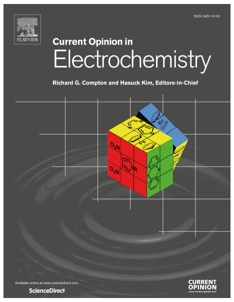

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Electrochemical Cascade Reactions for Electro-Organic Synthesis

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Abstract

Electrochemical cascades are an attractive tool for use in organic synthesis, providing an elegant pathway for one-pot synthesis of important chemical feedstocks. These cascade reactions typically consist of an electrochemical redox even that enables several (two or more) subsequent spontaneous chemical reactions. While classic organic cascades typically require stoichiometric amounts of reagents, especially reactive redox reagents, electrochemical methods replace stoichiometric reagents with an applied potential, offering a more sustainable synthetic route with high atom economy. This review highlights advances in the rapidly growing field by highlighting the use of metal-mediated, metal-free, and bioelectrocatlytic cascade reactions in electro-organic synthesis. As electrochemical cascade systems embrace the complexity and advances of modern electrochemical catalysis, there is likely to be greater increases in selectivity and efficiency.

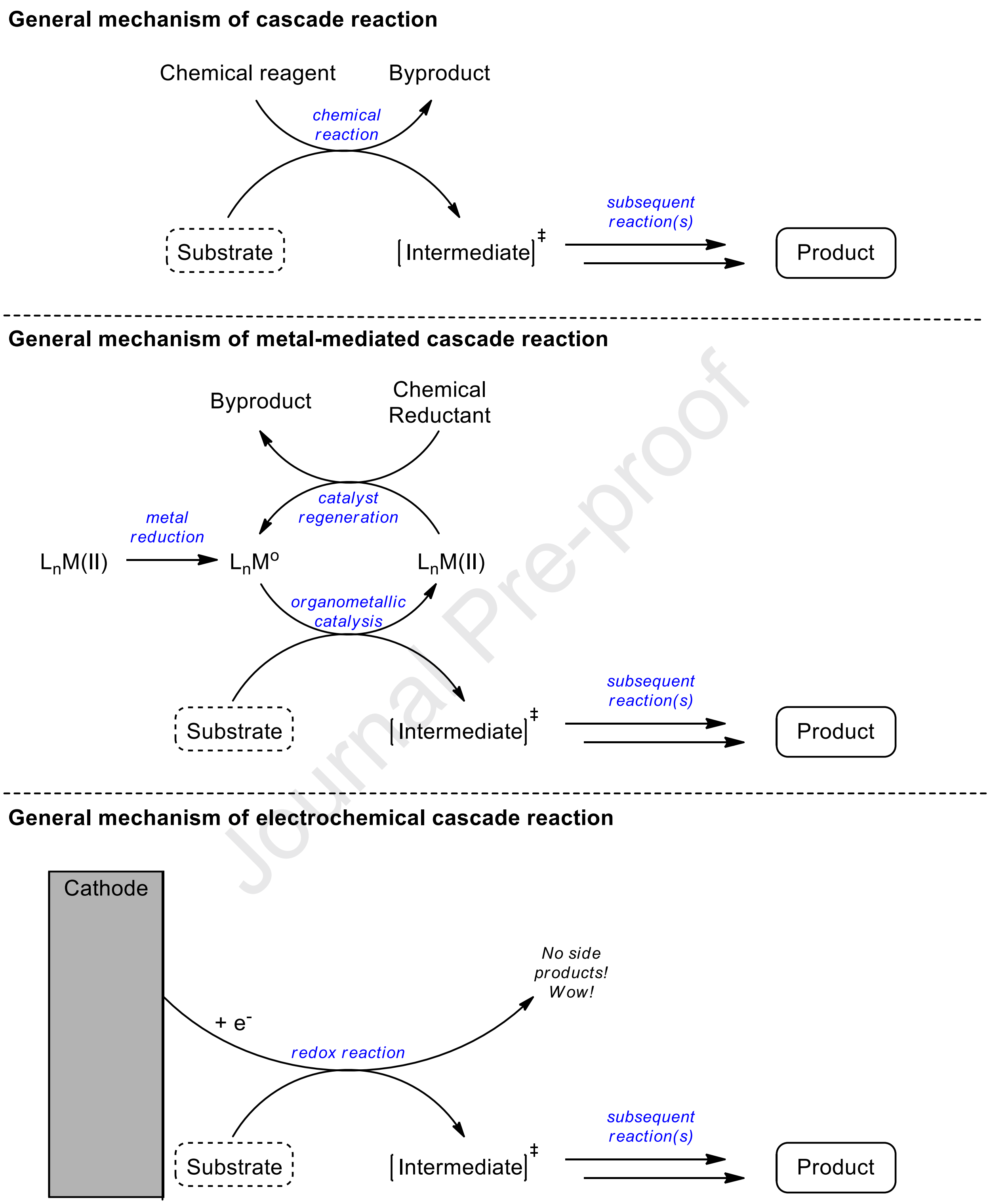
1. Introduction: Electrochemical Cascade Reactions

