ELECTROCHEMICALLY-DRIVEN, ENZYMATIC SYNTHESIS OF ORGANIC COMPOUNDS

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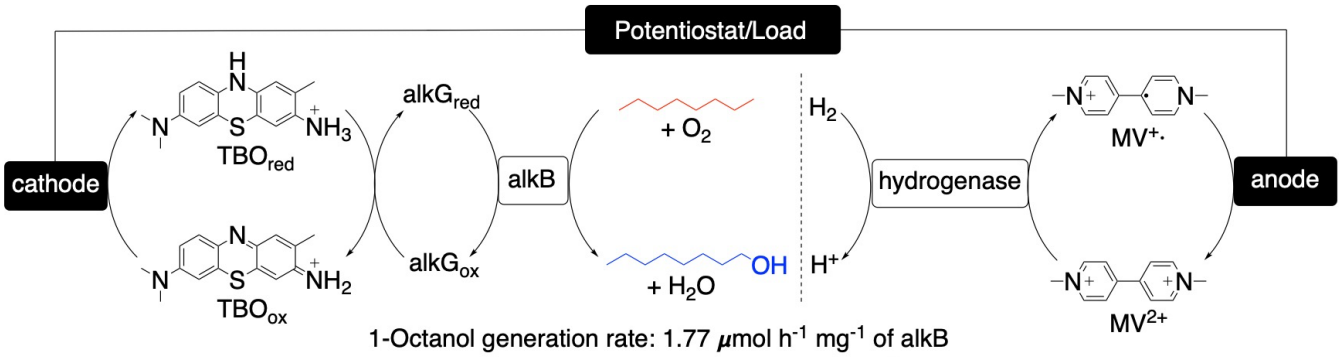
INTRODUCTION

Biocatalysis is a powerful tool in both organic synthesis and methodology development owing to its high specificity, activity and selectivity under mild reaction conditions. Electrocatalysis offers a clean and efficient alternative to traditional redox chemistry for generation of cofactors in biocatalytic systems, in which chemical oxidants or reductants are replaced by electricity. By coupling biocatalysis and electrocatalysis, "bioelectrocatalysis" aims to catalyze redox transformations at electrodes to prepare value-added molecules and renewable biofuels with the added features described above.[1]

ENZYMATIC ELECTROSYNTHESIS BY OXIDATION

Balancing reactivity and selectivity in the functionalization of inert aliphatic C-H bonds is difficult. Minteer and co-workers report a selective hydroxylation of terminal C-H bonds of alkanes catalyzed by alkane monooxygenase (alkB) in a biofuel cell with a coupled hydrogenase bioanode (Scheme 1).[2] Toluidine Blue O (TBO) shuttles electrons between the cathode and alkG/alkB which eliminates the need for unstable and costly NADH and NADH-reductase.

Scheme 1. AlkB Catalyzed Alkane C-H Hydroxylation in a Biofuel Cell



1-Octanol generation rate: 1.77 μmol h^{-1} mg^{-1} of alkB

Open circuit potential: 650 mV; Maximum current density: 318 μA cm^{-2}; Faradaic efficiency: 23%

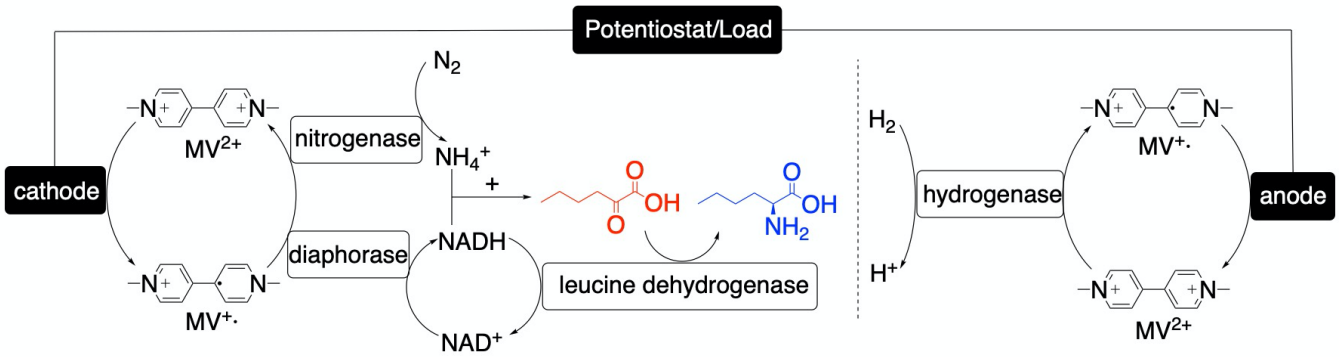
Peroxygenase is another promising biocatalyst for C-H functionalization. Holtmann and co-workers achieve the benzylic C-H hydroxylation of ethylbenzene by unspecific peroxygenase (AaeUPO).[3] Electrochemical, in-situ generation of H_2O_2 from O_2 protects the enzyme from deactivation by excess H_2O_2 and thus promotes the efficiency, which broadens its applicability.

ENZYMATIC ELECTROSYNTHESIS BY REDUCTION

The chemical inertness of N_2 introduces challenges in N_2 reductive fixation to valuable nitrogenous compounds. In 2017, Minteer and co-workers designed a bioelectrochemical Haber-Bosch mimic with a H_2/N_2 biofuel cell.[4] The reduction of N_2 to NH_3 catalyzed by MoFe nitrogenase and the oxidation of H_2

to H^+ by NiFe hydrogenase work together to fix N_2. To transform N_2 into nitrogenous organic compounds, enzyme cascades were developed by the same group using the system above. Prochiral α-keto acids, ammonia and NADH combine to synthesize amino acids by leucine dehydrogenase (Scheme 2).[5] Efficient regeneration of NADH by diaphorase and electron shuttle between electrodes and multiple enzymes by methyl viologen (MV) result in an impressive 87% Faradaic efficiency.

Scheme 2. Chiral Amino Acid Synthesis by Upgraded Bioelectrocatalytic N_2 Reduction System



L-Norleucine generation rate: 36 μmol L^{-1} h^{-1}, >99% *ee*

NH_3 conversion ratio: 92%; Maximum current density: ~42 μA cm^{-2}; Faradaic effiency: 87%

CONCLUSION AND FUTURE DIRECTIONS

Bioelectrocatalysis has been applied to various oxidation and reduction systems for the synthesis of organic compounds. Whereas biocatalysis provides uniquely high selectivity and reactivity, electrochemistry helps recycle expensive cofactors, generate substrates in situ and easily provide tunable potentials. However, the reaction types heavily rely on the innate reactivity of enzymes in the above examples. The choices of electron mediators are limited in consideration of enzymatic affinity and redox potential. Scaled-up biofuel cells are needed for higher current density output and product generation.

Enzymes with new-to-nature reactivities and better stability need further developments to employ such sophisticated systems. New, artificial electron mediators with high affinity towards enzymes and broad redox potentials could be designed to enhance the electron transfer efficiency. More biocompatible electrodes with better conductivity need to be invented from new material design and novel electrode modification methods.

REFERENCES

1. Minteer, S. D. et al. *Chem. Rev*. **2020**, *120*, 12903-12933.
2. Minteer, S. D. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 8969-8973.
3. Holtmann, D. et al. *J. Mol. Catal. B Enzyme*. **2016**, *133*, S137-S142.
4. Minteer, S. D. et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 2680-2683.
5. Minteer, S. D. et al. *J. Am. Chem. Soc.* **2020**, *142*, 4028-4036.