

Organic Electrochemistry: Molecular Syntheses with Potential

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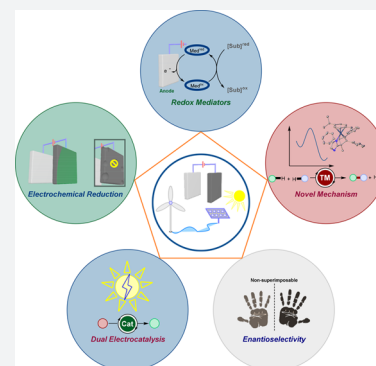


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ABSTRACT: Efficient and selective molecular syntheses are paramount to *inter alia* biomolecular chemistry and material sciences as well as for practitioners in chemical, agrochemical, and pharmaceutical industries. Organic electrosynthesis has undergone a considerable renaissance and has thus in recent years emerged as an increasingly viable platform for the sustainable molecular assembly. In stark contrast to early strategies by innate reactivity, electrochemistry was recently merged with modern concepts of organic synthesis, such as transition-metal-catalyzed transformations for *inter alia* C–H functionalization and asymmetric catalysis. Herein, we highlight the unique potential of organic electrosynthesis for sustainable synthesis and catalysis, showcasing key aspects of exceptional selectivities, the synergism with photocatalysis, or dual electrocatalysis, and novel mechanisms in metallaelectrocatalysis until February of 2021.



1. INTRODUCTION

Organic synthesis arguably represents the key discipline for the bottom-up assembly and late-stage diversification of molecular compounds with transformative applications to *inter alia* medicinal chemistry, drug development, and material sciences as well as chemical and pharmaceutical industries.¹ While scientists have in the past decade increasingly exploited the enabling platforms of photochemistry,² artificial intelligence,³ mechanochemistry,⁴ or flow technology,⁵ molecular electrosynthesis has largely laid dormant until very recently.⁶ Particularly, organic electrochemistry has in recent years overcome some of its past limitations as a niche technique.⁷ Electroorganic synthesis can indeed be traced back to the 19th century with Faraday's hydrolysis of acetic acid to hydrocarbons⁸ and Kolbe's electrochemical decarboxylative dimerization (Figure 1).⁹ Hence, in the early twentieth century, Hickling proposed that reactions could be conducted under potentiostatic control, rather than constant-current electrolysis.¹⁰ These findings were based on the emerging interest in polarographic methods at that time, such as voltammetry—the detection of current as a function of the potential at a solid working electrode—developed by Heyrovský among others.¹¹ In the mid-twentieth century, electrochemistry has been identified as an economically attractive approach for scalable commodity chemicals, for instance, the Simons fluorination process,¹² Monsanto adiponitrile processes,¹³ or later, the BASF Lysmeral synthesis via anodic benzylic oxidation,¹⁴ indicating the scalability of electroorganic synthesis, particularly in a paired electrosynthesis regime.^{14b,15} Yoshida introduced the concept of electroauxiliaries to selectively lower the electrochemical potential of substrates in the late twentieth century.¹⁶ The use of redox mediators for indirect

electrolysis could be traced back to 1900, when inorganic redox mediators were applied to the synthesis of quinones,¹⁷ while the principles of indirect electrolysis were formalized by Steckhan in the 1980s.¹⁸ Additional key achievements on the direct exploitation of electric current were made by Little,¹⁹ Schäfer,²⁰ Lund,²¹ Moeller,²² Amatore,²³ Jutand,²⁴ and Yoshida.²⁵ On the basis of these pioneering contributions, electrosynthesis gained significant momentum for sustainable organic syntheses (Figure 1).²⁶

The resurgence of this strategy stems from, among other things, an alternative array of reaction mechanisms that are exclusively feasible by electrochemistry or synergistically by photoelectrochemistry.²⁷ Here, electrons can be used as traceless redox equivalents to achieve exceptional selectivities, thus avoiding stoichiometric redox reagents and undesired byproduct generation.²⁸ The development of commercial electrochemical equipment,²⁹ has enabled most user-friendly access of electrosynthesis. Furthermore, the often exceedingly mild reaction conditions and the frequent use of protic solvents encompasses electrosynthesis as an environmentally benign strategy for molecular assembly.³⁰ On a different note, electrochemistry has the ability to regulate reactivity and selectivity by the precise control of the applied potential.^{6a,31} Thus, this unique tunability translates into an unmatched chemoselectivity of electrochemistry compared with com-

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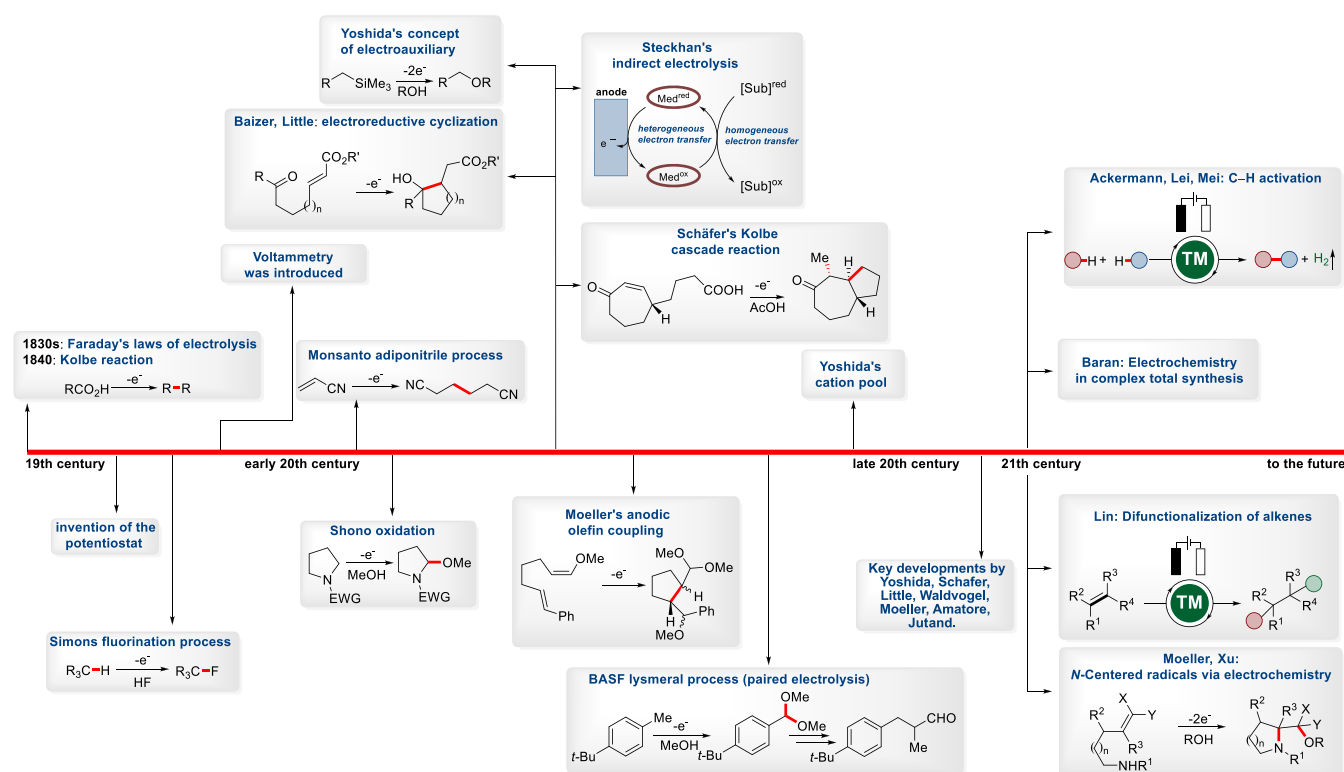


Figure 1. Selected milestones of representative electroorganic chemistry.

monly used chemical redox reagents.³² Particularly, the concept of indirect electrolysis with redox mediators can improve the efficiency and chemoselectivity of electrosynthesis (Figure 2). Synergistic electrocatalysis has gained particular recent impetus within the renaissance of electroorganic syntheses, which has addressed several challenges encountered in modern organic syntheses.³³ Specifically, electrophotocatalysis combined the electrochemical and photochemical steps in

tandem pathways to generate a highly reactive intermediate, thus providing new avenues for contemporary reaction design and molecular transformations.^{27,34} The merger of electrosynthesis with transition metal catalysis enabled novel resource-economic bond functionalizations, which unearthed a variety of new reaction mechanisms.³⁵ Electrochemical reduction shows largely untapped potential for reductive organic syntheses through cathodic reduction with the aid of a sacrificial anode material.³⁶ Enantioselective electrosynthesis, a key research arena which is highly relevant for pharmaceutical and crop-protecting industries, provides greener synthetic methods unattainable by traditional means (Figure 2).³⁷

