

Perspective

Harnessing Radical Chemistry
via Electrochemical Transition
Metal CatalysisJiaqing Lu,^{1,2} Yukang Wang,^{1,2} Terry McCallum,^{3,*} and Niankai Fu^{1,2,*}

SUMMARY

The merger of transition metal catalysis and electroorganic synthesis has recently emerged as a versatile platform for the development of highly enabling radical reactions in a sustainable fashion. Electrochemistry provides access to highly reactive radical species under extremely mild reaction conditions from abundant native functionalities. Transition metal catalysts can be used as redox-active electrocatalysts to shuttle electrons, chiral information to organic substrates, and the reactive intermediates in the electrolytic systems. The combination of these strategies in this mechanistic paradigm thus makes the generation and utilization of radical species in a chemoselective manner and allows further application to more synthetically attractive enantioselective radical transformations. This perspective discusses key advances over the past few years in the field of electrochemical transition metal catalysis and demonstrates how the unique features of this strategy permit challenging or previously elusive transformations via radical pathways to be successfully achieved.

INTRODUCTION

Transition metal catalysis has been well recognized as a powerful tool for the production of fine chemicals, pharmaceuticals, and functional materials (Hegedus and Söderberg, 2010). It lies at the heart of modern synthetic chemistry and plays an indispensable role in both academia and chemical industry. Most importantly, it has been continually demonstrating new modes of chemical activation for the discovery of unprecedented reactivities and transformations. This exciting promise of transition metal catalysis mainly originates from the intrinsic characteristics of transition metals that are capable of having a variety of oxidation states. Transition metals can form complexes with reactants or even the reactive intermediates in the reaction systems, providing a versatile platform for the design of new mechanistic paradigms that allow the invention of valuable chemical reactions. Recently, significant advances have been made on the basis that a couple of metal catalysts can engage in single-electron transfer processes, and the manipulation of oxidation states of the metal catalysts is critical to the desired radical-based reactivities (Kochi, 1974; Tasker et al., 2014; Levin et al., 2016; Crossley et al., 2016; Twilton et al., 2017; Wang et al., 2018). The strategies of single-electron oxidative addition and single-electron transmetalation of the catalytic metal centers have been creatively applied to unlock new avenues for cross-coupling reactions (Kalyani et al., 2011; Ye and Sanford, 2012; Creutz et al., 2012; Tellis et al., 2014; Zuo et al., 2014; Kainz et al., 2016). As a prominent example, transition metal-catalyzed cross-coupling of alkyl radicals, in which challenging sp^3 -hybridized C–H bonds and electrophiles have been utilized as coupling partners for C–C bond-forming reactions, has become an important class of transformations within the arena of complex molecule synthesis (Chen et al., 2019; Milligan et al., 2019; Kaga and Chiba, 2017; Fu, 2017).

From a historical perspective, the use of electrochemistry to alter the oxidation states of transition metal catalysts is not a new idea and, in fact, electrochemistry has been actively employed as a powerful technique to interrogate the mechanisms of transition metal-catalyzed reactions (Jutand, 2008). Perhaps more interesting, electrochemistry is one of the most straightforward and practical means to produce radical species by using electrons as traceless “reagents” in a sustainable manner, which are usually unmatched in efficiency or cost by employing redox chemical reagents. In addition, electrolytic techniques allow chemists to dial in a minimally sufficient potential to precisely control the generation of those desired open-shell species or the pursued oxidation states of the metal catalysts, thereby ensuring mild reaction

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conditions for downstream chemical processes that may otherwise lead to degradation or by-product formation. These features make electroorganic synthesis a socially responsible approach to meeting the prevailing trends in modern organic chemistry (Francke and Little, 2014; Waldvogel and Janza, 2014; Yan et al., 2017). However, in sharp contrast to the well-known facts that both transition metal catalysis and electrochemistry have been used in organic synthesis for more than two centuries, their combinational use to explore new chemical spaces, especially in the context of radical chemistry, has just recently become a burgeoning research area (Sauer and Lin, 2018; Siu et al., 2020).

Radical Chemistry is beginning to reshape the field of retrosynthetic analysis and affecting the preparation of natural products, pharmaceuticals, and organic materials (Smith et al., 2018; Romero et al., 2018; Pitre et al., 2019). In this regard, the strategy of merging transition metal catalysis and photoredox catalysis has found enormous success in the development of radical reactions (Twilton et al., 2017). Specifically, single-electron transfer between an excited-state catalyst and an organic substrate gives rise to highly reactive open-shell intermediates, which could be utilized by transition metal catalysts for otherwise challenging bond formation. Moreover, the oxidation state of the key transition metal complexes could be manipulated by the photoexcited catalyst either via single-electron transfer or energy transfer to facilitate daunting elementary steps in coupling reactions. Most of the methodologies developed so far, however, require the use of stoichiometric oxidants or reductants, especially for redox transformations, and the redox properties of photoredox catalysts or redox agents cannot be easily modified, thus constraining their applications to certain contexts.

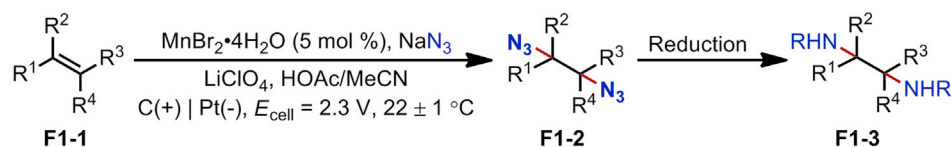
The purpose of this perspective is to highlight the key advances of electrochemical transition metal catalysis in harnessing radical chemistry. The use of redox-active metal catalysts as electrocatalysts not only substantially improve electron transfer kinetics between organic compounds and electrodes but also control the reactivities of the generated radical intermediates after electron transfer. The elegant strategy of metal-catalyzed C-H activation with electrochemistry as the driving force to replace redox agents and/or to tune the oxidation states of the metal complexes holds huge and largely untapped potential for sustainable organic synthesis (Sauermann et al., 2018; Meyer et al., 2019; Ma et al., 2018; Jiao et al., 2020a; Dwivedi et al., 2019). Recent advances in this area of research, especially the employment of environmentally friendly base metals as electrocatalysts for direct C-H bond functionalizations, have garnered massive attention from the chemistry community (Ackermann, 2020; Gandeepan et al., 2020). Although highly reactive open-shell species have a long history in electrochemistry, only recently have they been tactfully utilized in the context of transition metal catalysis, showcasing unique potential in organic transformations. Thus, emphases in this paper will be placed on the mechanistic hypotheses underpinning the radical reactions through using different transition metal catalysts under electrolytic conditions and we will conclude by providing an outlook of how we anticipate the field may develop in the future.

ELECTROCHEMICAL MANGANESE CATALYSIS

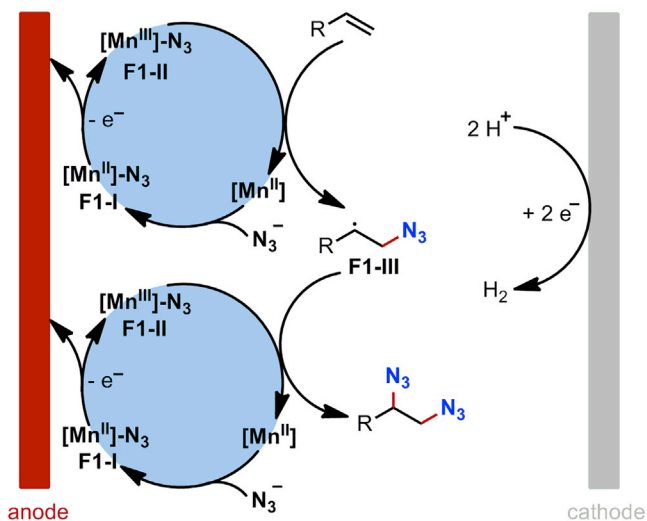
Mn^{III}-mediated oxidative radical processes for C–C and C–O bond formation reactions are among the most frequently executed processes in natural product syntheses during the past few decades (Snider, 1996). Additionally, C–N bond formation is also feasible via manganese chemistry, as demonstrated by Fristad and co-workers in the conversion of alkenes into diazides in 1985 (Fristad et al., 1985). Recently, the Groves group studied the ability of manganese in late-stage aliphatic C–H functionalizations (Liu and Groves, 2015) and reported a Mn-catalyzed aliphatic C–H azidation reaction that could efficiently convert secondary, tertiary, and benzylic C–H bonds into the corresponding azides (Huang et al., 2015). Despite significant advances as described above, the majority of the reported protocols required the use of stoichiometric chemical oxidants to turn over the catalytically active high oxidation state manganese species, which inevitably led to the formation of wasteful by-products, complicated product isolation processes, and diminished the sustainability of the protocols.

The preparation of vicinal diamines is of fundamental importance in organic synthesis as this kind of structural moiety is frequently encountered in privileged molecular scaffolds such as ligands/catalysts and medically relevant products. Despite substantial efforts, however, a generally unified methodological and efficient approach for their syntheses in a sustainable manner remains elusive and highly desirable in the chemistry community. Toward this end, Lin and co-workers developed a highly efficient electrochemical method for the diazidation of olefins using inexpensive MnBr₂ as the electrocatalyst (Figure 1A) (Fu et al., 2017a). This new electrocatalytic diazidation protocol showed little dependence on the electronic

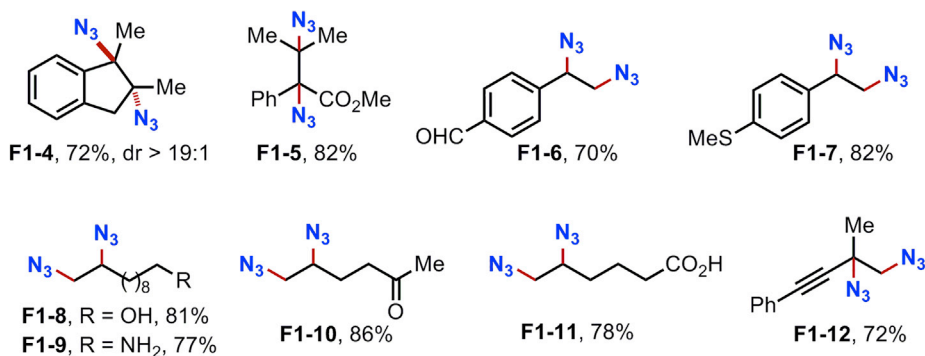
A Reaction conditions for alkene diazidation