Cascade reactions, also called tandem or domino reactions, integrate two or more subsequent reaction steps into a single reaction mixture and serve as an extremely valuable strategy for synthesizing and modifying target molecules. Cascade reactions offer high atom economy while simultaneously decreasing the time and effort required for organic synthesis. A notable example of this is seen in the synthesis of Nicolaou's 2005 synthesis of (+)-rugulosin, an anthraquinoid mycotoxin sought after for its anti-HIV properties[1]. In a single step after the addition of MnO_2, an anthracene derivative was shown to undergo oxidation, two enolization, complete dimerization, and two Micheal reactions resulting in the complete transformation to a tricyclic monomer in a seven-step cascade sequence. This particular sequence was dubbed the cytoskyrin cascade and many other cascades are shown throughout literature in the synthesis of natural products. Consequently, significant advances have been made to developing cascade-driven methodology, as shown through the sheer volume of reviews published in the recent decades[2-5].

Separately from the development of cascade reactions, electrochemical methods for organic synthesis have seen a sharp rise in popularity and utility in the last decade. Electrochemical methods allow for the addition or removal of single electrons of defined energy by applying an electric potential, providing simple and direct access to specific redox reactions. Application of a potential generates highly reactive intermediates, which in turn provide access to new avenues of reactivity unattainable with conventional chemical reductants. The application of electrochemical methodology to organic synthesis has yielded several landmark electrosynthetic transformations such as the electrochemical Birch reduction[6], O-arylation[7], and Aza-Wacker cyclization[8] reactions. Outside of conventional lab settings, electrochemistry has been seen in large processes like the Simons Fluorination[9] and the Monsanto adiponitrile process[10]. Organic electrosynthesis is recognized as a methodology capable of performing redox transformations of compounds in an environmentally friendly manner at scale and thus has seen eager adoption in the commercial manufacturing of organic products[11, 12].

Since electrochemical methods are capable of generating highly reactive intermediates, they are uniquely suitable for initiating a diverse array cascade reactions. Generally, a cascade reaction requires an energetic input (i.e. an applied potential or redox event) to promote downstream spontaneous organic reactions. Hence, olefins and single-electron intermediates are routinely seen in cascade reactions. Types of reactions promoted by this initial redox event are nucleophilic, electrophilic, radical, pericyclic or transition-metal-catalyzed reactions, classifications coined by Nicolaou[3]. The scope of electrochemical cascades has been demonstrated to be expansive, and by the nature of electrochemical organic synthesis a large number of reactions can be classified as electrochemical cascades. For this review, the simple classification will be made between metal-mediated, non-metal mediated, and biologically mediated cascade reactions.

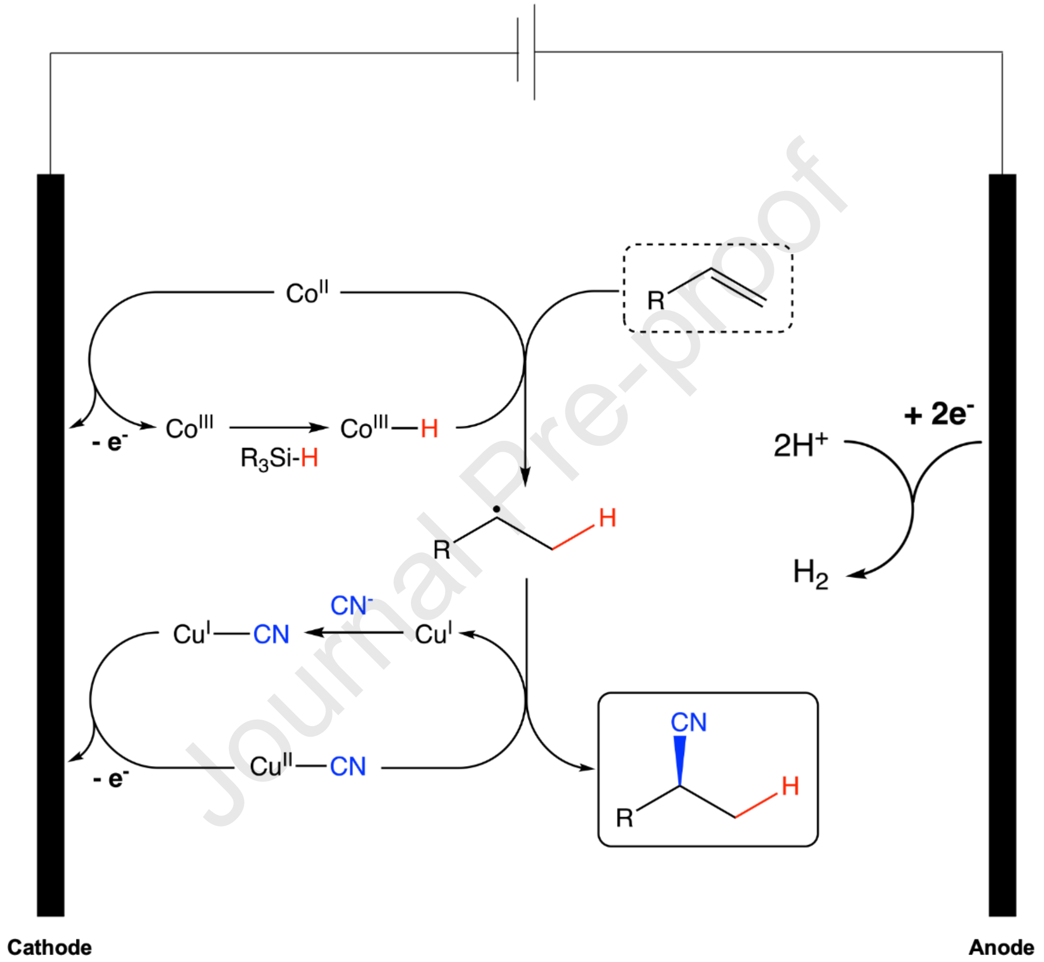
Electrochemical cascade reactions can undergo direct electron transfer or mediated-electron transfer reactions. In bioelectrosynthesis, mediated-electron transfer reactions are more commonly seen due to the limitations of active sites being deeply buried in insulating enzymes. Consequently, small molecule synthesis does not necessitate mediators; however, the use of electron transfer mediators has become more frequent in the past decade attributed to assisting in avoiding electrode passivation, exhibiting higher selectivity, as well as decreasing the needed redox potential for transformation[13]. In general, electrochemical cascade reactions are initiated through generating a reactive intermediate by either metal catalysis or redox chemistry. The reactive intermediate continues the cascade reaction until a product is formed, outlined in **Scheme 1**. This review highlights key examples of electrochemical cascade reactions from recent years. In particular, it emphasizes their application in the construction of high-value target molecules.



