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Integrating electrocatalysis with biocatalysis for asymmetric synthesis

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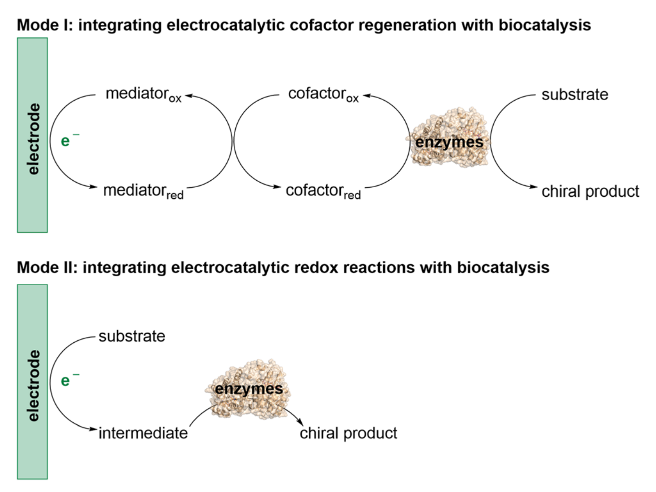
The integration of electrocatalysis with biocatalysis has recently been developed for the stereoselective synthesis of valuable compounds. This integration leverages the high efficiency and exquisite selectivity of enzymes along with the tunability of electrochemical reactions, providing a versatile approach for asymmetric synthesis with broad prospects. In this highlight, recent advances and future development directions in asymmetric synthesis that integrate electrocatalysis with biocatalysis are presented and discussed. We foresee that more valuable stereoselective transformations using this integrated strategy will be developed in the future.

Enzyme-based biocatalysis has become a powerful tool for generating enantiomerically pure chemicals in organic synthesis due to high enantioselectivity, gentle reaction conditions, and minimal by-product formation.[1] Enantioselective oxidoreductases, which account for the majority of known enzymes, play an essential role in redox reactions.[2] They have been extensively exploited to facilitate the efficient production of a variety of chiral compounds in asymmetric synthesis.[3] However, the inability to efficiently regenerate expensive reduced cofactors has restricted their application.[4] Electrochemistry offers an attractive and promising alternative for cofactor regeneration with the advantages of harnessing electricity as a clean energy source, getting rid of by-product generation, and simplifying the product separation process.[5] Integrating biocatalysis with electrocatalysis brings broader benefits, such as improved reaction efficiency, enhanced selectivity, and the environmentally benign and sustainable production of enantiopure chemicals.

Electrochemistry, a green and sustainable synthetic tool for organic transformations, has attracted considerable interest in synthetic chemistry.[6] For instance, electrochemical approaches have recently emerged as mild and efficient alternatives for the synthesis of organofluorines.[7] The application of electrons as cheap and renewable reagents avoids stoichiometric external oxidants or reductants and eliminates undesired by-product generation.[8] Furthermore, the reactivity and selectivity of electrochemical reactions can be regulated by precisely controlling the applied potential and electric current.[9] However, asymmetric electrosynthesis remains a challenging field of development and typically requires costly transition metals and chiral catalysts.[10] Additionally, the high reactivity of oxidatively or reductively generated radicals or reactive intermediates poses a challenge for asymmetric electrosynthesis.[11] Integrating electrocatalysis with biocatalysis provides a versatile approach for achieving stereo-control in electrochemistry.

The integration of biocatalysis and electrocatalysis is intriguing due to the combined merits of the high efficiency and exquisite selectivity of enzymes along with the tunability of electrochemical reactions.[12] This emerging strategy provides a powerful way to tune substrate and product selectivity, further enriching catalytic strategies to explore more valuable stereoselective transformations for asymmetric synthesis. There are two main modes involved in this integration (Scheme 1). In the first mode, (modified) electrodes are used to regenerate



Scheme 1 Modes in the integration of electrocatalysis and biocatalysis.