B Proposed catalytic cycle



C Representative products



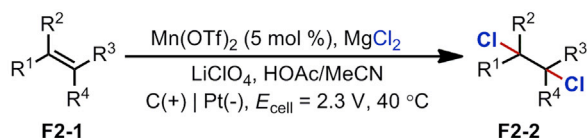
D Tandem diazidation and reduction



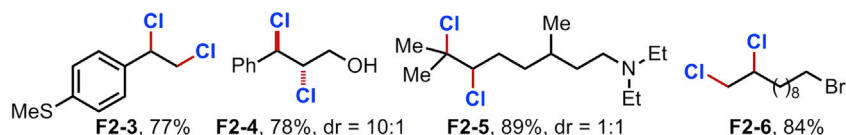
Figure 1. Mn-Catalyzed Electrochemical Diazidation of Alkenes

properties or substitution patterns of the alkene substrates. Notably, tetrasubstituted alkenes, notoriously challenging substrates due to the steric hindrance in synthetic chemistry, could be smoothly converted into the highly congested diazide products with good efficiency. Furthermore, the ability of electrochemistry to dial in the potential at the minimum level required for the desired redox transformation conferred the reaction high degrees of chemo-selectivity; substrates bearing alcohol, aldehyde, enolizable ketone,

A Reaction conditions for alkene dichlorination



B Representative products



C Novel radical reactivity patterns

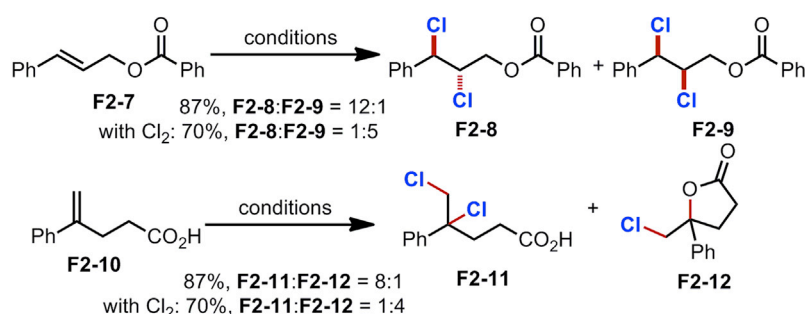


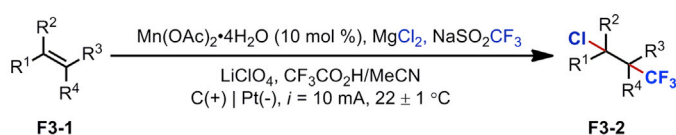
Figure 2. Mn-Catalyzed Electrochemical Dichlorination of Alkenes

carboxylic acid, amine, sulfide, and alkyne groups all proved compatible with the electrocatalytic system (Figure 1C). On the basis of well-established azide reduction methods, 1,2-diazides including those containing reductively labile groups were demonstrated to be chemoselectively reduced to the corresponding diamines, thereby presenting a generic and practical diamine synthesis protocol (Figure 1D).

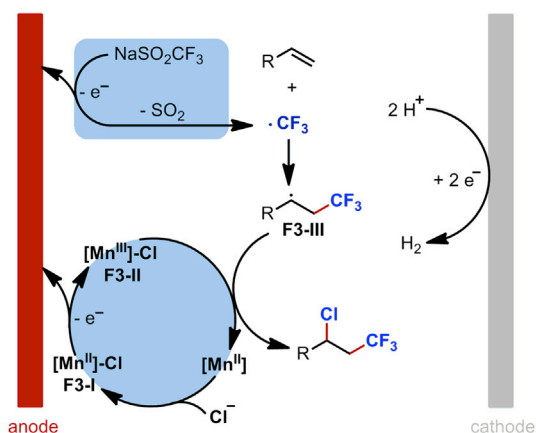
Mechanistic studies highlighted the strategy of combing electrochemistry and redox-metal catalysis in regulating the generation and reactivity of radical intermediates in the reaction system (Figure 1B). In the presence of HOAc, cyclic voltammetry studies showed that azide anion exhibited an irreversible oxidation peak at 0.84 V versus ferrocenium/ferrocene (Fc⁺⁰). Upon introduction of the Mn catalyst, the generation of the putative azidyl transfer agent in the form of [Mn^{III}]-N₃ **F1-II** formed through ligand exchange from [Mn^{II}]-X (X = Br, or OAc) to [Mn^{II}]-N₃ **F1-I** and subsequent anodic oxidation with much lower potential (with an onset potential of ca. 0.5 V versus Fc⁺⁰). Controlled experiments supported this hypothesis—the catalytic diazidation could occur with anodic potential as low as 0.5 V versus Fc⁺⁰. These observations indicated that the direct oxidation of azide anion to the corresponding azidyl radical contributed minimally to the desired reactivity, thus making the reaction conditions extremely mild and enabling exceptional chemoselectivity. Based on mechanistic studies and previous work by others (Fristad et al., 1985; Liu and Groves, 2015; Huang et al., 2015) the authors proposed that both equivalents of N₃[·] were transferred from [Mn^{III}]-N₃ **F1-II** to the olefin to yield the diazide product (Figure 1B). A silent feature of this mechanism is that the proposed [Mn^{III}]-N₃ complex has the potential to trap and functionalize C-centered radical intermediates for more C–N bond constructions (*vide infra*).

The proposed mechanism for electrochemical Mn-catalyzed alkene diazidation reaction was also applicable to Mn^{III}-mediated alkene dichlorination reaction (Fu et al., 2017b). As thus, Lin and co-workers developed an electrochemical Mn-catalyzed dichlorination of alkenes using MgCl₂ as the chlorine source. Analogously, a wide variety of alkenes were successfully transformed to the dichloroalkanes in high efficiency under conditions similar to the diazidation reaction system. From a mechanistic perspective, it is worth noting that the radical nature of this reaction provides unique chemo- and stereo-selectivity patterns

A Reaction conditions for alkene chlorotrifluoromethylation



B Proposed catalytic cycle



C Representative products

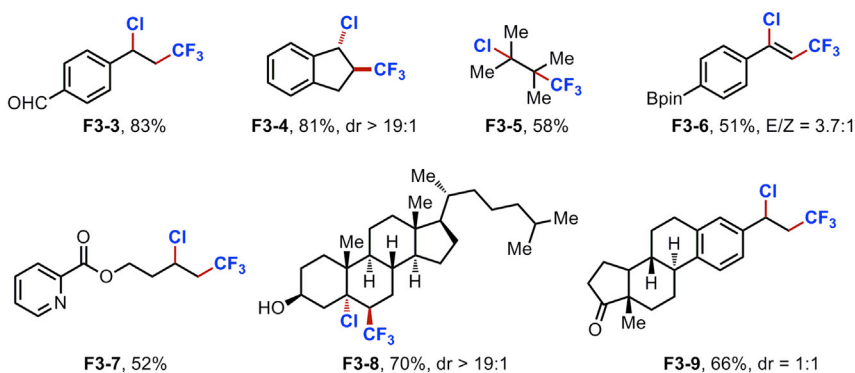


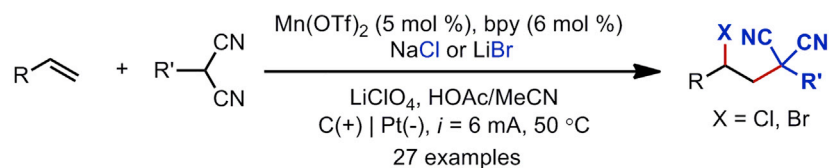
Figure 3. Mn-Catalyzed Electrochemical Chlorotrifluoromethylation of Alkenes

that are unattainable with traditional electrophilic chlorination approaches, under mild reaction conditions (Figure 2).

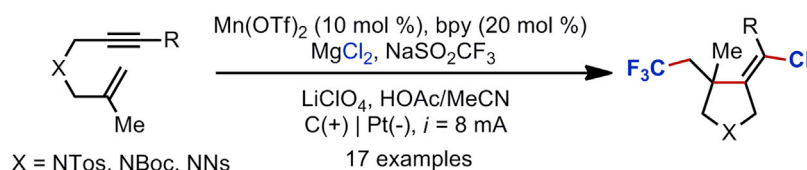
Heterodifunctionalization of alkenes allows chemists to rapidly increase the complexity of molecules bearing olefinic moieties. Achieving this challenging objective via radical approaches require the simultaneous generation of two distinct highly reactive open-shell species and control over their chemo- and regio-selective additions across the alkene. To this end, Lin and co-workers devised the strategy of anodically coupled electrolysis (ACE), an electrochemical process that combines two parallel oxidative events for alkene heterodifunctionalization in a chemo- and regio-selective manner (Sauer and Lin, 2018).

The Lin group first demonstrated this strategy in the context of chlorotrifluoromethylation of alkenes (Ye et al., 2018a). The cost-effective Langlois reagent, $\text{CF}_3\text{SO}_2\text{Na}$, was employed as the trifluoromethyl radical source, whereas bench stable MgCl_2 was used as the chlorine atom precursor for this propose. Importantly, cyclic voltammetry data showed that the oxidation potentials required for the generation of transient trifluoromethyl radical ($\text{CF}_3\cdot$) and persistent chlorine radical $[\text{Mn}^{\text{III}}]\text{-Cl}$ F3-II were similar to each other. The chemo- and regio-selectivities of the following radical installations were guided by the persistent radical effect (Leifert and Studer, 2020), whereupon the addition of $\text{CF}_3\cdot$ to the alkene, the incipient C-centered

