Advances on the Merger of Electrochemistry and Transition Metal Catalysis for Organic Synthesis

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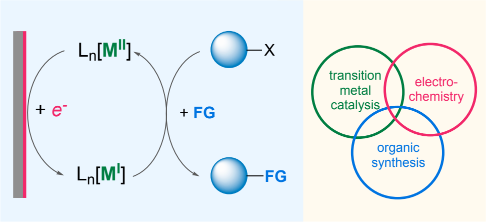
Abstract

Synthetic organic electrosynthesis has grown in the past few decades by achieving many valuable transformations for synthetic chemists. Although electrocatalysis has been popular for improving selectivity and efficiency in a wide variety of energy-related applications, in the last two decades, there has been much interest in electrocatalysis to develop conceptually novel transformations, selective functionalization, and sustainable reactions. This review discusses recent advances in the combination of electrochemistry and homogeneous transition-metal catalysis for organic synthesis. The enabling transformations, synthetic applications, and mechanistic studies are presented alongside advantages as well as future directions to address the challenges of metal-catalyzed electrosynthesis.



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1. INTRODUCTION

Electroorganic synthesis has become an established and environmentally friendly alternative to classical organic synthesis for the functionalization of organic compounds since dangerous and toxic redox reagents are replaced by an electric current.[1-3] The electrochemical step constitutes a key process for the in-situ generation of reactive intermediates, allowing reactions to be carried out in mild conditions. Moreover, electrosynthesis in the presence of redox mediators provides several advantages.[4] For example, reactions can be performed under lower potentials that lead to fewer side reactions, novel, and sustainable transformations can be discovered, and reaction selectivities can be fine-tuned. Therefore, organic electrochemistry provides interesting and useful alternatives to conventional synthetic methods and constitutes a valuable tool for the organic chemist.

1.1 Electrosynthesis: direct and mediated electrosynthesis

Electrosynthesis involves the electron transfer between an electrode and a molecule (substrate or mediator) followed by a chemical reaction to achieve the desired organic transformation. The reaction can be performed via direct or mediated (indirect) electrolysis. Direct electrolysis involves a heterogeneous electron-transfer between an electrode and a substrate of interest to generate a reactive intermediate. This is then followed by a chemical reaction with another molecule or functional group to obtain the desired product. Figure 1A is an example of a Shono oxidation of amines via direct electrolysis.[5,6] An amine (or amide) substrate is anodically oxidized to the iminium intermediate, which then undergoes nucleophilic addition with nucleophiles (e.g. alcohols) to generate the functionalized product.

In mediated (or indirect) electrosynthesis, a redox mediator (stoichiometric or catalytic) with a lower redox potential than the substrates undergo electron-transfer at the electrode to afford an electrochemically generated reagent that triggers the rection of interest (Figure 1B).[4] During the last four decades, commonly employed organic redox mediators for anodic oxidations are triarylamines and nitroxyl radicals. Major advantages of redox-mediated electrolysis include: (a) to avoid problems associated with heterogeneous electron transfer, such as overpotentials, (b) electrolysis can be conducted at lower potentials than the redox potential of the substrate, (c) accelerate the reaction rate, and (d) achieve higher selectivities by circumventing potential side reactions.[4] In most cases, when the mediator is a transition-metal (molecular electrocatalyst), they are used in catalytic amounts and many advances in this area have been developed in the last two decades. By definition, redox mediation implies a homogeneous outer-sphere electron transfer reactivity between the reduced or oxidized mediator and the substrate and this process is not covered in this review. Molecular electrocatalysis implies a metal-mediated electron transfer to a substrate, and in most cases, the molecular metal catalyst is involved in the bond-breaking and bond-forming steps to generate the desired product.