The current Outlook highlights representative recent concepts for the electrocatalytic diversification of organic molecules beyond their innate reactivity, until 2021. Thus, we focus on the selectivity control by modern redox mediators, dual electrocatalysis, new mechanistic innovation, electrochemical reduction, and asymmetric electrocatalysis, while conventional organic electrosynthesis has been comprehensively summarized elsewhere.^{31,38}

2. REDOX MEDIATORS: UNIQUE SELECTIVITY CONTROL IN ORGANIC ELECTROCHEMISTRY

Direct electrolysis enables molecules to undergo electron transfer directly at the electrode surface. In contrast, with indirect electrosynthesis, a redox mediator which is more easily oxidized or reduced than the substrate, acts as the electron-transfer-shuttle from the heterogeneous electrode surface to the homogeneous dissolved substrates.^{19a,39} The concept of indirect electrolysis offers several advantages. In many cases, the indirect approach results in improved reaction efficacy and better chemoselectivity by avoiding undesirable side reactions. The facile homogeneous redox process of the mediator eliminates kinetic inhibition of the heterogeneous electron

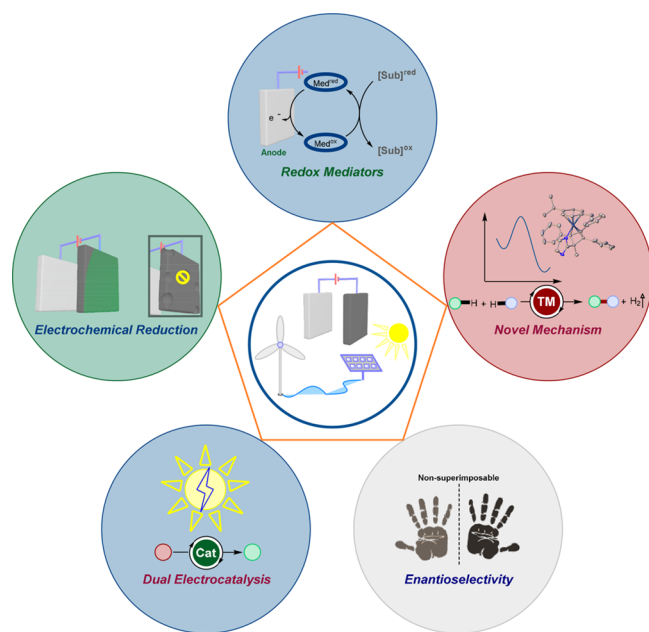
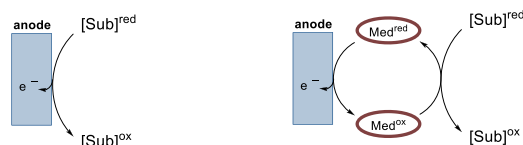


Figure 2. Prospects of modern concepts in organic electrosynthesis and electrocatalysis.

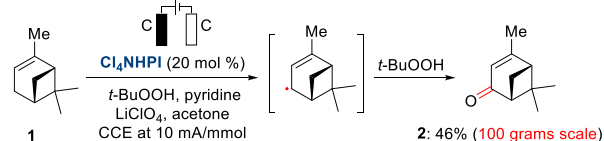
transfer and structural modification of the mediator offer direct selectivity control (Scheme 1A).^{18b,19a,40} In this context, the

Scheme 1. Case Studies in Redox Mediator in Organic Electrosynthesis⁴⁴

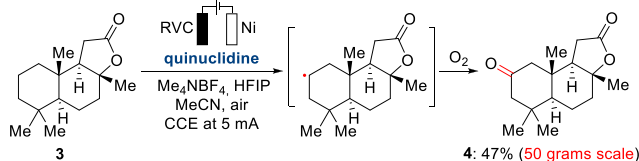
A) Direct electrochemical oxidation vs. indirect electrochemical oxidation



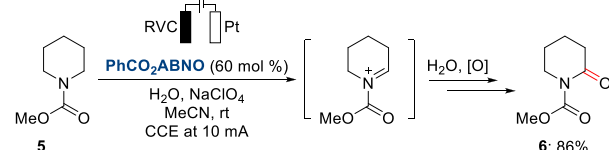
B) Allylic C–H oxidation with Cl₄NHPI (TCNHPI) as the mediator



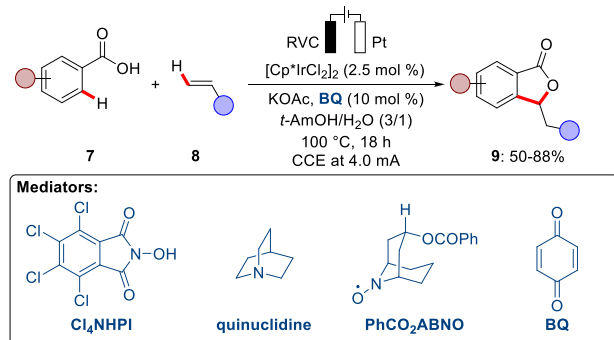
C) Unactivated C–H oxidation with quinuclidine as the mediator



D) Activated C–H oxidation with PhCO₂ABNO as the mediator



E) Iridaelectro-catalyzed C–H activation with BQ as the mediator



^aCl₄NHPI = tetrachloro-*N*-hydroxyphthalimide, BQ = *p*-benzoquinone, CCE = constant current electrolysis.

beneficial effects of redox mediators were recently exemplified for the challenging selective anodic oxidation of activated C–H bonds, which proved to be useful for the transformation of natural products. The electrochemical direct allylic oxidation pioneered by Shono, can engage the electrogenerated alkyl radical with the subsequent fragmentation of the cyclobutane ring to enable the direct oxidation of α -pinene (1).⁴¹ A major advance was made by Masui, employing *N*-hydroxyphthalimide (NHPI) as an electron carrier to facilitate allylic C–H oxidations.⁴²

Taking inspiration from these findings, Baran discovered that the use of a modified tetrachloro-derivative of NHPI, namely tetrachloro-*N*-hydroxyphthalimide (Cl₄NHPI), significantly improved the reaction outcome (Scheme 1B).⁴³ Comparing the reversible redox potentials of NHPI ($E_{1/2}$ =

0.78 V vs. Ag/AgCl) and Cl₄NHPI ($E_{1/2}$ = 0.87 V vs. Ag/AgCl), a slightly higher redox couple of Cl₄NHPI was indicative of the stronger oxidative character of the more electron-deficient *N*-oxyl radical. A 100 gram-scale reaction highlighted the synthetic utility of the approach, including the selective functionalization of steroids, monoterpenoids, and triterpenoids.

The redox mediator strategy was likewise implemented in the oxygenation of annulated hydrocarbons with quinuclidine as the mediator (Scheme 1C).⁴⁴ The indirect electrochemical process enabled the anodic oxidation to proceed at relatively low potentials compared with direct oxidation. Thus, chemoselective oxidation of unactivated C–H bonds proved to be amenable. The accessible electrooxidation allowed for the successful oxidation of sclareolide 4 on a 50 g-scale.

In contrast to traditional Shono oxidations by direct electron transfer to the electrode, Stahl developed the α -C–H oxygenation of cyclic carbamates 5 using bicyclic aminoxyl as a mediator (Scheme 1D).⁴⁵ Here, the anodically generated oxoammonium species promoted the oxidation of the substrate 5 to form the substrate-derived iminium ion, which reacted with H₂O in a two-electron oxidation to afford the desired product 6. Notably, the redox mediator benefited from an oxidizing potential being 1.0 V lower than the direct one-electron oxidation of the substrate. Hence, a good functional-group tolerance and broad substrate scope were shown to be viable.