Scheme 1. Generalized schema for a) cascade reactions, b) metal-mediated cascade reactions, c) electrochemical cascade reactions. All of these cascades are initiated by the generation of a reactive intermediate.

2.1 Metal-Mediated Cascade Reactions

DiStasio and Lin devised the enantioselective hydrocyanation of alkenes using dual electrocatalysis[14]. This electrochemical cascade reaction takes advantage of a cobalt-mediated hydrogen atom transfer followed by a copper-catalyzed cyanation reaction yielding the hydrocyanation product (depicted in **Scheme 2**) with high functional group tolerance. Additionally, this reaction is a rare example of enantioselectivity in electroorganic synthesis; here, enantioselectivity was induced by using a chiral S-box ligand for the copper-mediated cyanation in the second catalytic cycle of the cascade.



Scheme 2. Schematic depiction of an enantioselective hydrocyanation reaction carried out via a bimetallic cascade reaction. Adapted from ref. [14].

Jamison et al. demonstrated an electrochemically reduced nickel catalyzed coupling of N-hydroxyphthalimide (NHP) esters with aryl halides[15]. Typically, these low valent nickel couplings require the addition of stoichiometric amounts of metal reductants (e.g., Zn. Mn) to reduce Ni(I/II) to Ni(0) and also require sensitive organometallics as transmetalling agents. To avoid these methods, an electrochemical cascade is initiated by the decarboxylation of a NHP ester to form a highly reactive alkyl radical. The alkyl radical then feeds into a nickel cross electrophile coupling that is reduced by the cathode. This decarboxylative C_{sp^3}–C_{sp^2} cross-coupling showed broad substrate scope and practical usage of carboxylic acids as precursors for cross-coupling.

Kakiuchi et al. reported aromatic C-H halogenation with the use of palladium and hydrogen halides[16]. An electrochemical cascade begins with the complexation of Pd to the pyridine, followed by the ortho-palladation, the addition of an electrochemically generated halogen cation, and dissociation of the palladium to afford the product without the use of more reactive halogens or chemical oxidants, with the only byproduct being H_2. In contrast to most other reactions outlined, the cascade is not initiated by an electrochemical redox event, but takes place at the end of the cascade.

Xu and Lu reported electrochemical coupling of heteroarylamines with tethered alkynes to produce indoles and azaindoles.[17] These pharmaceutically relevant indoles typically require extensive protections/deprotections. With the implementation of an electrochemical cascade system that begins with ferrocene mediated oxidation of the substrate that undergoes an intramolecular radical cyclization. This synthesis is carried out with only H_2 as a byproduct. Furthermore, the use of ferrocene as the sole mediator makes this an attractive process in contrast to other methods which require precious metal catalysts.

Lei introduced a Mn-catalyzed electrochemical cascade coupling of Benzimidazo-fused polycyclic scaffolds and alkyl boronic acids[18]. Alkyl boronic acids are stable and widely available precursors that are often used in Suzuki type reactions, but to activate these acids it often requires stoichiometric amounts of oxidant. Instead, this reaction proceeds via electrochemical activation of alkyl boronic acid to afford a radical, which is the first step of the cascade that affords the Benzimidazo-fused polycyclic scaffold. This strategy avoids the explosive diazo compounds and expensive transition metal catalysts, making an electrochemical cascade reaction a much safer, greener, and economical option in this synthesis.