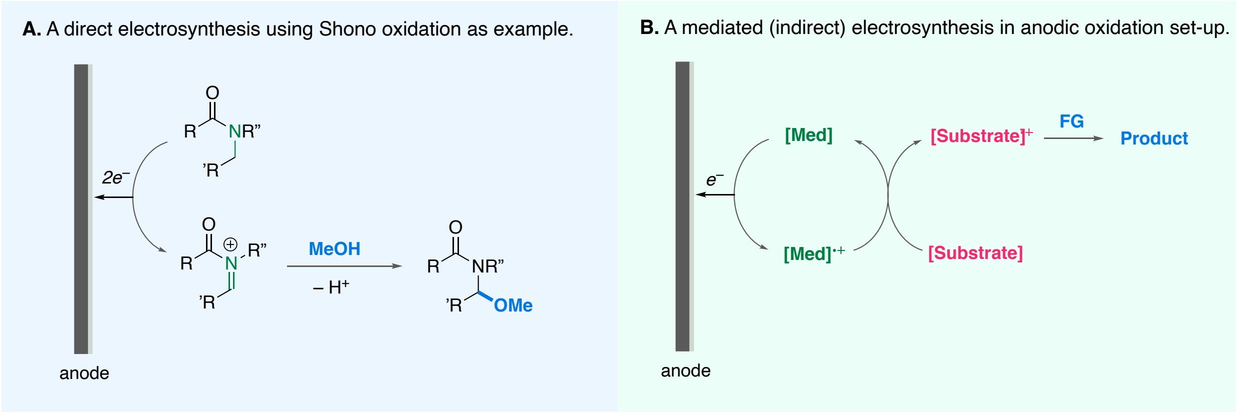


Figure 1. Direct and indirect (mediated) electrosynthesis in the context of anodic oxidation reactions.

1.2 Transition metal electrocatalysis

Transition metal (TM) catalysis has been well established in achieving many selective organic transformations. Transition metals have a very rich reactivity with many functional groups in organic molecules.[7] In most cases, their reactivities are mechanistically understood and can be predicted. With the fast-growing advancements in catalyst and ligand design, many highly selective and challenging bond-breaking and bond-forming steps can now be achieved. The utility of transition metals as catalytic mediators (TM-electrocatalysts) in electrosynthesis offers an important advantage in achieving high selectivity in substrate activation, functional group incorporation, bond-forming steps, and in achieving asymmetric reactions. In addition, electrochemistry offers additional advantages to this integration. For example, the presence of both cathodic reduction and anodic oxidation happening in an undivided cell, allows the access and control of the necessary oxidation states of the TM in each elementary step in a catalytic cycle.

Figure 2 shows the mechanism of the well-established Pd or Ni-catalyzed Buchwald-Hartwig amination[8,9] and a recently developed Ni-electrocatalyzed amination reaction of aryl halides.[10,11] In a Buchwald-Hartwig type amination, a Pd(0) or Ni(0) source (or chemically generated from stable M(II) precursors) undergoes oxidative addition to aryl halides to generate an aryl-M(II) intermediate. A base-mediated amine incorporation then generates the aryl-M(II)-amido complex. Reductive elimination, usually driven by the catalyst (bearing select phosphine ligands) or elevated temperature generates the aryl amine product and regeneration of M(0) active catalyst. In the Ni-catalyzed electrochemical amination, cathodic reduction of Ni(II) precatalyst to Ni(I) is followed by oxidative addition to aryl halides to generate aryl-Ni(III) intermediates. These intermediates are susceptible to another cathodic reduction to generate a more stable aryl-Ni(II) intermediate that can undergo a base-promoted incorporation of amine. An anodic oxidation of the aryl-Ni(II)-amine complex generates the reactive aryl-Ni(III)-amine intermediate that can readily undergo reductive elimination at room temperature. Recent mechanistic studies using voltammetric studies show the viability of a sequential two-electron reduction of Ni(II) to Ni(I) and Ni(0), thus, providing the possibility of aryl halide activation via oxidative addition of Ni(I) or Ni(0).[12]