Recently, the redox mediator strategy was successfully extended to metalla-electrocatalyzed C–H activation. With regard to studies by Jutand, on *p*-benzoquinone as a redox mediator for Fujiwara–Moritani type reactions,^{39c} Ackermann showed the beneficial effect of redox mediators for iridaelectrocatalyzed C–H alkenylations of benzoic acids 7 (Scheme 1E).⁴⁶ Here, a variety of sensitive functional groups, including cyano, ester, halide, and even labile iodo, were fully tolerated. The efficacy and chemoselectivity of the iridium electrocatalysis were considerably improved by the aid of the redox mediator. The robustness of the iridaelectro-catalyzed C–H activation⁴⁷ was further exploited for the assembly of medically relevant steroids and peptides.

It is noteworthy that the concept of modern redox mediators has proven to be beneficial for various aspects of organic electrosynthesis and innovative electrocatalysis (*vide infra*).⁴⁸ Also, novel electrode materials⁴⁹ have recently proven to have a major impact on the selectivity of specific organic electrochemical transformations. For instance, on the basis of the pioneering studies on biaryl formations in electrosynthesis,⁵⁰ recent impetus has been gained in electrooxidative coupling reactions to enable unprecedented substitution patterns and selectivity regimes, particularly by the aid of boron-doped diamond (BDD) electrodes, along with 1,1,1,3,3,3-hexafluoro-propan-2-ol (HFIP) as the solvent.^{26c,51}

3. DUAL ELECTROCATALYSIS IN ORGANIC SYNTHESIS

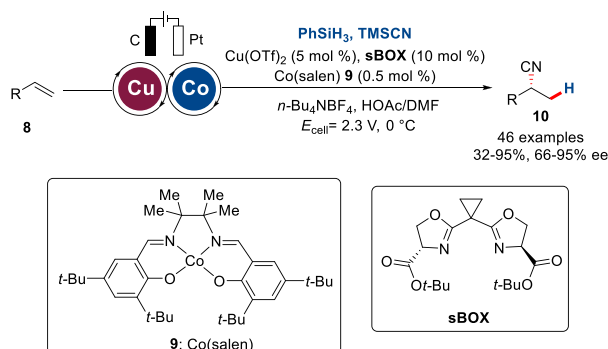
3.1. Synergistic Dual Catalysis for Electrochemistry.

In contrast to indirect electrolysis, dual electrocatalysis enables two distinct catalytic transformations that go beyond electron transfer, including but not being limited to, group transfer reactions, hydrogen atom transfer, or two individual catalytic concepts, such as mediated electrochemistry and photoredox catalysis. It was shown to be an efficient strategy to improve catalytic performance, chemoselectivity, and overall catalytic

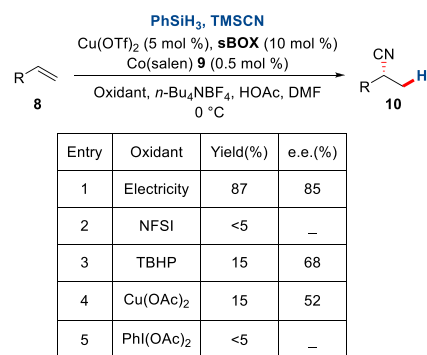
efficacy.⁵² In a representative elegant example, Lin recently utilized a novel chiral bisoxazoline (sBOX) ligand to establish asymmetric alkene hydrocyanation reactions within a dual electrocatalytic manifold by employing Co(salen) **9** and Cu(sBOX) as the catalysts (Scheme 2A).⁵³ The proposed

Scheme 2. Synergism of Dual Electrocatalysis in Practice: (A) and (B) Enantioselective Dual Electrocatalysis; (C) C–H Oxygenation by Synergistic Catalysis^a

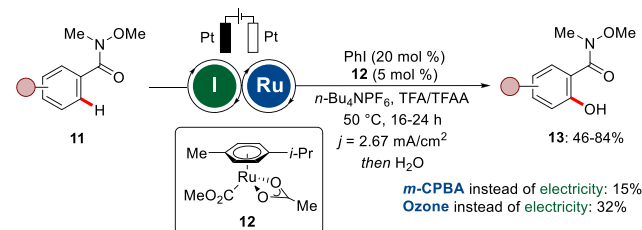
A) Dual electrocatalysis for enantioselective hydrocyanation of alkenes



B) Control experiments for enantioselective hydrocyanation of alkenes



C) Dual electrocatalysis for C–H oxygenation



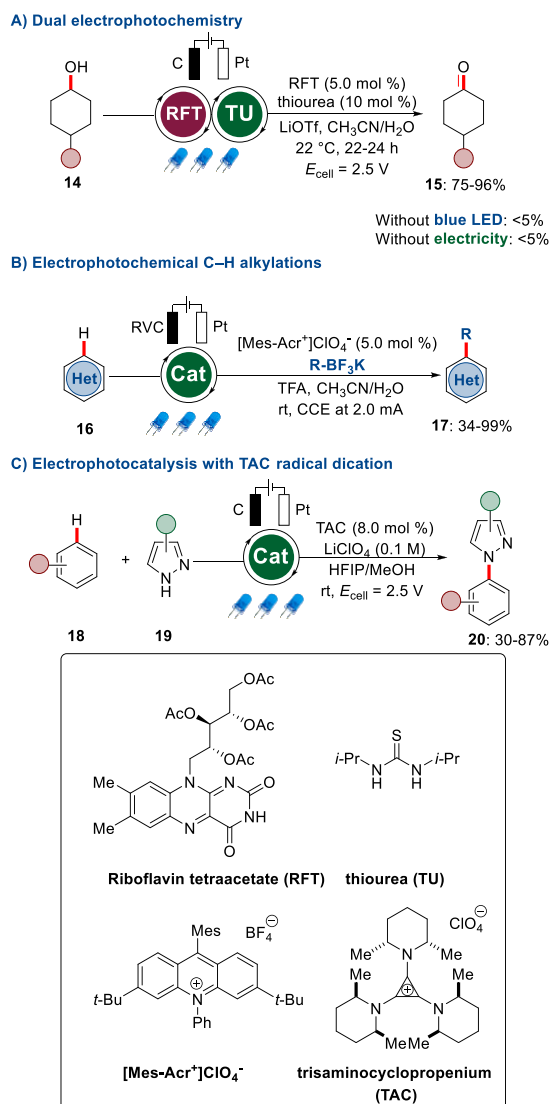
^aNFSI = N-fluorobenzenesulfonimide, TBHP = *tert*-butyl hydroperoxide.

catalytic scenario consists of initial formation of the catalytically competent [Co^{III}]-H species, formed from the anodically oxidized cobalt(III)salen complex and a hydrosilane. Subsequent hydrogen-atom transfer (HAT)⁵⁴ between the formal [Co^{III}]-H intermediate and olefin **8** furnishes the new C–H bond, along with a carbon-centered radical. The radical species now enters a second electrocatalytic cycle that is responsible for the asymmetric cyanide transfer. Here, the thus formed radical species is proposed to undergo single-electron oxidative addition to a [Cu^{II}]-CN complex, generating a copper(III) adduct. Finally, reductive elimination from the chiral complex

delivers the enantio-enriched nitrile **10** and a reduced copper(I) complex, which is easily reoxidized via anodic oxidation. The merger of two distinct electrocatalytic radical reactions, namely, cobalt-catalyzed hydrogen-atom transfer (HAT) and copper-catalyzed radical cyanation,⁵⁵ was the key to put into practice the asymmetric hydrocyanation of alkenes. Moreover, the electrocatalysis protocol featured significantly improved yields, chemoselectivities, and enantioselectivities compared with transformations using chemical oxidants, as was exemplified by the failure of topical oxidants such as *N*-fluorobenzenesulfonimide (NFSI), *tert*-butyl hydroperoxide (TBHP), Cu(OAc)₂, and PhI(OAc)₂ (Scheme 2B).

Hypervalent iodine(III) reagents have been extensively studied as strong chemical oxidants for oxidative transformations.⁵⁶ However, they commonly need to be synthesized and meticulously handled, and their use often results in stoichiometric waste products. Recently, Ackermann merged the catalytic electro-regeneration of hypervalent iodine(III) reagents⁵⁷ with ruthenaelectro-catalyzed C–H oxygenations (Scheme 2C).⁵⁸ The iodoarenes and ruthenium dual electrocatalytic strategy provided a unique avenue toward sustainable C–H oxygenations. Commonly used chemical oxidants, required to generate the hypervalent iodine(III) reagent, such as *m*-CPBA or ozone, indeed failed to deliver the desired product **13** with satisfactory yields. These results highlight that the hypervalent iodine reagent does not only operate as the electron-shuttle (*vide supra*) but can rather be classified as a transfer reagent of carboxylate anions, while likewise mediating the oxidative generation of high-valent ruthenium(IV) intermediates.⁵⁹ Notably, a series of weakly-*O*-coordinating amides **11** was thereby selectively converted to the corresponding oxygenated products **13**. The dual electrocatalysis proved also viable for selective C–H oxygenations of aromatic ketones or simple arenes in the absence of an external.

