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TUTORIAL REVIEW

A Tutorial on Asymmetric Electrocatalysis

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Electrochemistry has emerged as a powerful means to enable redox transformations in modern chemical synthesis. This tutorial review delves into the unique advantages of electrochemistry in the context of asymmetric catalysis. While electrochemistry has historically been used as a green and mild alternative for established enantioselective transformations, in recent years asymmetric electrocatalysis has been increasingly employed in the discovery of novel asymmetric methodologies based on reactions mechanisms unique to electrochemistry. This tutorial review first provides a brief tutorial introduction to electrosynthesis, then explores case studies on homogenous small molecule asymmetric electrocatalysis. Each case study serves to highlight a key advance in the field, starting with the historic electrification of known asymmetric transformations and culminating with modern methods relying on unique electrochemical mechanistic sequences. Finally, we highlight case studies in the emerging reasearch areas at the interface of asymmetric electrocatalysis with biocatalysis and heterogeneous catalysis.

1. Introduction

The preparation of enantiopure compounds has been a focal point of organic synthesis for decades, given the prevalence of chiral centers in biological settings and the influence of homochirality on macroscopic material properties, and asymmetric catalysis is one of the most effective strategies for forging asymmetric bonds.[1] Relative to alternative approaches based on chiral auxiliaries,[2] chiral pool synthesis,[3] or chiral resolution,[4] asymmetric catalysis offers advantages such as fewer reaction steps, greater generalizability, and improved atom economy. An important sub-category of asymmetric catalytic reactions are redox reactions, in which prochiral starting materials may be oxidized or reduced to provide enantioenriched products in the chiral environment of a catalyst. Notably, the 2001 Chemistry Nobel Prize was awarded jointly to K. Barry Sharpless, for his development of oxidative asymmetric catalysis, and to William S. Knowles and Ryoji Noyori, for their work on asymmetric hydrogenation (reduction).[5–7] Twenty years later, the 2021 Chemistry Nobel Prize was awarded to Benjamin List and David MacMillan for their pioneering work in organocatalysis—including the formal oxidation of carbonyl compounds via enamine catalysis, which remains a cornerstone in the field today.[8,9]

In recent decades, electrocatalysis has emerged as an enabling tool for redox transformations in chemical synthesis.[10–12] In an electrosynthetic transformation, organic substrates are oxidized or reduced by directly injecting or removing electrons at a cathode or anode, respectively. The application of electricity as an external, tunable energy source enables thermodynamically challenging transformations to take place at sufficiently reducing or oxidizing potentials. Electrochemistry additionally offers the experimentalist granular control over the applied electrode potential and therefore the opportunity to achieve selective electron-transfer to desired species or functional groups in complex settings featuring multiple reacting sites. Moreover, as sustainability grows increasingly central to modern chemistry research, electrochemistry has been hailed as a promising avenue for the decarbonization of the chemical and pharmaceutical industries, through its use of electricity as an alternative to wasteful and potentially hazardous chemical agents. Owing to these unique features, electrochemistry has begun to penetrate every corner of organic synthesis over the past several years, including asymmetric catalysis.

The earliest developments in asymmetric electrocatalysis were focused on the translation of known enantioselective redox transformations carried out with chemical reagents into electricity-driven processes.[13,14] While these pioneering contributions served as important proof-of-principle that electrochemistry is compatible with asymmetric catalysis, only relatively recently, beginning in the 2010s, have the unique capabilities of electrochemical synthesis been extensively exploited to expand the scope of known chemical transformations and for the development of novel enantioselective reactions. In this tutorial review, we present a focused discussion of the unique advantages of electrochemistry in the context of asymmetric catalysis through selected literature examples (for more comprehensive surveys of advances in asymmetric electrochemistry, the reader is referred to a number of excellent review articles[15–21]). In Section 2, we provide a brief introduction to electrosynthesis and discuss some advantages of electrolysis over traditional

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methodologies. In Section 3, we present several case studies of homogeneous small molecule asymmetric electrocatalysis that serve to highlight key advances in the field. Finally, Section 4 explores new developments in asymmetric electrocatalysis at the interface of heterogenous catalysis and biocatalysis.

2. A Brief Introduction to Organic Electrosynthesis

This section aims to provide a concise overview of the historical development and technical basics of organic electrosynthesis, with a focus on mechanistic considerations that are pertinent to asymmetric electrocatalysis. For more comprehensive reviews of electrosynthesis and electrocatalysis, the reader is referred to recent reviews.[10–12,22] Furthermore, for practical tutorials on electrosynthesis, we refer readers to essays by Baran,[23] Schotten and Williams,[24] and Hilt.[25]

2.1. The history and renaissance of organic electrosynthesis

The history of organic electrosynthesis (Fig. 1) is almost as old as the history of modern organic chemistry. Faraday discovered one of the first C–C bond-forming reactions in 1834,[26] generating ethane from the anodic decarboxylation of acetate, just six years after the landmark Wöhler urea synthesis.[27] Following a more detailed study by Kolbe in 1848, this oxidative double-decarboxylative coupling of carboxylic acids became known as the Kolbe electrolysis.[28] Kolbe also reported the first reductive organic electrosynthesis in 1845 when he electrolyzed trichloromethane sulfonic acid to provide the dechlorinated methyl sulfonic acid, employing zinc electrodes.[29] These seminal contributions laid the groundwork for the use of electrochemistry in organic synthesis, culminating in the discovery of notable transformations such as the Hofer-Moest reaction (1902)[30] and the Shono oxidation (1975)[31] as well as the invention of industrial processes for the production of fine chemicals such as lysmeral and adiponitrile.[32,33] However, while the field of organic chemistry continued to flourish and expand throughout the 1900s and early 2000s, electrochemistry was marginalized and often considered as a niche subject by the broader synthetic community.

In the mid-2010s, electrosynthesis experienced a resurgence, and in 2022, the number of publications in the field reached its peak since the 1920s.[11,34] This renaissance has been driven by several factors, one of the most prominent being that electrochemistry has unlocked a vast reaction space previously uncharted using traditional chemical or photochemical strategies. As organic synthesis continues to be a rate-limiting factor in the discovery of novel functional molecules such pharmaceuticals, agrochemicals, and materials,[35] interest in novel organic transformations and synthetic strategies continues to grow.[36–38] With its many distinct characteristics and capabilities, electrochemistry is uniquely suited for the invention of reaction methodologies and to enable efficient pathways for previously challenging or even impossible syntheses. Additionally, with increasing attention on the environmental impact of chemical synthesis, electrochemistry stands as a desirable "green" alternative to traditional redox modalities using stoichiometric chemical oxidants and reductants.

Finally and importantly, another driving factor for the recent broad adoption of electrochemistry in the synthetic community is the development of commercial standardized reactors, ranging from microscale high-throughput screening platforms (HTe^-Chem[39]) to batch preparative electrolysis setups (Electrasyn 2.0[40], IKA Screening System[41]) to continuous flow systems that allow for kilogram-scale operation of electrosynthetic transformations.[42] These readily available electrolysis reactors have now been adopted by numerous academic and industrial laboratories around the world and have helped further propel the emergence of organic electrochemistry as a prominent subfield of organic chemistry.

2.2. Components of an electrochemical reaction

In traditional chemical redox reactions, free energy is supplied in the form of oxidants or reductants, whose oxidizing or reducing potentials are innate properties that cannot be tuned. In contrast, in electrosynthesis, the oxidizing or reducing power afforded by electricity can be precisely dialed in. Each electrochemical system consists of two redox half reactions, the reductive half reaction at the cathode and the oxidative half reaction at the anode. Often, only one of the two half reactions is of interest to convert a given starting material to the desired product in a net-oxidative or net-reductive transformation. The electrode at which the desired transformation takes place is referred to as the working electrode. The other redox half reaction provides the source of redox equivalents by indirectly consuming the electrons (in a net oxidation) or holes (in a net reduction) generated at the working electrode. This process takes place at the counter electrode, ultimately converting a sacrificial reagent to often innocuous side products. Because the thermodynamic driving force of an electrochemical reaction is provided by an external power supply, the sacrificial reagent does not need to be potent enough to directly oxidize or reduce the stating material, thereby allowing for the desired transformation to take place under milder conditions, and often with improved chemoselectivity and atom economy relative to analogous chemical transformations. The development of an electrosynthetic reaction requires tuning of common reaction parameters, such as catalyst, additive, concentration, and temperature, as well as parameters specific to electrochemistry, which are discussed in the following paragraphs.[42] Overall, although operating an electrochemical reaction may initially appear to be labor intensive to non-specialists, it presents several attractive advantages that may prove ultimately beneficial for specific synthetic applications (as discussed in detail in Section 3 through various case studies).

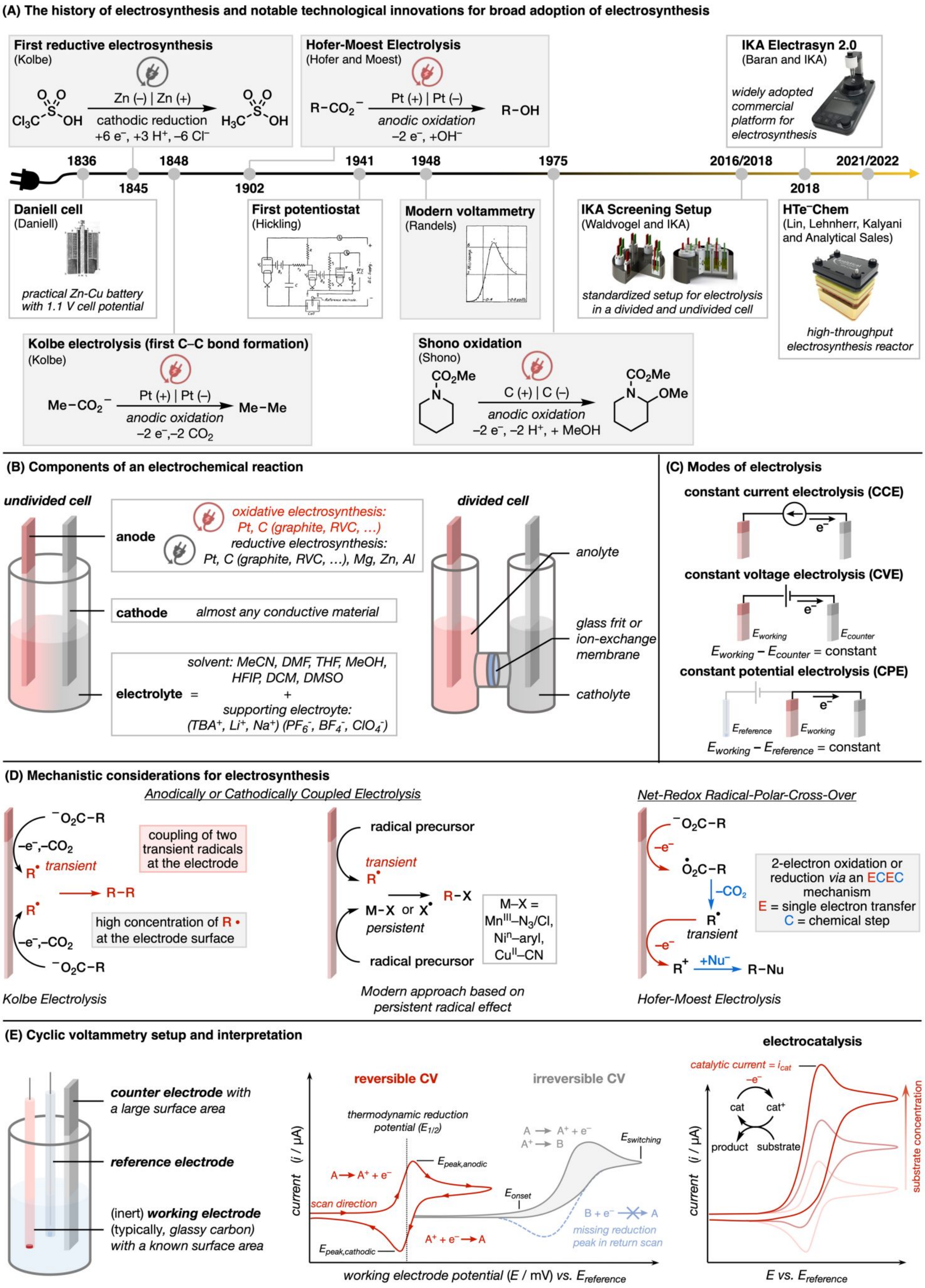

Fig. 1 Brief introduction to electrochemistry in organic synthesis.

Reactor. Electrosynthetic reactions can be carried out in two types of electrolysis vessels, an undivided cell or a divided cell (Fig. 1B).[25] In an undivided cell, the anode and cathode are placed in the same compartment, resulting in a simple setup employing common laboratory apparatuses such as flasks, vials, or beakers. In this system, both oxidative and reductive half reactions happen in the same solution. While the counter electrode reaction often does not interfere with the working electrode reaction, it has been shown in certain systems that this redox half reaction can either productively or deleteriously affect the desired transformation.[43] If the latter is true, a divided cell can be employed to suppress undesired cross reactivity between anodic and cathodic half reactions. In such a system, the anodic and cathodic compartments are separated by a glass frit, which allows for slow diffusion of any charged or uncharged species, or an ion-exchange membrane, which is permeable to ions but not neutral species. With this division, the redox half reactions taking place at the opposite electrodes operate independently and interfere minimally with one another.[44]

Electrodes. In theory, any conducting material can be used as an electrode in electrosynthesis. Two main factors are often considered when choosing an electrode, the stability of the electrode material under the applied potentials and its reactivity in the desired redox transformation. During electrolysis, the rate at which an electron transfer event takes place is not only determined by its intrinsic thermodynamic potential (given by the Nernst equation), but also the ability of the electrode surface to interact with the chemical entities before and after electron transfer. Thus, driving a given redox half reaction also requires the application of an overpotential—which is strongly dependent on the electrode material—in addition to the thermodynamic potential. The overpotential can be considered as the kinetic barrier for electron transfer, and overpotentials are documented in literature for common processes such as the hydrogen evolution reaction (HER) and the reduction of alkyl halides.[45] Guided by knowledge of the stability and reactivity of electrode materials, the initial screening of electrodes is often also carried out on a trial-and-error basis. While considering electrode material can be daunting to beginners, this additional parameter also offers the opportunity for the discovery of novel reactivities and the optimization of reaction outcomes.