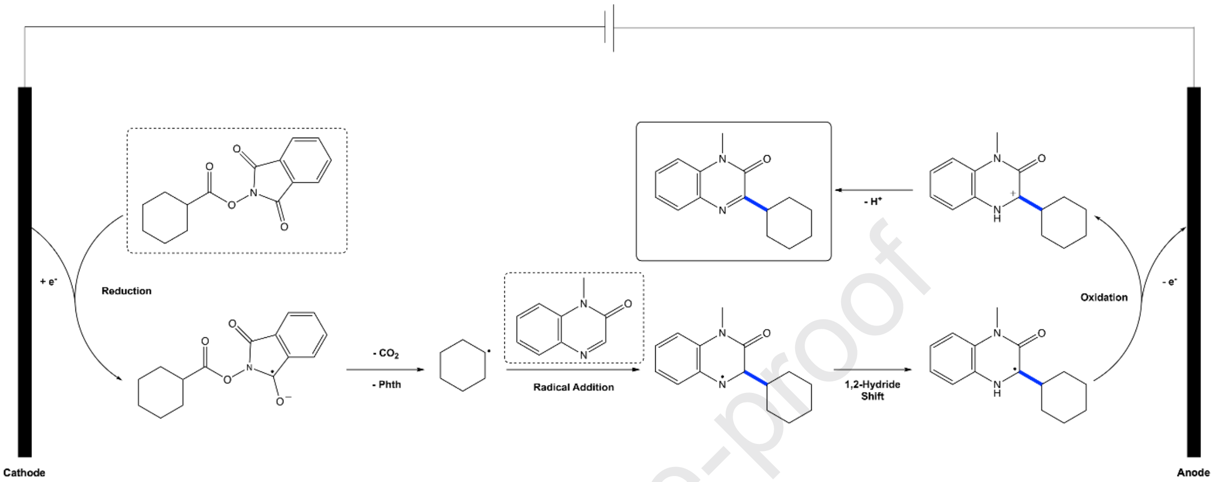
The Xu lab reported an electrochemically-induced polycyclic N-heteroaromatic generation through tandem diyne cyclizations[19]. Previously this cascade was initiated through tributyltin hydride single-electron transfer[20]; here, it was achieved by constructing polycyclic aromatic hydrocarbons with a urea substituent with a greater susceptibility to oxidation. Ferrocene is used as a redox mediator that radicalizes the amine via electrochemical oxidation that initiates a cyclization in tandem through radical interactions with the diynes. As a result, multiple cyclizations can form across the diynes simultaneously in a one-pot protocol. This reaction was shown at the gram-scale and boasts compatibility across a broad substrate scope with different functional groups at moderate yields.

2.2 Metal-Free Electrochemical Cascades

Minteer and Baran reported a metal-free electroreductive olefin-ketone coupling[21]. This electrochemical cascade is initiated by the electrochemical reduction of a ketone that performs homolytic cleavage of the olefin that eventually affords the coupled product. The precision of electrochemistry allows for the inclusion of air and water in the synthesis of the valuable tertiary alcohol, something typically not available with the organolithium and Grignard reagents.

In 2020 Wang introduced an electrochemical decarboxylative C3 alkylation of a wide range of quinoxalin-2(1H)-ones with NHP esters[22]. The cascade is initiated by the reduction of a

NHP ester to afford the reactive alkyl radical species that selectively adds to the C3 position of the quinoxalin-2(1H)-one. This product undergoes a 1,2–hydride shift, then electrochemically oxidized, and worked up to afford the product. This late-stage functionalization of the quinoxalinones was achieved through an undivided cell under constant current, and demonstrated use with a 3V battery in place of a potentiostat.



Scheme 3. Schematic depiction of a decarboxylative alkylation reaction that proceeds via the redox-active ester NHP; the redox-active nature of the NHP allows initiation of an electrochemical cascade reaction. Adapted from ref [22]

In 2013, Wang and Zha devised the one-pot synthesis of α-ketoamides via anodic oxidation from acetophenones and amines by using dioxygen as a reagent[23]. This electrochemical cascade reaction begins as an iodine-mediated radical initiation of the acetophenone, which is oxidized by O_2, eventually producing the desired α-ketoamide, without the use of transition metal catalysts or reactive halogenating reagents. This was applied to a variety of substrates to produce the desired α-ketoamides, including the uncommon use of primary aliphatic amines.

Sun and Zeng showed the transition metal-free synthesis of α-amino ketones through α-C-H functionalization of ketones[24]. Through the use of an electrochemical cascade iodination of the acetophenone, this is achieved with catalytic iodide to form the iodo-ketone, which undergoes nucleophilic substitution to afford the α-amino ketone. This electrochemical cascade increases yields from traditional methods while avoiding stoichiometric molecular iodide or iodide and a co-oxidant, making for a much greener synthesis.