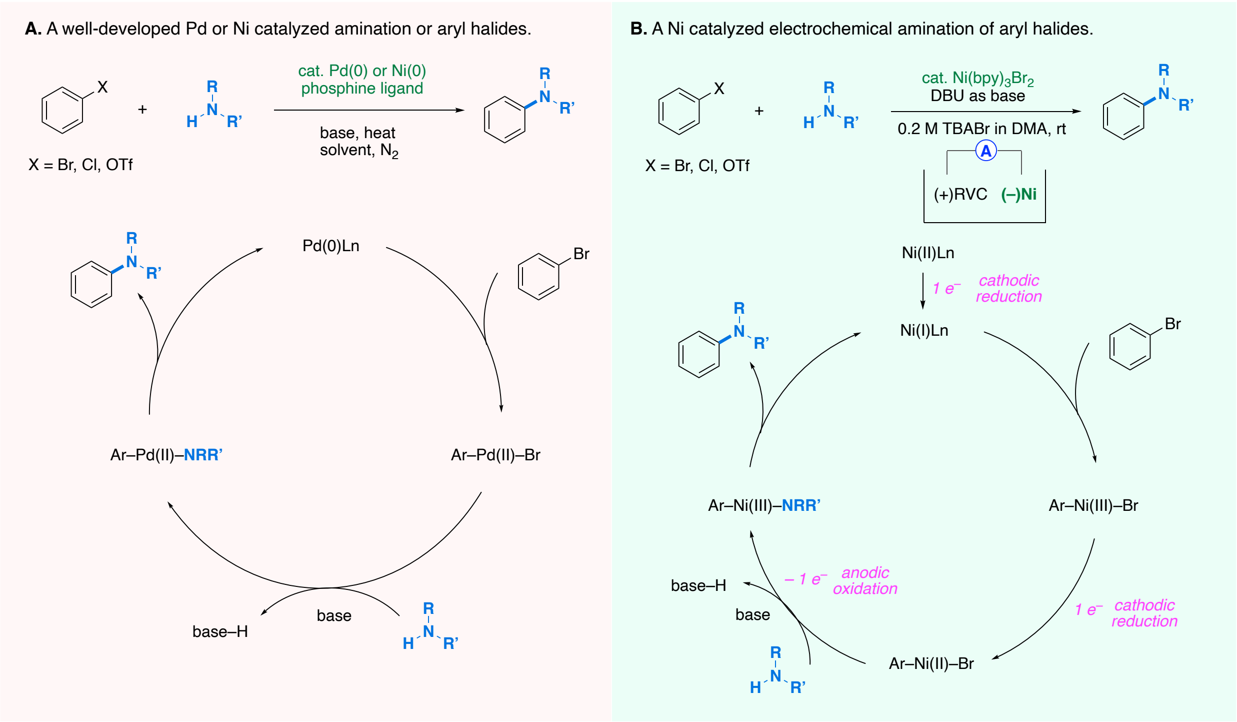


Figure 2. Pd or Ni catalyzed (non-electrochemical and electrochemical) amination of aryl halides for the synthesis of aryl amines.

The ability of metal-catalyzed electrosynthesis in controlling redox states of the catalyst allows the transformation to preclude the use of highly air-sensitive M(0) catalysts and phosphine ligands as well as access to the desired Ni(III) intermediates. As such, the reactions can be performed at room temperature and in air. Importantly, the mechanistic implications can certainly be adopted in other challenging redox organic reactions.

1.3 Scope of this review

Over the years, a variety of review articles have been published that summarize the impressive advances made in the field of organic electrochemistry. Pioneering reviews include those by Wawzonek and Weinberg in 1968.[13] Anodic oxidation and/or cathodic reduction processes were reviewed by Shono[6] and more recently by Boydston,[14] Lei,[15] Moeller,[3,16] Schafer,[17] Wright,[18] and Yoshida.[19] Progress in mediated electrosynthesis was reviewed by Francke and Little,[4] and more recently by Stahl[20] and Lin.[21] The synthetic application in complex settings have been described recently by Baran.[1,22] Bioelectrosynthesis were reviewed by Freguia and Virdis,[23] and more recently by Zhu[24] and Minteer.[25,26] The utility of alternating current electrolysis in organic synthesis was described by Luo.[27] Electrosynthesis in flow chemistry was described by Atobe,[28] Noel,[29] and Pletcher.[30] More recently, functional group-specific electrochemical transformations have also been reviewed, for instance, C-H functionalizations by Ackerman,[31] Karkas,[32] and Mei,[33] synthesis of heterocycles by Zeng[34] and Onomura,[35] fluorination of organic compounds by Fuchigami,[36] dehydrogenative biaryl synthesis by Waldvogel,[37] transformations involving *N*-centered radicals by Xu,[38] cationic intermediates by Yoshida,[39] carboxylic acids by Zhang[40] and Lam,[41] and olefin and alkyne functionalization by Ahmed,[42,43] Sun and Han,[44] and Lin.[45,46]

This review provides an overview of the recent developments on the integration of homogeneous transition-metal catalysis and electrochemistry for organic synthesis with an emphasis on reaction development and mechanistic insight. The use of electrochemical methods to elucidate elementary steps in organometallic compounds was reviewed by Jutand[47] in 2008 and are not covered in this review. The TM-electrocatalytic activation or reduction of small molecules (e.g. CO_2 reduction to CO, methane, light alkanes) are recently reviewed and were excluded in this overview, as well, since they are focused on energy applications and not organic synthesis.[48]

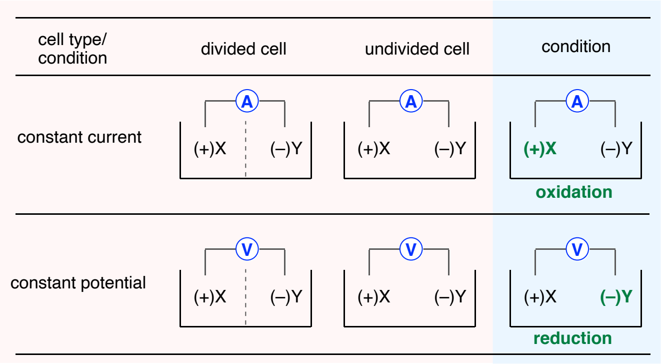


Figure 3. Cell notations used in this review. The following notations are used to easily differentiate the electrochemical conditions used (constant current vs constant potential electrolysis, the use of a divided vs undivided cell, and anodic oxidation vs cathodic reduction) in a given reaction scheme. A, constant current electrolysis; V, constant potential electrolysis; (+)X, anode material, (-)Y, cathode material.