To help support confidence in electrode choice, we offer some considerations for those new to electrosynthesis. Common working electrodes for anodic electrolysis include carbon-based materials, such as graphite, glassy carbon, and boron-doped diamond, as well as platinum, owing to their stability at highly oxidizing potentials.[45,46] Common working electrodes for cathodic electrolysis include carbon as well as metals and their alloys, such as nickel, platinum, brass, and nichrome.[45,46] In addition to plate- or wire-shaped electrodes, porous electrodes may be used to enhance the rate of electron transfer as a result of their greater surface areas. Several porous conducting materials are readily available such as carbon felt, carbon cloth, reticulated vitreous carbon (RVC), and nickel foam.

Two criteria are often considered when selecting suitable counter electrode reactions. The first is that the reaction should not interfere with the desired working electrode reaction (assuming that the system is not operating under a paired electrolysis scenario), and the second is that the process should be fast that it does not become the rate-limiting process in the overall reaction. For anodic oxidation, the most common counter electrode reaction is the HER, where protons from mild acids (e.g., water, alcohols, acetic acid) are reduced at the cathode to generate hydrogen as an innocuous side product. Platinum, stainless steel, and nickel are the most commonly used counter electrodes, owing to their low overpotentials (and correspondingly fast kinetics) for HER. Alternatively, if the reaction is sensitive to protic conditions, the reduction of other mild oxidants such as quinones and oxygen may be adopted.

In cathodic electrolysis, sacrificial anodes made form metals with low reduction potentials (e.g., magnesium, zinc, aluminium) are most frequently employed as counter electrodes. During electrolysis, these metals are oxidized to the corresponding cations and are dissolved into the electrolyte solution or precipitate as insoluble salts. While these cations are electrochemically inert, they may or may not interact with the homogenous reactants as Lewis acids.[47,48] Alternatively, recent advances have shown that homogenous sacrificial reductants can be employed in lieu of sacrificial metal anodes, in combination with an inert electrode such as carbon and platinum.[49] The most common sacrificial reductants are amines (e.g., triethylamine and diisopropylethylamine) and phosphines (e.g., triphenylphosphine). In such a system, the counter electrode itself is not consumed during the electrolysis. As such, these homogeneous systems are more amenable to large-scale synthesis and make it possible to integrate electroreductive reactions with continuous flow technology, thereby providing an additional avenue to conveniently scale up such transformations. Nonetheless, the oxidation of the sacrificial reductants often results in the release of protons into solution, which may interfere with the desired working electrode reaction.

Electrolyte. The reaction medium in electrolysis is referred to as the electrolyte. The electrolyte typically consists of a polar solvent and a supporting electrolyte that is added to ensure conductivity. Typically, redox inert salts are employed as supporting electrolytes (for example, cations: Li^+, Na^+, NR_4^+ with R = alkyl; anions: PF_6^-, BF_4^-, TfO^-, ClO_4^-). While the supporting electrolyte does not actively participate in the reaction, its identity and concentration has a crucial role in the reaction yield and selectivity, as it dictates the composition and microstructure of the interface between the solution and the electrode where most electrochemical reactions take place.[50,51] Solvents that are used in electrosynthesis need to dissolve the supporting electrolyte and remain intact under the applied anodic and cathodic potentials.[52] Typical solvents used include acetonitrile, dimethylformamide, methanol, water, tetrahydrofuran, and dichloromethane. Solvents frequently used in traditional asymmetric catalytic reactions that rely on weak non-covalent interactions, such as toluene, hexanes, and diethyl ether, are typically not tolerated in electrosynthesis due to their low dielectric constants.[23]

Electrocatalyst. To improve the kinetics of an electron transfer event or to impart additional selectivity, a homogeneous or heterogeneous electrocatalyst can be used.[10] In homogenous electrocatalysis, a molecular catalyst (e.g., a transition metal complex, halide, aminoxyl radical, etc.) is oxidized or reduced at an inert working electrode surface (e.g., carbon or platinum) and then reacts with the substrate to generate the product. In contrast, in heterogenous electrocatalysis, the surface of the electrode (e.g., a metal oxide) directly acts as the catalyst, which functions by chemically interacting with the substrate and lowering the kinetic barrier for its oxidation or reduction. Both homo- and heterogeneous electrocatalytic strategies can be used in asymmetric catalysis and are discussed in Sections 3 and 4, respectively.

2.3. Modes of electrolysis

There are three distinct modes of electrolysis that are commonly employed in organic electrosynthesis (Fig. 1C).[53] The most common mode of operation is constant current electrolysis (CCE). In this scenario, a current of a set magnitude is applied between the working and counter electrodes until a desired amount of charge has been passed to achieve full conversion of the starting material.[53] The total charge is often 2 F/mol, as most organic electrosynthetic reactions involve overall two-electron oxidation or reduction, although sometimes charge is passed in excess of this amount to ensure complete conversion when competing side reactions can also occur. The reaction time needed can be exactly calculated using the equation charge = current × time. Because electrosynthetic reactions are typically limited by the rate of electron transfer, CCE allows for precise control over the reaction rate. Additionally, the current can be optimized to match the catalyst turnover frequency, thereby suppressing any racemic background reactions that are not promoted by the catalyst. In contrast, similar control in traditional chemical systems is often challenging to achieve, and often accomplished either through the slow release or slow addition of reagents.[54]

A second mode of electrolysis is constant potential electrolysis (CPE). Precise control over the applied potential at the working electrode is achieved using a three-electrode setup, including a reference electrode.[53] In this case, a constant potential is applied between the working and the reference electrodes, and the potential at the counter electrode is automatically adjusted to sustain the current needed for the working electrode reaction. In an electrocatalytic reaction, the potential of the working electrode is often conveniently set around the halfwave potential ($E_{1/2}$) of the catalyst. The advantage of this technique is that it allows for exquisite selectivity for the desired electron transfer at the set potential and, in combination with cyclic voltammetry (see Section 2.4), can offer insights into the reaction mechanism. However, owing to the use of an additional reference electrode, CPE is often considered to be operationally involved and is difficult to integrate with high-throughput experimentation.

A third mode of operation is constant voltage electrolysis (CVE), where a constant cell voltage is applied between working and counter electrodes. In this case, the observed current is dependent on the identity and concentration of the species reacting at the two electrodes. As the reaction progresses and substrate is depleted, the current decreases, and for some transformations the progressive decrease in current can suppress undesired side reactions (such as over-oxidation or over-reduction). This mode of electrolysis boasts advantages of both CCE and CPE, as it utilizes a convenient two-electrode setup and provides a means to maintain relatively stable electrode potentials for improved chemoselectivity.

2.4. Mechanistic considerations for electrosynthesis

In electrochemistry, reagents undergo single-electron transfers at electrode surfaces.[55] Most formally two-electron reduction or oxidation reactions proceed via sequential single electron transfer events with intermediate chemical steps.[55] Of note, the chemoselectivity for single-electron transfers—which is based on redox potentials and kinetics—often does not correlate with the selectivity for concerted two-electron redox chemistry, which couples group- or atom-transfer to the formal electron transfers.[38] For instance, conjugate π systems (e.g., extend aromatic groups) that are largely inert under traditional two-electron redox conditions may be readily activated in a single electron paradigm, granting access to radical cations or radical anions.[56] In contrast, aliphatic ketones can undergo facile reduction to the corresponding alcohols with hydride agents but are often resistant to single-electron reduction.[56] Functional groups such as alkenes can participate in both chemical and electrochemical redox processes, but they give rise to distinct species in each case: a chemical reaction with peracids yields epoxides, whereas single-electron anodic oxidation of alkenes produces radical cations that can undergo diverse difunctionalization or cycloaddition reactions. This orthogonal selectivity serves as a basis for the excellent and complementary functional group tolerance observed in many electrochemical protocols, which is particularly attractive in the transformation of polyfunctional molecules.[38,57]

It is also instructive here to highlight how electrochemical transformations differ mechanistically from chemical and photochemical redox reactions. In chemical reactions utilizing conventional oxidants and reductants, the reagents are dissolved and distributed evenly in the reaction mixture. Likewise, photoredox chemistry provides a homogenous source of redox equivalents, which however is highly dilute due to the requirement of photon absorption prior to electron transfer.[36] In contrast, electron transfer in electrochemistry occurs at the electrode-solution interface. This localization of redox activity facilitates the buildup of high concentration of reactive intermediates in a confined space. In addition, the magnitude of the applied driving force or even the polarity of current can be altered on demand during electrolysis. Finally, electrochemistry affords access to highly biased potentials not readily attained in chemical or photochemical systems, and therefore allows for reactivity far from thermodynamic equilibrium, while under mild conditions.[10] These features give rise to unique mechanistic sequences (Fig. 1D), such as cathodically or anodically coupled electrolysis (for the latter, see Section 3.3, case study 5), net-reductive or oxidative radical-polar crossover (for the latter, see Section 3.3, case study 6), and rapid alternating polarity electrolysis, some of which have been employed recently in the realm of asymmetric electrocatalysis to enable reactions that are not achievable with traditional chemical approaches.

2.5. Cyclic voltammetry as a tool for studying reaction mechanisms

Electrochemistry has traditionally been utilized in various analytical applications, with voltammetry and spectroelectrochemistry serving as common tools for studying highly reactive and non-isolable intermediates.[58,59] These analytical techniques have been extensively covered in accessible tutorial reviews. [58,59] Here, we provide only a brief background of cyclic voltammetry to facilitate understanding of case studies involving electroanalysis in the development of asymmetric electrocatalysis.

Cyclic voltammetry (CV) is the most commonly employed electroanalytical technique for organic redox reactions (Fig. 1E).[59] Cyclic voltammograms are measured in a three-electrode setup with a working electrode, a counter electrode, and a reference electrode. [60] This brief discussion will focus on oxidation, although the same principles also apply to reduction. During a simple CV experiment, the current is recorded as the potential at the working electrode is linearly increased (i.e., anodic sweep) at a constant sweeping rate (measured in mV/s) until an artificially set switching potential is reached. The potential is then decreased (i.e., cathodic sweep) until it returns to the original value. The measured current—which results from both the capacitive charging of the working electrode (background) and the oxidation of the analyte (faradaic current)—is then plotted against the potential at the working electrode.

The faradaic current is correlated with the concentration of the analyte in the bulk solution, the rate of electron transfer, and the diffusion of the analyte (A) to the electrode surface. In systems where the electron transfer is facile and the overall redox reaction is diffusion limited, which is the case for most electrocatalytic systems, a current peak will be observed. If the oxidized form of the analyte generated in the anodic sweep (A^+) is stable on the timescale of the CV scan, it will be reduced during the cathodic sweep back to the original analyte, leading to a reduction peak with the same area as the oxidative peak—a characteristic of a reversible reaction on the CV timescale. In contrast, the absence of a clear and symmetrical reduction peak indicates that the oxidized analyte undergoes a chemical reaction on the CV timescale. The timescale is in turn related to the scan rate, which is a tunable experimental parameter. Scanning between 0–500 mV takes 0.5 seconds at a scan rate of 1000 mV/s but requires 3.3 minutes at a scan rate of 5 mV/s. For a reversible redox couple, the average potential of the anodic and cathodic peaks ($E_{1/2}$) quantifies the thermodynamic redox potential of the A^+/A redox couple. In the case of irreversible oxidation, cyclic voltammetry still enables the qualitative estimation of the redox potential in the form of half-peak potential or current onset potential for the oxidation.

Cyclic voltammetry can be used to quantify the kinetics of electrocatalysis. Most electrocatalysts exhibit a reversible CV response, as their oxidized/reduced forms must remain sufficiently stable to allow for multiple turnovers without undergoing decomposition. When a substrate is introduced to the catalyst solution, the observed anodic current increases, and the cyclic voltammogram of the catalyst becomes irreversible. The reaction between the substrate and the oxidized catalyst regenerates the original catalyst, which is then re-oxidized at the electrode. Through this process, each catalyst molecule undergoes multiple oxidations, resulting in an enhanced anodic current, the magnitude of which can be correlated with the turnover frequency and substrate concentration. Quantitative analysis enables the determination of rate constants for the reaction between the active catalyst and the substrate, as well as the rate law. This approach has been employed in the development of asymmetric catalytic reactions, as illustrated in Section 4.