A Haloalkylation of alkenes



B Radical ene-yne cyclization



C Chloro- and azidophosphinoylation of alkenes

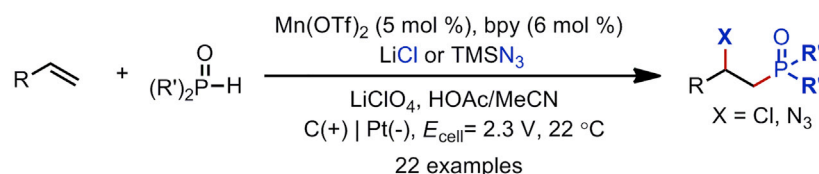


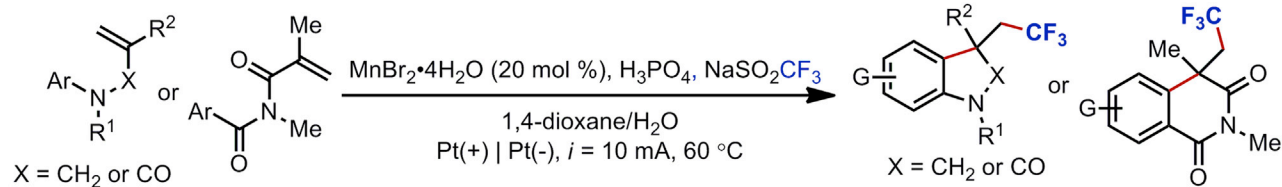
Figure 4. Mn-Catalyzed Electrochemical Heterodifunctionalization of Alkenes

radical **F3-III**, would be intercepted by the persistent radical $[\text{Mn}^{\text{III}}]\text{-Cl}$ **F3-II** to deliver the desired product (Figure 3B). Under the optimized reaction conditions, many alkenes with oxidatively labile functional groups, including aldehydes, enolizable ketones, and boronates, were compatible with the electrocatalytic system, giving the desired chlorotrifluoromethylation adducts in good yields. Several natural product-derived substrates proved suitable for the reaction conditions (Figure 3C). The unique feature of exceptional substrate generality of this electrocatalytic protocol has been highlighted by direct comparison with previously reported photochemical methods, in which the C-centered radical **F3-III** was proposed to be further oxidized to the carbocation intermediate for C–Cl bond formation (Oh et al., 2014). Notably, the electrocatalytic protocol could be further expanded to the difunctionalization of alkynes, indicating a facile capture of the corresponding highly reactive vinyl radical intermediate by the simultaneously generated $[\text{Mn}^{\text{III}}]\text{-Cl}$ **F3-II** species (Figure 3).

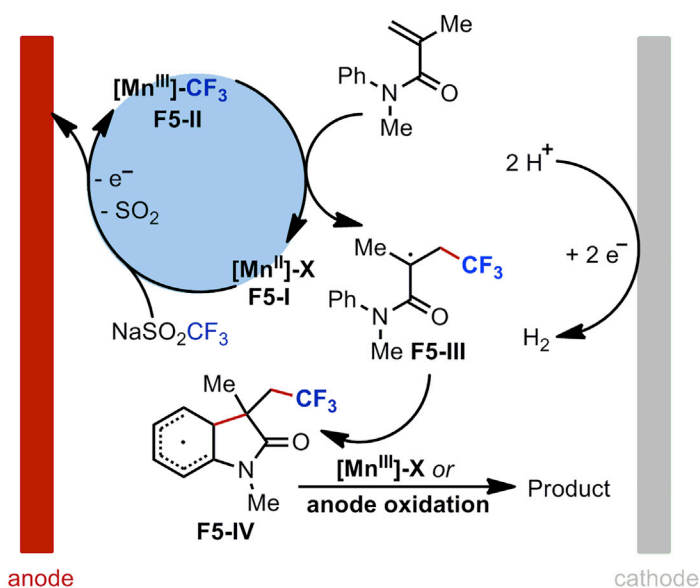
Later on, Lin and co-workers successfully applied the ACE strategy to (1) the haloalkylation of alkenes by which vicinal C–C and C–Cl bonds could be readily constructed in a single synthetic operation using malononitriles or cyanoacetates as the carbon source and NaCl as the chlorine source, respectively (Figure 4A) (Fu et al., 2019a); (2) the synthesis of halotrifluoromethylated pyrrolidines by Mn-catalyzed electrochemical radical ene-yne cyclization of 1,6-ene-yne substrates (Figure 4B) (Ye et al., 2018b); (3) the chloro- and azido-phosphinoylation of alkenes in which electrochemically generated $[\text{Mn}^{\text{III}}]\text{-X}$ was proposed for oxidizing secondary phosphine oxides to the corresponding electrophilic P-centered radical and functionalizing the C-centered radicals as group transfer agents (Figure 4C) (Lu et al., 2019).

Mo and co-workers reported a Mn-catalyzed electrochemical trifluoromethylation/ $\text{C}_{\text{sp}}^2\text{-H}$ functionalization cascade for the synthesis of CF_3 -containing azaheterocycles using $\text{CF}_3\text{SO}_2\text{Na}$ as the trifluoromethyl radical precursor (Figure 5) (Zhang et al., 2019a). A wide range of substrates were readily accommodated in this electrochemical approach, producing a diverse variety of trifluoromethylated heterocycles in good yields (Figure 5C). A gram-scale synthesis was demonstrated under ambient atmospheric conditions to give the oxindole product in synthetically acceptable isolated yield. Based on experimental observations and mechanistic studies, the authors suggested that the electrochemical generation of Mn species **F5-II**

A Reaction conditions



B Proposed catalytic cycle



C Representative products

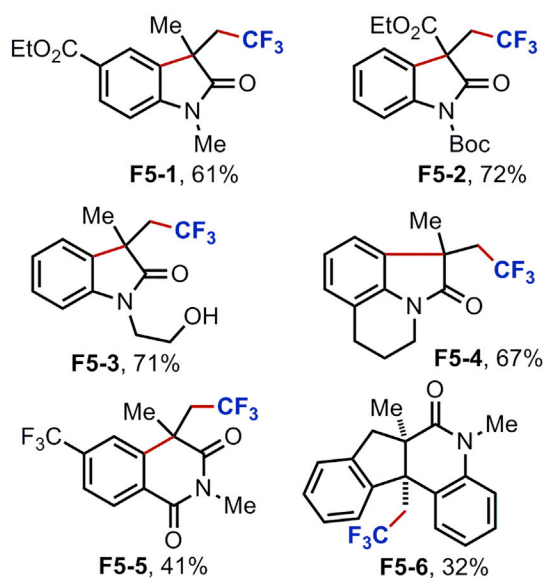


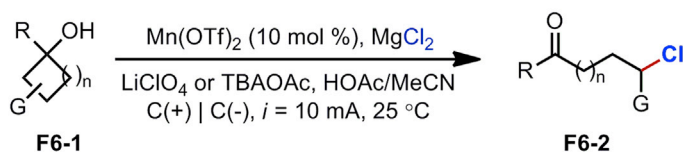
Figure 5. Mn-Catalyzed Electrochemical Synthesis of CF_3 -Containing Azaheterocycles

acted as a latent CF_3 radical to initiate the reaction. After the generation of C-centered radical F5-III, intramolecular cyclization would deliver F5-IV that underwent a single electron oxidation to furnish the final product (Figure 5B).

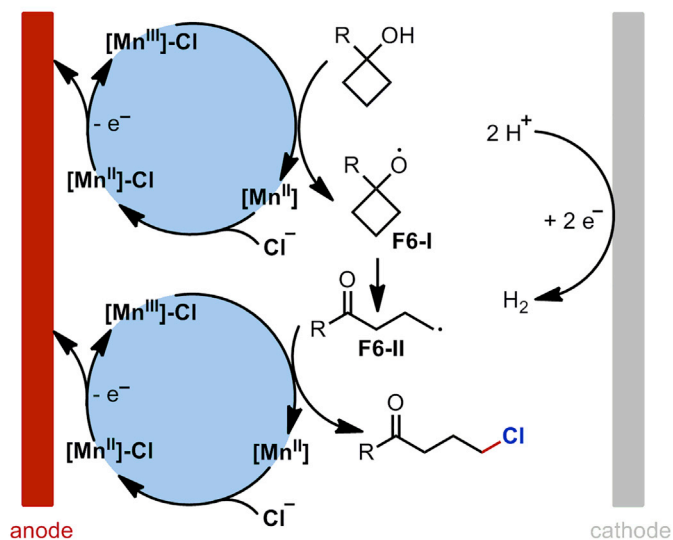
Alkoxy radicals are traditionally highly challenging intermediates to generate from alcohols because of the high bond dissociation energy of RO-H bonds (105 kcal/mol). Morrill, Browne, and co-workers have highlighted the capacity of electrochemically generated $[\text{Mn}^{\text{III}}]\text{-Cl}$ species in the electrochemical deconstructive chlorination of cycloalkanols for synthesizing β - and γ -chlorinated ketones via alkoxy radicals (Allen et al., 2019). This electrochemical method exhibited good functional group tolerance. Interestingly, many of the 7-, 8-, 9-, and 10-membered ring benzyl chloride products could be synthesized when benzo-fused cyclobutanols were employed as the substrates. Perhaps more notably, the authors demonstrated the combinational use of recirculating flow electrochemistry and continuous inline purification technologies for gram scale synthesis. A plausible reaction mechanism involving the electrochemical generation of $[\text{Mn}^{\text{III}}]\text{-Cl}$ species was proposed. This intermediate underwent ligand exchange with the cycloalkanol to form a Mn^{III} alkoxide, and subsequent homolysis afforded the alkoxy radical F6-I en route to the C-centered radical F6-II via β -scission. Alternatively, a reversible β -scission of the Mn^{III} alkoxide to directly give the ring-opening induced C-centered radical intermediate F6-II was also possible. Finally, the C-centered radical F6-II could be intercepted by $[\text{Mn}^{\text{III}}]\text{-Cl}$ species to deliver the chlorinated product (Figure 6).

In combination with a cathodic oxygen reduction reaction, Chen and co-workers were able to utilize the electrochemically generated $[\text{Mn}^{\text{III}}]\text{-Cl}$ species for oxychlorination of styrenes for the synthesis of

A Reaction conditions for deconstructive chlorination of cycloalkanols



B Proposed catalytic cycle



C Representative products

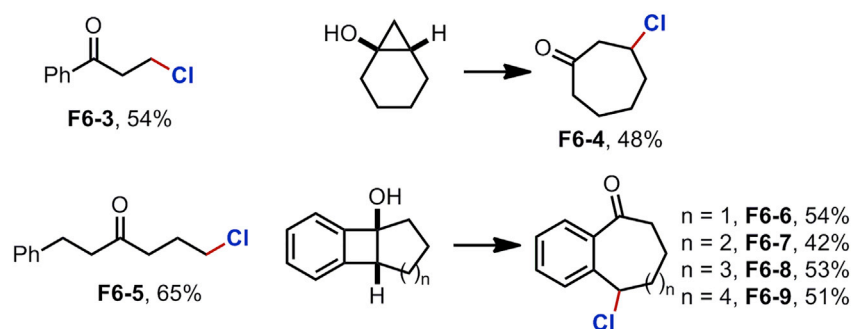


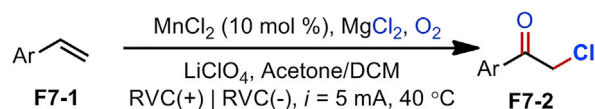
Figure 6. Mn-Catalyzed Electrochemical Deconstructive Chlorination of Cycloalkanols

synthetically versatile chloroacetophenones (Tian et al., 2019). The electrochemically produced $[\text{Mn}^{\text{III}}]\text{-Cl}$ was proposed to react with styrene to generate transient C-centered radical F7-II. At the same time, superoxide (O_2 radical anion) F7-I was cathodically generated *in situ* from oxygen. The persistent radical F7-I could then couple with the transient C-centered radical F7-II to generate intermediate F7-III, which was proposed to undergo decomposition to yield the benzylic alcohol intermediate F7-IV. Finally, further oxidation of F7-IV at the anode or by superoxide F7-I would deliver the product (Figure 7B). A diverse array of chloroacetophenones could be smoothly obtained using this protocol, but electronically unbiased aliphatic alkenes were not suitable substrates (Figure 7).