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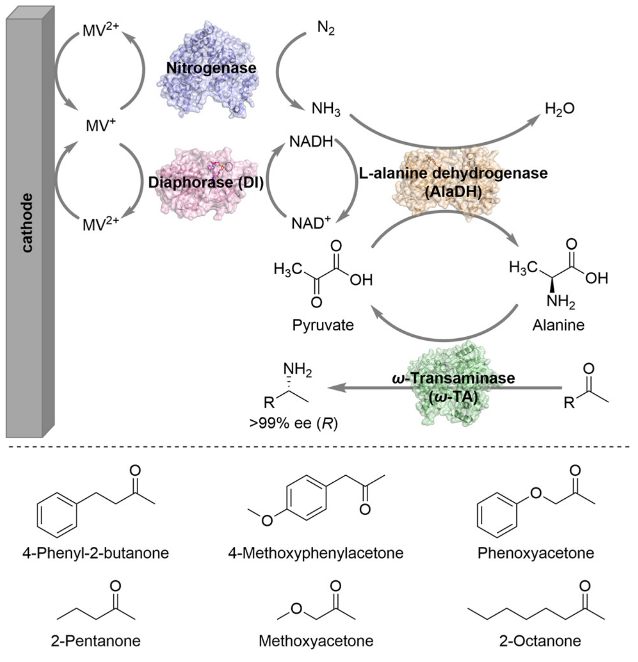
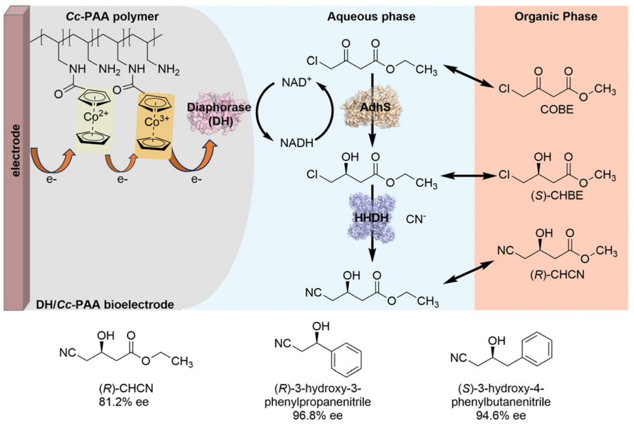
cofactors for the cofactor-dependent oxidoreductases to achieve their natural redox activity. The second mode involves the electroenzymatic cascade reaction, where the electrocatalytic redox reaction initially converts the substrate or co-substrate into an intermediate, which is subsequently catalyzed by the enzymes to generate the chiral product. Although the application of this combined strategy in asymmetric organic synthesis is still in its infancy, recent breakthroughs indicate that it holds great promise for the exploration of novel asymmetric reactions. Herein, we highlight recent advances in asymmetric synthesis that integrate electrocatalysis with biocatalysis and discuss future directions in this field.

The Minteer group constructed an enhanced bioelectrocatalytic platform for N_2 fixation that combines nitrogenase, diaphorase (DI), L-alanine dehydrogenase (AlaDH), and *ω*-transaminase (*ω*-TA) with electrodes to convert N_2 into chiral amine intermediates in one-pot under mild conditions (Scheme 2).[13] This bioelectrocatalytic system used an H-shaped dual-chamber reactor with oxidized methyl viologen (MV^{2+}) as an electron mediator. The cathode directly provides electrons for reduced MV^+, realizing the efficient regeneration of MV^+. The reduced MV^+ then donates electrons to nitrogenase to facilitate the reduction of N_2 to NH_3. DI consumes reduced MV^+ to regenerate NADH, while MV^+ is recycled by the cathode. AlaDH, using NADH as a coenzyme, captures NH_3 and transfers it to the acceptor pyruvate to generate alanine. Then the amino group of alanine is transferred by *ω*-TA to various ketone substrates, ultimately generating enantiomerically pure chiral amine intermediates. Notably, AlaDH consumes the by-product pyruvate to reproduce alanine, shifting the reaction equilibrium towards the amine product side. Employing this system, different prochiral ketones could be aminated to produce the corresponding chiral amines with perfect stereoselectivity (>99% ee).



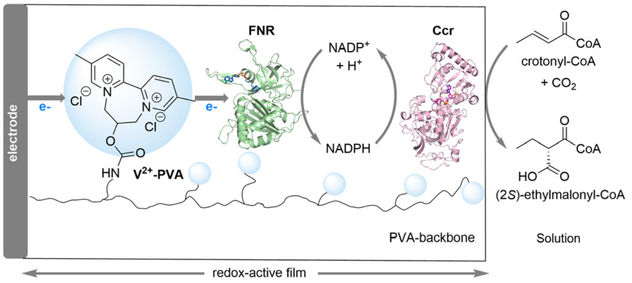
Scheme 2 A bioelectrocatalytic platform converts N_2 into chiral amine intermediates (mode I).