3. Case studies in asymmetric electrocatalysis

The case studies discussed below were chosen to highlight key conceptual, mechanistic, and practical advances in asymmetric electrocatalysis. Case studies 1 and 2 present examples where, in lieu of strong chemical redox reagents, metal catalysts are turned over on the anode or cathode to achieve Sharpless dihydroxylation[57] or cross-electrophile coupling (XEC),[58] respectively. Alternatively, electricity can be used as an elegant means to access reactive electrophiles or nucleophiles that are challenging to prepare and isolate. An example of this approach is demonstrated in case study 3, where chiral enamine nucleophiles react with electrogenerated electrophiles in an organocatalytic system.[13,61,62] Electrochemistry can also provide a selective and mild avenue for the turnover of a redox-active catalyst, thereby expanding the functional group tolerance; this approach is demonstrated in case study 4, where desymmetrization of diols containing labile olefins is achieved.[57] Finally, case studies 5 and 6 highlight two reaction systems that are uniquely enabled by electrochemistry. In case study 5, formation of chiral benzylic nitriles is realized through anodically coupled electrolysis.[51,63–65] In case study 6, valuable chiral 1,4-dicarbonyls compounds are obtained from two enol equivalents through a cross-nucleophile coupling *via* an oxidative radical-polar crossover.[66]

3.1. Electrifying known transformations by replacing stoichiometric chemical redox agents

There are many examples in the literature of reactions carried out electrochemically using relatively innocuous reagents that would otherwise require far more reactive species when performed using traditional chemical routes. As such, electrosynthesis can in principle be used to carry out desired transformations in a safer, more scalable, and greener fashion than traditional redox approaches.[67] For example, in electrochemical syntheses, halide salts can be oxidized at the anode to provide reactive halogen species, with the sole by-product being hydrogen generated from proton reduction at the cathode, whereas the equivalent chemical reaction would require the use of an electrophilic halogen source.[68] Indeed, as discussed in this section, the earliest examples of asymmetric electrocatalysis leveraged an electric current to provide the redox equivalents in lieu of stoichiometric chemical oxidants and reductants to improve the greenness, safety, and scalability of well-established traditional asymmetric catalysis.

3.1.1. Effecting catalyst turnover using electricity

Case study 1: electrocatalytic Sharpless dihydroxylation

In traditional redox reactions, energy is needed in the form of chemical oxidants or reductants. In many cases, these same transformations can also be driven by an external electric current,[10] obviating the need for strong chemical oxidants and reductants. Consequently, such reactions can be carried out using milder conditions and with greater atom economy and scalability.[67] For instance, oxidative reactions can often be carried out under electrochemical conditions using an anode as the electron sink in lieu of a conventional stoichiometric oxidant.[67] The anode can either be used to turn over the oxidant, thereby reducing its loading to only a catalytic quantity, or to directly remove electrons from the reaction substrate, thus eliminating the use of a strong oxidant entirely. In many examples in the literature protons are used as mild terminal oxidants, which indirectly accept electrons removed from the substrate and are then reduced on the cathode to innocuous H_2 by-product.[67]

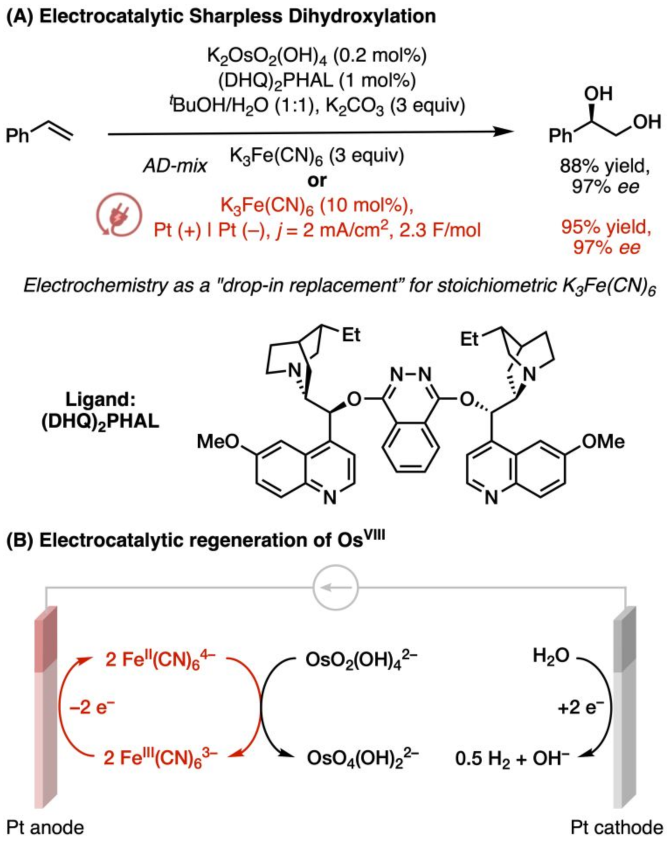

Fig. 2 (A) Chemical and electrochemical conditions for the Sharpless Dihydroxylation. (B) Scheme for the mediated anodic regeneration of Os^{VIII}.

This principle was demonstrated in one of the earliest examples of asymmetric electrocatalysis from Torii and co-workers,[14] wherein an electric current was used to drive the venerable Sharpless dihydroxylation[69] towards the synthesis of enantioenriched vicinal diols. The reaction developed by Sharpless relied on stoichiometric quantities of the highly toxic and volatile OsO_4, which adds to an alkene enantioselectively in the presence of a quinine-derived chiral ligand; following hydrolysis of the resulting osmate ester, the corresponding diol product is obtained.[69] Subsequent development of a catalytic system using $K_3Fe(CN)_6$ as a stoichiometric oxidant significantly enhanced the practicality of the system and culminated in the commercialization of "AD-mix", which contains the ligand, K_2CO_3 as a buffer, terminal oxidant $K_3Fe(CN)_6$, and $K_2OsO_2(OH)_4$ as a non-volatile Os source (Fig. 2A).[70] While this protocol significantly improved the safety and synthetic utility of the methodology, the reaction still generates two equivalents of $K_4Fe(CN)_6$ waste.[71] To circumvent this issue, Torii and co-workers employed electrochemical regeneration of $Fe(CN)_6^{3-}$ through anodic oxidation of $Fe(CN)_6^{4-}$, leveraging the rapid electrokinetics of this reversible redox process.[14] In this electrocatalytic system, water (a co-solvent with tert-butanol) serves as an innocuous terminal oxidant, while $K_3Fe(CN)_6$ instead serves as a redox mediator. As such, the loading of this salt could be reduced from three equivalents to 10 mol%, with the only stoichiometric by-product being hydrogen that is released at the cathode (Fig. 2B). No other changes to the original AD-mix system or optimization were required, and the electrolysis tolerated a panel of alkene substitution patterns, with enantioselectivities and yields comparable to those achieved under chemical conditions. Of note, this work was an improvement over a similar previous contribution by Amundson,[72] and more recently, Moeller adopted the same transformation in a photoelectrochemical system using a photovoltaic to drive the electrocatalytic reaction with sunlight as the ultimate energy source.[73]

Akin to the dihydroxylation, Torii and co-workers rendered the Jacobsen epoxidation electrocatalytic by replacing the perquisite hypochlorite with chloride and electricity.[74] The same principle has also been employed by Page and Marken in organocatalytic olefin oxidation using iminium-based catalysts. In this system, the catalyst react with an electrochemically generated persulfate or percarbonate to provide an electrophilic chiral oxaziridine, which is primed for face-selective oxygen-atom transfer to an alkene nucleophile.[75]

A more recent example of using electrochemistry to achieve known reactivity under milder conditions was reported by Ackermann and co-workers.[76] Their laboratory previously pioneered a series of oxidative Co-catalyzed C–H functionalization reactions that relied on stoichiometric silver(I) or copper(II) salts or molecular oxygen as oxidants. Molecular oxygen is a desirable oxidant that generates water as the only by-product, although it can present an explosion hazard at larger scales.[76] Ackerman and colleagues replaced stoichiometric oxidants with anodic oxidation, thereby achieving good atom economy and an improved safety profile, with H_2 produced as a sole by-product.[76] Moreover, they rendered this class of transformations enantioselective using chiral phosphoric acids, synthesizing a wide range of point or axially chiral products, notably allowing for the desymmetrization of various phosphorous (P)-stereogenic compounds.[77]

Case study 2: cathodic reductions in asymmetric cross-electrophile coupling

Electrosynthetic approaches are often more scalable, reproducible, and exhibit improved kinetic profiles when compared to corresponding traditional routes that employ heterogeneous oxidants and reductants.[32,33] For instance, metal powders (e.g., Mg, Zn, or Mn) frequently employed in reductive coupling reactions can in principle be replaced by cathodic reduction coupled with a bulk metal sacrificial anode (see Section 2.2).[11] While the overall reaction remains the same, by separating substrate reduction and oxidation of the metal reductant, the electrochemical system can circumvent several challenges encountered with the use of metal powders. For example, strongly reducing metal powders are pyrophoric and often require pre-activation *via* acid washes and storage under inert conditions to prevent passivation. Further, because metal particle size and activity can vary from batch to batch,[78] reaction reproducibility may be negatively affected, and kinetic studies can become subject to particle size and stir-rate dependencies. Finally, the scale up of reactions relying on metal powders is also challenging, due in large part to difficulties in controlling the mass transport and heterogenous reaction rate as well as the need to remove excessive reductant via filtration.

In contrast, an electrochemical reduction employing a bulk sacrificial anode (often a commercially available metal plate or rod) does not suffer from the above drawbacks. Indeed, these electrodes typically do not require pre-activation because upon application of an electric current, any oxide layer on the anode metal surface will be removed and dissolved in the solution. These electrodes are also readily recovered and reused. Further, as discussed in Section 2.3, the rate of an electrochemical reaction is proportional to the magnitude of the current, which thus makes these reaction systems more reproducible and easier to regulate.

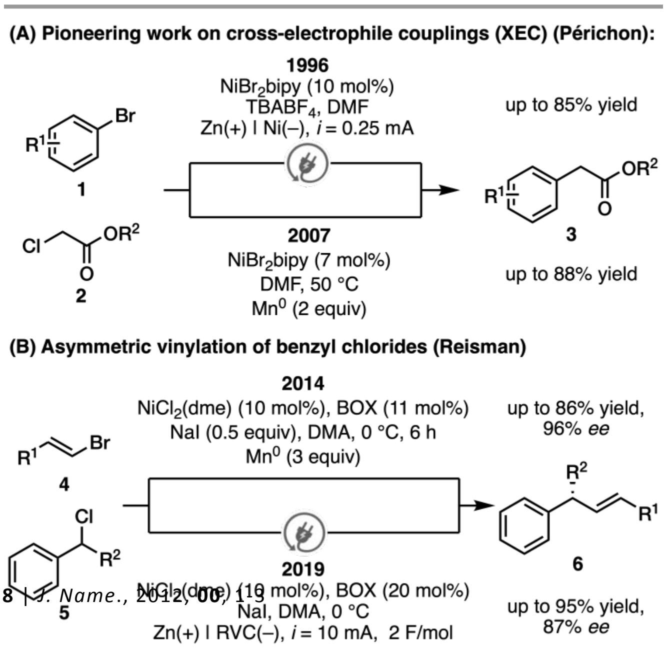

Fig. 3 Ni catalysed reductive cross electrophile coupling. (A) Périchon first developed an electrochemical approach for XEC followed by a chemical route. (B) The asymmetric XEC from Reisman was first enabled by metal reductant and then electrochemistry.

Transition metal-catalyzed reductive cross-electrophile coupling (XEC) reactions are one class of transformations that have been significantly optimized through the use of cathodic reductions in electrosynthesis. These reactions have become a ubiquitous tool to forge C–C bonds in organic synthesis, due to the improved commercial and synthetic availability of electrophiles when compared to analogous carbon-nucleophiles, which are typically prepared by metal insertion to the corresponding organohalides.[79] Ni catalysts are typically employed in these reactions, where a commonly proposed mechanism starts with oxidative addition of an aryl halide to an in-situ generated Ni^0 complex.[80] The resulting Ni^{II}–aryl adduct combines with an alkyl radical (generated *in situ*) and then undergoes reductive elimination to release the cross-coupling product and a Ni^I intermediate. This Ni^I species reacts with an alkyl halide to generate the aforementioned alkyl radical and Ni^{II}, which is reduced by a metal powder reductant or electrochemistry to regenerate the active Ni^0 species. More recently, Ni-catalyzed XEC reactions have also been rendered enantioselective using suitable chiral ligands such as bisoxazolines (BOX).[78,81]

In 1996, Périchon and co-workers reported the first electrochemical XEC reaction between aryl halides (**1**) and activated alkyl halides (**2**) (Fig. 3A).[82] In this study, $NiBr_2bipy$ was introduced to an undivided cell equipped with a Ni or stainless-steel cathode and an Al or Zn sacrificial anode. In 2007, Périchon demonstrated that the same transformation can also be carried out using Mn powder as the chemical reductant at an elevated temperature under very similar conditions.[83] As a side note, this system represents a rare example of a well-established transformation in modern organic synthesis that was developed first using electrochemistry and then expanded to non-electrochemical conditions. This scenario has, however, become more common in recent years following the renaissance of organic electrosynthesis, as also exemplified in Section 3.3.

In 2014, Reisman and co-workers reported an asymmetric variant of the $C(sp^2)$–$C(sp^3)$ XEC reaction between vinyl bromides (**4**) and benzyl chlorides (**5**), catalyzed by Ni ligated with a chiral BOX ligand in the presence of Mn^0 as the terminal reductant,[81] under similar conditions to those reported by Périchon in 2007[83] (Fig. 3B). Although this reaction provides a broad range of coupling products (**6**) with high enantioselectivity, the authors noted that the heterogeneous metal reductant gave rise to reproducibility issues due to the unpredictable stirring effects and batch-to-batch variability in metal activity, and the reaction generates excessive waste.[81] These issues were circumvented in an electrochemical approach that the authors developed in a follow up study in

2019.[78] In the new reaction, Mn^0 was replaced with an RVC cathode and a sacrificial Zn anode, and NaI was used as supporting electrolyte. In addition to providing a conducting solution, NaI was previously shown to enhance the reactivity and enantioselectivity in the chemical system,[81] in part due to activation of the electrophiles through halide exchange. These reaction conditions were readily carried out on a synthetically relevant, gram-scale in a batch reactor simply by increasing the electrode size and the applied current.

3.1.2: In-situ generation of reactive intermediate via electrochemical activation of reactants.