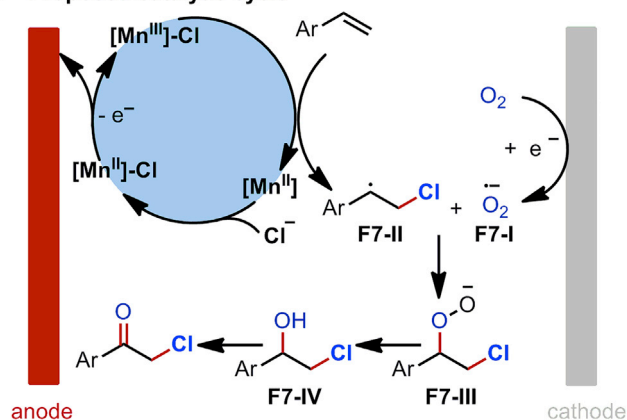
ELECTROCHEMICAL COPPER CATALYSIS

Utilizing the ability of copper to mediate the oxidative transformation of alkyl radicals into alkenes, Baran and co-workers described an electrochemical approach for the synthesis of the decalin core of pyrone

A Reaction conditions for oxychlorination of styrenes



B Proposed catalytic cycle



C Representative products

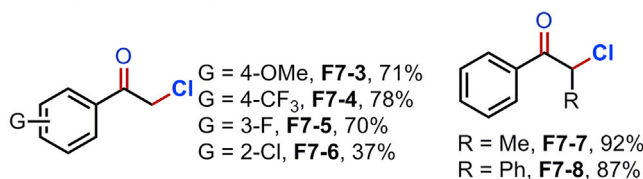
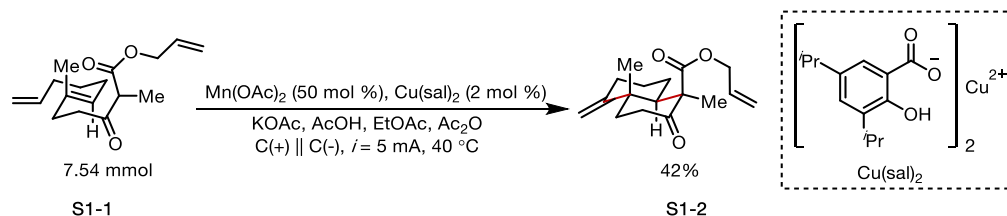


Figure 7. Mn-Catalyzed Electrochemical Oxychlorination of Styrenes

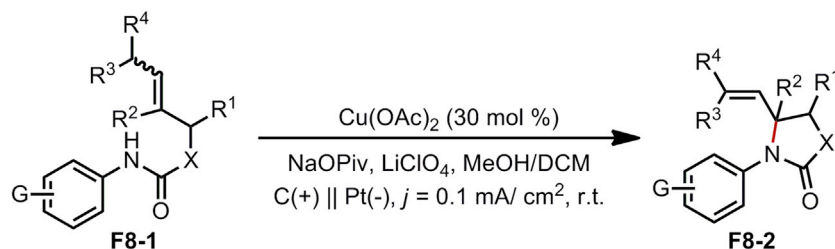
diterpenes via oxidative radical polycyclization by a Mn/Cu dual electrocatalytic process (Merchant et al., 2018). The electrolysis in a divided cell using catalytic amounts of Mn(OAc)₂ and copper catalyst could deliver the desired product in a comparable yield relative to classic chemical oxidation conditions. Thus, the adoption of electrochemistry in this protocol significantly reduces the metal-based waste and simplifies/accelerates the workup procedure in large-scale synthesis (Scheme 1).

Later, Hu and co-workers incorporated copper catalysis into electrochemical oxidation in the context of formal aza-Wacker cyclization for the synthesis of *N*-heterocycles (Figure 8A) (Yi and Hu, 2019). The copper catalyst was found essential for employing secondary and primary alkyl radical intermediates for the final alkene-forming step, thus making this work substantially different from the previous reports by Xu et al. (Xiong et al., 2017; Xiong and Xu, 2019). An extensive variety of 5-membered *N*-heterocycles including oxazolidinone, imidazolidinone, thiazolidinone, pyrrolidinone, and isoindolinone were prepared in a divided cell under mild conditions (Figure 8C) (usually at room temperature). Mechanistic studies demonstrated

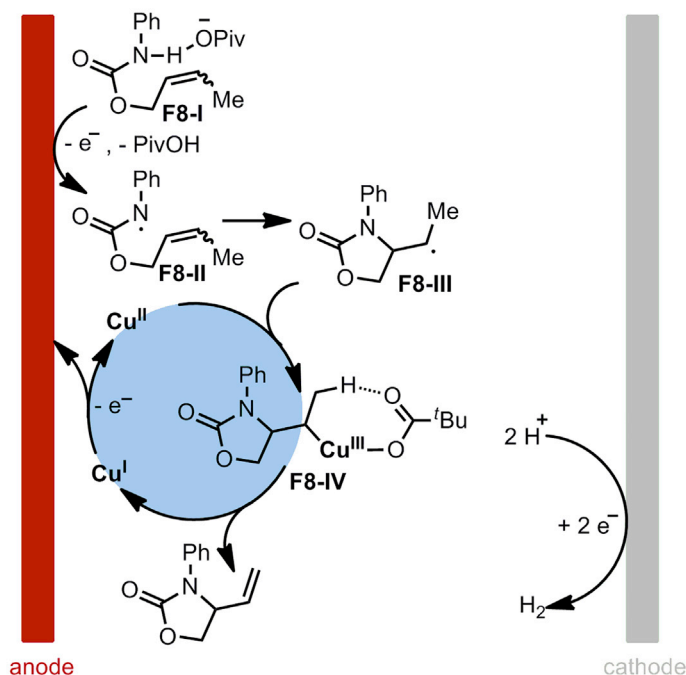


Scheme 1. Electrochemically Mediated Radical Polyene Cyclization

A Reaction conditions for formal aza-Wacker cyclization



B Proposed catalytic cycle



C Representative products

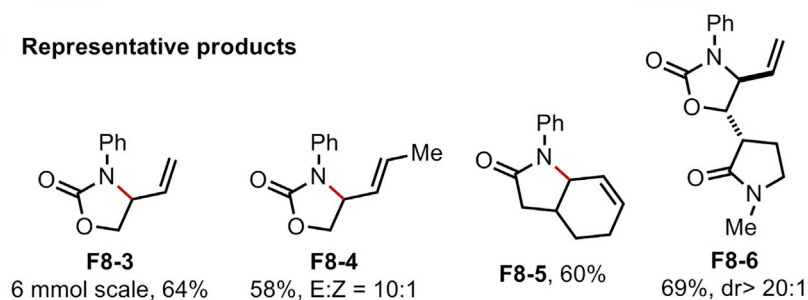


Figure 8. Electrochemical Cu-Catalyzed Formal aza-Wacker Cyclization

that generation of the key amidyl radical species **F8-II** was not influenced by the introduction of copper catalyst, yet the addition of NaOPiv facilitated this process through the formation of a substrate-base complex **F8-I**. A kinetically favored 5-*exo-trig* cyclization of **F8-II** would then generate the alkyl radical intermediate **F8-III**, which could be trapped by the electrochemically produced Cu^{I} species to give a formal Cu^{III} alkyl intermediate **F8-IV**. Subsequent elimination of this Cu^{III} alkyl intermediate **F8-IV**, probably promoted by the base in the reaction system, afforded the desired alkene product and regenerated the Cu^{I} species, with the latter oxidized at the anode to enter the next catalytic cycle (Figure 8B).

Recently, Lin and co-workers demonstrated enantioselective electrocatalysis (Lin et al., 2019; Chang et al., 2020) in the context of Cu-catalyzed radical cyanation reactions (Wang et al., 2018). Since the copper ions