3.2. Electrophotocatalysis. The use of a dual electrocatalysis approach by electrophotocatalysis^{27,34,60} broadens the possibilities for elegant reaction design and expands the viable scope of photoredox catalysis. While important contributions for electrophotosynthesis have been made by *inter alia* Xu,^{61,62} Lambert,⁶³ Lin,^{64,67} Wickens,⁶⁵ and our group,⁶⁶ among others,^{34c,d} selected examples shall be discussed in the following section. Seminal work by Lin for the oxidation of alcohols **14** relied on riboflavin tetraacetate (RFT) and thiourea as the cocatalyst. Previous photochemical flavin-catalyzed aerobic oxidation of alcohols was thus far limited to benzylic alcohols. The dual electrophotocatalytic system enabled the oxidation of more challenging unactivated aliphatic alcohols **14** under exceedingly mild reaction conditions (Scheme 3A).⁶⁷ Likewise, a chemical oxidant-free C–H alkylation of heteroarenes **16** with organotrifluoroborate salts was elegantly carried out by means of electrophotocatalytic activation (Scheme 3B).⁶¹ Highly oxidizing excited state organic dye [Mes-Acr⁺]* (*E*^{red} = 2.06 V vs SCE in MeCN) was generated from irradiation of the organic dye ion [Mes-Acr⁺]. Then, a single-electron transfer (SET) delivers acridinyl radical (Mes-Acr[•]) and an alkyl radical, respectively. Anodic electro-oxidation of the acridinyl radical (Mes-Acr[•]) subsequently regenerates the ground state cationic catalyst [Mes-Acr⁺]. On a different note, the C–H/N–H coupling of azoles **19** was realized by Lambert using a trisaminocyclopropenium (TAC) ion as the electrophotocatalyst (Scheme 3C).^{63c} The electrophotocatalysis relied on the electrochemical oxidation of

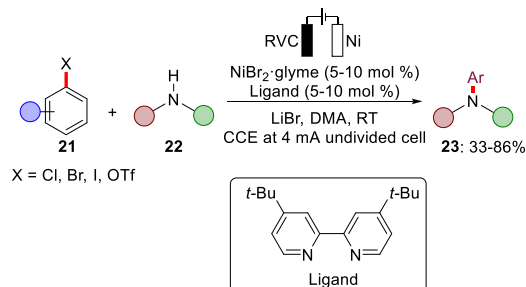
Scheme 3. Recent Progress in Electrophotocatalysis^a

^aRFT = riboflavin tetraacetate, TFA = trifluoroacetic acid, TAC = trisaminocyclopropenium, HFIP = 1,1,1,3,3,3-hexafluoro-propan-2-ol, CCE = constant current electrolysis.

trisaminocyclopropenium ion (TAC⁺) to the corresponding radical dication (TAC²⁺), followed by visible light photoexcitation to generate the highly potent oxidizer TAC^{2+*} ($E = 3.33$ V vs SCE). The highly oxidizing photoexcited TAC radical dication (TAC^{2+*}) enabled facile oxidation of inert simple arenes **18**.

4. UNRAVELLING NOVEL MECHANISTIC INSIGHTS: ORGANIC METALLA-ELECTROCATALYZED TRANSFORMATIONS

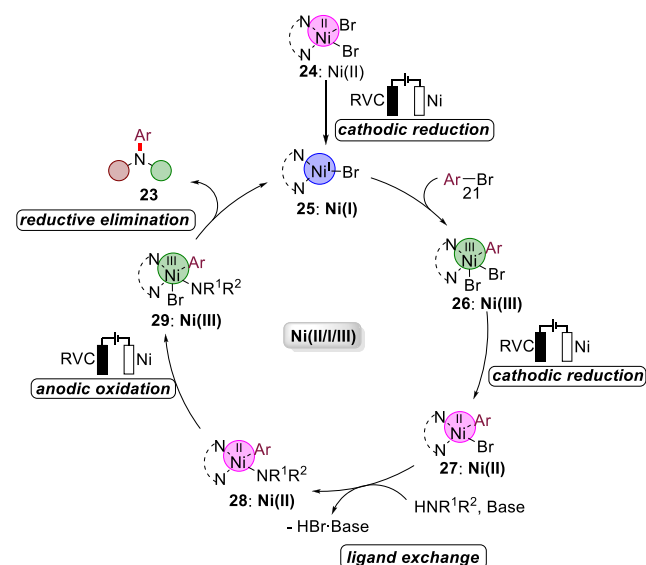
4.1. Novel Findings for Electrochemical Cross-Couplings. Despite considerable progress, cross-couplings by nickel catalysis often suffered from the need of air-sensitive nickel(0) catalysts, strong alkoxide bases, and high temperatures.⁶⁸ Electrochemical nickel-catalyzed cross-couplings have set the stage for C–C and C–heteroatom formations under significantly milder reaction conditions.⁶⁹ Recently, electrochemical nickel-catalyzed aminations of aryl halides and triflates **21** were demonstrated (Scheme 4).⁷⁰ Detailed

Scheme 4. Nickelaelectro-Catalyzed Amination^a

^aCCE = constant current electrolysis.

mechanistic studies of the electrocatalytic aryl aminations with the aid of cyclic voltammetry, kinetic studies, and DFT calculations unraveled the novel paired electrolysis working mode, responsible for the exceedingly mild reaction conditions (Scheme 5).⁷¹ Initially, cathodic reduction of the nickel(II)

Scheme 5. Mechanistic Rationale



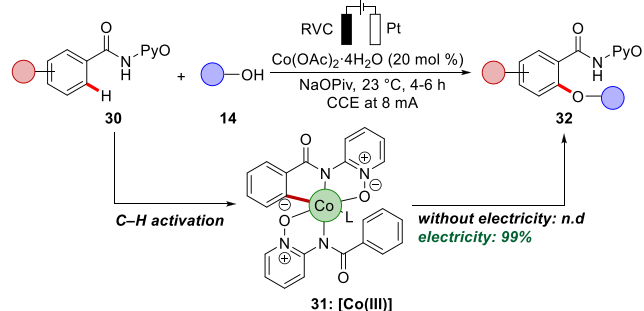
precursor **24** delivers a nickel(I) species **25**. Then, oxidative addition of aryl halide **21** furnishes the nickel(III) intermediate **26**, and a second cathodic reduction generates the nickel(II) species **27**. Along with ligand exchange with the amine, intermediate **28** is anodically oxidized to the nickel(III) complex **29**. Thereafter, the desired product **23** is formed via reductive elimination, while the catalytically competent complex **25** is regenerated.

4.2. New Mechanistic Insights: Metalla-Electrocatalyzed C–H Activation. Transition-metal-catalyzed C–H activation has surfaced as a particularly powerful tool for step-economical molecular syntheses, with major prospects for materials sciences and the pharmaceutical industry, among others.⁷² The merger of C–H activation and electrochemistry thus acts as an ideal platform for modern sustainable molecular syntheses by the aid of electrochemical anodic oxidation and cathodic reduction processes.⁷³ The application of analytical techniques such as voltammetry, spectrophotometry or *in operando* techniques, such as React-IR, NMR spectroscopy, and electrospray ionization mass spectrometry (ESI-MS), as well as computation, have set the stage for novel insights into

the catalyst's modes of action. Thus, electrochemistry allowed for the identification of new paradigms in metallaelectrocatalysis by characterization of short-lived intermediates and detailed insights into often fundamental single electron transfer (SET) processes.