Case study 3: carbonyl α-functionalization via organocatalysis

As discussed in Section 2.3, electrochemistry provides a controlled approach for the generation of redox equivalents, much like a syringe pump for electrons and holes, that promotes the conversion of reactants, reagents, and catalysts to their activated states. This feature was illustrated in case studies 1 and 2 wherein the catalyst turnover was achieved with an electrode rather than by means of the use of a strong, stoichiometric oxidant or reductant. In this case study, we discuss three related examples in which anodic oxidation was utilized for the *in situ* generation of reactive intermediates from reactants. The relevant intermediates from the first and second examples may also be prepared separately, from respective precursors, and then subjected to the same reaction system. However, the adoption of electrochemistry in those cases allowed for the direct use of more stable and more readily available precursors, without pre-activation. Of note, all three transformations have previously been achieved using chemical oxidants under non-electrochemical conditions, but the electrochemical approaches offer several advantages, including the avoidance of hazardous by-products (Jørgensen[13] and Mei[61]) and simplified reaction conditions (Luo[62]). These examples illustrate the general concept of anodically generated electrophiles, which have been employed in various mechanistically related asymmetric electrocatalytic systems that will not be discussed this review.[84–86]

Enamine organocatalysis is one of the most efficient strategies for α-functionalization of carbonyl compounds.[87] These transformations often involve initial condensation of an amine organocatalyst with an aldehyde or ketone to generate a highly nucleophilic enamine, which can then react with an array of electrophiles. While many electrophiles are isolable, bench-stable reagents, electrochemistry can be used to access a broader chemical space through *in situ* generation of highly reactive electrophiles. Jørgensen and co-workers leveraged this strategy for the regio- and stereo-selective synthesis of meta-substituted anilines via α-arylation of aldehydes (**8**) (Fig. 4A).[13] Anodic oxidation of para-N-tosylaminophenol (**7**) results in umpolung (i.e., polarity reversal) generating an electrophilic benzoquinone imine derivative (**10**), which then reacts with enamines (**11**) derived from a prolinol-based chiral secondary amine catalyst to forge a new C–C bond. The resultant intermediate (**12**) undergoes hydrolysis of the iminium ion followed by tautomerization of the cyclohexadienone unit and cyclization of the ensuing phenol onto the aldehyde group to complete the transformation. The enantioenriched products (**9**) attained could be further transformed into optically active 5-amino-2,3-disubstituted dihydrobenzofurans after deprotection of the N-tosyl group with SmI_2. This methodology was demonstrated for a variety of aldehydes with excellent enantioselectivity. Of note, the authors also achieved the same transformation using iodobenzene diacetate as a chemical oxidant in place of electrochemistry for substrate activation.[13] However, this process generated iodobenzene as a stoichiometric waste product, while the electrochemical protocol only produces H_2 from water reduction.

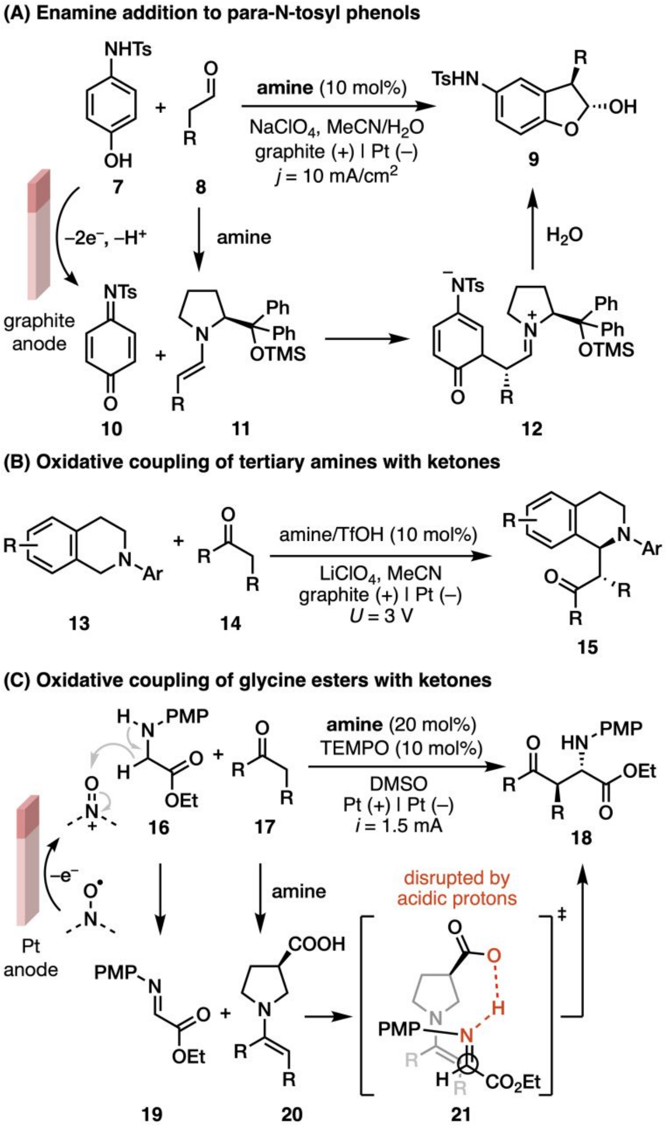

Fig. 4 (A) Electrochemical electrophile generation for enamine coupling. (B) Electrochemical synthesis of bicyclic β-aminoketones. (C) TEMPO-mediated selective amine oxidation for enamine coupling.

In separate studies, Luo,[62] Mei,[61] and their respective co-workers independently reported two asymmetric electrocatalytic Mannich-type reactions via generation of imine or iminium electrophiles *in situ* under the manifold of enamine catalysis. In the reaction from Luo, a tetrahydroisoquinoline (**13**) is first oxidized to the corresponding iminium ion, which then reacts with an enamine generated from a ketone (**14**) and a chiral primary amine catalyst (Fig. 4B).[62] Notably, this transformation has previously been achieved by Luo using photoredox catalysis,[88] although that route requires the use of a triple catalyst system—a Ru-based photocatalyst, a Co-based redox catalyst, and the organocatalyst—as well as nitrobenzene as the stoichiometric terminal oxidant. The electrochemical protocol substantially simplified the reaction conditions, requiring only the primary amine catalyst and trifluoroethanol as the sacrificial oxidant (which provides H^+), with carbon and platinum as the anode and cathode, respectively. This procedure afforded access to a range of bicyclic β-aminoketones (**15**) in good yield and diastereomeric ratio with excellent enantioselectivity.

The system from Mei is mechanistically related to that reported by Luo, and involves asymmetric oxidative coupling of a glycine ester (**16**) and ketone (**17**) via oxidation of the ester to the corresponding imine (**19**); the imine can then be attacked by an enamine (**20**) to generate the coupled product (**18**; Fig. 4C).[61] The synthesis of the same type of products has been reported previously using glyoxylic imines (**19**) directly as the electrophiles using the same catalyst scaffold,[89] but electrochemistry allows the reaction to be carried out directly from a more stable N-protected glycine ester. The authors found that under direct electrolysis conditions, the substrate was prone to rapid decomposition due to the low oxidation potential of the p-methoxyphenyl (PMP)-protected amine. The use of TEMPO as a redox mediator significantly increased the chemoselectivity of the oxidation. It is likely that the oxoammonium ion formed upon anodic oxidation of TEMPO mediates an inner-sphere hydride abstraction to furnish **19** (Fig. 4C). In contrast, the more sterically hindered amine in product **18** does not undergo hydride transfer with $TEMPO^+$, thus circumventing undesired product decomposition. The authors hypothesized that the enantioselectivity in this reaction is controlled by a weak interaction between the acidic proton of the amine catalyst and the imine (see transition state **21**). The authors found that when the same transformation was carried out chemically using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) or $TEMPO^+BF_4^-$, product was obtained with substantially lower enantiomeric excess (*ee*). They reasoned that protons generated during oxidation may disrupt the H-bonding interaction in the proposed transition state **21**, but that this is mitigated in the electrochemical system because H^+ is reduced simultaneously on the cathode, resulting in an overall neutral medium.

3.2. Improving reaction scope and functional group compatibility

Case study 4: aminoxyl radical peptides

In addition to improving reaction sustainability and scalability, the electrification of synthetic redox transformations may also improve the reaction scope, by enabling the use of substrates with functional groups that are incompatible with strong oxidants or reductants.[90,91] Indeed, the electrode potential in an electrocatalytic reaction can be manually set (in constant potential or voltage mode) or automatically adjusted (in constant current mode) to a magnitude needed for oxidizing or reducing the catalyst, allowing for the use of milder and more controlled conditions than when using chemical redox agents.[53] Therefore, functional groups that are not redox active at a given potential will remain intact. Further, as discussed in Section 2.4, electrochemical processes rely on single-electron transfer events to enact redox transformations, which differs from the majority of common oxidants or reductants that initiate redox processes *via* atom transfer. As such, functional groups that are sensitive to oxygen transfer (e.g., epoxidation) or hydride transfer (e.g., hydrogenation) may be inert under electrolytic conditions.[38,56]

The use of electrochemistry to expand reaction scope has been showcased in numerous non-asymmetric transformations and has also recently been demonstrated by Lin, Miller, Sigman, and co-workers in the development of an aminoxyl radical-catalyzed oxidative desymmetrization of *meso*-diols.[57] By incorporating an achiral aminoxyl moiety into a modular, peptide-based scaffold,[92] they synthesized over 70 catalysts and then screened them against a panel of 15 structurally diverse model substrates. This optimization process was carried out using a chemical oxidant and resulted in the identification of optimal catalyst **22**, which afforded high *ee* across all 15 model substrates as well as additional substrates including 1,5-, 1,4-, and 1,3-diols with distinct steric and electronic profiles (Fig. 5A). While this methodology displays an unusually broad substrate scope with respect to structural diversity, its functional group compatibility was hampered by the use of the harsh oxidant trichloroisocyanuric acid (TCCA) to turn over the catalyst. In particular, a large number of commercial *meso*-diols containing alkene functional groups (**23**) were incompatible with this approach, due to direct chlorination by TCCA.

An exhaustive panel of over 50 chemical oxidants was screened in search of conditions that tolerated alkenes, but all of these alternative conditions were unsuccessful due to oxidation of the alkene or lowered reactivity and selectivity. As such, the authors instead turned to an electrochemical approach to overcome the limitations of strong chemical oxidants. Traditional anodic oxidation reactions typically utilize protic acids as sacrificial oxidants, but these proved incompatible with the reaction system, likely due to their acidity disrupting hydrogen bonding between the diols and the catalyst. Thus, the key was to identify a sacrificial oxidant that would not decompose sensitive substrates, but would still provide a counter cathodic reaction for the desired electrocatalytic oxidation to occur in the presence of an electric driving force. Sacrificial oxidants were rapidly screened using the commercial HT*e*$^-$Chem reactor,[39] and dialkyl azodicarboxylates and diacyl peroxides were identified as suitable candidates. The optimal oxidant was found to be diisopropyl azodicarboxylate, which afforded the product (**24**) in good yields and high enantioselectivity for several alkene containing substrates, while producing diisopropyl hydrazine-1,2-dicarboxylate by-product upon reduction (Fig. 5B).

Of note, traditionally electrochemistry has been perceived to be incompatible with asymmetric catalytic methodologies that rely on weak non-covalent interactions, because

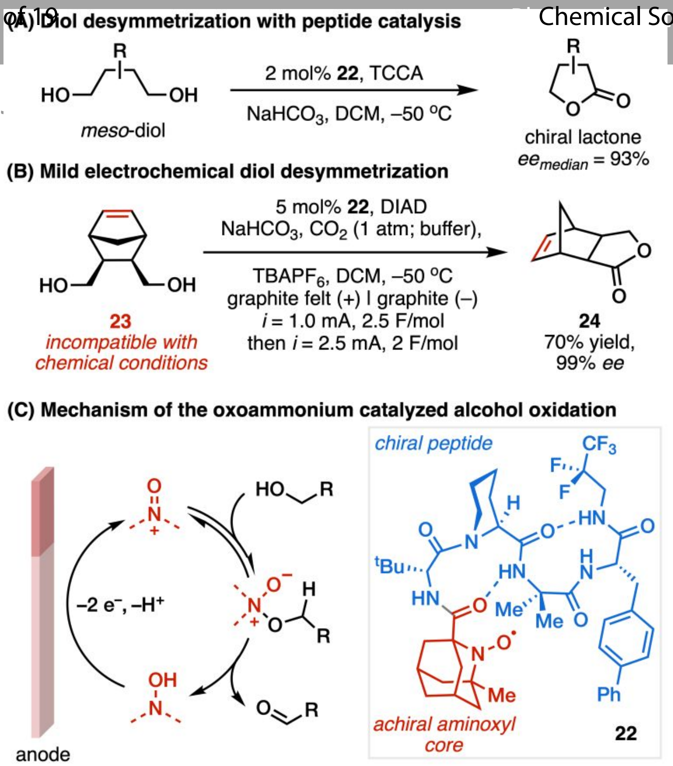

Fig. 5 (A) Desymmetrization of *meso*-diols to produce enantioenriched lactones using a chiral peptide catalyst. (B) Electrochemical protocol for desymmetrization allowed for tolerance of alkenes. (C) Mechanism of oxoammonium mediated alcohol oxidation.

electrolysis is most often carried out in polar electrolyte media.[93] This work challenged this view and showed that electrochemistry can be compatible with enantioselective reactions that are achieved through weak catalyst-substrate interactions, thus laying groundwork for future endeavors in this area.