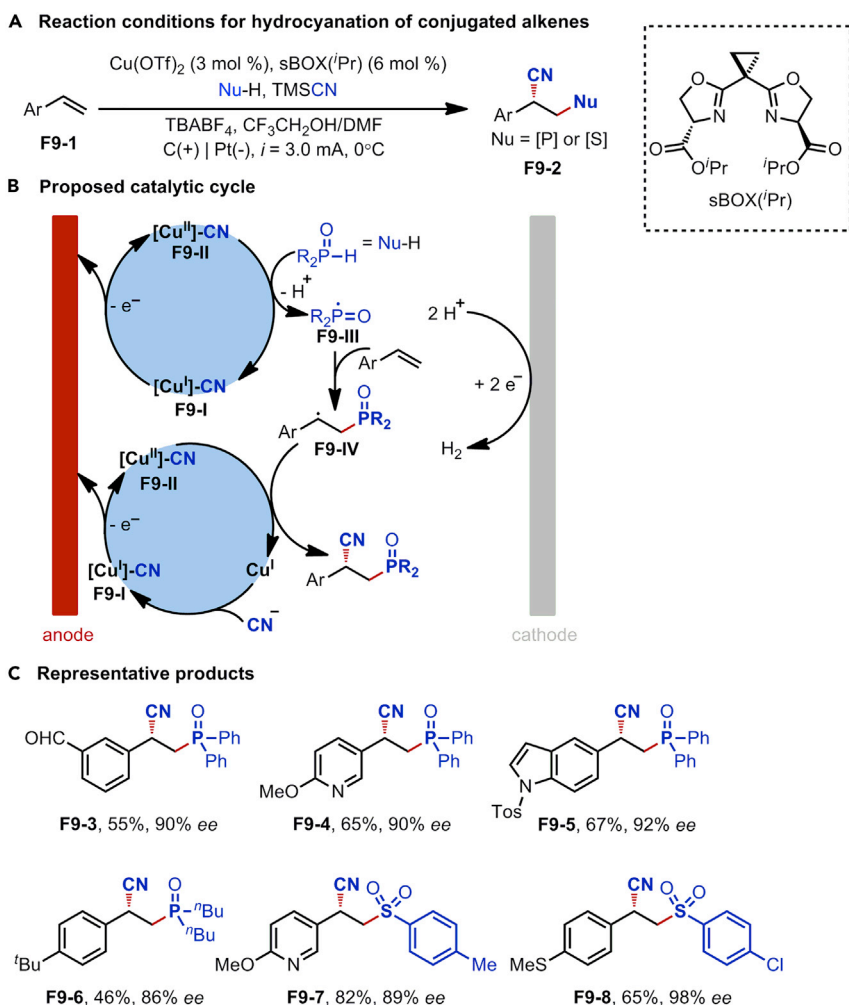


Figure 9. Electrochemical Cu-Catalyzed Enantioselective Cyanofunctionalization of Vinylarenes

are substantially easier to reduce than protons, resulting in the copper plating onto the cathode and loss of catalytic activity, most Cu-catalyzed electrochemical reactions are carried out in divided cells. To address this challenge and render copper electrocatalytic processes enantioselective in a more practically useful undivided cell, the choice of reaction medium, proton source, and ligand is critical.

The enantioselective alkene cyanophosphinoylation achieved by installing two functional handles in a single operation would provide unique structural patterns that could be further elaborated to synthetically valuable chiral molecules (Zhang et al., 2019b). The Lin research group reported the development of a highly enantioselective method for the copper-catalyzed electrochemical cyanophosphinoylation of styrenes (Fu et al., 2019b). Mechanism-informed ligand design led to the discovery of a new family of serine-derived chiral bisoxazoline ligands (sBOXs) with pendant ester substituents, which could boost the enantioselectivity of the reaction from 84% ee to 94% ee. The implementation of ACE ensured the required parallel anodic generation of two radicals—the transient phosphinoyl radical F9-III and the persistent [Cu^{II}]-CN radical complex F9-II in the catalytic system. Upon the addition of the highly electrophilic transient P-centered radical F9-III to the electron-rich alkene, the nascent C-centered radical F9-IV could be trapped by the persistent radical [Cu^{II}]-CN complex F9-II to furnish the C-CN bond (Figure 9B). Further mechanistic studies indicated that the generation of the P-centered radical species F9-III was catalyzed by the electrochemically generated Cu^{II} species. In addition, the authors were able to expand the reaction scope to the cyanosulfonylation of vinylarenes using sulfinic acids as the transient radical precursors (Figure 9).

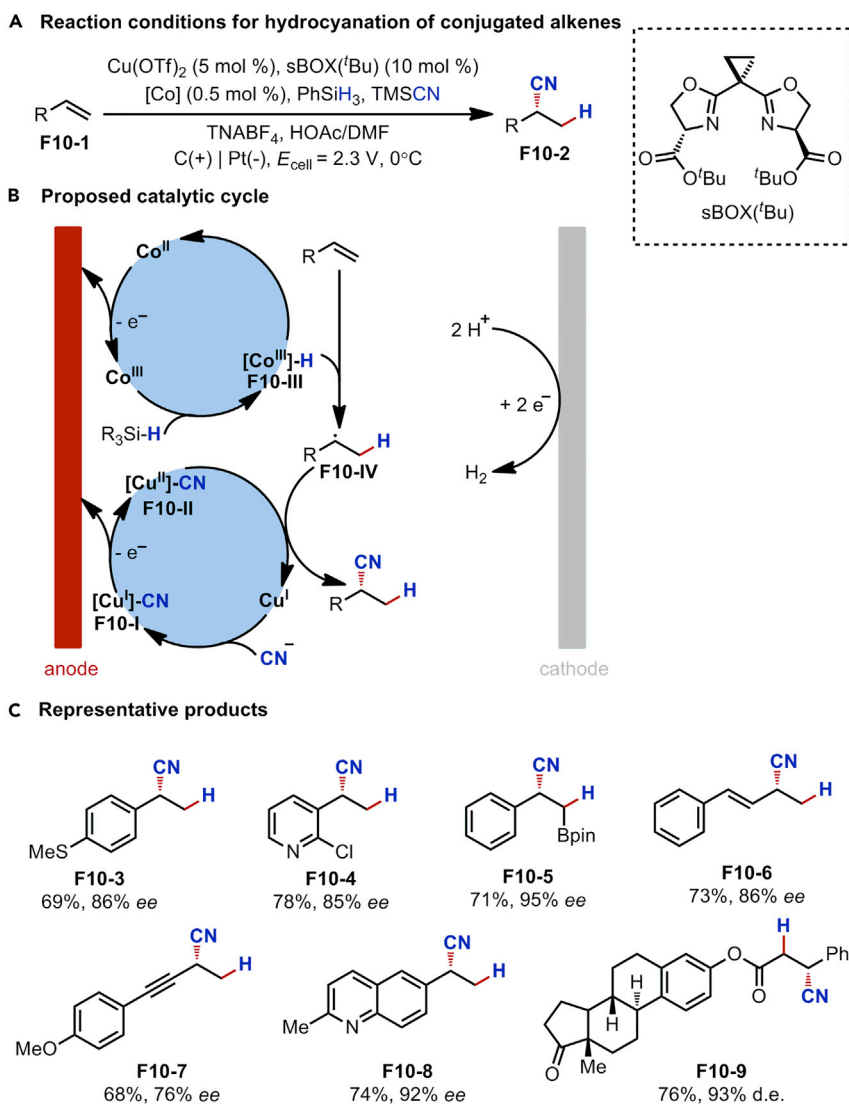
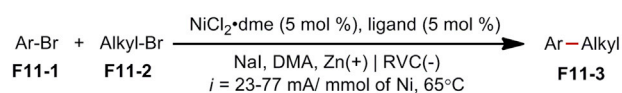
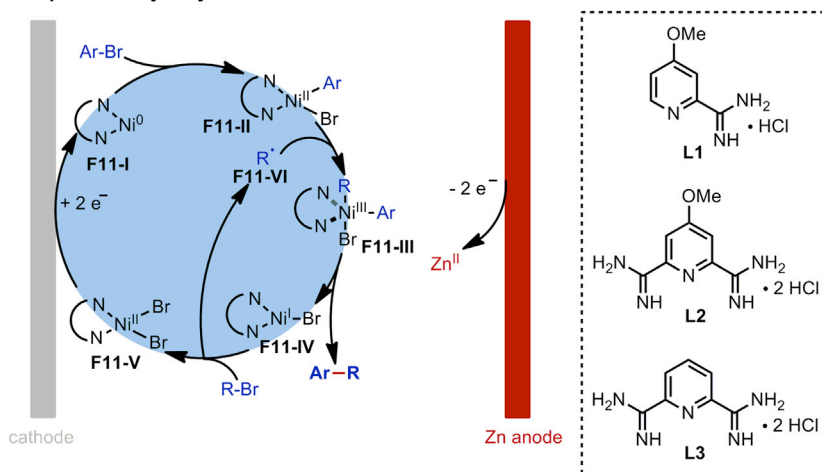
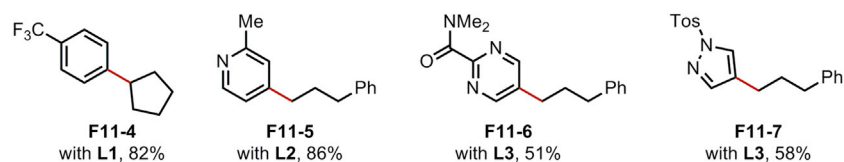


Figure 10. Dual Co/Cu Electrocatalytic Enantioselective Hydrocyanation

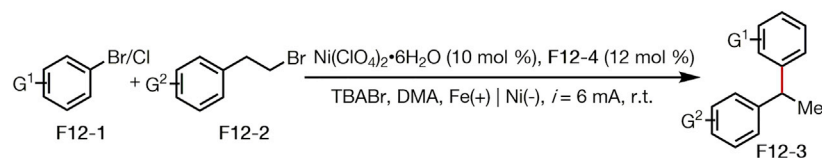
Enantioselective alkene hydrocyanation represents one of the most efficient and straightforward approaches for synthesizing chiral nitriles, which are versatile synthetic intermediates and prevalent in pharmaceuticals and bioactive compounds (Figure 10A). Unfortunately, there is no generic method featuring high enantioselectivity with a broad substrate scope and high functional group tolerance. To address this synthetic challenge, Lin, DiStasio, and colleagues devised a dual Co/Cu electrocatalytic system, in which two canonical radical reactions, cobalt-catalyzed hydrogen atom transfer (HAT) (Crossley et al., 2016) and copper-catalyzed radical cyanation (Wang et al., 2018), were synergistically combined to accomplish a highly enantioselective hydrocyanation of a wide range of conjugated alkenes (Figure 10B) (Song et al., 2020). Again, sBOXs ligands turned out to be the optimal choice. Notably, challenging substrates including internal alkenylarenes, dienes, enynes, and allenes with a variety of synthetically useful functional groups could be well applied in the electrocatalytic system (Figure 10C). The authors also showcased the unique features of electroorganic synthesis to precisely control the chemo-selectivity of oxidation-sensitive electron-rich substrates via electrode potential regulation, which would have otherwise been very difficult to do with chemical oxidants. Finally, a number of detailed quantum mechanical calculations were carried out and supported the chiral catalyst's ability to impart a combination of attractive and repulsive non-covalent interactions to direct the enantio-determining C–CN bond forming step (Song et al., 2020).