As a pertinent example, cobalt electrocatalysis allowed for a series of C–H transformations, such as C–H oxygenations,⁷⁴ C–H aminations,⁷⁵ C–H/N–H annulations with alkynes,⁷⁶ isocyanides and allenes,⁷⁷ as well as with carbon monoxide.⁷⁸ The catalyst's *modus operandi* was probed through in-depth mechanistic studies.⁷⁹ The well-defined cobalt(III) cyclometalated complex **31** was utilized in a series of key stoichiometric reactions. In contrast to alkyne and allene annulations, the C–H oxygenation (Scheme 6) could only be

Scheme 6. Cobaltalelectro-Catalyzed C–H Oxygenation^a

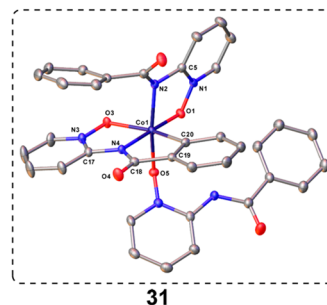


^aCCE = constant current electrolysis.

induced under anodic oxidative conditions, thus providing unique mechanistic support for an oxidation-induced reductive elimination⁸⁰ by a cobalt(III/IV/II) regime. The hypothesis was further supported by means of cyclic voltammetry (CV) of the isolated cyclometalated complex **31**, a Hammett–Zuman plot, and DFT calculations (Figure 3).

Electrochemical transformations of unactivated C–H bonds were not limited to cobalt catalysis. Nickel catalysts, in comparison to precious metals, are earth-abundant, cost-effective, and less toxic.⁸¹ In this context, 3d nickelalelectrocatalyzed C–H activation has recently been recognized as amenable strategy for the construction of organic molecules in a sustainable and user-friendly fashion.⁶⁹ Hence, C–H amination of amides proved to be viable, representing the proof-of-concept for the feasibility of C–H transformations by nickelalelectrocatalysis.⁸² In addition, the versatile electrocatalysis proved to be effective for the challenging C–H alkoxylation with secondary alcohols **14**.⁸³ Particularly, chemical oxidants were not able to efficiently promote the envisioned C–H alkoxylation reaction with challenging secondary alcohols **14** (Scheme 7). Cyclic voltammograms of nickel(III) cycles **34** displayed an oxidation wave at a relatively low potential of 0.50 V vs Fc^{0/+} (Figure 4). Moreover, detailed mechanistic investigations provided strong support for an oxidation-induced reductive elimination via a nickel(III/IV) manifold (Scheme 8), in contrast to previously reported nickel(II/III/I)-catalytic cycles facilitated by chemical oxidants.⁸⁴ The broadly applicable nickelalelectro-catalyzed C–H activation approach gained further momentum for the effective conversion of synthetically useful alkyl iodides under ambient condition.⁸⁵

A) Crystal structure of cobalt(III) cyclometalated complex **31**



B) Cyclic voltammetry of cobalt(III) cyclometalated complex **31**

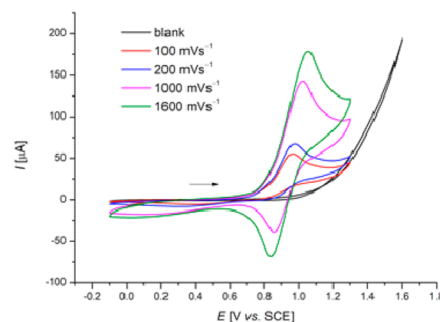
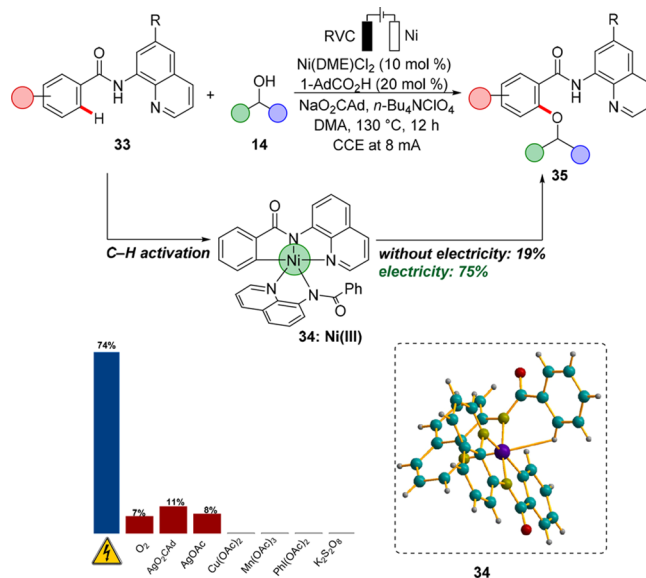


Figure 3. Cyclic voltammograms of cobaltacycles **31** in MeOH (3.5 mM) at different scan rates. The voltammograms were recorded in 0.1 M *n*-Bu₄NPF₆ at 273 K. Reprinted with permission from ref 79. Copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA.

Scheme 7. Nickelalelectrocatalysis: Electricity vs Chemical Oxidants^a



^aCCE = constant current electrolysis.

Iron-catalyzed C–H arylations were realized with dichloroisobutane (DCIB) as the chemical oxidant.⁸⁶ DCIB is a cost-intensive vicinal dihalide (\$4086/mol);⁸⁷ however, it is often an essential oxidant. In order to address these limitations, direct electrochemical C–H arylation by iron catalysis was devised under mild reaction temperature. Thus, the vicinal-dichloride DCIB could be replaced by electricity as the green

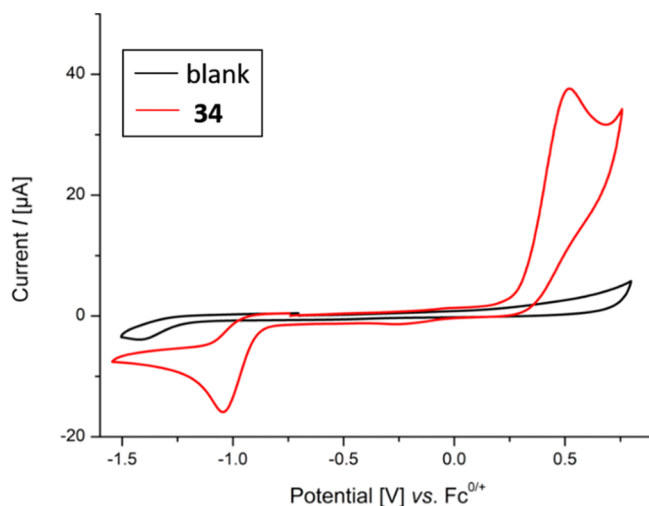
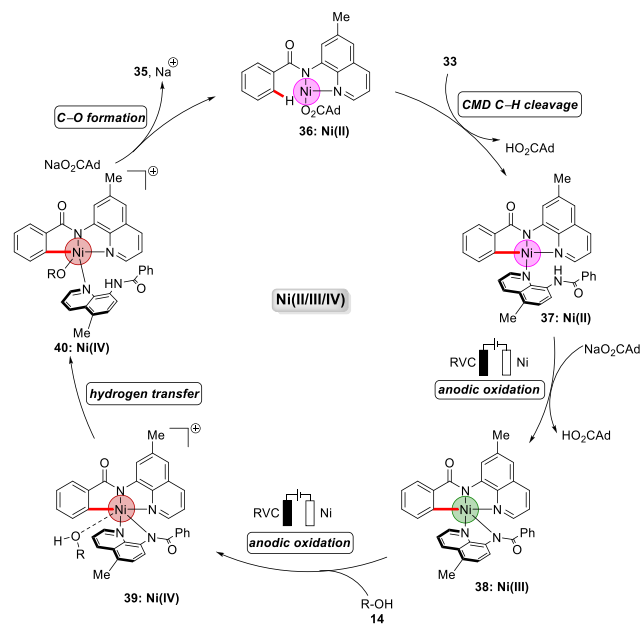


Figure 4. Cyclic voltammograms of nickelacycle **34** in DMA (0.1 mM) at 100 mV/s scan rate. The voltammograms were recorded in 0.1 M *n*-Bu₄NBF₄.