3.3 Enabling novel transformations using electrochemistry

Sections 3.1 and 3.2 showcased the many benefits of electrochemistry as an alternative to traditional chemical oxidation and reduction in asymmetric redox catalysis. However, perhaps one of the most attractive aspects of electrosynthesis is the vast chemical reaction space that it can unlock. In an electrochemical reaction, the electron transfer occurs in a very narrow and compact solution layer on the electrode surface. The localization of redox activity and the resultant high concentration of reactive intermediates within a confined space can give rise to unique mechanistic consequences, as highlighted in the case studies discussed below.

Case study 5: anodically coupled enantioselective hydrocyanation of alkenes

The dimerization of two transient alkyl radicals has not traditionally been possible using chemical approaches, due to the exceedingly short lifetimes and resultant low concentrations of these species. However, in the classic Kolbe electrolysis, this very reactivity is observed, owing to the generation of a high concentration of alkyl radicals at the anode surface *via* the oxidative decarboxylation of carboxylic acids.[94,95] This notion can also be extended to the cross coupling of open-shell intermediates to achieve more complex and synthetically useful transformations. Recently, anodically (or cathodically) coupled electrolysis has been strategically employed in reaction discovery, wherein two distinct species are oxidized (or reduced) in parallel at the same electrode to provide two radicals with orthogonal reactivities (Fig. 1D).[96] This pair of reactive intermediates, often consisting of one transient radical and one persistent radical, can either directly combine or sequentially react with another closed-shell substrate (e.g., an alkene) to provide new products (Fig. 1D, middle).[10] Anodically coupled electrolysis has in particular been successfully employed in various electrochemical cyanation reactions in recent years, as discussed below.[51]

The asymmetric hydrocyanation of alkenes (**25**) provides convenient access to chiral nitriles (**26**)—valuable intermediates in the preparation of numerous pharmaceutical ingredients—from readily available alkenes and cyanide (CN⁻). However, while alkene hydrocyanation has become an important process in the chemical industry,[97] the development of highly enantioselective variants of this transformation remained a largely unsolved challenge until recently. In 2019, towards addressing this challenge, Lin and co-workers developed a Cu-catalyzed asymmetric electrocatalytic cyanofunctionalization reaction for the synthesis of bifunctional chiral nitriles.[63] This reaction combines two known radical reactivities in the same anodically coupled electrolysis system. First, the single-electron oxidation of a diarylphosphine gives rise to a transient P-centered radical; this oxidation was later revealed by cyclic voltammetry experiments to be mediated by a Cu^{I}/Cu^{II} redox couple (**Electrocatalytic cycle 1**; Figs. 6A and 6B). This radical then adds to a styrene to generate a transient benzylic radical. In a second anodic event, a Cu^{I}(BOX) catalyst is oxidized to give Cu^{II}(BOX), which forms the resting state Cu^{II}(BOX)–CN upon cyanide ligation (**Electrocatalytic cycle 2**; Fig. 6A; here, trimethylsilyl cyanide (TMSCN) was employed as a soluble source for slow release of cyanide anions). This persistent Cu^{II}(BOX)–CN complex and the transient radical then react with one another *via* radical combination to produce a putative alkyl–Cu^{III}(BOX)–CN intermediate. This intermediate undergoes an enantiodetermining reductive elimination to complete the cyanofunctionalization and regenerate the Cu^{I}(BOX). By using a different transient radical precursor, *p*-toluenesulfinic acid, this catalytic strategy was further extended to achieve cyanosulfonylation, giving product.

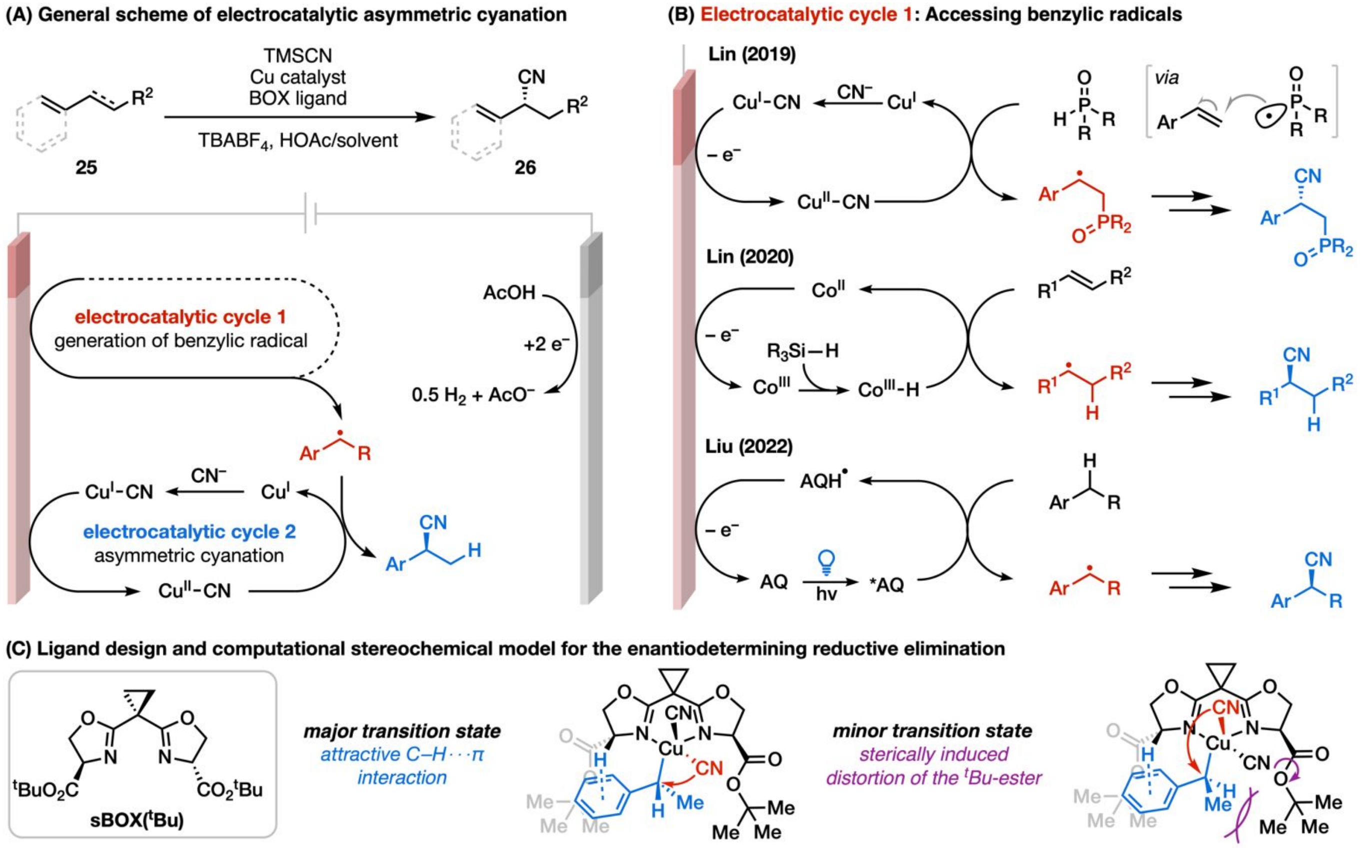

Fig. 6 (A) Mechanism of dual-electrocatalytic asymmetric cyanation. (B) The cyanophosphinoylation developed by Lin and coworkers using diphenylphosphine oxide as phosphine source, 3 mol% $Cu(OTf)_2$ as catalyst, conducted electrolysis with felt(+) | Pt(–) in TFE and DMF mixture at 0 °C at a constant current of 3 mA for 2 F/mol (upper); hydrocyanation from the Lin lab utilizing $PhSiH_3$ as hydride source, 0.5 mol% Co(salen) and 5 mol% $Cu(OTf)_2$ as catalyst, and with DMF as solvent to perform the electrolysis at 0 °C with a constant cell voltage of 2.3 V for 10 h, with carbon felt(+) | Pt(–) (middle); Liu used 5 mol% $Cu(MeCN)_4BF_4$ and 5 mol% anthraquinone as electrophotocatalyst, which was activated by a 420 nm LED to conduct the electrolysis with RVC(+) | Pt/Ti(–) in a mixture of acetonitrile and 1,2-dichloroethane at 2-3 mA depending on the substrate (lower). (C) Ligand design and stereochemical model for sBOX ligands.

Of note, Cu-promoted enantioselective C–CN bond formation was originally pioneered by Liu and Stahl in 2016 in the context of benzylic C–H cyanation with *N*-fluorobenzenesulfonimide (NFSI) as an oxidant.[98] The work from Lin[63] was the first to demonstrate that this fundamental reactivity can be harnessed in an electrocatalytic system to achieve previously unknown transformations. A key factor that allowed these highly enantioselective cyanofunctionalizations to take place in a highly polar electrolyte medium was the development of a new class of serine-derived bisoxazoline ligands (sBOX) (Fig. 6C). Upon coordination with Cu, these ligands present second-sphere ester groups with acidic α-proton, which were shown through density functional theory calculations to enable additional stabilizing noncovalent interactions in the selectivity-determining transition states.

Building on this work, Lin and co-workers then substituted the first electrocatalytic cycle (i.e., the oxidation of diphenylphosphine oxide) with a Co^{III}–H catalyzed hydrogen atom transfer (HAT) cycle, thus enabling a previously elusive transformation, the highly enantioselective hydrocyanation of conjugated alkenes (Fig. 6B).[51] In this case, catalytic amounts of a Co(salen) complex and Cu(sBOX) in the presence of $PhSiH_3$ and TMSCN promoted formation of enantioenriched benzyl nitriles via effective sequential addition of a H atom and a cyano group across an olefin. Control experiments showed that a diverse panel of chemical oxidants (including single-electron oxidants) failed to produce nearly the same levels of yield and enantioselectivity in this transformation. The authors reasoned that electrochemistry provides several advantages in this particular system. First, anodic oxidation provides a clean and direct means to activate both catalysts simultaneously, whereas in a chemical system, one would need to identify an oxidant that can efficiently react with both catalysts but also does not generate byproducts that poison either catalyst. Second, due to the localization of a high concentration of anodically generated Cu^{II}(BOX)–CN intermediates within the diffusion layer of the electrode, the benzylic radical generated from the first electrocatalytic cycle can undergo rapid cyanation. In contrast, in a chemical oxidation, this radical may react competitively with a chemical oxidant, which is present in a higher concentration, to yield undesired carbocation trapping products; such products were indeed observed in several aforementioned control experiments. Finally, in this electrochemical setting, an unproductive side reaction between the reductant $PhSiH_3$ and a strong oxidant and the potential associated safety hazard are avoided.

This unique dual electrocatalytic mechanism is compatible with a broad scope of alkenes with functional groups such as benzyl halides, benzaldehyes, and aryl boronic esters. Furthermore, the reaction is applicable not only to terminal styrenes with electron-withdrawing and electron-donating substituents, but also to internal alkenylarenes and other conjugated alkenes such as dienes and enynes. In addition, because Co-catalyzed HAT to unactivated, alkyl-substituted alkenes was facile, this reaction method also allowed for the efficient synthesis of simple alkyl nitriles albeit with low enantioselectivities due to intrinsic difficulties in differentiating two C(sp^3) alkyl substituents.

Following the initial development of electrocatalytic cyanation reactions, in 2022 Liu, Wang, and co-workers disclosed an electrophotocatalytic system to overcome the challenges encountered in the original C–H cyanation from Liu and Stahl (Fig. 6B).[64] In their previous report, NFSI was used both to oxidatively turn over the Cu catalyst and as a hydrogen-atom acceptor (HAA) to achieve benzyl C–H abstraction. However, this system was ineffective in promoting the C–H cyanation of substrates containing electron-deficient arenes, including many pharmaceutically relevant *N*-heterocycles. Furthermore, the strongly oxidizing NFSI limited the functional group compatibility. In the new dual catalytic system, the HAT event is decoupled from the Cu cycle through the introduction of 2-chloro-anthraquinone (AQ) in the first electrocatalytic cycle of an anodically coupled electrolysis (Fig. 6B).[64] In its ground state, AQ is a mild functional group-tolerant oxidant that only becomes capable of C–H activation upon photoexcitation. In this system, the anodic oxidation regenerates AQ from the semiquinone generated upon HAT. Advantageously, a number of commercially available anthraquinone derivatives offer the opportunity for systematic tuning of the HAT process, independent of the Cu catalytic cycle. This benzylic cyanation approach is compatible with a broad panel of (hetero)arenes and competent for the late-stage functionalization of complex pharmaceuticals and natural product derivatives, and significantly expanded on the NFSI oxidant system. In a related work, Xu employed a similar strategy to achieve a decarboxylative asymmetric cyanation, employing a cerium electrophotocatalyst for the decarboxylation of phenylacetic acids to generate the prerequisite benzylic radicals.[65]

Case study 6: Sequential electron-transfer enables enol ether-enolate cross coupling

Due to the short lifetimes of highly reactive intermediates such as radicals, radical ions, and excited state species, achieving efficient sequential single-electron transfer events to a single substrate can often be challenging using chemical redox agents or photocatalysis. On the other hand, electrochemistry is uniquely suited to promote successive electron transfers to the same substrate; with constant flux of electrons and holes inside the diffusion layer of the electrode, radical and radical ion intermediates generated on the electrode can readily and immediately accept or give up additional electrons to become closed-shelled ionic species, thereby participating in what is known as a radical-polar crossover.[11,12] This reactivity is observed in classic named electrolysis reactions, such as the Hofer-Moest reaction[30] or the Shono oxidation,[31] and it has more recently been strategically employed for the development of cross-electrophile couplings of alkyl electrophiles.[99]

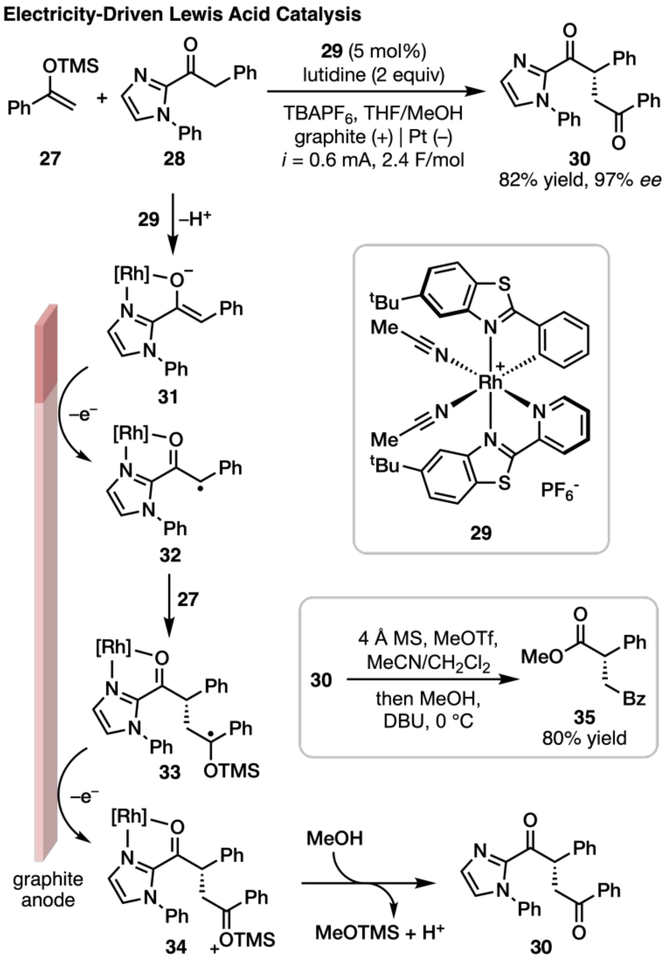

Fig. 7 Electrochemically enabled Lewis acid catalysis supresses homocoupling.