A Reaction conditions for cross-electrophile coupling reaction**B Proposed catalytic cycle****C Representative products****Figure 11. Electrochemical Ni-Catalyzed Cross Electrophile Coupling Reaction****ELECTROCHEMICAL NICKEL CATALYSIS**

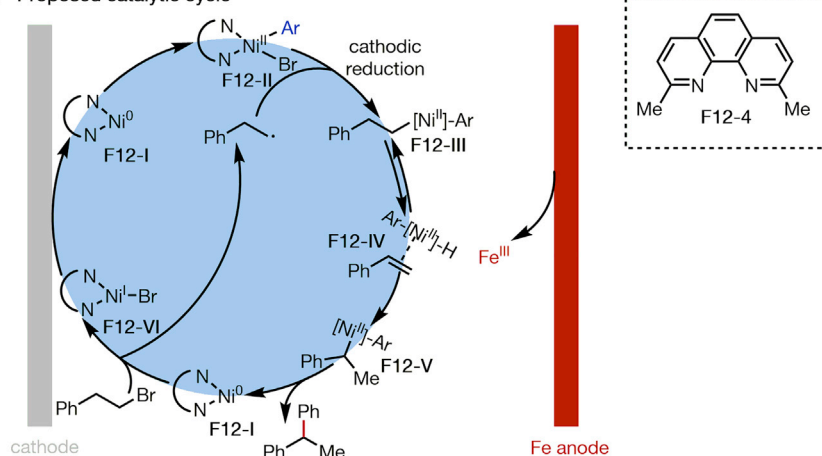
Given the well-accepted ability of nickel to engage in single electron transfer and radical-capture mechanisms (Tasker et al., 2014; Twilton et al., 2017) the combinatorial use of electrochemical reduction and nickel catalysis has been devised for nickel catalyst activation and turnover to avoid the use of conventional metal powder reductants in cross-electrophile coupling reactions (Durandetti and Périchon, 2004). The electrochemical reduction method offers the ability to tune the rate of catalyst activation via current passed through the electrocatalytic system, which is vital to reaction condition optimization.

In 2017, Hansen and co-workers reported an electrochemical method for nickel-catalyzed reductive $C_{sp^2}\text{--}C_{sp^3}$ cross electrophile couplings between aryl and alkyl bromides (Figure 11A) (Perkins et al., 2017). A chemically inert reticulated vitreous carbon (RVC) cathode was selected for reduction for its high surface area, while a sacrificial metal rod anode was used in an undivided cell. It is important to note that the coupling reaction could not be promoted with iron powder as the reductant, but it can work well with iron as the anode. This indicated that the nickel catalyst was activated by cathodic reduction rather than the anode metal surface. Furthermore, electron-deficient pyrimidine and pyrazole were generally poor substrates when using zinc powder as reductant as direct zinc insertion into the aryl bromides was proposed to compete with productive Ni-catalyzed processes. Using electrochemical reduction, however, both substrates could be smoothly applied, and reaction yields were substantially increased (Figure 11C). It was proposed that Ni(0) F11-I entered the catalytic cycle via reduction of Ni(II) F11-V at the cathode while the metal rod anode was oxidized (Figures 11B). The cathodically generated Ni(0) species F11-I then underwent oxidative addition with Ar-Br to produce Ni(II) aryl complex F11-II. The alkyl radical formed by single-electron transfer between Ni(I) species F11-IV and alkyl bromide can be captured by Ni(II) aryl complex F11-II to give the high-valent Ni(III) complex F11-III, which upon reductive elimination yielded the product and reconstituted the Ni(I) species F11-IV. In addition, cyclic voltammetry data excluded the possibility that Zn^{2+} in solution was reduced to Zn metal at the cathode to influence the reaction.

A Reaction conditions for cross-electrophile coupling reactions



B Proposed catalytic cycle



C Representative products

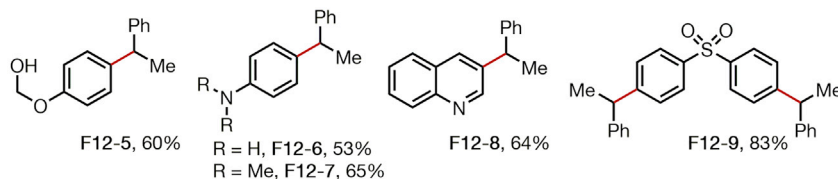
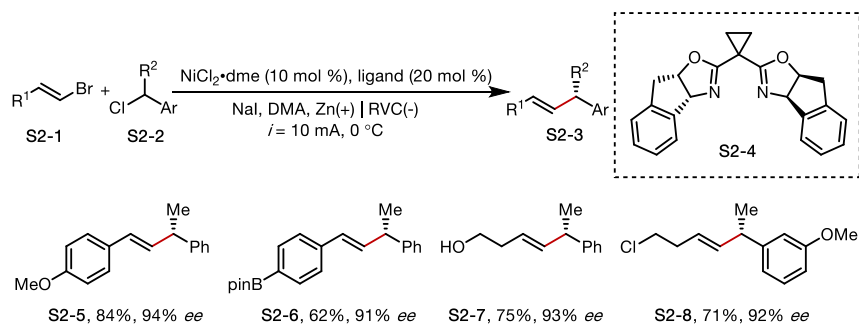


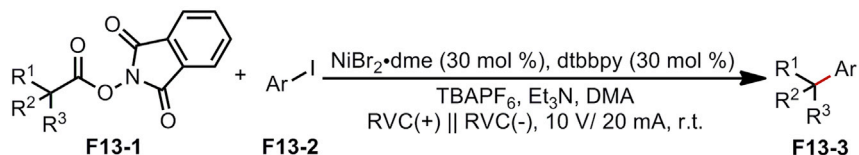
Figure 12. Electrochemical Ni-Catalyzed Reductive Relay Cross-Coupling Reaction

Quite recently, Mei and co-workers reported a highly regioselective electrochemical Ni-catalyzed reductive relay cross-coupling between aryl bromides or chlorides and alkyl bromides for the synthesis of 1,1-diarylethanes that are core structures in a wide variety of natural products and biologically active molecules (Figure 12A) (Jiao et al., 2020b). The methyl groups on the ligand F12-4 were crucial for the desired reactivities (Peng et al., 2017; Chen et al., 2017). The electrocatalytic system exhibited good substrate generality with aryl bromides; a wide range of functional groups including ether, hydroxy, and amino groups could be smoothly incorporated to produce the products in good yields (Figure 12C). Aryl chlorides were also demonstrated to be competent coupling partners. Mechanistic studies supported a mechanism in which the Ni(0) complex F12-I was generated at the cathode and acted as the catalytically active species in the reaction system and Ni(0) reacted more readily with aryl halides than alkyl halides. A more complete

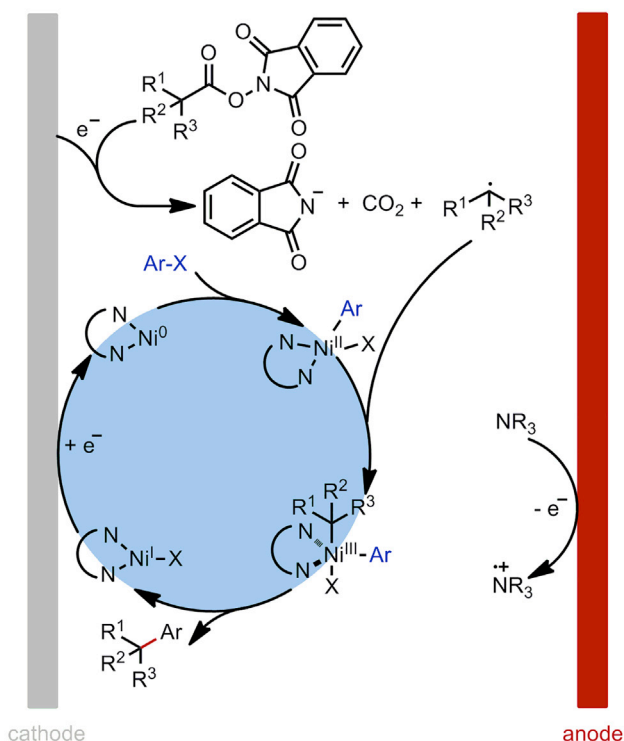


Scheme 2. Electrochemical Ni-Catalyzed Electroreductive Coupling of Alkenyl and Benzyl Halides

A Reaction conditions for decarboxylative C-C coupling



B Proposed catalytic cycle



C Representative products

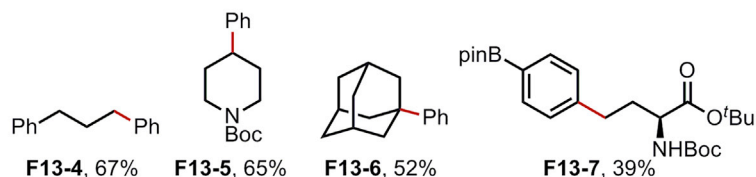
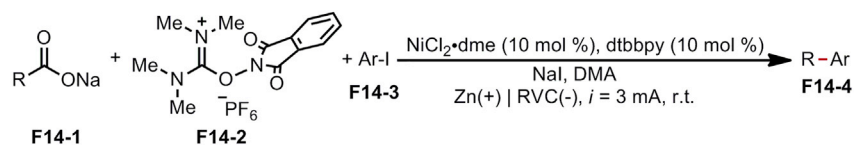


Figure 13. Electrochemical Ni-Catalyzed Decarboxylative C–C Coupling

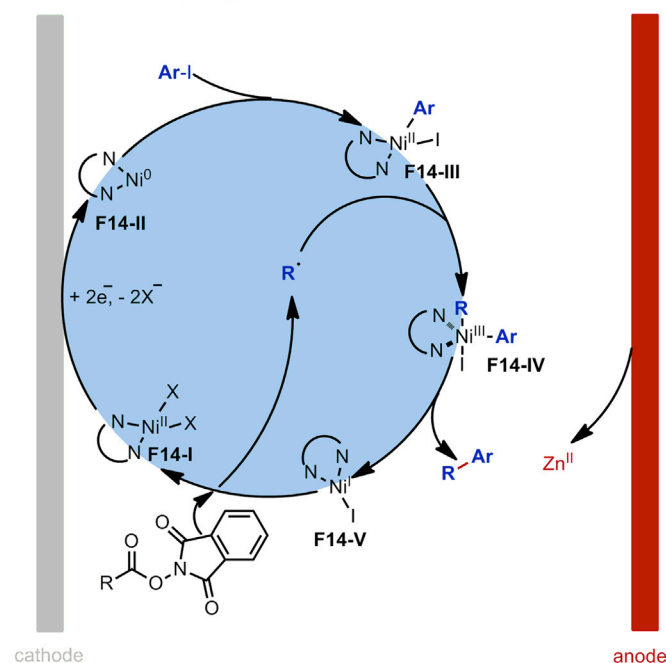
depiction of the presumed mechanism for the reaction is shown below. Oxidative addition of aryl halides to cathodically generated $\text{Ni}(\text{I})$ **F12-I** gives $\text{Ni}(\text{II})$ **F12-II**, then cathodic reduction of **F12-II** affords an $\text{ArNi}(\text{I})$ species that can trap alkyl radical to generate $\text{Ni}(\text{II})$ **F12-III**. After that, β -hydride elimination and re-addition of nickel hydride gives rise to the thermodynamically favored benzylic alkylnickel intermediate **F12-V**, setting the stage for reductive elimination to yield the desired product. The generated $\text{Ni}(\text{I})$ species was proposed to react with the alkyl bromide to afford the alkyl radical and $\text{Ni}(\text{I})$ species **F12-VI**, with the latter being reduced at cathode to initiate the next catalytic cycle (Figure 12B). Independently, the Rueping group reported a similar electrochemical Ni-catalyzed chain-walking cross-electrophile coupling system for the synthesis of 1,1-diaryllalkane derivatives (Kumar et al., 2020).