Boydston and coworkers have developed a robust general procedure converting aldehydes to esters through oxidative electrolysis[25]. This cascade reaction is executed at a low chemical potential through a Breslow intermediate state before proceeding with esterification from the alcohol in solution. The electrolysis produces only the desired ester and hydrogen as a result of cathodic reduction. Furthermore, the ester formation has been demonstrated on a diverse range of substrates at near quantitative yields.

The Baran group has developed a scalable, inexpensive oxidation for remote alcohol and ketone generation that proceeds via an electrochemical cascade[26]. By employing a quinuclidine mediator across Ni/RVC electrode and HFIP, electrochemical oxidations can be performed on high-value products on distant methylene positions. Mechanistically, the oxidation is proposed to proceed through a radical abstraction assisted by a quinuclidine radical cation. The radical coordinates with O_2 before aerobic oxidation.

Senboku and coworkers developed a method for simultaneous aryl halide-olefin coupling and carboxylation utilizing a Pt and Mg electrode setup[27]. Mechanistically, this reaction is initiated through a single electron reduction at the aryl-halide, which undergoes radical cyclization in conjunction with the olefin. Finally, the radical coordinates with carbon dioxide resulting in a sequential radical cyclization-carboxylation in a single reaction step.

Xu and Moeller devised an amide-olefin cyclization technique to generate substituted pyrrolidine and piperidine rings[28]. The cascade is initiated by electrochemically oxidizing the olefin to generate a radical and a carbocation. The amine interacts with the radical to perform a cyclization. After hydrogen abstraction occurs due to the oxidative conditions, a pi bond reforms, which will be cis-methoxylated. The methodology can effectively cyclize five-membered rings, benefitting from LiOMe base and methanol solvent. Coupling can be performed at low temperatures in excellent yields.

Sun and Little developed a method for indoline synthesis under constant current electrolysis of n-substituted styrene[29]. Facile and environmentally-friendly, the transformation proceeds through an iodinium intermediate through the addition of $n\text{-}Bu_4NI$, which promotes cyclization before getting quenched by methanol solvent. The synthesis works solvent-less in moderate yields to good yields under various functional groups.

2.3 Bioelectrocatalytic Cascades

Biological cascades have also been adapted for use in electrosynthetic methodologies. Building off of naturally occurring modes of reactivity, these bioelectrosynthetic cascades can offer value-added products from cheap feedstocks that are not naturally occurring[30]. For example, Chen *et al.* reported a one-pot conversion of inert hydrocarbons to imine products, greatly simplifying existing synthetic pathways[31]. The first step of this cascade reaction was C-H activation and conversion of the hydrocarbon to primary alcohol, electrochemically mediated by the alkB protein. The alcohol was subsequently oxidized to an aldehyde by the $AcCO_6$ enzyme, and finally underwent reductive amination to produce the imine via the NfRedAm enzyme in an electrochemically mediated process. This multistep, multi-enzyme cascade shows the power and utility of bioelectrocatalysis in the synthesis of non-naturally occurring products.

Another key advantage of bioelectrocatalytic cascade reactions for organic synthesis is the inherent selectivity of biological systems. Electroorganic methods often progress through radical intermediates making enantioselective reactions rare. In contrast, enzymes and the electrochemical reactions they catalyze offer significant selectivity, including enantioselectivity. An example of this in cascade form was reported for the enzymatic electrosynthesis of chiral amines[32] and amino acids[33]. This cascade reaction operates via the electrochemical conversion of N_2 to NH_3 via the nitrogenase enzyme (and methyl-viologen redox mediator). The produced NH_3 is then utilized in the amination of racemic pyruvate to the chiral alanine via L-alanine dehydrogenase enzyme.

Finally, the cascade concludes via the transfer of the amine from alanine to a ketone substrate via w-transaminase resulting in the chiral amine product in 99% enantiomeric excess.

While these bioelectrocatalytic reactions are selective, a major limitation is the aqueous solubility of the organic products. To this end, Dong *et al.* reported a bioelectrochemical cascade that utilized a biphasic electrolyte in the synthesis of chiral beta-hydroxy nitriles[34]. In this system, a cascade reaction which converts 4-chloroacetoacetate to (R)-ethyl-4-cyano-3-hydroxybutyrate was carried out electrochemically via an S-specific alcohol dehydrogenase (AdhS) and a mutant halogen halohydrin dehalogenase (HHDH). Utilization of *tert*-butyl ether as organic phase allowed for increased uploading of the starting material, increased stability of cascade intermediates and increased Faradaic efficiency of the overall reaction. The ratio of product conversion was 8 times higher *with* the organic phase present, highlighting the impact of this strategy.