Leveraging the paradigm of radical-polar crossover, Meggers and co-workers demonstrated electricity-driven chiral Lewis acid catalysis for the oxidative cross-coupling of 2-acyl imidazoles with silyl enol ethers (Fig. 7).[66] This reaction proceeds through a chemical–electrochemical–chemical–electrochemical (CECEC) mechanism that involves three chemical (C) and two electron-transfer (E) steps. It commences with the chelation of the rhodium catalyst (**29**) to the substrate (**28**), followed by deprotonation to generate an enolate intermediate (**31**). A single-electron anodic oxidation results in umpolung of the enolate, delivering the rhodium-bound electrophilic α-carbonyl radical (**32**). This radical is then trapped by the nucleophilic silyl enol ether (**27**) to form a secondary ketyl radical (**33**). Upon a second anodic oxidation and desilylation, the enantioenriched product (**30**) is obtained, which could be further converted to the corresponding methyl ester (**35**). Using a chiral C_2-symmetric Rh complex (**29**), the C–C coupling process is rendered highly enantioselective (up to 97% *ee*). Importantly, the catalyst-substrate complex (**31**) has a considerably lower oxidation potential than the model silyl enol ether (respectively, 0.52 and 1.72 V *vs.* Ag/AgCl), and as such this protocol can be carried out under relatively mild conditions and is highly selective for the desired product. The Rh catalyst was also critical for restricting the formation of **32** to low concentrations, statistically suppressing homocoupling. Indeed, oxidative cross-nucleophile coupling of two enol equivalents has traditionally been hampered by the fact that the more easily oxidized enol is also more nucleophilic, resulting solely in homocoupling of the enol ether, as was also observed in the absence of a catalyst in this work.

Interestingly, control experiments revealed that this transformation cannot be promoted efficiently using photochemical or chemical redox approaches in lieu of electrochemistry under similar conditions. Indeed, significant side reactions occurred and the desired products were only obtained in 8–11% yield. Although not specifically discussed by the authors, we posit that the superior performance of the electrochemical approach stems from the fact that the working electrode provides a high concentration of redox equivalents within the diffusion layer, where the transformations of reactive intermediates take place.[36] In contrast, in the photochemical or chemical reactions, there is a very low statistical likelihood of short-lived radical intermediates such as **32** and **33** encountering another dilute redox equivalent (i.e., another molecule of a chemical oxidant or excited photooxidant), and therefore side reactions can become competitive.

4. Enzymatic and Heterogeneous Electrocatalysis

In the previous section, we discussed the use of homogeneous small molecule catalysts in electrosynthesis, wherein the catalyst designs and modes for asymmetric induction mirror those in conventional organic asymmetric catalysis. In this section, we will discuss three distinct modes of asymmetric electrocatalysis. Section 4.1 discusses the use of electrochemistry to turnover enzyme catalysts in the context of asymmetric bioenzymatic synthesis. In Sections 4.2 and 4.3, asymmetry is induced through the modification of an electrode, either by rendering the electrode itself chiral through embedding (redox inert) chiral molecules into the surface (Section 4.2), or by covalently tethering small molecule chiral catalysts to the electrode surface (Section 4.3).

4.1. Electroenzymatic catalysis

Enzymes can execute a diverse range of reactions with exceptional chemo-, regio-, and stereoselectivities that are often unrivalled by small molecule catalysts. As such, enzymes are appealing alternatives to synthetic catalysts for select synthetic applications.[100] Nonetheless, the use of enzymes can be complex and costly due to their reliance on exogenous redox cofactors, coenzymes, or terminal oxidants or reductants. Using electrochemistry, electrons can in principle be used in place of these auxiliary reaction components, thereby enabling these intricate reaction cascades with fewer reagents.

Direct electron transfer to enzymes typically requires high overpotentials because active sites are often buried within the protein and are not accessible to the electrode surface; the high voltages in turn can lead to enzyme degradation and poor productivity. As such, indirect electrolysis with a catalytic mediator (i.e., an electrocatalyst) that can be regenerated at mild potentials is generally employed to enable rapid homogenous electron transfer. Elegant work by Minteer and co-workers leveraged cathodically generated persistent methyl viologen radical ($MV^{\bullet+}$) as a mediator to turn over nitrogenase and diaphorase enzymes in a nitrogen-fixation cascade (Fig. 8A).[101] This reaction is unprecedented in non-enzymatic settings due to the inertness of molecular nitrogen.[101] In this work, N_2 was enzymatically reduced to NH_3,[102] which was then used to generate alanine for the asymmetric reductive amination of ketones (**37**) by an ω-transaminase to produce valuable chiral amines (**36**).

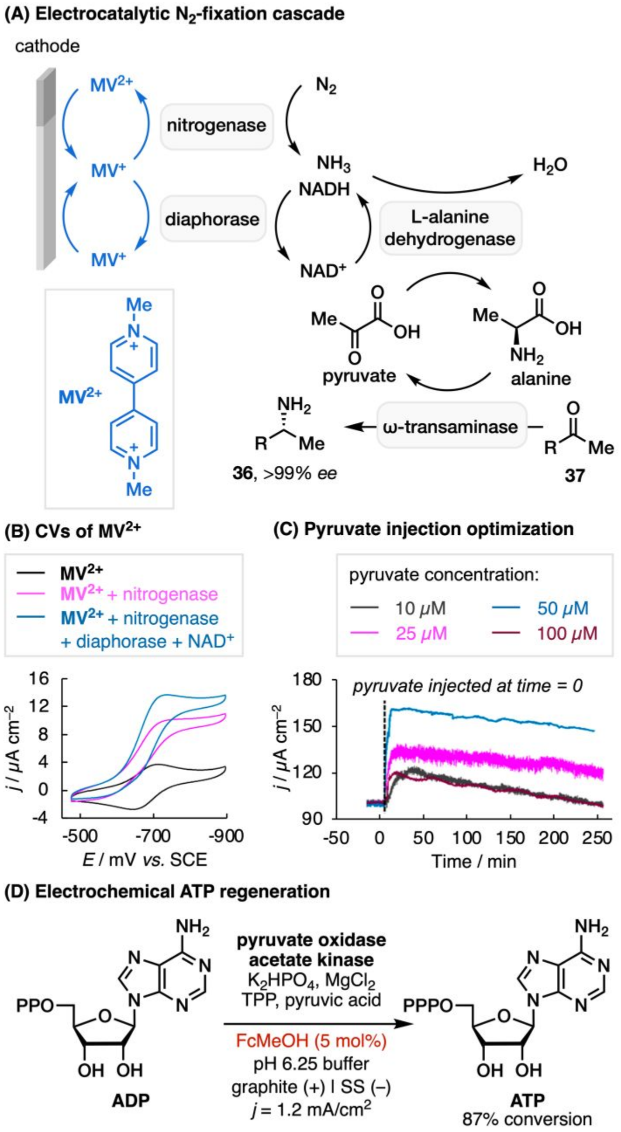

Fig. 8 (A) Enzymatic cascade for the asymmetric reductive amination with molecular nitrogen. (B) Cyclic voltammograms supporting catalytic turnover of nitrogenase and diaphorase with methyl viologen radical. Reprinted (adapted) with permission from Chen et. al., J. Am. Chem. Soc., 2019, 141, 4963–4971. Copyright 2019 American Chemical Society (C) Reaction condition screening through constant potential electrolysis in the presence of varying pyruvate concentrations. (D). Electrocatalytic ATP regeneration.

Cyclic voltammetry experiments revealed catalytic current enhancement upon addition of nitrogenase to the mediator and further enhancement upon addition of diaphorase, indicating catalytic turnover of both enzymes by $MV^{\bullet+}$ (Fig. 8B). Based on these experiments, the working potential during preparative electrolysis was set at −0.85 V *vs.* SCE, slightly past the reduction potential of methyl viologen, to maintain a high electron flow while mitigating any enzyme or substrate degradation at higher potentials.

As discussed in Section 2.3, the magnitude of current in an electrolysis is directly proportional to the reaction rate, thus, the current could be used to monitor the progress of the reaction by correlating the decrease in current density over time with the increase in concentration of the desired amine product. Traditional reaction process analysis depends on monitoring the formation of intermediates and products and then mathematically calculating the rate constants. In contrast, current is a convenient and direct measure of rate that is more sensitive and more responsive to reaction progress than concentration. In the electroenzymatic system from Minteer, this technique was applied to optimize the concentration of pyruvate (Fig. 8C). The authors found that 50 µM pyruvate afforded the highest current density and almost twice the concentration of product compared to 10 or 100 µM injections.

Electrochemistry has additionally been employed in enzymatic catalysis for the regeneration of valuable co-factors. For instance, adenosine triphosphate (ATP) is ubiquitous in all organisms and provides the chemical driving force for many biochemical processes. Thus, the efficient in vitro regeneration of this co-factor from ADP is of significant interest in biocatalysis, particularly in preparative scale systems due to the high cost of ATP. In 2022, Merck developed an electrocatalytic ATP regeneration system,[103] drawing inspiration from a previous method[104] that relied on oxidative decarboxylative phosphorylation of pyruvate with O_2, catalysed by the enzyme pyruvate oxidase (Fig. 8D). Using molecular oxygen as the terminal oxidant has several limitations. For example, catalase must be added to decompose H_2O_2 formed as a by-product of O_2 reduction, and special engineering considerations are required for efficient mass transfer and to avoid safety issues.[105,106] In place of O_2, the Merck team utilized electrochemistry to turn over the pyruvate oxidase cofactor, flavin adenine dinucleotide (FAD), by reoxidising the reduced form (FADH2) using ferrocene derived mediators. Crucial to optimization was matching the rate of FAD turnover with that of other enzymes in the system, otherwise there would be a shortage of phosphate and a build-up of oxidized mediator, a corresponding increase in the cell potential, and ultimately enzymatic failure due to over-oxidation. The optimized system from Merck was showcased through the synthesis of several complex chiral pharmaceutically relevant molecules, in yields equal to or greater than systems using O_2. Using a flow system, the strategy was also successfully implemented for cofactor recycling in a complex ATP-dependent biocatalytic cascade for the synthesis of a precursor of the antiviral molnupiravir (>20 g scale with 96% conversion).

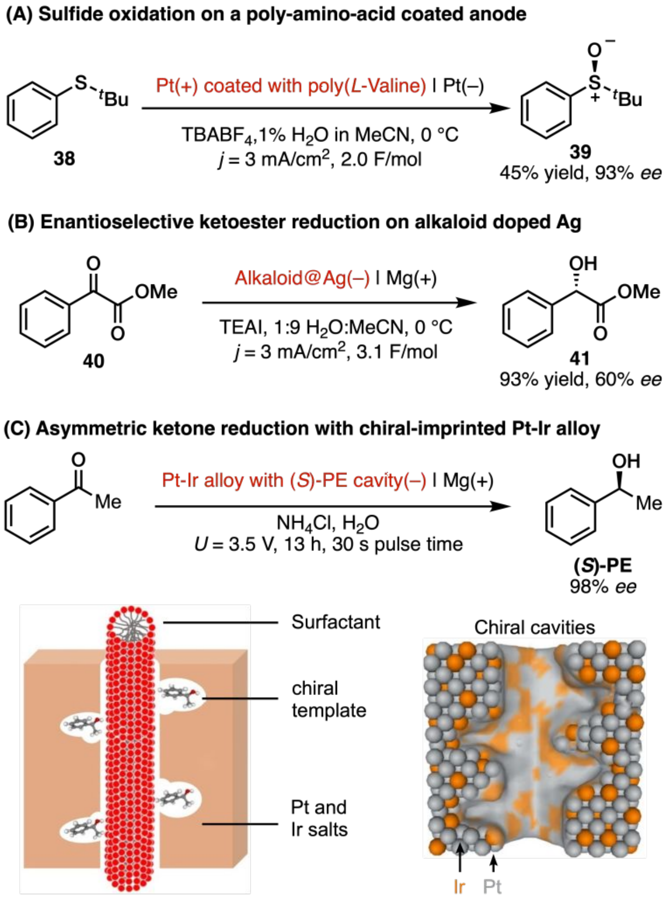

Fig. 9 Chiral electrodes for asymmetric electrosynthesis. (A) Chiral environment created by polymer coating. (B) Organocatalysts entrapped on electrode. (C) Chiral cavity encoded on electrode, reproduced from S. Butcha et. al., *Nat. Commun.*, 2021, **12**, 1314.