Electrochemical activation of Ni catalysts was also utilized by Reisman and co-workers to affect the enantioselective reductive coupling of alkenyl and benzyl halides (DeLano and Reisman, 2019). The

A Reaction conditions for decarboxylative C-C coupling



B Proposed catalytic cycle



C Representative products

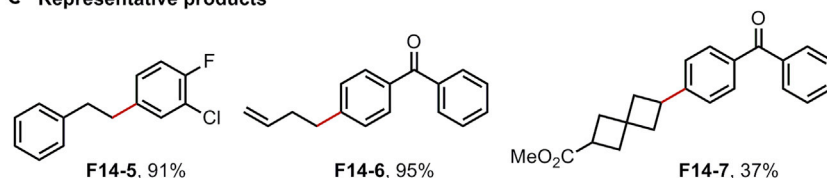
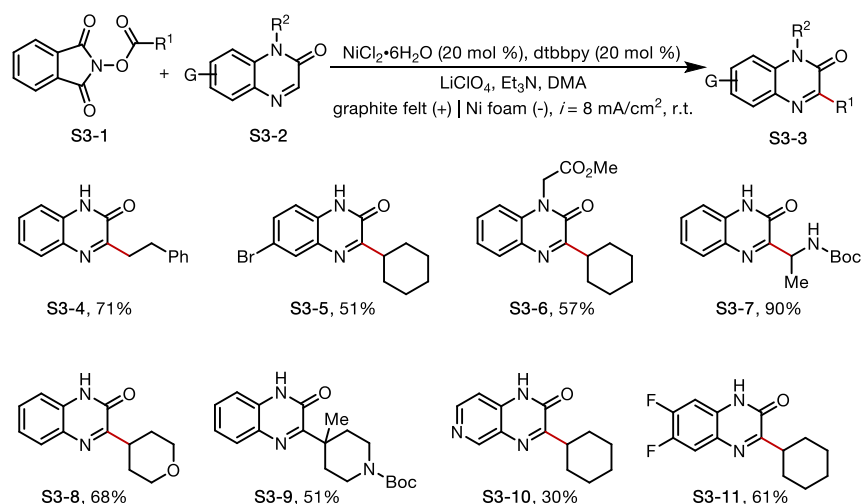


Figure 14. One-Pot Electrochemical Ni-Catalyzed Decarboxylative C–C Coupling

electrochemical protocol could mitigate issues such as capricious stirring effects, variability of metal sources, and safety issue on large scales posed by superstoichiometric use of metal powder reductants (Cherney et al., 2013). In the presence of $\text{NiCl}_2 \cdot \text{dme}$ (10 mol%), indanyl-substituted BOX ligand **S2-4** (20 mol%) and NaI (1.0 equivalent), electrolysis in an undivided cell equipped with an RVC cathode and a sacrificial Zn anode could afford products bearing allylic stereogenic centers with good to excellent enantioselectivity under mild conditions. NaI was used as electrolyte and it also functioned as an additive to facilitate the reaction. However, it has been observed that lowering the loading of NaI or ligand was detrimental to the reaction outcomes. It is worth noting that this electrocatalytic protocol could be readily carried out on gram scale and did not require an excess of either of the coupling partners (Scheme 2).

The capacity of carboxylic acids to act as an adaptive functionality renders them ideal starting materials in organic synthesis (Hu et al., 2020). In this context, redox-active esters from readily available alkyl carboxylic acids have been recently recognized as versatile alkyl halide surrogates for applications in metal-catalyzed cross-coupling reactions (Murarka, 2018). The introduction of alkyl radical species by using redox-active *N*-hydroxyphthalimide (NHP) esters into an electrocatalytic cycle was reported by Bio and co-workers in 2018 (Li et al., 2018). In the presence of homogeneous nickel catalyst, an electrochemical reductive coupling of



Scheme 3. Electrochemical Ni-Catalyzed Decarboxylative Coupling of NHP Esters with Quinoxalinones

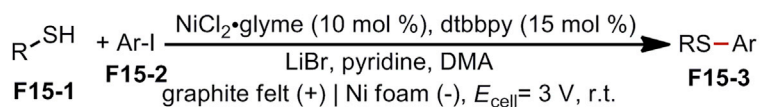
aryl iodides with alkyl NHP esters in a divided cell was accomplished with broad substrate compatibility. Mechanistically, the authors believed that the short-lived alkyl radical species were directly generated on the solid-state electrode surface via electrochemical reduction, then intercepted by the nickel catalyst for C–C bond formation. Et₃N was used as the terminal reductant that provided electrons to the reaction system. The reaction performed better in a divided cell likely owing to competitive anodic oxidation of catalytically active low-valent nickel species in an undivided cell. Notably, an operationally simple continuous flow condition was further demonstrated for large-scale synthesis using commercially available electrochemical flow reactor (Figure 13).

Later, Loren and co-workers reported a nickel-catalyzed electroreductive decarboxylative coupling of carboxylate salts and aryl iodides, proceeding through *in situ* generation of NHP esters from alkyl carboxylates and *N*-hydroxyphthalimide tetramethyluronium hexafluorophosphate (PITU) (Koyanagi et al., 2019). A sacrificial zinc electrode and an RVC electrode were used as the anode and cathode, respectively. It is noteworthy that the present electrochemical decarboxylative coupling could proceed well with only 10 mol% of nickel catalyst loading. The results of cyclic voltammetry studies provided evidence that the starting Ni(II) complex F14-I could be selectively reduced at the cathode owing to its lower reduction potential with respect to the redox-active NHP esters. The cathodically generated Ni(0) species F14-II then underwent oxidative addition with Ar–I and gave rise to Ni(II) aryl complex F14-III. The alkyl radical formed by single-electron transfer between Ni(I) species F14-V and redox-active NHP esters can be captured by the Ni(II) aryl complex F14-III to furnish the high-valent Ni(III) complex F14-IV, which upon reductive elimination gave the desired product and reconstituted the Ni(I) species F14-V (Figure 14).

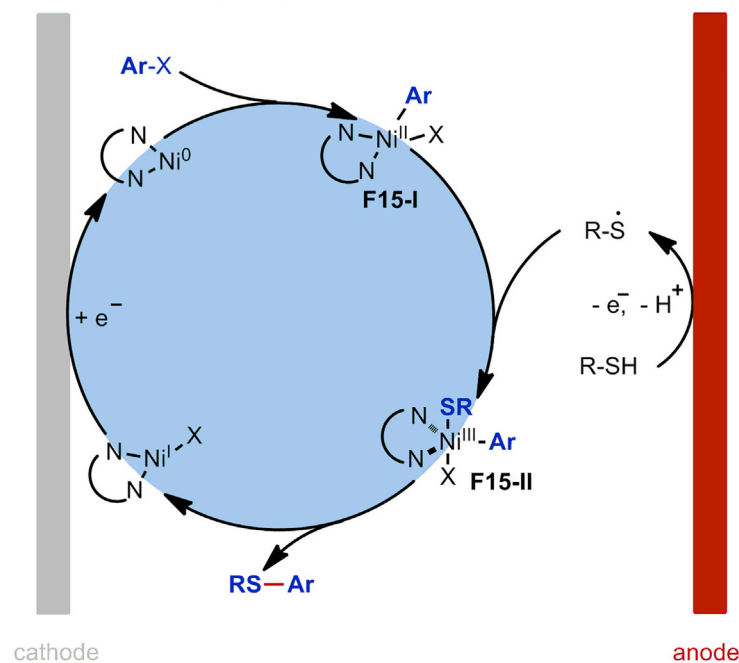
Zeng and co-workers developed a method of Ni-catalyzed electrochemical reductive coupling of NHP esters with quinoxalinones for the synthesis of 3-alkylated quinoxalinones (Lian et al., 2019). Reaction condition optimization demonstrated that graphite felt and nickel foam were the optimal electrode materials and reactions were conducted in an undivided cell with Et₃N as the sacrificial reductant. The Ni catalyst primarily acted as an electron mediator to facilitate electron transfer between cathode and redox-active NHP esters. Under optimized conditions, a diverse range of biologically important 3-alkylated quinoxalinones were obtained in good yields (Scheme 3).