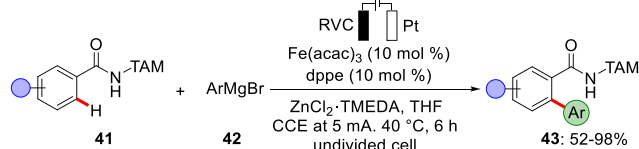
Scheme 8. Proposed Catalytic Cycle for Nickelaelectro(II/III/IV)-Catalyzed C–H Activation



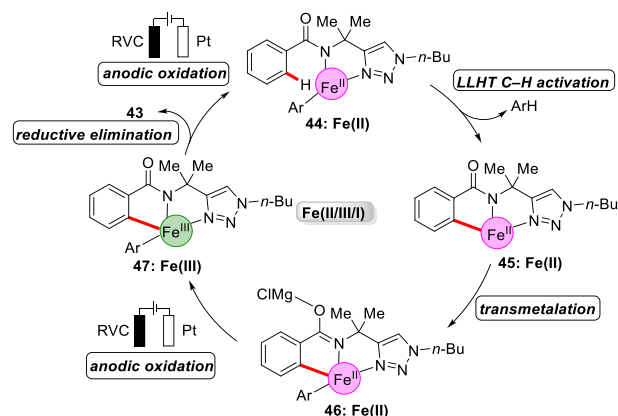
terminal oxidant (Scheme 9A).⁸⁷ The performance of the electrocatalysis was indeed significantly increased compared with the DCIB-mediated transformation. Detailed mechanistic studies by experiments and computation (Scheme 9B) featured an iron(II) complex as the active catalyst. Initially, a ligand-to-ligand hydrogen transfer (LLHT) delivers cyclometalated iron(II) intermediate **45**.⁸⁸ The following transmetalation generates the iron-complex **46** and set the stage for an oxidation-induced reductive elimination. Thus, subsequent anodic oxidation delivered the iron(III) complex **47**, which then undergoes reductive elimination to generate the desired product **43**. Finally, the active catalyst is regenerated through anodic oxidation. Furthermore, the metallaelectrocatalysis strategy was implemented in an electrochemical manganese-catalyzed C–H arylation of amides without zinc additives.

Scheme 9. Electrochemical C–H Arylation under Iron and Manganese Catalysis^a

A) Iron-catalyzed electrochemical C–H arylation



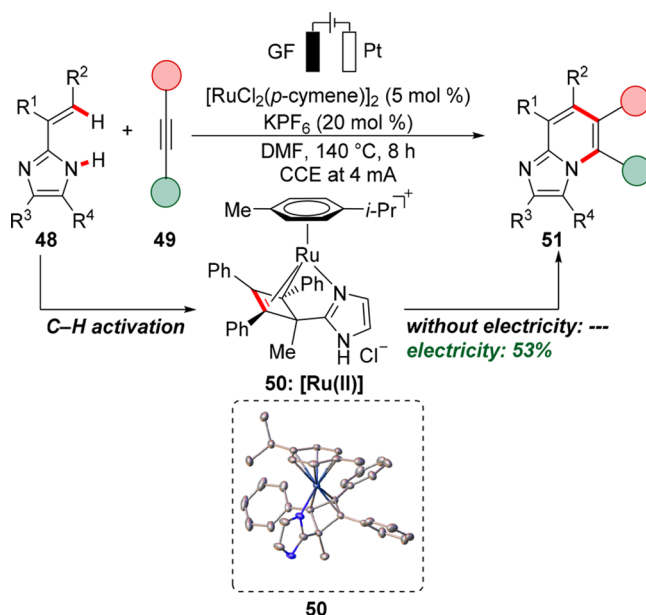
B) Key mechanistic steps



^adppe = 1,2-bis(diphenylphosphino)ethane, TAM = triazolyl-dimethylmethyl, CCE = constant current electrolysis.

While 3d metallaelectro-catalyzed C–H activations largely involve bidentate directing groups to encompass positional-selectivity, 4d and 5d transition metals have likewise benefited from key mechanistic insights by electrocatalysis. For instance, within the synthesis of bridgehead *N*-fused [5,6]-bicyclic heteroarenes **51** through ruthenaelectro-catalyzed dehydrogenative C–H/N–H annulation of imidazoles **48** with alkynes **49**, novel mechanistic scenarios were uncovered (Scheme 10).⁸⁹

Scheme 10. Ruthenaelectro(II/III/I)-Catalyzed Alkyne Annulations^a

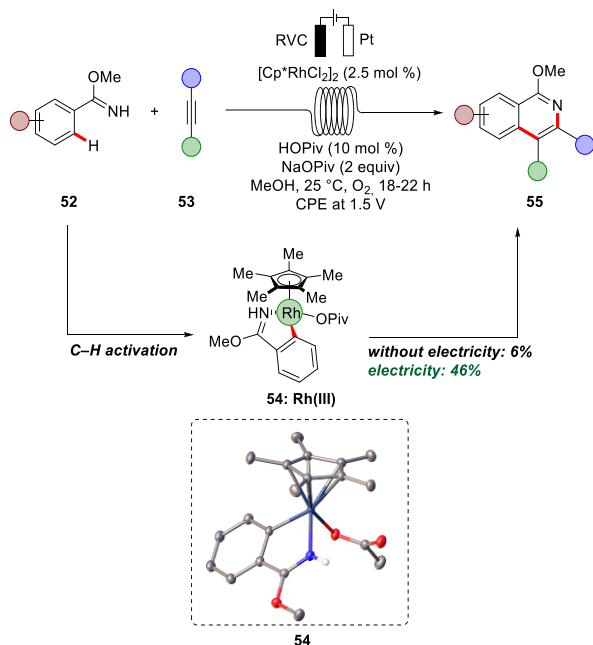


^aCCE = constant current electrolysis.

Notably, two ruthenium(II) complexes were isolated and fully characterized. The formation of product **51** was observed when electricity was applied, thus providing support for an oxidation-induced reductive elimination within an unusual ruthenium-(II/III/I) regime, which is in stark contrast to the previously reported mechanisms with chemical oxidants.⁹⁰

The robust rhodaelectrocatalytic C–H activation⁹¹ allowed electrochemical flow techniques⁹² to establish challenging flow-rhodaelectro-catalyzed C–H/N–H alkyne annulations with imidates **52** (Scheme 11).⁹³ Using cyclic voltammetry and

Scheme 11. Rhodaelectro-Catalyzed C–H Activation^a



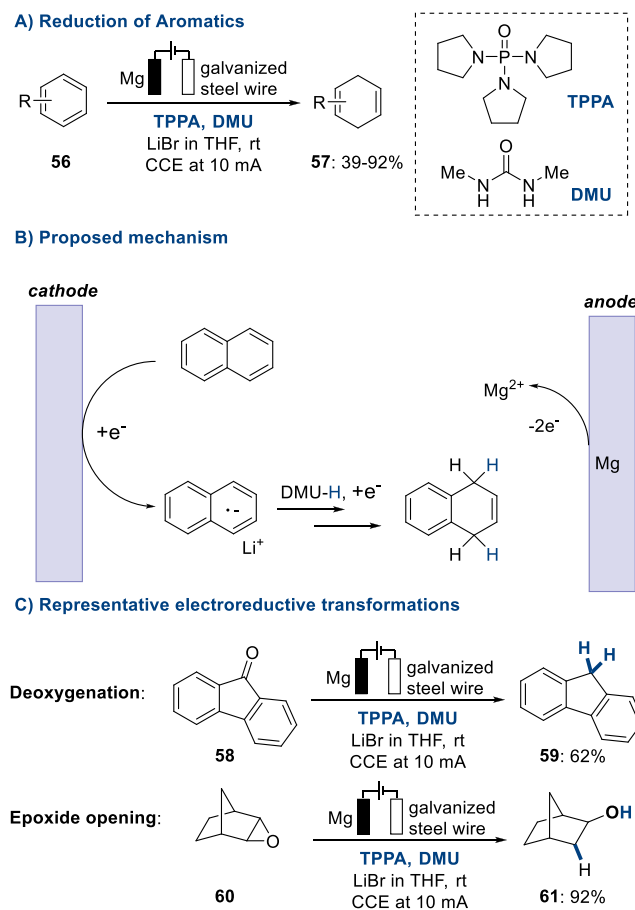
^aCPE = constant potential electrolysis.

further detailed mechanistic studies by experiment provided novel insights for the rhodaelectrocatalytic manifold. Sufficient formation of product **55** was solely observed when electricity was applied to oxidize the isolated rhoda(III)cyclometalated complex **54**, thus providing support for an oxidation-induced reductive elimination within a rhodium(III/IV/II) regime. The generality of this strategy was demonstrated in several innovative transformations. A multiple C–H domino electrooxidative alkyne annulation was developed for accessing aza-polycyclic aromatic hydrocarbons (aza-PAHs).⁹⁴ Novel rhodium-cyclometalated complexes were fully characterized and identified as key intermediates, which demonstrated the order of the three subsequent C–H activation events. Very recently, Xu concurrently reported a mechanistically related phosphorylation with *N*-coordinating directing groups.⁹⁵ Ackermann further developed a rhodium-catalyzed electrochemical C–C activation. The rhodaelectro-catalyzed C–C alkenylation confers advantages of chemo- and position-selectivities to access the hindered 1,2,3-substituted arenes, which were not accessible by a C–H scission strategy.⁹⁶