To overcome the low efficiency of cofactor regeneration and substrate solubility problems in oxidoreductase-based asymmetric synthesis, Minteer and colleagues developed a novel two-phase bioelectrocatalytic system. This system enables the efficient synthesis of chiral β-hydroxy nitriles by integrating alcohol dehydrogenase (AdhS), halohydrin dehalogenase (HHDH) with diaphorase (DH)-modified electrodes (Scheme 3).[14] Diaphorase (DH) was immobilized on the electrode surface with a cobaltocene-modified poly(allylamine) redox polymer to form DH/*Cc*-PAA bioelectrode. In this bioelectrode, *Cc*-PAA polymer mediates the transfer of electrons from the electrode to DH, which further utilizes the electrons to catalyze the reduction of NAD^+ to efficiently regenerate the reduced cofactor NADH. NADH-dependent AdhS then catalyzes the reduction of the model substrate COBE to (*S*)-CHBE by consuming NADH. HHDH catalyzes the dehalogenation and cyanation of (*S*)-CHBE to (*R*)-CHCN. Notably, the use of methyl *tert*-butyl ether (MTBE) as the second organic phase enhances substrate loading, prevents spontaneous substrate hydrolysis, alleviates substrate inhibition of HHDH activity, improves product yields, and prolongs the lifetime of DH/*Cc*-PAA bioelectrode. By applying this two-phase bioelectrocatalytic system, different chiral β-hydroxy nitriles could be produced with high enantioselectivity (up to 96% ee).



Scheme 3 Two-phase bioelectrocatalytic system for the efficient synthesis of chiral β-hydroxy nitriles (mode I).

In recent years, the integration of electrochemistry and biocatalysis for the conversion of CO_2 into value-added chemicals has garnered significant attention.[15] The Plumere group presented a bioelectrocatalytic approach that combines electricity-driven cofactor NADPH regeneration with enzymatic CO_2 fixation for the stereoselective C–C bond formation (Scheme 4).[16] They employed 2,2′-viologen modified polyvinyl alcohol (V^{2+}-PVA) hydrogel as the redox polymer to co-immobilize ferredoxin $NADP^+$ reductase (FNR) with NADPH-dependent crotonyl-CoA carboxylase/reductase (Ccr) on electrode. The V^{2+}-PVA/FNR films showed excellent electrocatalytic activity and stabi-



Scheme 4 A bioelectrocatalytic approach for CO_2 fixation and the stereoselective C–C bond formation (mode I).

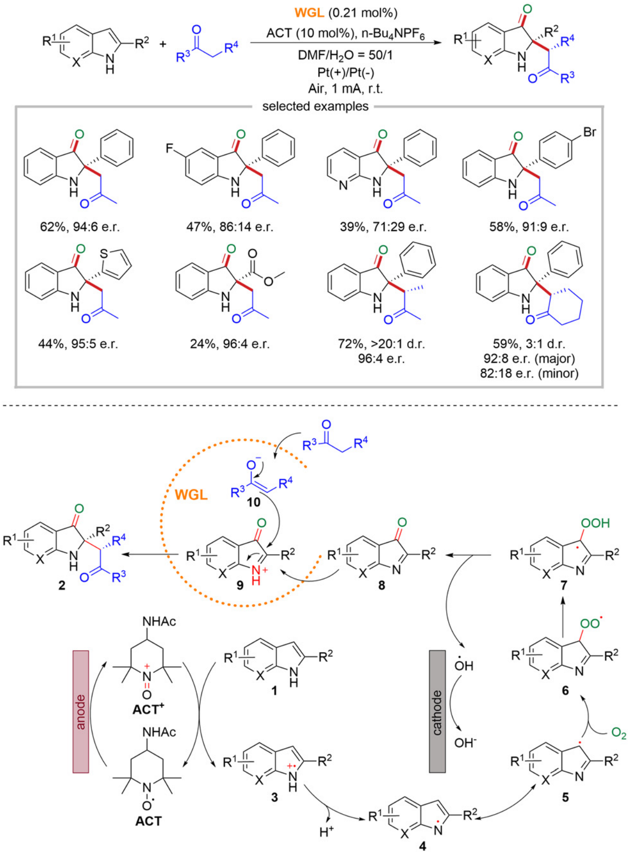
lity, providing efficient electron transfer from the electrode to FNR for reducing $NADP^+$ to NADPH. Sufficient supply of NADPH enabled the Ccr-catalyzed incorporation of CO_2 into crotonyl-CoA for the stereoselective generation of (2*S*)-ethylmalonyl-CoA. After optimization of conditions, the system was successfully scaled up to achieve a maximum yield of 57% and a faradaic efficiency of 91%.

The free diffusion of Ccr in solution generally leads to a significant decrease in reaction yields. Therefore, by co-immobilizing the enzymes within a smaller volume, the proximity of the biocatalysts facilitates rapid diffusive transport of intermediates and cofactors among the active sites of the enzymes, resulting in increased reaction rates and enhanced electrocatalytic performance.