4.2. Electrode Modification

Much of this review has focused on homogeneous asymmetric electrocatalysis. Nevertheless, all electrolysis inherently relies on electron transfer at the electrode surface. As such, the heterogenous solvent-electrode interface provides a potential general lever to introduce asymmetry. Further, chirally modified electrodes in theory can be recycled and reused without the need for elaborate product-catalyst separation procedures. These attractive features have sparked decades of basic research with several selected examples of electrode modification discussed below, though few practical synthetic applications have been reported to date.[17]

In 1984, Nonaka and co-workers developed a poly(amino acid)-coated electrode to perform the first highly enantioselective transformation on a chiral electrode (Fig. 9A).[107] In this case, a Pt anode was first chemically modified by the reaction of surface oxides with *N*-[3-(trimethoxysilyl)propyl]pyrrole, then subjected to anodic oxidation in the presence of pyrrole to form a polypyrrole polymer film covalently bound to the electrode surface. The electrode was then dip-coated in a solution of poly(L-valine) to prepare a chiral electrode with a poly(L-valine) film on the surface. This electrode was then used as an anode to run asymmetric thioether oxidation to furnish chiral sulfoxides (**39**), giving 93% *ee* and 45% yield for the model substrate (**38**). The authors also noted that the anode could be reused, but the enantioselectivity decreased by about 20% *ee* over four runs.

In 2014, Lu and Wang utilized organically doped metals as electrodes to conduct enantioselective hydrogenation of methyl benzoylformate (**40**).[108] In particular, alkaloid@Ag electrodes were prepared by reduction of $AgNO_3$ by NaH_2PO_2 in an aqueous solution of either cinchonine or its isomer cinchonidine, which resulted in the alkaloid molecules becoming trapped within Ag nanograins. The resulting powders were then pressed into a coin and used as an electrode. When the alkaloid@Ag electrodes were used as cathodes for reduction of **40**, the authors could consistently achieve higher than 90% yield and approximately 60% *ee* (of either the *S* or *R* enantiomer) over 10 runs with the same electrode (Fig. 9B). In comparison, if the alkaloid was used as an additive with a pure Ag cathode, the enantioselectivity decreased dramatically to 25% *ee*, highlighting the advantage of immobilizing the chiral catalyst.

In addition to the chemical modification of electrodes, nanoscale engineering has more recently enabled physically modified chiral electrodes to be explored in asymmetric electrosynthesis.[109] Here, a chiral-imprinted porous metal or alloy is used as electrode to induce enantioselectivity. For instance, Kuhn and co-workers prepared a Pt-Ir alloy electrode by electrodepositing Pt and Ir around a supramolecular template structure consisting of cylindrical aggregated surfactant (Fig. 9C). When enantiomerically pure (*S*)-1-phenylethanol (*S*-PE) was incorporated as the co-template (Fig. 9C), the resulting alloy electrode could be used for selective electroreduction of acetophenone to *S*-PE. When pulsed potential electrolysis was used to facilitate adsorption of racemic substrates into the chiral cavity, S-PE could be obtained in 98% *ee* in the first run, with approximately a 10% decrease in *ee* over the course of two additional runs with the same electrode.

4.3. Chiral-on-electrode

An alternative strategy for the chiral modification of electrode surfaces is the covalent tethering of traditional small molecule catalysts to the electrode surface. In 1993, Bobbitt and co-workers developed a chiral aminoxyl radical catalyst (SPIROXYL) for enantioselective diol oxidation to the corresponding chiral lactone using mCPBA as the oxidant.[110] Unfortunately, this work was limited to a single substrate with poor enantioselectivity. In 2002, the same group rendered this methodology electrocatalytic to turnover the aminoxyl radical, furnishing lactone (**43**) from the corresponding diol (**42**) in 87% yield with 38% ee (Fig. 10A).[111] Although the use of electrochemistry made this transformation milder, it did not immediately improve the enantioselectivity of the reaction. However, when the catalyst was covalently attached to the surface of the electrode, an excellent 98% ee was achieved, along with a 9% increase in yield. Furthermore, the catalyst turnover number increased from 40 to 500. Three additional lactones were all obtained in good to excellent yield and enantioselectivity, using constant current electrolysis on a 0.5 mmol scale in a divided cell.

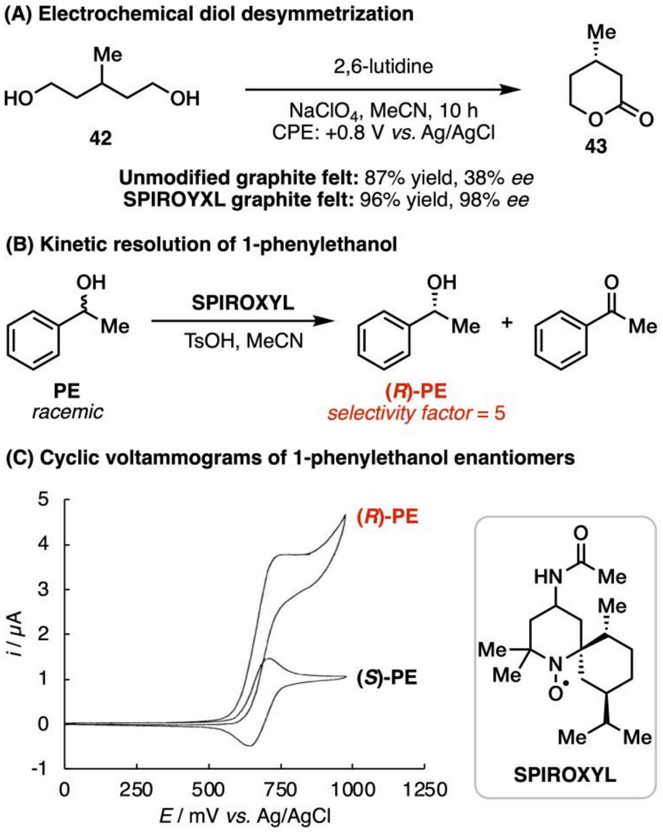

Fig. 10 (A) Electrochemical diol desymmetrization with unmodified GF and SPIROXYL modified GF electrodes. (B) Kinetic resolution of 1-phenylethanol using SPIROXYL. (C). 1-phenylethanol enantiomers display different current responses in cyclic voltammograms of (6*R*,7*S*,10*R*)-SPIROXYL (0.1 mM) in $NaClO_4/CH_3CN$ (0.1 M) and 2,6-lutidine (3.2 mM) in the presence of *R*-PE or *S*-PE (1.6 mM) at a scan rate of 25 mV/s. Reproduced with permission from Kashiwagi et. al., Chem. Pharm. Bull. (Tokyo), 1999, 47, 1051–1052. Copyright 1999 The Pharmaceutical Society of Japan.

The surface modification was accomplished by coating graphite felt electrodes with polyacrylic acid, then treating them with SPIROXYL–NH_2 in the presence of dicyclohexylcarbodiimide as an amide coupling agent. Remaining carboxyl groups were then cross-linked or butylated. Cyclic voltammetry of the modified electrodes demonstrated the reversible redox couple corresponding to the single electron oxidation of aminoxyl radical to oxoammonium ion, showing that the coating could mediate the transfer of electrons. The loading of electroactive SPIROXYL present on the electrode surface was assessed by integrating the oxidation current wave of the cyclic voltammogram and applying Faraday's Law (charge = current × time). This revealed that approximately 20% of the carbonyl groups of the polymer layer of the electrode were modified with SPIROXYL.

In their 1993 work, Bobbitt and co-authors could also achieved a kinetic resolution of racemic 1-phenylethanol (PE) if they pre-generated the active oxoammonium form of SPIROXYL (Fig. 10B).[110] The (S)-enantiomer reacted about five times faster than the (R)-enantiomer. Later mechanistic work by Anzai and co-workers showed that the two enantiomers mirrored this trend in cyclic voltammetry studies of a SPIROXYL derivative (Fig. 10C).[112] The anodic peak current of R-PE was enhanced compared to that of S-PE, showing that the rate of catalyst recycling on the CV time scale was far greater for the (R)-enantiomer. These electroanalytical results are consistent with the observed kinetic resolution in preparative experiments with SPIROXYL and demonstrate that cyclic voltammetry can serve as a tool to probe selectivity in kinetic resolutions.

5. Conclusions

Asymmetric electrocatalysis has emerged as a powerful and enabling strategy to set stereocenters in a redox non-neutral paradigm, with numerous unique advantages. As discussed in Section 3.1, electrochemistry has historically provided an alternative approach to turn over known redox-active catalysts in a controlled, sustainable, and potentially safer manner. In recent years, the focus of the electrosynthetic community has shifted towards the discovery of unprecedented reactions enabled by the unique reaction mechanisms accessible to electrochemistry, including anodically and catholically coupled electrolysis and redox non-neutral radical-polar crossover (ECEC) (see Section 3.3.).

Looking forward, the development of synthetically relevant asymmetric variants of established racemic electrosynthetic methodologies represents one of the greatest standing challenges in contemporary organic electrosynthesis. For instance, while all three of the named reactions introduced in the historic overview in Section 2.1 (Kolbe electrolysis (1848), Hofer-Moest electrolysis (1902), Shono oxidation (1975)) have found numerous synthetic applications from total synthesis to industrial applications, no asymmetric catalytic variants have been developed to date likely as a result of the lack of catalytic variants of these direct electrolysis methods. Thus, rendering the plethora of established direct electrolysis enantioselective could require entirely reimagining the synthetic approaches. Indeed, in 2023 the Baran group developed the first enantioselective doubly decarboxylative cross coupling 175 years after the report of the Kolbe electrolysis.[113] In this method, two carboxylic acids, activated as redox active esters, are reductively decarboxylated in a cathodically paired electrolysis in the presence of a chiral nickel complex. This approach represents a drastic departure from the traditional oxidative decarboxylation found in the Kolbe electrolysis. By melding classic approaches with modern innovations, this example illuminates the potential for accessing asymmetric variants of known electrosynthetic transformations. Furthermore, the discovery of a robust chiral strategy to embed chiral information at core components of an electrochemical reaction (e.g., electrodes) could aid in addressing the challenge of rendering direct electrolysis enantioselective (see promising studies in Section 4.2), but much more development remains needed towards these objectives.

Author Contributions

All authors contributed to writing the original draft and reviewing and editing the manuscript.

Conflicts of interest

There are no conflicts to declare.

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References

1 E. N. Jacobsen, A. Pfaltz and H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer Berlin Heidelberg, 2004.
2 Y. Gnas and F. Glorius, *Synthesis*, 2006, 1899–1930.
3 Z. G. Brill, M. L. Condakes, C. P. Ting and T. J. Maimone, *Chem. Rev.*, 2017, **117**, 11753–11795.
4 Y. Teng, C. Gu, Z. Chen, H. Jiang, Y. Xiong, D. Liu and D. Xiao, *Chirality*, 2022, **34**, 1094–1119.
5 W. S. Knowles, *Adv. Synth. Catal.*, 2003, **345**, 3–13.
6 R. Noyori, *Adv. Synth. Catal.*, 2003, **345**, 15–32.
7 K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2002, **41**, 2024–2032.
8 N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370–4371.
9 B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396.
10 L. F. T. Novaes, J. Liu, Y. Shen, L. Lu, J. M. Meinhardt and S. Lin, *Chem. Soc. Rev.*, 2021, **50**, 7941–8002.
11 M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230–13319.
12 A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2018, **57**, 5594–5619.
13 K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2010, **49**, 129–133.
14 S. Torii, P. Liu and H. Tanaka, *Chem. Lett.*, 1995, **24**, 319–320.
15 D. I. Park, S. Jung, H. J. Yoon and K. Jin, *Electrochimica Acta*, 2021, **397**, 139271.
16 K.-J. Jiao, Z.-H. Wang, C. Ma, H.-L. Liu, B. Cheng and T.-S. Mei, *Chem Catal.*, 2022, **2**, 3019–3047.
17 Q. Lin, L. Li and S. Luo, *Chem. – Eur. J.*, 2019, **25**, 10033–10044.
18 C. Margarita and H. Lundberg, *Catalysts*, 2020, **10**, 982.
19 X. Chang, Q. Zhang and C. Guo, *Angew. Chem. Int. Ed.*, 2020, **59**, 12612–12622.
20 P. Chakraborty, R. Mandal, N. Garg and B. Sundararaju, *Coord. Chem. Rev.*, 2021, **444**, 214065.
21 M. Ghosh, V. S. Shinde and M. Rueping, *Beilstein J. Org. Chem.*, 2019, **15**, 2710–2746.

22 S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2018, **57**, 6018–6041.

23 C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata and P. S. Baran, *Acc. Chem. Res.*, 2020, **53**, 72–83.

24 C. Schotten, T. P. Nicholls, R. A. Bourne, N. Kapur, B. N. Nguyen and C. E. Willans, *Green Chem.*, 2020, **22**, 3358–3375.