5. ELECTROCHEMICAL REDUCTION FOR UNIQUE CHEMOSELECTIVITIES AND SMALL MOLECULE TRANSFORMATIONS

Electrochemical reduction offers molecular synthesis by means of cathodic reductive electrolysis to generate radical anions.^{6c,30c,36} This strategy was successfully applied for the reduction of various functional groups such as aldehydes,⁹⁷ ketones,⁹⁸ esters, or amides.⁹⁹ An early example of electrochemical Birch reduction of benzene was disclosed by Kashimura, who employed Mg electrodes, LiClO₄ as a supporting electrolyte, and *t*-BuOH as a proton donor in dry THF to afford 1,4-cyclohexadienes **58** as the related product.¹⁰⁰ However, the approach was limited to simple hydrocarbons and continuous sonication was required, which impedes its application to practical synthesis. To address these drawbacks, a scalable reductive electrosynthetic strategy was devised by Baran (Scheme 12A), introducing tris(pyrrolidino)-

Scheme 12. Electrochemical Birch Reduction^a



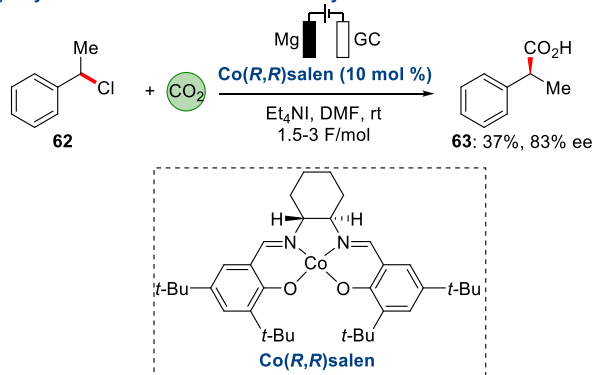
^aTPPA = tris(pyrrolidino)phosphoramidate, DMU = 1,3-dimethylurea, CCE = constant current electrolysis.

phosphoramidate (TPPA) as an overcharge protectant, and dimethylurea (DMU) was used as the proton source, as well as manganese as the sacrificial anode material of choice (Scheme 12B).¹⁰¹ The robustness of this electrochemical Birch reduction led to unprecedented levels of functional group tolerance as well as broadly reductive transformations including ketone **58** deoxygenations and reductive ring-opening of epoxides **60** and furans (Scheme 12C).

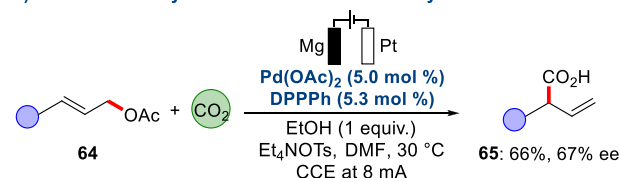
Carbon dioxide evolution is of major environmental concern as a significant source of greenhouse gas emissions.¹⁰² However, CO₂ has also proven to be an easily available, yet non-toxic source of C₁ synthon in modern organic synthesis. The utilization of CO₂ as a building block in organic synthesis have been studied in detail,¹⁰³ whether for carboxylations,¹⁰⁴ carbonylations as CO surrogates,¹⁰⁵ methylation of amines,¹⁰⁶ synthesis of polycarbonates, or cyclic carbonates¹⁰⁷ from epoxides. The kinetic and thermodynamic stability of CO₂, however, translates into the requirement of superstoichiometric amounts of strong reducing agents, such as Mn or Et₂Zn. Innovative electrochemical approaches for the environmentally benign reduction of CO₂ for C–C bond formation reactions are highly desirable.^{24,108} There is precedent for electroreductive cross-coupling of organohalides with CO₂.^{104d,109} Lu and Wang reported an enantioselective electrochemical carboxylation, utilizing chiral cobalt salen complexes (Scheme 13A). This example illustrated the

Scheme 13. Case Studies in Electrochemical Reduction of CO₂^a

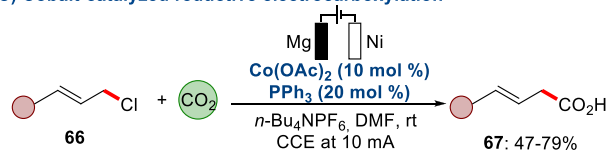
A) Asymmetric reductive electrocarboxylation



B) Palladium-catalyzed reductive electrocarboxylation



C) Cobalt-catalyzed reductive electrocarboxylation



^aDPPPh = 1,2-Bis(diphenylphosphino)benzene.

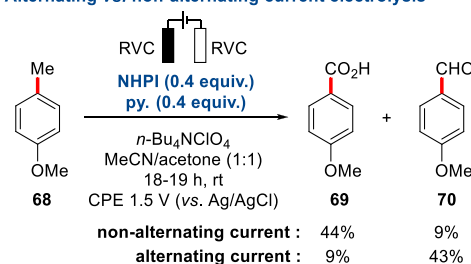
possibility of an asymmetric electroreductive carboxylation of inexpensive and optically inactive alkyl chloride **62** for the first time.¹¹⁰ Subsequently, Mei displayed an elegant palladium-catalyzed electroreductive carboxylation of allyl esters **64** with CO₂ in a highly regioselectivity manner (Scheme 13B).¹¹¹ In contrast, Ackermann showcased earth-abundant cobalt-catalysis for electroreductive carboxylation of allylic chlorides **66** with a simplified undivided cell setup and nontoxic solvent to achieve the synthesis of styrylacetic acid derivatives **67** in good yield and regioselectivity (Scheme 13C).¹¹² Despite efforts into designing and employing electrochemical means for the reduction of CO₂ for organic syntheses, multifarious

challenges, such as the high selectivity of CO₂ transformations and the need for a sacrificial anode remained unsolved to model a multifacet cross-coupling reaction with CO₂ as a synthon to enrich organic synthesis with sustainable methods.

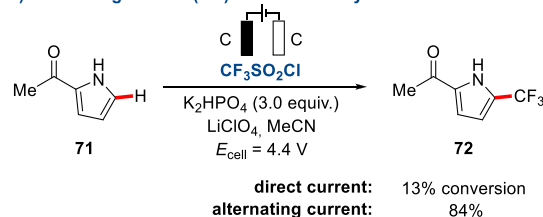
The technique of switching polarity direction of the electrodes, such as alternating current (AC), during the reaction could avoid passivation on the electrode surface, thereby increasing the lifetime of the electrodes. This underexplored approach could be the key in unlocking some of the problematic reaction, chemoselectivity issues and avoiding the use of sacrificial anodes.¹¹³ Recent developments by Reid highlighted the ability of inverting chemoselectivity by alternating current electrolysis for the selective oxidation of 4-methyl anisole (**68**). The in-depth mechanistic studies confers deeper understanding of AC vs non-alternating constant potential (CPE) electrolysis (Scheme 14A),¹¹⁴ here enabled

Scheme 14. Alternating Current (AC) Electrolysis

A) Alternating vs. non-alternating current electrolysis



B) Alternating current (AC) in trifluoromethylation



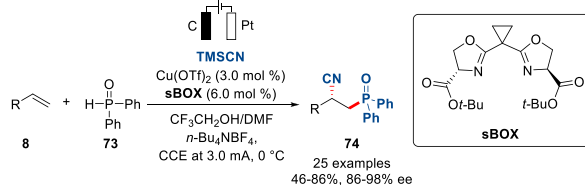
with the aid of the redox mediator NHPI (*vide supra*). Luo and Nguyen likewise devised the successful usage of AC electrolysis for the trifluoromethylation of heteroarenes **71** (Scheme 14B).¹¹⁵ Within their study, alternating current significantly enhanced the overall efficacy of the electrosynthetic transformation by the direct conversion of otherwise unstable intermediates in a confined space.