3. Conclusions: Outlook and Directions of Electrochemical Cascades

As the field of organic electrosynthesis has been driven by synthetic chemistry's embrace of the complexity of electrochemistry, we expect that the field of electrochemical cascades will benefit from expansion to multi-disciplinary electrochemical methods, including electro-photoredox[35] reactions and the use of complex solid-state catalysts such as metal-organic frameworks[36]. The integration of these fields will allow even greater synthetic challenges to be overcome. While the electrocatalysis community has been focused for decades on imparting selectivity for small molecule activation (CO_2, O_2, etc.) to electrode surfaces with new catalysts and nanostructures, the organic electrochemical community has only recently begun to explore the possibilities of surface-catalyzed electrochemical organic reactions[37]. In particular, advances in bimetallic or multimetallic nanoparticles[38] are of natural interest to the field of electrochemical cascade reactions, and could allow the execution of multiple, different metal-catalyzed reactions in a single cascade. Similarly, the use of nanostructures and electrode microenvironments[39, 40] (i.e. interfacial concentration profiles, pH gradients, or electric fields) to induce selectivity for CO_2 reduction products could be adapted to electro-organic cascades to influence the types of chemical steps in the cascade, such as inducing radical-polar crossover steps[41].

The principal challenge in electrochemical organic synthesis is the search for the "chiral electron", an electrochemical method with general enantioselectivity that can be extended to a variety of chemical transformations. Cascade electrosynthetic methods present a phenomenal opportunity to explore *induced* chirality via multistep chemical reactions. In a cascade reaction, the electrochemical step need not be enantioselective, but chirality could be induced at later steps in the cascade via a number of chiral auxiliaries such as a chiral catalysts[14] or chiral electrode[42]. While these concepts on their own are not novel, there is only a small amount of literature on them in the context of a multistep cascade reactions. The success of the multistep bioelectrocatalytic cascades in achieving enantioselectivity is encouraging of this approach.

While the list of cascade reactions here is by no-means exhaustive, it shows that there have been major developments in the use of electrochemical cascade reactions for organic synthesis. These developments coincide with the recent re-emergence of electrochemical methods in organic chemistry and take advantage of the selectivity afforded by electrochemical methods. It is this selectivity that allows the use of one-pot cascade reactions, saving time and resources in synthetic routes. Ultimately, these methods shift the field of electroorganic chemistry towards the central goal of *sustainable* and *selective* chemical reactions. The future of this field will depend on embracing the complexity of multi-disciplinary electrochemical systems to further enhance the selectivity of these multistep reactions.

Acknowledgements

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References

1. Nicolaou, K. C.; Lim, Y. H.; Papageorgiou, C. D.; Piper, J. L., Total Synthesis of (+)-Rugulosin and (+)-2,2′-epi-Cytoskyrin A through Cascade Reactions. *Angewandte Chemie International Edition* **2005,** *44* (48), 7917-7921.
2. Padwa, A.; Bur, S. K., The domino way to heterocycles. *Tetrahedron* **2007,** *63* (25), 5341-5378.
3. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G., Cascade Reactions in Total Synthesis. *Angewandte Chemie International Edition* **2006,** *45* (43), 7134-7186.
4. Nicolaou, K. C.; Chen, J. S., The art of total synthesis through cascade reactions. *Chemical Society Reviews* **2009,** *38* (11), 2993-3009.
5. Grondal, C.; Jeanty, M.; Enders, D., Organocatalytic cascade reactions as a new tool in total synthesis. *Nature Chemistry* **2010,** *2* (3), 167-178.
6. Peters, B. K.; Rodriguez, K. X.; Reisberg, S. H.; Beil, S. B.; Hickey, D. P.; Kawamata, Y.; Collins, M.; Starr, J.; Chen, L.; Udyavara, S.; Klunder, K.; Gorey, T. J.; Anderson, S. L.; Neurock, M.; Minteer, S. D.; Baran, P. S., Scalable and safe synthetic organic electroreduction inspired by Li-ion battery chemistry. *Science* **2019,** *363* (6429), 838-845.
7. Zhang, H. J.; Chen, L.; Oderinde, M. S.; Edwards, J. T.; Kawamata, Y.; Baran, P. S., Chemoselective, Scalable Nickel-Electrocatalytic O -Arylation of Alcohols. *Angewandte Chemie International Edition* **2021,** *60* (38), 20700-20705.
8. Yi, X.; Hu, X., Formal Aza-Wacker Cyclization by Tandem Electrochemical Oxidation and Copper Catalysis. *Angewandte Chemie International Edition* **2019,** *58* (14), 4700-4704.
9. Simons, J. H., Production of Fluorocarbons. *Journal of The Electrochemical Society* **1949,** *95* (2), 47.
10. Danly, D. E., Development and Commercialization of the Monsanto Electrochemical Adiponitrile Process. *Journal of The Electrochemical Society* **1984,** *131* (10), 435C-442C.
11. Pletcher, D.; Green, R. A.; Brown, R. C. D., Flow Electrolysis Cells for the Synthetic Organic Chemistry Laboratory. *Chemical Reviews* **2018,** *118* (9), 4573-4591.
12. Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R., Organic electrosynthesis: a promising green methodology in organic chemistry. *Green Chemistry* **2010,** *12* (12), 2099-2119.
13. Francke, R.; Little, R. D., Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chemical Society Reviews* **2014,** *43* (8), 2492-2521.