Armstrong and co-workers reported a unique approach for driving and controlling enantioselective conversions by coupling nanoconfined enzyme cascades with bidirectional electrocatalysis.[17] They co-confined ferredoxin $NADP^+$ reductase (FNR) and alcohol dehydrogenase (ADH) variants within the nanopores of an indium tin oxide (ITO) layer to form (FNR + ADH)@ITO electrode. FNR catalyzed the rapid and reversible $NADP^+$/NADPH interconversion in a bidirectional manner controlled by the applied electrode potential. At the same time, ADH immediately recycled $NADP^+$ or NADPH to catalyze redox interconversions between ketone and secondary alcohol enantiomers. The deracemization of alcohols could be efficiently achieved through a two-stage process in one pot with two (FNR + ADH)@ITO electrodes in sequence. In the first stage, an electrode containing an enantioselective ADH variant selectively oxidized the undesired alcohol enantiomer to ketone. After a quick switch to the electrode containing another ADH variant with opposing enantioselectivity and a pH adjustment, the ketone was irreversibly reduced to the desired alcohol enantiomer with >90% ee in the second stage.

The majority of the established strategies that integrate biocatalysis and electrocatalysis were limited to oxidoreductases, while electrochemistry is used for cofactors regeneration.[18] In 2022, Guan and co-workers reported an innovative approach that combined enzymes other than oxidoreductases with electrosynthesis, going beyond cofactor regeneration and expanding the scope and synthetic potential of the integrated strategy.[19] They take advantage of the catalytic promiscuity of hydrolase with electrosynthesis for the asymmetric synthesis of complex chiral compounds (Scheme 5). Specifically, they carried out the enantioselective oxidative cross-coupling of 2-substituted indoles and simple ketones in an undivided electrochemical cell with wheat germ lipase (WGL) as the biocatalyst, platinum sheets as electrodes, 4-acetamido 2,2,6,6-tetramethyl-1-piperideoxy (ACT) as the redox mediator, $n\text{-}Bu_4NPF_6$ as electrolyte, and DMF/H_2O as the solvent. A wide range of 2,2-disubstituted 3-carbonyl indoles featuring a stereogenic quaternary carbon center could be successfully obtained with good yields (up to 78%), excellent enantioselectivity (up to 96 : 4 e.r.) and diastereoselectivity (>20 : 1 d.r.).

With regard to the mechanism, ACT is initially oxidized at the anode to generate ACT^+, which subsequently oxidizes substrate **1** to the N-centered radical cation **3** *via* single electron transfer. Then N-centered radical cation **3** undergoes deprotonation to generate N-centered radical **4.** Its resonance structure, the C-centered radical **5,** reacts with O_2 to produce radical **6,** which further undergoes hydrogen transfer to afford radical **7.** Subsequently, radical **7** cleaves a hydroxyl radical to produce intermediate **8.** In the active site of WGL, intermediate **8** is protonated to form the electrophilic cationic intermediate **9,** while ketone loses a proton to generate enolate **10,** which then

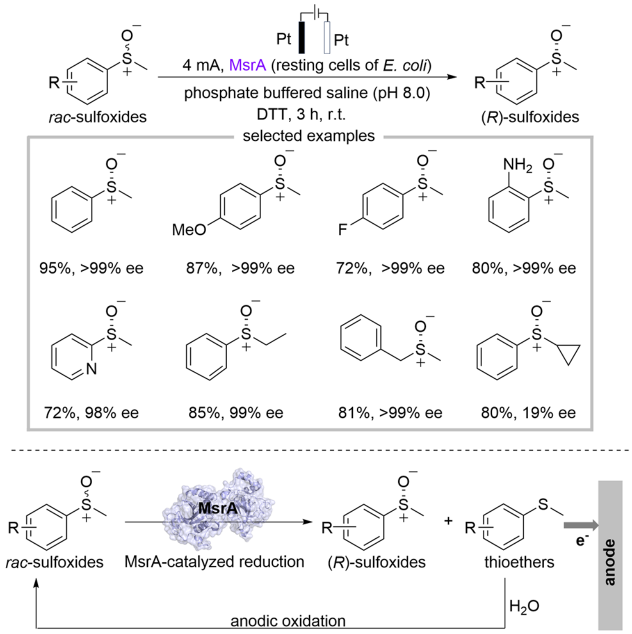


Scheme 5 Integration of the catalytic promiscuity of lipase (WGL) with electrosynthesis for asymmetric oxidative cross-coupling reaction (mode II).