This review is organized based on the substrates being activated by the electrochemically generated TM electrocatalyst and their mechanistic feature. Majority of the reports in the past two decades focused on the functionalization of organohalides and pseudohalides, alkenes, carbon-hydrogen bonds, as well as functional group interconversions of alcohols (and deprotection of alcohols), organoboron, and organosilicon reagents. Within each topic, the review is organized based on the type of transformation (bond-forming step or product formed) or the metal catalyst involved. A set of graphical cell notations (Figure 3) were utilized to represent the electrochemical parameters of each reaction, including cell type (divided vs undivided), electrolytic conditions (constant current vs constant potential), and electrode compositions. This is meant to aid the reader to rapidly identify classes of reactions and setups without needing to refer to the text or the article. The aim of this review is to encourage researchers to explore and to adopt organic electrosynthesis, a technique with considerable potential, to the general synthetic organic toolbox.

2 ELECTROCATALYTIC REACTIONS OF ORGANOHALIDES

Organic halides are among the most sought substrates or electrophiles in metal-catalyzed reactions due to their commercial availability, stability, and low toxicity. Importantly, they have very rich and generally more understood reactivity with low valent transition metals.[7] The activation of organohalides with chemically or electrochemically generated low valent metal catalysts typically undergoes via three major mechanistic pathways: (a) halogen abstraction to generate carbon-centered radical, (b) direct oxidative addition to generate organometallic intermediates, or via (c) two-step halogen abstraction and radical rebound mechanism. In all cases, organohalides are converted to reactive species, typically as organometallic intermediates that can undergo coupling reactions with various partners to achieve new functional groups.

2.1 Organohalide activation, protodehalogenations, and dimerization

Among the earliest reports of metal-catalyzed electro-organic reactions (reported in 1970s) were protodehalogenation and dimerization of organohalides (Figure 4).[49-51] These reductive reactions are typically catalyzed by cobalt (e.g. vitamin B_{12}, cobalt-salen) to yield the reduced product or dimer. These early reports, however, were underutilized for organic synthesis mainly due to the very poor selectivity in products (protodehalogenation vs dimerization and other byproducts). Nonetheless, they prompted the mechanistic studies done on organohalide activation with electrogenerated low-valent metals[52-54] that led to many electrochemical transformations of organohalides to generate various carbon-carbon and carbon-heteroatom bonds and are discussed throughout the rest of Section 2. Protodehalogenation was found to be the major pathway when reactions were performed in ionic liquids, or when bidentate ligands such as bipyridines are used, or titanocene electrocatalysts were used. These strategies were utilized in several electrochemical reductive dehalogenations of halogenated pesticides.

Recently, mechanistic studies by the groups of Minteer and Sigman, Toste and Chang, and Diao, using electrochemical methods and catalyst design has provided relevant mechanistic pathways and approaches to control selectivity in the activation of organohalides with cobalt catalysts.[52,53,55-57] We expect that the fundamental mechanistic studies will soon be adapted in the context of selective electrocatalysis for organic synthesis.