25 G. Hilt, *ChemElectroChem*, 2020, **7**, 395–405.

26 M. Faraday, *Philos. Trans. R. Soc. Lond.*, 1997, **124**, 77–122.

27 C. Wentrup, *Eur. J. Org. Chem.*, 2022, **2022**, e202101492.

28 H. Kolbe, *Justus Liebigs Ann. Chem.*, 1849, **69**, 257–294.

29 H. Kolbe, *Justus Liebigs Ann. Chem.*, 1845, **54**, 145–188.

30 H. Hofer and M. Moest, *Justus Liebigs Ann. Chem.*, 1902, **323**, 284–323.

31 T. Shono, H. Hamaguchi and Y. Matsumura, *J. Am. Chem. Soc.*, 1975, **97**, 4264–4268.

32 M. M. Baizer, *J. Appl. Electrochem.*, 1980, **10**, 285–290.

33 D. S. P. Cardoso, B. Šljukić, D. M. F. Santos and C. A. C. Sequeira, *Org. Process Res. Dev.*, 2017, **21**, 1213–1226.

34 *Scifinder*^{n} search accessed on 06/06/2023, showed that the percentage of publications containing the keyword "electrolysis" in the subset of publications including the keyword "organic" in 2022 was 0.78% and higher than at any year since 1926. Further, since 2016 there has been a steady increase per year providing indicating a renaissance in electrosynthetic chemistry.

35 D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, *Nat. Chem.*, 2018, **10**, 383–394.

36 N. E. S. Tay, D. Lehnherr and T. Rovis, *Chem. Rev.*, 2022, **122**, 2487–2649.

37 F. Parsaee, M. C. Senarathna, P. B. Kannangara, S. N. Alexander, P. D. E. Arche and E. R. Welin, *Nat. Rev. Chem.*, 2021, **5**, 486–499.

38 G. Laudadio, M. D. Palkowitz, T. El-Hayek Ewing and P. S. Baran, *ACS Med. Chem. Lett.*, 2022, **13**, 1413–1420.

39 J. Rein, J. R. Annand, M. K. Wismer, J. Fu, J. C. Siu, A. Klapars, N. A. Strotman, D. Kalyani, D. Lehnherr and S. Lin, *ACS Cent. Sci.*, 2021, **7**, 1347–1355.

40 Description - ElectraSyn 2.0 Package, https://www.ika.com/en/Products-LabEq/Electrochemistry-Kit-pg516/ElectraSyn-20-Package-20008980/, (accessed 8 June 2023).

41 C. Gütz, B. Klöckner and S. R. Waldvogel, *Org. Process Res. Dev.*, 2016, **20**, 26–32.

42 J. Rein, S. Lin, D. Kalyani and D. Lehnherr, in *The Power of High-Throughput Experimentation: General Topics and Enabling Technologies for Synthesis and Catalysis (Volume 1)*, American Chemical Society, 2022, vol. 1419, 167–187.

43 G.-Q. Sun, P. Yu, W. Zhang, W. Zhang, Y. Wang, L.-L. Liao, Z. Zhang, L. Li, Z. Lu, D.-G. Yu and S. Lin, *Nature*, 2023, **615**, 67–72.

44 J. Yoshida, A. Shimizu and R. Hayashi, *Chem. Rev.*, 2018, **118**, 4702–4730.

45 A. M. Couper, D. Pletcher and F. C. Walsh, *Chem. Rev.*, 1990, **90**, 837–865.

46 D. M. Heard and A. J. J. Lennox, *Angew. Chem.*, 2020, **132**, 19026–19044.

47 W. Zhang, W. Guan, J. I. Martinez Alvarado, L. F. T. Novaes and S. Lin, *ACS Catal.*, 2023, 8038–8048.

48 S. Manabe, C. M. Wong and C. S. Sevov, *J. Am. Chem. Soc.*, 2020, **142**, 3024–3031.

49 M. C. Franke, V. R. Longley, M. Rafiee, S. S. Stahl, E. C. Hansen and D. J. Weix, *ACS Catal.*, 2022, **12**, 12617–12626.

50 G. Xu and K. D. Moeller, *Org. Lett.*, 2010, **12**, 2590–2593.

51 L. Song, N. Fu, B. G. Ernst, W. H. Lee, M. O. Frederick, R. A. DiStasio and S. Lin, *Nat. Chem.*, 2020, **12**, 747–754.

52 O. R. Luca, J. L. Gustafson, S. M. Maddox, A. Q. Fenwick and D. C. Smith, *Org. Chem. Front.*, 2015, **2**, 823–848.

53 M. Rafiee, M. N. Mayer, B. T. Punchihewa and M. R. Mumau, *J. Org. Chem.*, 2021, **86**, 15866–15874.

54 S. E. Denmark, W. E. Kuester and M. T. Burk, *Angew. Chem. Int. Ed.*, 2012, **51**, 10938–10953.

55 D. H. Evans, *Chem. Rev.*, 2008, **108**, 2113–2144.

56 H. G. Roth, N. A. Romero and D. A. Nicewicz, *Synlett*, 2016, **27**, 714–723.

57 J. Rein, S. D. Rozema, O. C. Langner, S. B. Zacate, M. A. Hardy, J. C. Siu, B. Q. Mercado, M. S. Sigman, S. J. Miller and S. Lin, *Science*, 2023, **380**, 706–712.

58 N. Elgrishi, K. J. Rountree, B. D. McCarthy, E. S. Rountree, T. T. Eisenhart and J. L. Dempsey, *J. Chem. Educ.*, 2018, **95**, 197–206.

59 C. Sandford, M. A. Edwards, K. J. Klunder, D. P. Hickey, M. Li, K. Barman, M. S. Sigman, H. S. White and S. D. Minteer, *Chem. Sci.*, 2019, **10**, 6404–6422.

60 S. Minteer, J. Chen, S. Lin, C. Crudden, S. Dehnen, P. V. Kamat, M. Kozlowski, G. Masson and S. J. Miller, *ACS Catal.*, 2023, **13**, 4468–4469.

61 Z.-H. Wang, P.-S. Gao, X. Wang, J.-Q. Gao, X.-T. Xu, Z. He, C. Ma and T.-S. Mei, *J. Am. Chem. Soc.*, 2021, **143**, 15599–15605.

62 N. Fu, L. Li, Q. Yang and S. Luo, *Org. Lett.*, 2017, **19**, 2122–2125.

63 N. Fu, L. Song, J. Liu, Y. Shen, J. C. Siu and S. Lin, *J. Am. Chem. Soc.*, 2019, **141**, 14480–14485.

64 W. Fan, X. Zhao, Y. Deng, P. Chen, F. Wang and G. Liu, *J. Am. Chem. Soc.*, 2022, **144**, 21674–21682.

65 X.-L. Lai, M. Chen, Y. Wang, J. Song and H.-C. Xu, *J. Am. Chem. Soc.*, 2022, **144**, 20201–20206.

66 X. Huang, Q. Zhang, J. Lin, K. Harms and E. Meggers, *Nat. Catal.*, 2019, **2**, 34–40.

67 Y. Yuan and A. Lei, *Nat Commun*, 2020, **11**, 802.

68 L. G. Gombos and S. R. Waldvogel, *Sustain. Chem.*, 2022, **3**, 430–454.

69 S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 4263–4265.

70 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.

71 L. Ahrgren and L. Sutin, *Org. Process Res. Dev.*, 1997, **1**, 425–427.

72 A. R. Amundsen and E. N. Balko, *J. Appl. Electrochem.*, 1992, **22**, 810–816.

73 B. H. Nguyen, R. J. Perkins, J. A. Smith and K. D. Moeller, *Beilstein J. Org. Chem.*, 2015, **11**, 280–287.

74 H. Tanaka, M. Kuroboshi, H. Takeda, H. Kanda and S. Torii, *J. Electroanal. Chem.*, 2001, **507**, 75–81.

75 P. C. B. Page, F. Marken, C. Williamson, Y. Chan, B. R. Buckley and D. Bethell, *Adv. Synth. Catal.*, 2008, **350**, 1149–1154.

76 N. Sauermann, T. H. Meyer and L. Ackermann, *Chem. – Eur. J.*, 2018, **24**, 16209–16217.

77 T. von Münchow, S. Dana, Y. Xu, B. Yuan and L. Ackermann, *Science*, 2023, **379**, 1036–1042.

78 T. J. DeLano and S. E. Reisman, *ACS Catal.*, 2019, **9**, 6751–6754.

79 M. J. Goldfogel, L. Huang and D. J. Weix, in *Nickel Catalysis in Organic Synthesis*, John Wiley & Sons, Ltd, 2020, 183–222.

80 S. Biswas and D. J. Weix, *J. Am. Chem. Soc.*, 2013, **135**, 16192–16197.

81 A. H. Cherney and S. E. Reisman, *J. Am. Chem. Soc.*, 2014, **136**, 14365–14368.

82 M. Durandetti, J.-Y. Nédélec and J. Périchon, *J. Org. Chem.*, 1996, **61**, 1748–1755.

83 M. Durandetti, C. Gosmini and J. Périchon, *Tetrahedron*, 2007, **63**, 1146–1153.

84 F.-Y. Lu, Y.-J. Chen, Y. Chen, X. Ding, Z. Guan and Y.-H. He, *Chem. Commun.*, 2020, **56**, 623–626.

85 Y. Hussain, D. Sharma, N. Kotwal, I. Kumar and P. Chauhan, *ChemSusChem*, 2022, **15**, e202200415.

86 X. Chang, J. Zhang, Q. Zhang and C. Guo, *Angew. Chem. Int. Ed.*, 2020, **59**, 18500–18504.

87 S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471–5569.

88 Q. Yang, L. Zhang, C. Ye, S. Luo, L.-Z. Wu and C.-H. Tung, *Angew. Chem. Int. Ed.*, 2017, **56**, 3694–3698.

89 H. Zhang, M. Mifsud, F. Tanaka and C. F. Barbas, *J. Am. Chem. Soc.*, 2006, **128**, 9630–9631.

90 B. R. Rosen, E. W. Werner, A. G. O'Brien and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5571–5574.

91 B. Liu, S. Duan, A. C. Sutterer and K. D. Moeller, *J. Am. Chem. Soc.*, 2002, **124**, 10101–10111.

92 A. J. Metrano, A. J. Chinn, C. R. Shugrue, E. A. Stone, B. Kim and S. J. Miller, *Chem. Rev.*, 2020, **120**, 11479–11615.

93 H. Wynberg and B. Greijdanus, *J. Chem. Soc. Chem. Commun.*, 1978, **0**, 427–428.

94 H. J. Schäfer, *Angew. Chem. Int. Ed. Engl.*, 1981, **20**, 911–934.
95 Y. Hioki, M. Costantini, J. Griffin, K. C. Harper, M. P. Merini, B. Nissl, Y. Kawamata and P. S. Baran, *Science*, 2023, **380**, 81–87.
96 J. C. Siu, N. Fu and S. Lin, *Acc. Chem. Res.*, 2020, **53**, 547–560.
97 United States, US3547972A, 1970.
98 W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl and G. Liu, *Science*, 2016, **353**, 1014–1018.
99 W. Zhang, L. Lu, W. Zhang, Y. Wang, S. D. Ware, J. Mondragon, J. Rein, N. Strotman, D. Lehnherr, K. A. See and S. Lin, *Nature*, 2022, **604**, 292–297.
100 C.-H. Wong, *Science*, 1989, **244**, 1145–1152.
101 H. Chen, R. Cai, J. Patel, F. Dong, H. Chen and S. D. Minteer, *J. Am. Chem. Soc.*, 2019, **141**, 4963–4971.
102 R. D. Milton, R. Cai, S. Abdellaoui, D. Leech, A. L. De Lacey, M. Pita and S. D. Minteer, *Angew. Chem. Int. Ed.*, 2017, **56**, 2680–2683.
103 S. Ruccolo, G. Brito, M. Christensen, T. Itoh, K. Mattern, K. Stone, N. A. Strotman and A. C. Sun, *J. Am. Chem. Soc.*, 2022, **144**, 22582–22588.
104 J. A. McIntosh, T. Benkovics, S. M. Silverman, M. A. Huffman, J. Kong, P. E. Maligres, T. Itoh, H. Yang, D. Verma, W. Pan, H.-I. Ho, J. Vroom, A. M. Knight, J. A. Hurtak, A. Klapars, A. Fryszkowska, W. J. Morris, N. A. Strotman, G. S. Murphy, K. M. Maloney and P. S. Fier, *ACS Cent. Sci.*, 2021, **7**, 1980–1985.
105 A. Hoschek, B. Bühler and A. Schmid, *Angew. Chem. Int. Ed.*, 2017, **56**, 15146–15149.
106 A. Gavriilidis, A. Constantinou, K. Hellgardt, K. K. (Mimi) Hii, G. J. Hutchings, G. L. Brett, S. Kuhn and S. P. Marsden, *React. Chem. Eng.*, 2016, **1**, 595–612.
107 T. Komori and T. Nonaka, *J. Am. Chem. Soc.*, 1984, **106**, 2656–2659.
108 H. Yang, D. Chi, Q. Sun, W. Sun, H. Wang and J. Lu, *Chem. Commun.*, 2014, **50**, 8868–8870.
109 S. Butcha, S. Assavapanumat, S. Ittisanronnachai, V. Lapeyre, C. Wattanakit and A. Kuhn, *Nat. Commun.*, 2021, **12**, 1314.
110 Z. Ma, Q. Huang and J. M. Bobbitt, *J. Org. Chem.*, 1993, **58**, 4837–4843.
111 Y. Kashiwagi, F. Kurashima, S. Chiba, J. Anzai, T. Osa and J. M. Bobbitt, *Chem. Commun.*, 2003, 114–115.
112 Y. Kashiwagi, K. Uchiyama, F. Kurashima, C. Kikuchi and J. Anzai, *Chem. Pharm. Bull. (Tokyo)*, 1999, **47**, 1051–1052.
113 Y. Gao, B. Zhang, J. He and P. S. Baran, *J. Am. Chem. Soc.*, 2023, **145**, 11518–11523.