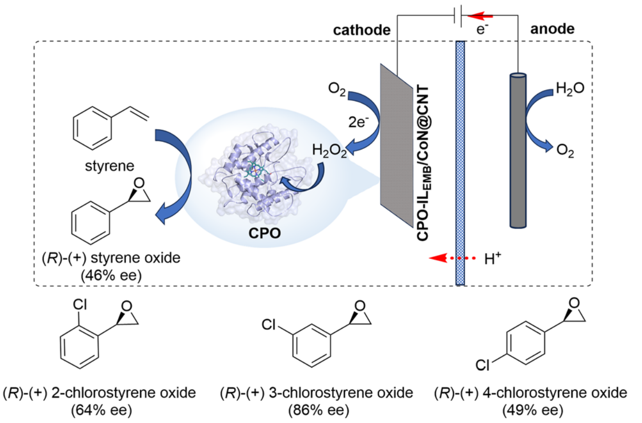
nucleophilically attacks intermediate **9** to yield the final product **2**.

Xu's group reported a deracemization strategy for achieving chiral sulfoxides through the combination of electrocatalysis and biocatalysis (Scheme 6).[20] The deracemization process was conducted in an undivided cell with platinum electrodes, methionine sulfoxide reductase A (MsrA) as the biocatalyst, dithiothreitol (DTT) as terminal reductants, and the phosphate buffered saline (PBS) as the electrolyte solution under 4 mA constant current in the atmosphere. Chiral sulfoxides can be achieved up to 95% yield with 99% ee by integrating MsrA-catalyzed reduction for kinetic resolution of racemic sulfoxides with the non-stereoselective anodic oxidation of thioethers. This strategy can be successfully applied to a wide range of substituted sulfoxides, showing good functional group tolerance. Remarkably, the reaction can be easily scaled up. Mechanistic experiments revealed that the anodic oxidation of thioethers proceeded *via* a radical pathway, and H_2O served as the oxygen atom source during the anodic oxidation process.

Recently, Chen and co-workers developed a one-pot electroenzymatic cascade platform that integrated the advantages of enzymatic catalysis and electrocatalysis for efficient asymmetric epoxidation of styrene derivatives (Scheme 7).[21] Chloroperoxidase (CPO), a heme-containing peroxidase, was functionalized using 1-ethyl-3-methylimidazolium bromide (IL_{EMB}) and immobilized on cobalt nitrogen-doped carbon nanotubes (CoN@CNT) to form CPO-IL_{EMB}/CoN@CNT biohybrid. This biohybrid was then dropped on electrode surfaces. The electrochemical measurements showed that CoN@CNT has excellent electrocatalytic properties for oxygen reduction, producing H_2O_2 with high Faradaic efficiency and rate. *In situ* electrogenerated H_2O_2 was directly utilized by CPO to catalyze the asymmetric epoxidation of styrene, with the merit of maintaining the high catalytic activity of CPO. In a sealed H-type electrolytic cell, CPO-IL_{EMB}/CoN@CNT achieved 27% styrene conversion within 30 min and yielded 46% ee of chiral styrene oxide with a cascade catalytic efficiency 17 times higher than that of free CPO-IL_{EMB} in solution. The universality of this electroenzymatic cascade platform was further validated by the successful epoxidation of various chloro-substituted styrene derivatives with high enantioselectivity (49–86% ee).



Scheme 6 Combination of electrocatalysis and biocatalysis for chiral sulfoxides (mode II).



Scheme 7 A one-pot electroenzymatic cascade platform for asymmetric epoxidation of styrenes (mode II).

In this highlight, the latest advances in asymmetric synthesis that integrate electrocatalysis and biocatalysis have been demonstrated. This versatile approach has gained prominence as it combines the advantages of both electrocatalysis and biocatalysis. By utilizing electricity as a clean energy source and employing enzymes with high stereoselectivity and even with catalytic promiscuity as biocatalysts, the green and efficient production of chiral chemicals can be achieved without the need for stoichiometric redox reagents while minimizing the production of by-products. Based on these inspiring breakthroughs, future development direction should focus on the following aspects.

(1) Exploring new types of enzymes for integration with electrocatalysis, which will greatly diversify the reaction types and broaden the application range.

(2) Further design and construction of novel and efficient electroenzymatic cascade reaction systems with good compatibility between enzymes and electrodes, which is crucial for realizing more enantioselective transformations.

(3) Applications of protein engineering such as directed evolution to enhance the activity and stability of enzymes under electrochemical and non-aqueous conditions to achieve new and interesting reactivity.

(4) Design and application of aqueous–organic biphasic media and improved enzyme immobilization techniques as pertinent strategies to improve reaction productivity.

(5) Exploring the non-natural activities of enzymes driven by electricity to achieve novel-to-nature reactivity,[22] which will

enhance the versatility of enzymes and open up exciting possibilities for new synthetic pathways and the discovery of novel reactions.