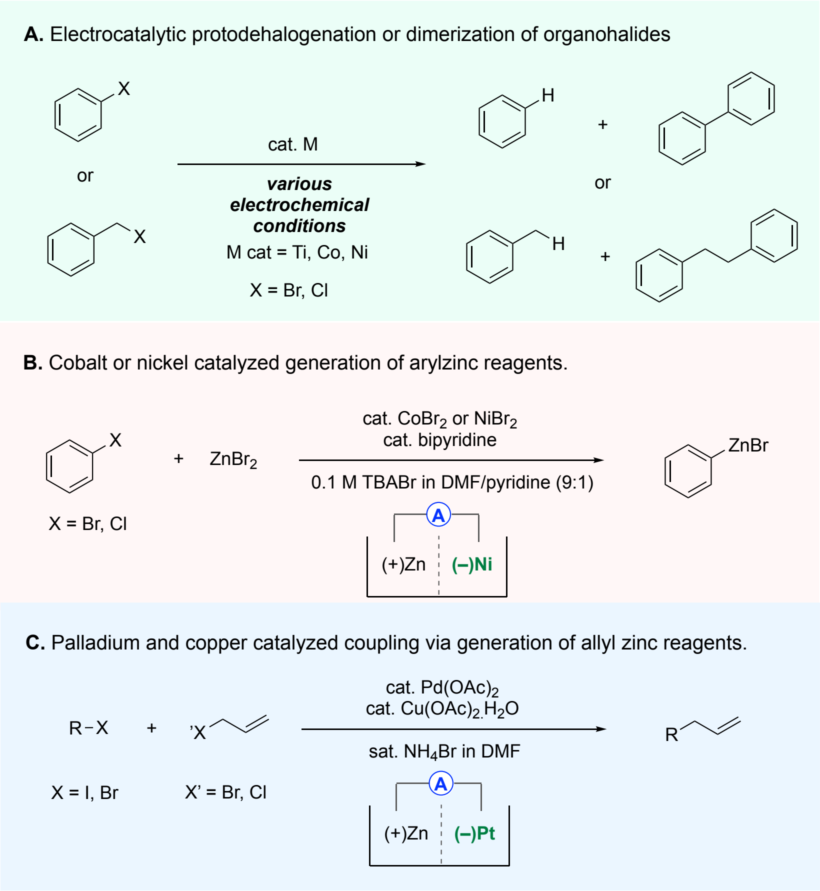


Figure 4. Electrocatalytic protodehalogenation and dimerization organohalides, and generation of arylzinc reagents.

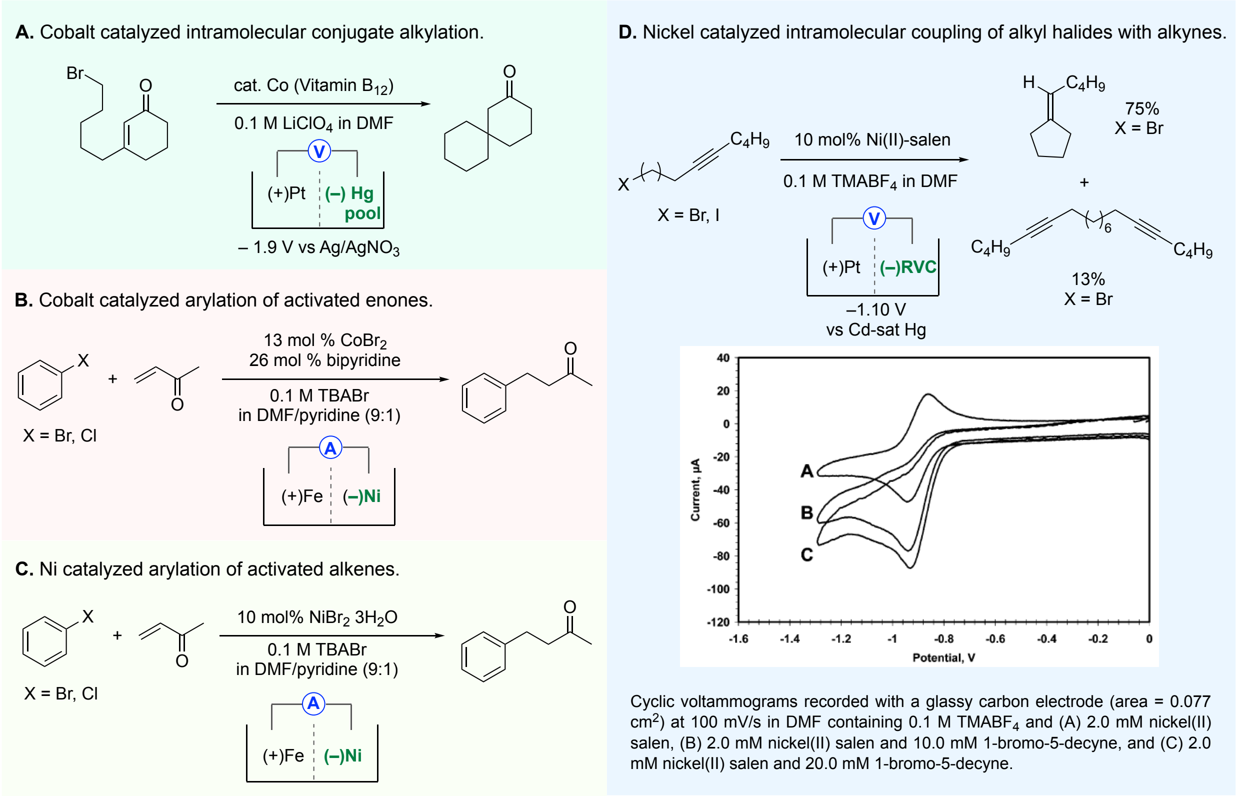
2.2 Generation of organozinc reagents and their coupling reactions