6. ENANTIOSELECTIVE ELECTROCHEMICAL TRANSFORMATIONS

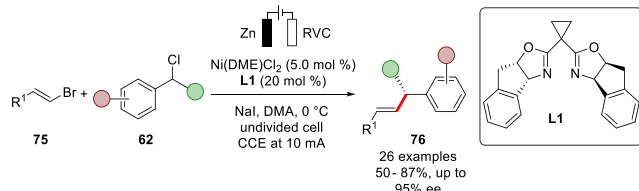
Enantioselective electrochemical synthesis was envisioned for the synthesis of enantiomerically enriched, chiral compounds by electrochemical synthetic methods.³⁷ Organic electrosynthesis offers the possibility to perform reactions under exceedingly mild reaction conditions such as low temperatures, which are typically required to achieve highly enantioselective transformations. The existing methods of asymmetric electrochemical synthesis relied on the participation of an external source of chirality, such as chiral auxiliaries, chiral catalysts, chiral reagents, chiral electrodes,¹¹⁶ chiral electrolytes,¹¹⁷ or chiral solvents.¹¹⁸ Very recently, Lin devised the enantioselective cupraelectro-catalyzed cyanophosphinoylation of alkenes **8** (Scheme 15A).¹¹⁹ By merging two distinct oxidative

Scheme 15. Enantioselective Electrocatalytic Transformations

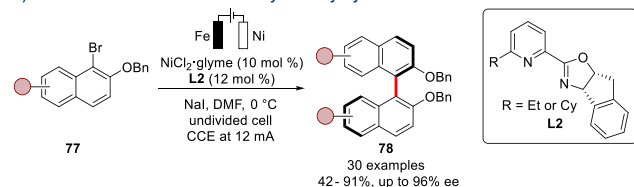
A) Enantioselective cupraelectrocatalyzed cyanofunctionalization



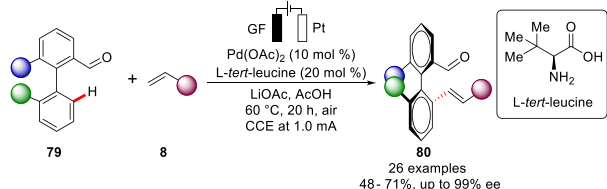
B) Enantioselective electroreductive nickel-catalyzed cross-couplings



C) Enantioselective nickelaelectro-catalyzed biaryl synthesis



D) Enantioselective palladaelectro-catalyzed C–H activations



events, challenging enantioselective transformations of alkenes **8** with diphenylphosphine oxide **73** were made possible.¹²⁰ The stereoselectivities were well-controlled with the aid of chiral ligands for the envisioned heterodifunctionalization of alkenes.^{37d,121} The designed bis(oxazoline) (sBOX)¹²² was found to be the key to success for the enantio-determining C–CN formation. The same copper catalyst was thereafter found to be essential for the chiral induction within a dual electrocatalytic approach (*vide supra*).⁵³ As to reductive transformations, Reisman established enantioselective electrochemical nickel-catalyzed cross-couplings of alkenyl bromides **75** and benzyl chlorides **62** by employing a chiral bis(oxazoline) ligand **L1** (Scheme 15B).¹²³ Likewise, Mei reported the nickel-catalyzed electroreductive enantioselective homocoupling of aryl bromides **77** to furnish axially chiral biaryl compounds **78** (Scheme 15C).¹²⁴ The high levels of asymmetric induction relied on the newly designed chiral pyridine-oxazoline ligands **L2**. Compared with previously proposed nickel(II) intermediates, Mei suggested a nickel(0/II/I) pathway for this transformation. To avoid elements of prefuctionalization, Ackermann developed asymmetric palladaelectro-catalyzed C–H olefinations with high position-, diastereo-, and enantio-control under mild reaction conditions (Scheme 15D).¹²⁵ A transient directing group strategy was utilized leading to the atroposelective organometallic C–H activation. Here, the authors were able to assemble axially chiral biaryl scaffolds **80** by organic electrocatalysis.

7. OUTLOOK

Recent years have witnessed a remarkable renaissance of organic electrosynthesis. The resurgence of molecular electrochemistry was spurred by key conceptual developments, which are considerably environmentally benign yet economically attractive transformations. Particularly, the merger of electro-synthesis with transition-metal catalysts within synergistic catalysis regimes has set the stage for novel functionalizations. These findings had partially involved redox mediators and were guided by model mechanistic insights. Thereby, innovative strategies for the full control of chemo-, position-, diastereo-, and even enantio-control were identified, also enabling asymmetric electrocatalysis. In spite of these indisputable advances, key challenges remain to be overcome to render organic electrosynthesis the central position it fully deserves (Figure 5). While reductive cross-couplings are efficient tools

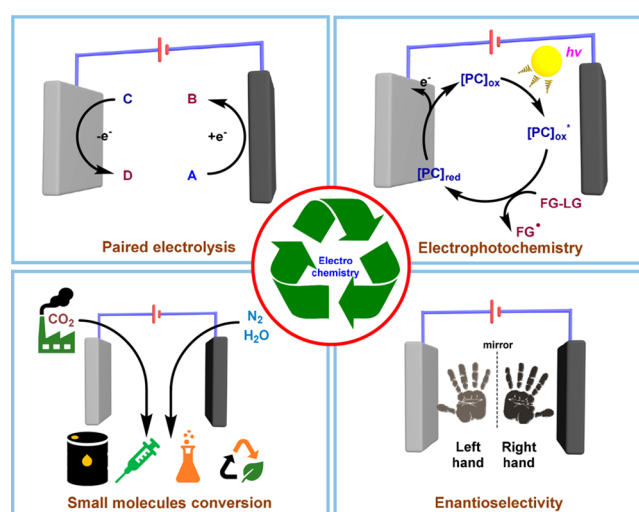


Figure 5. Selected perspectives of the synthetic electrochemistry.

for C–C formation, electroreductive reactions have largely incited by the need for sacrificial electrodes.¹²⁶ However, there were advances made to bypass this limitation by paired electrolysis or alternating current.¹¹³

Paired electrolysis refers to parallel electrochemical processes where two desirable half reactions are performed simultaneously. The combination of two half-reactions that consequently give the desired product(s), thereby maximizing the energy efficiency. Paired electrolysis can be considered as the gold standard for industrial settings due to the optimal overall usage of applied energy for two simultaneous desirable processes on both electrodes; this could be either through parallel, sequential divergent, or convergent processes.^{15c,127} The approach of paired electrolysis was recently exploited by Waldvogel and Morandi for reversible halide-shuttle reactions.¹²⁸ The innovative concept was particularly powerful for electrochemical vicinal dihalogenations of various olefins, using simple dihalogenated solvents as the halide source.

The synergism of electrochemistry and photochemistry has sparked significant current interest with numerous electro-photocatalytic reactions being disclosed to achieve extreme redox potentials for otherwise difficult molecular transformations.^{27,34a,129} The quest for a well-designed electro-photocatalyst for an allied co-operation with electrocatalysis as well as inherent scalability remains a considerable hurdle.

Electrochemical conversion of small molecules has indeed thrived within recent years; however, there have been limited efforts to further utilize them in organic synthesis.¹³⁰ Introducing CO₂ as a C1 synthon provides a greener alternative for organic synthesis in conjunction with electrochemical methods. The global outlook for chemical synthesis has been reaching out far for more renewable methodologies and chemical sources, and we expect more advances to be made in this direction toward efficient conversion of CO₂ and N₂ to useful synthetic materials.

Recent developments in asymmetric electrochemical transformations have led to synthetic applications in the organic synthesis with good functional group tolerance and high enantioselectivity.³⁷

The rapid development of electrosynthesis strongly depends on detailed mechanistic insights into electroorganic reactions. In this Outlook, we detailed how the oxidation-induced reductive elimination progress operates with *inter alia* cobalt, nickel, ruthenium, and rhodium cyclometalated intermediates by electrochemical analyses. Thus, this technique is anticipated to continue to unravel the mechanism of electrosynthesis by characterization of short-lived intermediates and provide further insights into fundamental single electron transfer (SET) processes.^{80a,131}

In summary, electrosynthesis offers a green platform with the prospect for sustainable molecular synthesis for peptide chemistry,¹³² biochemistry,¹³³ and material sciences.¹³⁴ Furthermore, the ideal levels of resource economy of electrochemistry hold great potential for large-scale industrial manufacturing.

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Notes

The authors declare no competing financial interest.

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