14. Song, L.; Fu, N.; Ernst, B. G.; Lee, W. H.; Frederick, M. O.; Distasio, R. A.; Lin, S., Dual electrocatalysis enables enantioselective hydrocyanation of conjugated alkenes. *Nature Chemistry* **2020, *12* (8), 747-754.
Achieving enantioselective hydrocyanation using electrochemically reduced cobalt hydrogenation and copper cyanation. This is a rare case of enantioselective electrochemical reactions.

15. Li, H.; Breen, C. P.; Seo, H.; Jamison, T. F.; Fang, Y.-Q.; Bio, M. M., Ni-Catalyzed Electrochemical Decarboxylative C–C Couplings in Batch and Continuous Flow. *Organic Letters* **2018,** *20* (5), 1338-1341.
16. Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T., Palladium-Catalyzed Aromatic C−H Halogenation with Hydrogen Halides by Means of Electrochemical Oxidation. *Journal of the American Chemical Society* **2009,** *131* (32), 11310-11311.
17. Hou, Z. W.; Mao, Z. Y.; Zhao, H. B.; Melcamu, Y. Y.; Lu, X.; Song, J.; Xu, H. C., Electrochemical C−H/N−H Functionalization for the Synthesis of Highly Functionalized (Aza)indoles. *Angewandte Chemie International Edition* **2016,** *55* (32), 9168-9172.
18. Yuan, Y.; Zheng, Y.; Xu, B.; Liao, J.; Bu, F.; Wang, S.; Hu, J.-G.; Lei, A., Mn-Catalyzed Electrochemical Radical Cascade Cyclization toward the Synthesis of Benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one Derivatives. *ACS Catalysis* **2020,** *10* (12), 6676-6681.
*19. Hou, Z.-W.; Mao, Z.-Y.; Song, J.; Xu, H.-C., Electrochemical Synthesis of Polycyclic N-Heteroaromatics through Cascade Radical Cyclization of Diynes. *ACS Catalysis* **2017,** *7* (9), 5810-5813.
Xu and coworkers report an electrochemically-induced radical cascade cyclization process to form three rings in a single step. This cyclization reaction is initiated by electrochemically reducing a tethered-urea group with a ferrocene catalyst. Used in the synthesis of polycyclic aromatic hydrocarbons.

20. Pati, K.; dos Passos Gomes, G.; Harris, T.; Hughes, A.; Phan, H.; Banerjee, T.; Hanson, K.; Alabugin, I. V., Traceless Directing Groups in Radical Cascades: From Oligoalkynes to Fused Helicenes without Tethered Initiators. *Journal of the American Chemical Society* **2015,** *137* (3), 1165-1180.
21. Hu, P.; Peters, B. K.; Malapit, C. A.; Vantourout, J. C.; Wang, P.; Li, J.; Mele, L.; Echeverria, P.-G.; Minteer, S. D.; Baran, P. S., Electroreductive Olefin–Ketone Coupling. *Journal of the American Chemical Society* **2020, *142* (50), 20979-20986.
Minteer and Baran labs show a scalable, chemoselective method to coupling unactivated olefins and ketones free of chemical reductants. By using electrochemical approach, this coupling avoids issues encountered with Grignard reagents in multistep syntheses.

*22. Niu, K.; Song, L.; Hao, Y.; Liu, Y.; Wang, Q., Electrochemical decarboxylative C3 alkylation of quinoxalin-2(1H)-ones with N-hydroxyphthalimide esters. *Chemical Communications* **2020,** *56* (78), 11673-11676.
Using quinoxalin-2(1H)-ones with N-hydroxyphthalimide esters to achieve alkylation without the use of metal catalysts. This demonstrates direct reduction/oxidation of the substrate with high functional group tolerance.

23. Zhang, Z.; Su, J.; Zha, Z.; Wang, Z., A novel approach for the one-pot preparation of α-ketoamides by anodic oxidation. *Chemical Communications* **2013,** *49* (79), 8982-8984.
24. Liang, S.; Zeng, C.-C.; Tian, H.-Y.; Sun, B.-G.; Luo, X.-G.; Ren, F.-z., Electrochemically Oxidative α-C–H Functionalization of Ketones: A Cascade Synthesis of α-Amino Ketones Mediated by NH4I. *The Journal of Organic Chemistry* **2016,** *81* (23), 11565-11573.

25. Finney, E. E.; Ogawa, K. A.; Boydston, A. J., Organocatalyzed Anodic Oxidation of Aldehydes. *Journal of the American Chemical Society* **2012,** *134* (30), 12374-12377.
*26. Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran, P. S., Scalable, Electrochemical Oxidation of Unactivated C–H Bonds. *Journal of the American Chemical Society* **2017,** *139* (22), 7448-7451.
Distant functionalization of unactivated C-H bonds was demonstrated by the Baran and coworkers. This simple methodology utilizes a quinuclidine mediator to perform electrochemical oxidation across remote methylene positions.