Gosmini and Perichon in 1990s to 2000s have reported highly efficient electrochemical generation of arylzinc reagents from aryl bromides and chlorides.[58-60] These reactions were realized using nickel and cobalt electrocatalysts with sacrificial Zn anode and a stoichiometric amount of zinc dihalides. Their preliminary reports using nickel/bipyridine as mediator required high excess of bipyridine ligands to stabilize the low valent nickel catalyst and restrict the formation of biaryls. Significant improvements in the reaction conditions were obtained using cobalt chloride and pyridine as the electrocatalyst. The scope and functional group tolerance of these reactions were comparable to those chemical methods of generating arylzinc reagents. Arylzinc reagents are very important carbon-based nucleophiles or coupling partners to obtain many functionalized aryl products. Gosmini and Perichon have reported the subsequent utility of the electrochemically generated arylzinc reagents in various functionalization and cross-coupling reactions to generate unsymmetrical biaryls, aryl iodides, and aryl ketones.

Notably, Huang recently reported a robust method for alkyl iodide allylation using electrocatalytic palladium in aqueous media (Figure 4C).[61] Using Zn as a sacrificial anode, it was proposed that the reaction proceeds by the initial generation of organozinc reagents from allyl halides followed by Pd-catalyzed coupling. This report shows modest yields utilizing a ligand-free catalyst with a co-catalytic copper to chemoselectively synthesize an alkyl/allylic halide coupling product. This protocol is effective for coupling a large variety of alkyl halides, including activated and unactivated primary, second and tertiary halides, without exclusion of air or moisture.

2.3 Addition of organohalides to alkenes and alkynes

Foote and Imagawa reported electrocatalytic carbon-carbon bond-forming reactions by intramolecular coupling of primary alkyl bromides with enones via 1,4-addition (Figure 5A).[62] Cobalt electrocatalysts (Vitamin B_{12} and derivatives) were utilized for the electroreductive coupling reaction to generate bicyclic ketones in good yields. This work prompted the development of various intermolecular conjugate addition reactions of organohalides.[63,64] Gosmini reported the Co/bypyridine conjugate addition of aryl bromides and iodides with terminal enones using iron as a sacrificial anode (Figure 5B).[65] Moderate yields of the addition products were obtained and the reaction condition was compatible with various substituents on the aryl group. However, the present conditions was found challenging when aryl chloride was used the electrophile, with yields typically very low. Condon and Nedelec reported a Ni-catalyzed electrochemical arylation of enones (Figure 5C).[66] Moderate to good yields were obtained. The use of aryl chlorides as substrates was also found to be challenging, but improved yields were obtained when the reactions were performed at 100 °C instead of 70 °C. This method was also utilized towards arylation of acrolein diethyl acetals to access beta-arylated aldehydes.



Cyclic voltammograms recorded with a glassy carbon electrode (area = 0.077 cm^2) at 100 mV/s in DMF containing 0.1 M $TMABF_4$ and (A) 2.0 mM nickel(II) salen, (B) 2.0 mM nickel(II) salen and 10.0 mM 1-bromo-5-decyne, and (C) 2.0 mM nickel(II) salen and 20.0 mM 1-bromo-5-decyne.