We envisage that the integration of biocatalysis and electrocatalysis will be a versatile approach for asymmetric synthesis, leading to more valuable stereoselective transformations and promising for a multitude of synthetic applications.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

Conflicts of interest

There are no conflicts to declare.

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References

1 (*a*) F. H. Arnold, Innovation by Evolution: Bringing New Chemistry to Life (Nobel Lecture), *Angew. Chem., Int. Ed.*, 2019, **58**, 14420–14426; (*b*) G. Qu, A. Li, C. G. Acevedo-Rocha, Z. Sun and M. T. Reetz, The Crucial Role of Methodology Development in Directed Evolution of Selective Enzymes, *Angew. Chem., Int. Ed.*, 2020, **59**, 13204–13231; (*c*) U. T. Bornscheuer, G. W. Huisman, R. J. Kazlauskas, S. Lutz, J. C. Moore and K. Robins, Engineering the third wave of biocatalysis, *Nature*, 2012, **485**, 185–194; (*d*) P. de María, G. de Gonzalo and A. Alcántara, Biocatalysis as Useful Tool in Asymmetric Synthesis: An Assessment of Recently Granted Patents (2014–2019), *Catalysts*, 2019, **9**, 802; (*e*) C. K. Winkler, J. H. Schrittwieser and W. Kroutil, Power of Biocatalysis for Organic Synthesis, *ACS Cent. Sci.*, 2021, **7**, 55–71; (*f*) Y. Lin, W. Xue, H. Li, B. Su, J. Lin and K. Y. Ye, Advances in Enzymatic Incorporation of Small Fluorine Modules, *Eur. J. Org. Chem.*, 2024, **27**, e202400003.

2 (*a*) X. Wang, T. Saba, H. H. P. Yiu, R. F. Howe, J. A. Anderson and J. Shi, Cofactor NAD(P)H Regeneration Inspired by Heterogeneous Pathways, *Chem*, 2017, **2**, 621–654; (*b*) M. Yuan, M. J. Kummer, R. D. Milton, T. Quah and S. D. Minteer, Efficient NADH Regeneration by a Redox Polymer-Immobilized Enzymatic System, *ACS Catal.*, 2019, **9**, 5486–5495.

3 (*a*) J. Dong, E. Fernández-Fueyo, F. Hollmann, C. E. Paul, M. Pesic, S. Schmidt, Y. Wang, S. Younes and W. Zhang, Biocatalytic Oxidation Reactions: A Chemist's Perspective, *Angew. Chem., Int. Ed.*, 2018, **57**, 9238–9261; (*b*) F. Hollmann, D. J. Opperman and C. E. Paul, Biocatalytic Reduction Reactions from a Chemist's Perspective, *Angew. Chem., Int. Ed.*, 2020, **60**, 5644–5665.

4 (*a*) R. A. Sheldon and D. Brady, The limits to biocatalysis: pushing the envelope, *Chem. Commun.*, 2018, **54**, 6088–6104; (*b*) H. Wu, C. Tian, X. Song, C. Liu, D. Yang and Z. Jiang, Methods for the regeneration of nicotinamide coenzymes, *Green Chem.*, 2013, **15**, 1773.

5 (*a*) C. Zhang, H. Zhang, J. Pi, L. Zhang and A. Kuhn, Bulk Electrocatalytic NADH Cofactor Regeneration with Bipolar Electrochemistry, *Angew. Chem., Int. Ed.*, 2022, **61**, e202111804; (*b*) Y. Li, G. Liu, W. Kong, S. Zhang, Y. Bao, H. Zhao, L. Wang, L. Zhou and Y. Jiang, Electrocatalytic NAD(P)H regeneration for biosynthesis, *Green Chem. Eng.*, 2024, **5**, 1–15; (*c*) H. K. Song, S. H. Lee, K. Won, J. H. Park, J. K. Kim, H. Lee, S. J. Moon, D. K. Kim and C. B. Park, Electrochemical Regeneration of NADH Enhanced by Platinum Nanoparticles, *Angew. Chem.*, 2008, **120**, 1773–1776; (*d*) L. Zhang, N. Vilà, G.-W. Kohring, A. Walcarius and M. Etienne, Covalent Immobilization of (2,2′-Bipyridyl) (Pentamethylcyclopentadienyl)-Rhodium Complex on a Porous Carbon Electrode for Efficient Electrocatalytic NADH Regeneration, *ACS Catal.*, 2017, **7**, 4386–4394.