The ability of metal-catalyzed electrocatalysis to mediate previous challenging bond constructions has been highlighted by recent publications describing valuable carbon–heteroatom bond-forming technologies (Kawamata et al., 2019). For example, Wang and co-workers studied Ullmann-type thiolation of aryl iodides under nickel-catalyzed electrochemical conditions (Figure 15A) (Wang et al., 2019). A simple undivided cell setup using graphene and nickel foam as anode and cathode, respectively, could afford the C–S cross-coupling products under mild conditions (Figure 15C). Mainly owing to the strong coordination of thiolates to metal centers, this type of transformation generally requires the use of strong base to generate

A Reaction conditions for C-S bond formation



B Proposed catalytic cycle



C Representative products

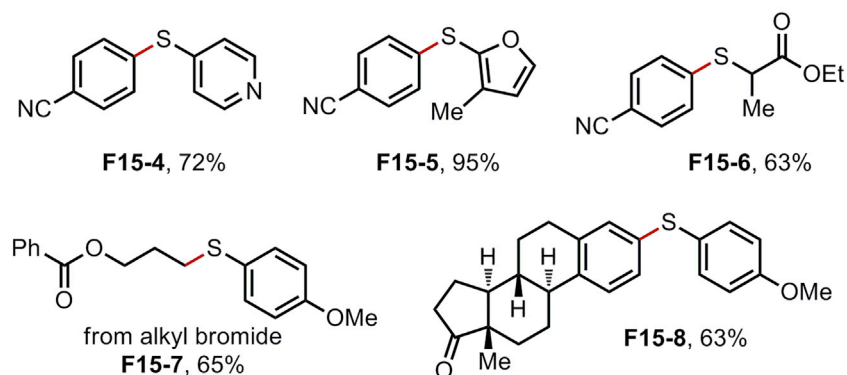
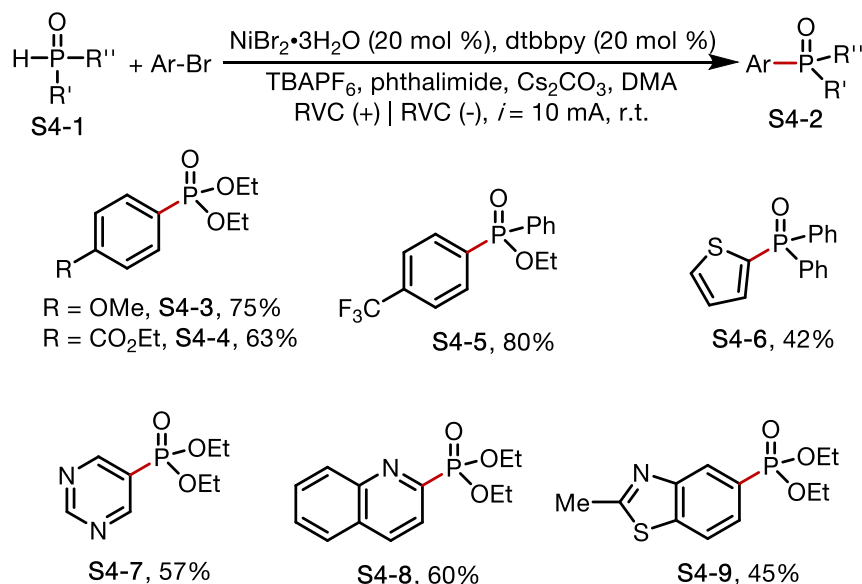


Figure 15. Electrochemical Ni-Catalyzed C-S Bond Formation

thiolates from thiols and elevated reaction temperature to drive the reaction. In contrast, the present electrocatalytic protocol enabled the coupling of both aryl iodides and one example of alkyl bromide with aryl and alkyl thiols at room temperature. Mechanistic studies including radical trapping experiments and cyclic voltammetry studies supported a mechanism in which the anodic oxidation of thiol to generate thiol radical species that was intercepted by Ar-Ni(II)-X **F15-I** to deliver a Ni(III) complex **F15-II**. Upon reductive elimination, the C-S coupling product was generated along with the formation of Ni(I)-X complex that was reduced at the cathode to enter the next catalytic cycle (Figure 15B). Leveraging similar principles, Mei and co-workers independently studied nickel-catalyzed thiolation of aryl halides and heteroaryl halides



Scheme 4. Electrochemical Ni-Catalyzed C-P Bond Formation

through electrochemistry (Liu et al., 2019). It was also suggested that a thiol radical involved pathway for the product formation was possible.

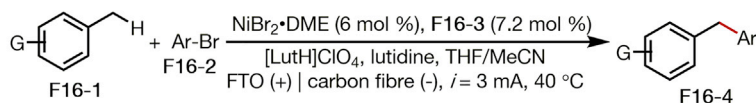
The use of electrochemically mediated Ni catalysis to facilitate C–P bond formation is also possible. In 2019, Xiang, Cui, and co-workers studied the nickel-catalyzed electrochemical coupling reaction of aryl bromides with dialkyl phosphites, ethyl phenylphosphinate, and diphenylphosphine oxide (Bai et al., 2019). This chemistry was possible using an operationally simple undivided cell. Mechanistically, a P-centered radical was proposed to interact with the Ni(II) complex to generate Ni(III) species en route to product formation via reductive elimination (Scheme 4). However, a similar reaction system developed by the Rueping group suggested the generation of phosphorus radical was not involved in the reaction (Zhu et al., 2020).

By leveraging the ability of Ni to trap radicals and form organonickel intermediates that are prone to C–C bond formation, Hu and co-workers realized an electrochemical Ni-catalyzed arylation of benzylic C–H bonds (Zhang and Hu, 2020). Generally, only 3 equivalents of toluene or its derivatives were sufficient to achieve synthetically useful reaction yields, but toluene derivatives containing an electron-withdrawing group seemed to be challenging substrates and 10 equivalents were required. The authors noted that fluorine-doped tin oxide (FTO)-coated glass was an essential anode for the success of this reaction. Mechanistically, the anodically generated benzylic radical **F16-I** was trapped by Ni(II) complex **F16-II** to produce high-valent Ni(III) complex **F16-III**, which upon reductive elimination furnished the product and Ni(I) species **F16-IV**. The Ni(I) species **F16-IV** was reduced to a Ni(0) species **F16-V** at the cathode to enter the next catalytic cycle. Alternatively, the oxidative addition between aryl bromide and Ni(I) species **F16-IV** could furnish Ni(III) species **F16-VI**, which was proposed to be reduced at the cathode to produce Ni(II) species **F16-II** for benzylic radical capture (Figure 16).

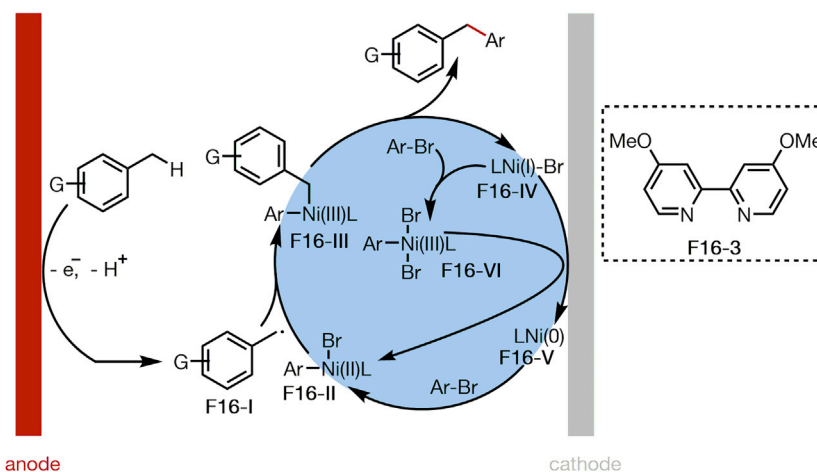
OUTLOOK

Over the past few years, the merger of transition metal catalysis and electroorganic synthesis has been demonstrated as a versatile platform for the development of new radical reactions. The leveraging of metal catalysis via the enabling technology of electroorganic synthesis has clearly opened new doors in the realm of radical chemistry for accessing previously challenging reactivities in a sustainable manner. As mentioned above, the advantages of combining transition metal catalysis and electrochemistry extend far beyond the aspect of radical species generation, obviated by the comparative use of stoichiometric amounts of chemical redox reagents. The metal-catalyzed radical capture mechanism can undoubtedly benefit from the extremely mild reaction conditions enabled by electrochemistry. In addition, redox-active metal catalysts

A Reaction conditions for direct arylation of benzylic C-H bonds



B Proposed catalytic cycle



C Representative products

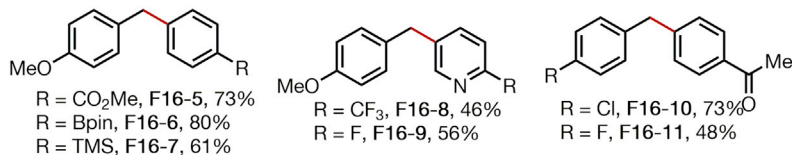


Figure 16. Electrochemical Ni-Catalyzed Arylation of Benzylic C–H Bonds

are usually employed as electrocatalysts to improve electron transfer kinetics, lower the potential required for radical generation, and, most importantly, impart selectivity control in the following chemical steps. Furthermore, electrochemistry can be of use in challenging elementary steps by direct modification of the oxidation state of the transition metal via single electron transfer. Nevertheless, there are a wide variety of redox-active metals yet to be engaged in electrocatalysis.

To date, enantioselective metal-catalyzed radical protocols demonstrating the utility of electrocatalysis are still limited, but such advances should be highly promising and are expected in this rapidly evolving research area in light of the mild and controllable reaction conditions for redox transformations and the sought-after sustainable characteristics offered by electrochemistry. The combination of electrochemistry with alternative catalytic strategies also allows capture of radical species to provide opportunities for stereoselective radical transformations. For example, combining chiral Lewis acid catalysis and electrochemistry offers new avenues for stereoselective radical transformations through dual catalytic manifold. The association of Lewis base substrates with chiral Lewis acid catalysts not only results in architecturally confined complexes but also facilitates and controls the generation of radical species, thus providing a powerful platform for the development of stereo-controlled radical bond-forming processes (Huang et al., 2018.; Zhang et al., 2019c).

Compared with conventional organic synthesis, however, the additional reaction parameters such as electrodes, electrolytes, and electrolysis potential inherently required in electrocatalytic systems do make the process of reaction condition optimization much more complicated. As such, harnessing the power of artificial intelligence and the implementation of automated high-throughput experimentation for

electroorganic synthesis are then highly desirable. At the same time, to make electroorganic synthesis a real green technology, the development of continuous-flow electroorganic synthesis without supporting electrolyte is also a practically important research direction (Pletcher et al., 2018). The development of new reactor technologies in electroorganic synthesis recently demonstrated by Jensen, Buchwald, and co-workers, that the distance between electrodes in microfluidic parallel flow channel has a huge influence on the selectivity of radical cross-coupling reactions (Mo et al., 2020). With the technology advances and in-depth understanding of mechanisms of electrochemical transition metal catalysis, we anticipate this research field will continue to grow at a remarkable pace, providing the organic community with new radical retrosynthetic routes for streamlined access to valuable chemical building blocks.

ANNOTATIONS

Electrochemical condition: (+) sign denotes the anode; (−) sign denotes the cathode; “|” denotes an undivided cell setup; “||” denotes a divided cell setup.

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AUTHOR CONTRIBUTIONS

All authors jointly conceptualized the paper and contributed to the original and revised drafts.

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