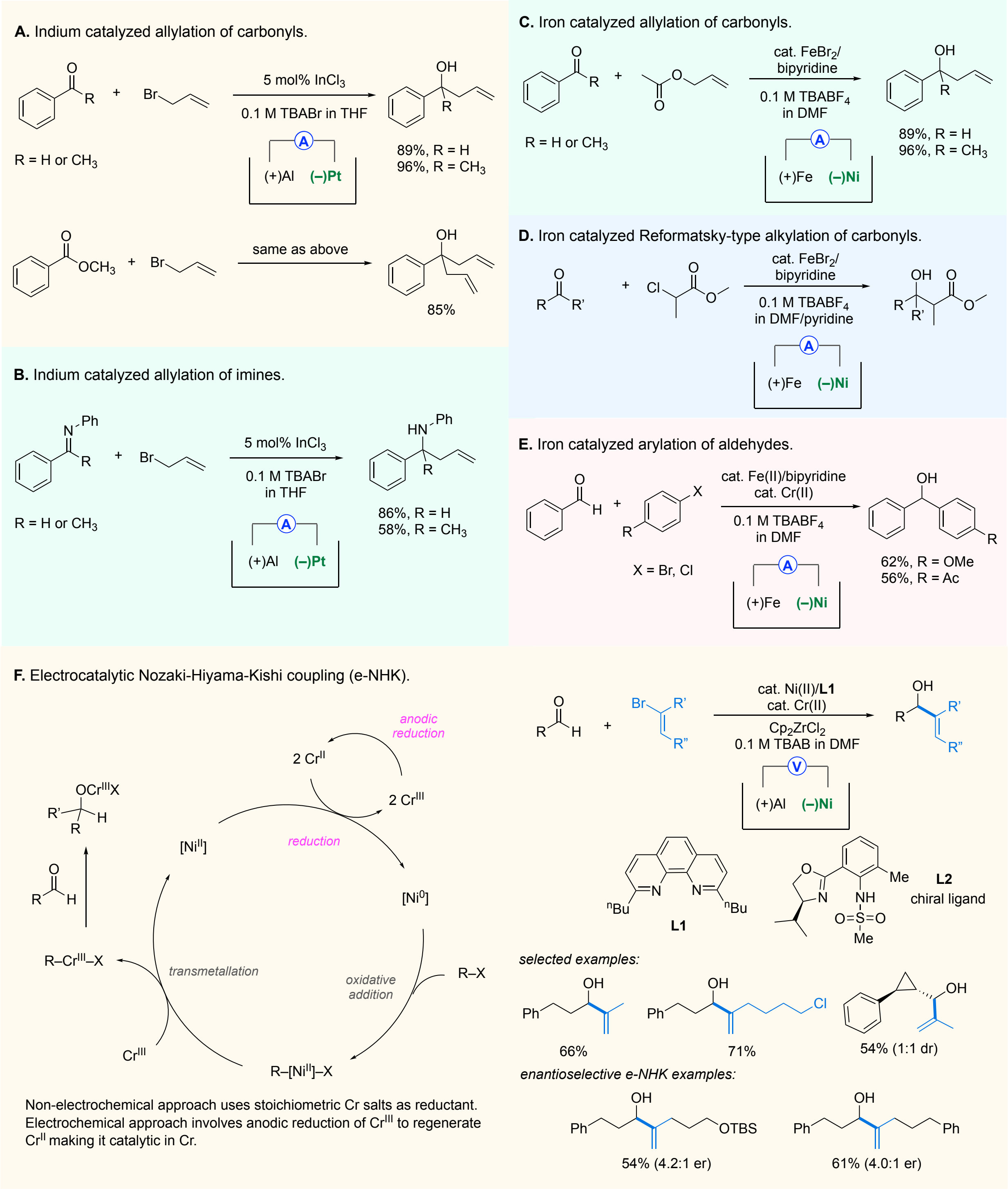
Figure 5. Electrocatalytic addition of organohalides to (activated) alkenes and alkynes. Cyclic voltamograms in (D) is reprinted from *J. Org. Chem.* **2006**, *71*, 623–628. Copyright (2006) American Chemical Society.

The reductive intramolecular cyclization of organohalides with unactivated alkenes and alkynes was also reported. The coupling of aryl bromide with unactivated alkyne was reported by Peters and co-workers using Ni-electrocatalysis (Figure 5D).[67,68] Bulk electrolyses were performed at reticulated vitreous carbon cathodes using nickel(II)-salen as the electrocatalyst.[67] Good yields of cyclic alkenes were obtained together with homocoupled byproducts. As shown in Figure 5D, cyclic voltammetry for the reduction of nickel(II)-salen in the presence of the substrate revealed that nickel(I)-salen catalytically reduces the organohalide at potentials more positive than those required for direct reduction.[68] During controlled-potential electrolysis of solutions containing nickel-salen and the substrate, catalytic reduction of the latter proceeds via one-electron cleavage of the carbon-halogen bond to form a radical intermediate that undergoes cyclization to afford the product. A tandem cyclization reaction of vinyl bromides with enones and unactivated alkenes was developed by Toyota and Ihara[69] using nickel electrocatalysis to generate tricyclic ketones in good yields.

Budnikova reported electrochemical fluoroalkylation of alkenes utilizing platinum electrodes in the presence of pyridine-substituted nickel catalysts.[70] Modest yields were obtained for dimerization of alkenes and upon treatment with tributyltin hydride, a monomer product can be generated under the same conditions. Nedelec reported a Cu-catalyzed electrochemical coupling of activated olefins and α,α,α-trichloro or gem-dichloro compounds to form halogenated cyclopropanes.[71] This reaction utilizes iron and nickel electrodes with copper bromide salt to generate a nucleophilic bimetallic copper-iron nucleophilic intermediate that can cyclize dichlorodiphenylmethane into an activated olefin. The reaction proceeds with low yields in direct electrolysis with an aluminum anode, but with moderate yields through indirect electrolysis with an iron anode.