6 (*a*) J. L. Röckl, D. Pollok, R. Franke and S. R. Waldvogel, A Decade of Electrochemical Dehydrogenative C,C-Coupling of Aryls, *Acc. Chem. Res.*, 2019, **53**, 45–61; (*b*) E. J. Horn, B. R. Rosen and P. S. Baran, Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method, *ACS Cent. Sci.*, 2016, **2**, 302–308; (*c*) S. R. Waldvogel and B. Janza, Renaissance of Electrosynthetic Methods for the Construction of Complex Molecules, *Angew. Chem., Int. Ed.*, 2014, **53**, 7122–7123; (*d*) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, Modern Electrochemical Aspects for the Synthesis of Value–Added Organic Products, *Angew. Chem., Int. Ed.*, 2018, **57**, 6018–6041.

7 (*a*) Y. Zheng, W. Lu, T. Ma and S. Huang, Recent advances in photochemical and electrochemical strategies for the synthesis of sulfonyl fluorides, *Org. Chem. Front.*, 2024, **11**, 217–235; (*b*) R. Shaw, N. Sihag, H. Bhartiya and M. R. Yadav, Harnessing photocatalytic and electrochemical approaches for C–H bond trifluoromethylation and fluoroalkylation, *Org. Chem. Front.*, 2024, **11**, 954–1014.

8 (*a*) J. C. Siu, N. Fu and S. Lin, Catalyzing Electrosynthesis: A Homogeneous Electrocatalytic Approach to Reaction Discovery, *Acc. Chem. Res.*, 2020, **53**, 547–560; (*b*) C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata and P. S. Baran, A Survival Guide for the "Electro-curious", *Acc. Chem. Res.*, 2019, **53**, 72–83.

9 (*a*) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu and L. Ackermann, Organic Electrochemistry: Molecular

Syntheses with Potential, *ACS Cent. Sci.*, 2021, **7**, 415–431; (*b*) M. Yan, Y. Kawamata and P. S. Baran, Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance, *Chem. Rev.*, 2017, **117**, 13230–13319.

10 (*a*) X. Chang, Q. Zhang and C. Guo, Asymmetric Electrochemical Transformations, *Angew. Chem., Int. Ed.*, 2020, **59**, 12612–12622; (*b*) K. Yamamoto, M. Kuriyama and O. Onomura, Anodic Oxidation for the Stereoselective Synthesis of Heterocycles, *Acc. Chem. Res.*, 2019, **53**, 105–120; (*c*) L. Li, Y. Li, N. Fu, L. Zhang and S. Luo, Catalytic Asymmetric Electrochemical α–Arylation of Cyclic β–Ketocarbonyls with Anodic Benzyne Intermediates, *Angew. Chem., Int. Ed.*, 2020, **59**, 14347–14351.

11 X. Huang, Q. Zhang, J. Lin, K. Harms and E. Meggers, Electricity-driven asymmetric Lewis acid catalysis, *Nat. Catal.*, 2018, **2**, 34–40.

12 (*a*) H. Chen, F. Dong and S. D. Minteer, The progress and outlook of bioelectrocatalysis for the production of chemicals, fuels and materials, *Nat. Catal.*, 2020, **3**, 225–244; (*b*) D. G. Boucher, E. Carroll, Z. A. Nguyen, R. G. Jadhav, O. Simoska, K. Beaver and S. D. Minteer, Bioelectrocatalytic Synthesis: Concepts and Applications, *Angew. Chem., Int. Ed.*, 2023, **62**, e202307780; (*c*) C. J. Long, Y. H. He and Z. Guan, Emerging Strategies for Asymmetric Synthesis: Combining Enzyme Promiscuity and Photo–/Electro–redox Catalysis, *Asian J. Org. Chem.*, 2023, **12**, e202200685.

13 H. Chen, R. Cai, J. Patel, F. Dong, H. Chen and S. D. Minteer, Upgraded Bioelectrocatalytic N_2 Fixation: From N_2 to Chiral Amine Intermediates, *J. Am. Chem. Soc.*, 2019, **141**, 4963–4971.

14 F. Dong, H. Chen, C. A. Malapit, M. B. Prater, M. Li, M. Yuan, K. Lim and S. D. Minteer, Biphasic Bioelectrocatalytic Synthesis of Chiral β-Hydroxy Nitriles, *J. Am. Chem. Soc.*, 2020, **142**, 8374–8382.

