 (a) E. J. Nanni, Jr. , D. T. Sawyer, S. S. Ball, T. C. Bruice, *J. Am. Chem. Soc.*, 1981, **103**, 2797-2802; (b) V. Sichula, P. Kucheryavy, R. Khatmullin, Y. Hu, E. Mirzakulova, S. Vyas, S. F. Manzer, C. M. Hadad, K. D. Glusac, *J. Phys. Chem. A,* 2010, **114**, 12138-12147; (c) P. Ménová, H. Dvořáková, V. Eigner, J. Ludvík, R. Cibulka, *Adv. Synth. Catal.*, 2013, **355**, 3451-3462; (d) T. Sakai, T. Kumoi, T. Ishikawa, T. Nitta, H. Iida, *Org. Biomol. Chem.*, 2018, **16**, 3999-4007.

15 (a) A. V. Guzzo, G. Tollin, *Arch. Biochem. Biophys.*, 1963, **103**, 244-248; (b) O. Heilmann, F. M. Hornung, J. Fiedler, W. Kaim, *J. Organomet. Chem.*, 1999, **589**, 2-10; (c) J. Casas, D. Pianca, N. Le Breton, A. Jouaiti, C. Gourlaouen, M. Desage-El Murr, S. Le Vot, S. Choua, S. Ferlay, *Inorg. Chem.*, 2024, **63**, 4802-4806.

16 C. Kemal, T. W. Chan, T. C. Bruice, *J. Am. Chem. Soc.*, 1977, **99**, 7272-7286.

17 (a) C. C. Ryerson, D. P. Ballou, C. Walsh, *Biochemistry*, 1982, **21**, 2644-2655; (b) D. Sheng, D. P. Ballou, V. Massey, *Biochemistry*, 2001, **40**, 11156-11167; (c) N. M. Kamerbeek, D. B. Janssen, W. J. H. van Berkel, M. W. Fraaije, *Adv. Synth. Catal.*, 2003, **345**, 667-678; (d) E. Romero, J. R. G. Castellanos, G. Gadda, M. W. Fraaije, A. Mattevi, *Chem. Rev.*, 2018, **118**, 1742-1769.

18 (a) S. Oae, K. Asada, T. Yoshimura, *Tetrahedron Lett.*, 1983, **24**, 1265-1268; (b) Y. Imada, H. Iida, S.-I. Murahashi, T. Naota, *Angew. Chem., Int. Ed.*, 2005, **44**, 1704-1706.

19 (a) E. Mirzakulova, R. Khatmullin, J. Walpita, T. Corrigan, N. M. Vargas-Barbosa, S. Vyas, S. Oottikkal, S. F. Manzer, C. M. Hadad, K. D. Glusac, *Nature Chem.*, 2012, **4**, 794-801; (b) X. Yang, J. Walpita, E. Mirzakulova, S. Oottikkal, C. M. Hadad and K. D. Glusac, *ACS Catal.*, 2014, **4**, 2635-2644.

20 (a) Y. Arakawa, K. Yamanomoto, H. Kita, K. Minagawa, M. Tanaka, N. Haraguchi, S. Itsuno, Y. Imada, *Chem. Sci.*, 2017, **8**, 5468-5475; (b) Y. Chevalier, Y. L. T. Ki, D. le Nouen, J. P. Mahy, J. P. Goddard, F. Avenier, *Angew. Chem., Int. Ed.*, 2018, **57**, 16412-16415.

21 T. C. Bruice, J. B. Noar, S. S. Ball, U. V. Venkataram, *J. Am. Chem. Soc.*, 1983, **105**, 2452-2463.

22 (a) M. Renz, B. Meunier, *Eur. J. Org. Chem.*, 1999, **1999**, 737-750; (b) G.-J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Chem. Rev.*, 2004, **104**, 4105-4123.

23 Y. L. Hu, Y. B. Xie, D. J. Li, *Bull. Chem. Soc. Ethiop.*, 2016, **30**, 297-306.

24 (a) A. Herman, J. L. Mathias and R. Neumann, *ACS Catal.*, 2022, **12**, 4149-4155; (b) Y. Mu, B. Q. Chen, H. N. Zhang, M. C. Fei, T. Y. Liu, N. Mehta, D. Z. Wang, A. J. M. Miller, P. L. Diaconescu, D. W. Wang, *J. Am. Chem. Soc.,* 2024, **146**, 13438-13444; (c) X. Luo, Y. Wang, B. Wu, Y. Wang, C. Li, M. Shao, B. Liu, Z. Wei, *J. Phys. Chem. Lett.*, 2024, **15**, 10435-10441.

25 S. S. Cha, Y. X. Chen, W. Du, J. X. Wu, R. Wang, T. Jiang, X. J. Yang, C. Lian, H. L. Liu and M. Gong, *Jacs Au*, 2024, **4**, 3629-3640.

26 J. H. Maalouf, K. Jin, D. Yang, A. M. Limaye, K. Manthiram, *ACS Catal.*, 2020, **10**, 5750-5756.

27 Reusable flavin catalysts immobilized on solid supports have been developed. For examples, see: (a) H. Schmaderer, P. Hilgers, R. Lechner and B. König, *Adv. Synth. Catal.*, 2009, **351**,

163-174; (b) J. Spackova, E. Svobodova, T. Hartman, I. Stibor, J. Kopecka, J. Cibulkova, J. Chudoba and R. Cibulka, *Chemcatchem*, 2017, **9**, 1177-1181; (c) Y. Arakawa, R. Kawachi, Y. Tezuka, K. Minagawa and Y. Imada, *J. Polym. Sci., Part A: Polym. Chem.*, 2017, **55**, 1706-1713; (d) T. Sakai, M. Watanabe, R. Ohkado, Y. Arakawa, Y. Imada and H. Iida, *ChemSusChem*, 2019, **12**, 1640-1645.

The data supporting this article have been included as part of the Supplementary Information.