27. Senboku, H.; Michinishi, J.-Y.; Hara, S., Facile Synthesis of 2,3-Dihydrobenzofuran-3-ylacetic Acids by Novel Electrochemical Sequential Aryl Radical Cyclization-Carboxylation of 2-Allyloxybromobenzenes Using Methyl 4-tert-Butylbenzoate as an Electron-Transfer Mediator. *Synlett* **2011,** *2011* (11), 1567-1572.
28. Xu, H.-C.; Moeller, K. D., Intramolecular Anodic Olefin Coupling Reactions and the Synthesis of Cyclic Amines. *Journal of the American Chemical Society* **2010,** *132* (8), 2839-2844.
29. Liang, S.; Zeng, C.-C.; Luo, X.-G.; Ren, F.-Z.; Tian, H.-Y.; Sun, B.-G.; Little, R. D., Electrochemically catalyzed amino-oxygenation of styrenes: n-Bu4NI induced C–N followed by a C–O bond formation cascade for the synthesis of indolines. *Green Chemistry* **2016,** *18* (7), 2222-2230.
30. Lee, Y. S.; Lim, K.; Minteer, S. D., Cascaded Biocatalysis and Bioelectrocatalysis: Overview and Recent Advances. *Annual Review of Physical Chemistry* **2021,** *72* (1), 467-488.
31. Chen, H.; Tang, T.; Malapit, C. A.; Lee, Y. S.; Prater, M. B.; Weliwatte, N. S.; Minteer, S. D., One-Pot Bioelectrocatalytic Conversion of Chemically Inert Hydrocarbons to Imines. *Journal of the American Chemical Society* **2022, *144* (9), 4047-4056.
A demonstration of converting chemically inert hydrocarbons to active imine products utilizing a multienzyme cascade reaction with electrochemical cofactor regeneration. This conversion was achieved under mild conditions.

32. Chen, H.; Cai, R.; Patel, J.; Dong, F.; Chen, H.; Minteer, S. D., Upgraded Bioelectrocatalytic N2 Fixation: From N2 to Chiral Amine Intermediates. *Journal of the American Chemical Society* **2019,** *141* (12), 4963-4971.
33. Chen, H.; Prater, M. B.; Cai, R.; Dong, F.; Chen, H.; Minteer, S. D., Bioelectrocatalytic Conversion from N2 to Chiral Amino Acids in a H2/α-Keto Acid Enzymatic Fuel Cell. *Journal of the American Chemical Society* **2020,** *142* (8), 4028-4036.
34. Dong, F.; Chen, H.; Malapit, C. A.; Prater, M. B.; Li, M.; Yuan, M.; Lim, K.; Minteer, S. D., Biphasic Bioelectrocatalytic Synthesis of Chiral β-Hydroxy Nitriles. *Journal of the American Chemical Society* **2020,** *142* (18), 8374-8382.
35. Liu, J.; Lu, L.; Wood, D.; Lin, S., New Redox Strategies in Organic Synthesis by Means of Electrochemistry and Photochemistry. *ACS Central Science* **2020,** *6* (8), 1317-1340.

36. Safaei, M.; Foroughi, M. M.; Ebrahimpoor, N.; Jahani, S.; Omidi, A.; Khatami, M., A review on metal-organic frameworks: Synthesis and applications. *TrAC Trends in Analytical Chemistry* **2019,** *118*, 401-425.

37. Harwood, S. J.; Palkowitz, M. D.; Gannett, C. N.; Perez, P.; Yao, Z.; Sun, L.; Abruña, H. D.; Anderson, S. L.; Baran, P. S., Modular terpene synthesis enabled by mild electrochemical couplings. *Science* **2022,** *375* (6582), 745-752.

38. Loza, K.; Heggen, M.; Epple, M., Synthesis, Structure, Properties, and Applications of Bimetallic Nanoparticles of Noble Metals. *Advanced Functional Materials* **2020,** *30* (21), 1909260.

39. Xing, Z.; Hu, X.; Feng, X., Tuning the Microenvironment in Gas-Diffusion Electrodes Enables High-Rate CO2 Electrolysis to Formate. *ACS Energy Letters* **2021,** *6* (5), 1694-1702.

40. Liu, M.; Pang, Y.; Zhang, B.; De Luna, P.; Voznyy, O.; Xu, J.; Zheng, X.; Dinh, C. T.; Fan, F.; Cao, C.; de Arquer, F. P. G.; Safaei, T. S.; Mepham, A.; Klinkova, A.; Kumacheva, E.; Filleter, T.; Sinton, D.; Kelley, S. O.; Sargent, E. H., Enhanced electrocatalytic CO2 reduction via field-induced reagent concentration. *Nature* **2016,** *537* (7620), 382-386.

41. Zhang, W.; Lin, S., Electroreductive Carbofunctionalization of Alkenes with Alkyl Bromides via a Radical-Polar Crossover Mechanism. *Journal of the American Chemical Society* **2020,** *142* (49), 20661-20670.

42. Butcha, S.; Assavapanumat, S.; Ittisanronnachai, S.; Lapeyre, V.; Wattanakit, C.; Kuhn, A., Nanoengineered chiral Pt-Ir alloys for high-performance enantioselective electrosynthesis. *Nature Communications* **2021,** *12* (1), 1314.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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