15 (*a*) R. Cai, R. D. Milton, S. Abdellaoui, T. Park, J. Patel, B. Alkotaini and S. D. Minteer, Electroenzymatic C–C Bond Formation from CO_2, *J. Am. Chem. Soc.*, 2018, **140**, 5041–5044; (*b*) M. Yuan, S. Sahin, R. Cai, S. Abdellaoui, D. P. Hickey, S. D. Minteer and R. D. Milton, Creating a Low–Potential Redox Polymer for Efficient Electroenzymatic CO_2 Reduction, *Angew. Chem., Int. Ed.*, 2018, **57**, 6582–6586; (*c*) S. K. Kuk, K. Gopinath, R. K. Singh, T.-D. Kim, Y. Lee, W. S. Choi, J.-K. Lee and C. B. Park, NADH-Free Electroenzymatic Reduction of CO_2 by Conductive Hydrogel-Conjugated Formate Dehydrogenase, *ACS Catal.*, 2019, **9**, 5584–5589; (*d*) G. Morello, B. Siritanaratkul, C. F. Megarity and F. A. Armstrong, Efficient Electrocatalytic CO_2 Fixation by Nanoconfined Enzymes via a C3-to-C4 Reaction That Is Favored over H_2 Production, *ACS Catal.*, 2019, **9**, 11255–11262; (*e*) Y. Guo, X. Hong, Z. Chen and Y. Lv, Electro-enzyme coupling systems for selective reduction of CO_2, *J. Energy Chem.*, 2023, **80**, 140–162; (*f*) X. Tan and J. Nielsen, The integration of bio-catalysis and electrocatalysis to produce fuels and chemicals from carbon dioxide, *Chem. Soc. Rev.*, 2022, **51**, 4763–4785.

16 L. Castañeda-Losada, D. Adam, N. Paczia, D. Buesen, F. Steffler, V. Sieber, T. J. Erb, M. Richter and N. Plumeré, Bioelectrocatalytic Cofactor Regeneration Coupled to CO_2 Fixation in a Redox–Active Hydrogel for Stereoselective C–C Bond Formation, *Angew. Chem., Int. Ed.*, 2021, **60**, 21056–21061.

17 L. Wan, R. S. Heath, C. F. Megarity, A. J. Sills, R. A. Herold, N. J. Turner and F. A. Armstrong, Exploiting Bidirectional Electrocatalysis by a Nanoconfined Enzyme Cascade to Drive and Control Enantioselective Reactions, *ACS Catal.*, 2021, **11**, 6526–6533.

18 (*a*) F. Hollmann, K. Hofstetter, T. Habicher, B. Hauer and A. Schmid, Direct electrochemical regeneration of monooxygenase subunits for biocatalytic asymmetric epoxidation, *J. Am. Chem. Soc.*, 2005, **127**, 6540–6541; (*b*) R. Wu, C. Ma and Z. Zhu, Enzymatic electrosynthesis as an emerging electrochemical synthesis platform, *Curr. Opin. Electrochem.*, 2020, **19**, 1–7; (*c*) H. Chen, T. Tang, C. A. Malapit, Y. S. Lee, M. B. Prater, N. S. Weliwatte and S. D. Minteer, One-Pot Bioelectrocatalytic Conversion of Chemically Inert Hydrocarbons to Imines, *J. Am. Chem. Soc.*, 2022, **144**, 4047–4056; (*d*) R. Wu, F. Li, X. Cui, Z. Li, C. Ma, H. Jiang, L. Zhang, Y. H. P. J. Zhang, T. Zhao, Y. Zhang, Y. Li, H. Chen and Z. Zhu, Enzymatic Electrosynthesis of Glycine from CO_2 and NH_3, *Angew. Chem., Int. Ed.*, 2023, **62**, e202218387.

19 C. J. Long, H. Cao, B. K. Zhao, Y. F. Tan, Y. H. He, C. S. Huang and Z. Guan, Merging the Non–Natural Catalytic Activity of Lipase and Electrosynthesis: Asymmetric Oxidative Cross–Coupling of Secondary Amines with Ketones, *Angew. Chem., Int. Ed.*, 2022, **61**, e202203666.

20 X. Duan, D. Cui, M. Wang, Y. Tian, J. Shi, Y. Wu, S. Liu, Z. Zhu and J. Xu, Deracemization of Sulfoxides Combining Electrocatalysis and Biocatalysis, *Chin. J. Chem.*, 2024, **42**, 3107–3112.

21 X. Zhu, Y. Ding, S. Li, Y. Jiang and Y. Chen, Electroenzymatic cascade reaction on a biohybrid boosts the chiral epoxidation reaction, *Sci. Bull.*, 2024, **69**, 483–491.

22 (*a*) D. C. Miller, S. V. Athavale and F. H. Arnold, Combining chemistry and protein engineering for new-to-nature biocatalysis, *Nat. Synth.*, 2022, **1**, 18–23; (*b*) Z. Liu and F. H. Arnold, New-to-nature chemistry from old protein machinery: carbene and nitrene transferases, *Curr. Opin. Biotechnol.*, 2021, **69**, 43–51.