2.4 Addition of organohalides to carbonyls and imines

The addition of organohalides to carbonyls or imines is a powerful reaction to forge new carbon-carbon bonds with the concomitant formation of alcohols or amines. Transition-metal electrocatalyzed methods for these transformations have been well reported. Hilt reported an In-electrocatalyzed allylation of aldehydes and ketones with allyl bromides to obtain alcohols (Figure 6A).[72] This reaction was proposed to go through electrochemical reduction of In(III) to In(I) followed by activation of allyl bromide. A sacrificial anode such as aluminum was found to be critical for the reaction. The optimized conditions were also found applicable to the allylation of esters to generate bis-allylated alcohols, as well as allylation of imines and aldimines to generate allylated amines (Figure 6B).[73] Electrochemical methods for allylation of carbonyls or imines mediated by Zn or Sn were also reported.[74,75] Electrochemical allylation of carbonyls using allyl acetates was reported by Durandetti using Fe(II)/bypridine as an electrocatalyst to obtain high yields of tertiary and secondary allyl alcohols (Figure 6C).[76] Electrochemical Reformatsky-type coupling of 2-halo-esters or nitriles to carbonyls were reported by Durandetti using Fe(II)/bipyridine as electrocatalysts (Figure 6D).[77] Ketones and aldehydes were also coupled with various alpha-halo esters and nitriles to generate beta-hydroxy esters and nitriles in good yields.



A. Indium catalyzed allylation of carbonyls.

B. Indium catalyzed allylation of imines.

C. Iron catalyzed allylation of carbonyls.

D. Iron catalyzed Reformatsky-type alkylation of carbonyls.

E. Iron catalyzed arylation of aldehydes.

F. Electrocatalytic Nozaki-Hiyama-Kishi coupling (e-NHK).

Non-electrochemical approach uses stoichiometric Cr salts as reductant. Electrochemical approach involves anodic reduction of Cr^{III} to regenerate Cr^{II} making it catalytic in Cr.

Figure 6. Electrocatalytic addition of organohalides to carbonyls and imines.

The Ni/Cr mediated addition of organohalides to carbonyls, also known as Nozaki-Hiyama-Kishi (NHK) coupling, is a highly interesting method for the construction of carbon-carbon bonds to form substituted alcohols. Non-electrochemical approaches uses nickel catalyst and stoichiometric chromium salt as reductant. As shown in Figure 6F, the reaction is initiated by a chromium mediated reduction of Ni(II) to Ni(0) followed by oxidate addition to form organometallic Ni(II) intermediate. Transmetallation with Cr(III) generate the organometallic Cr(II) complex that reacts with aldehydes or ketones to for alcohol products. The incorporation of electrochemistry for NHK method will allow the anodic reduction of Cr(III) to regenerate the Cr(II) reductant.

The electrocatalytic Nozaki-Hiyama-Kishi (e-NHK) coupling using Ni(II)/bipyridine as an electrocatalyst and catalytic chromium to generate benzylic alcohols was reported by Durandetti (Figure 6E).[78,79] Under similar conditions, the addition of various organo(pseudo)halides (vinyl halides, allyl acetates, and 2-chloroesters) to aldehydes was also found effective. A highly general and practical electrocatalytic Nozaki-Hiyama-Kishi (e-NHK) coupling was recently reported through a collaborative effort from Baran, Blackmond, and Reisman groups (Figure 6F).[80] Inspired by early proof-of concept work by Grigg,[81] Tanaka,[82] and Durandetti,[78,79] a careful choice of ligand, Cr, and Ni sources and optimization of electrochemical parameters allows one to avoid the use of superstoichiometric metallic reducing agents and dramatically expand the scope of those original reports. Application to Kishi's asymmetric variant as well as multiple realistic substrate classes is also demonstrated. The e-NHK can even enable non-canonical substrate classes, such as redox-active esters, to participate with low loadings of Cr when conventional chemical techniques fail. A combination of detailed kinetics, cyclic voltammetry, and in situ UV−vis spectroelectrochemistry of these processes illuminates the subtle features of this mechanistically intricate process. Specifically, electroanalytical studies illustrate the following: (1) the thermodynamic and kinetic redox properties of the Cr(III) are significantly different in the presence of Ni(II), (2) the e-NHK electron transfer processes likely proceed first by electrochemically reversible cathodic electron transfer to Cr(III) followed by electrochemically irreversible electron transfer from Cr(II) to the Ni(II) catalyst, (3) a Cr(III) species persists throughout the duration of the e-NHK, which could correspond to a putative resting state preceding rate-determining electron transfer observed under bulk electrolysis conditions, and (4) there does not appear to be an appreciable buildup of Cr(II) or low-valent Ni species by UV−vis spectroscopy during active electrocatalysis. The e-NHK can even enable non canonical substrate classes, such as redox-active esters, to participate with low loadings of Cr when conventional chemical techniques fail.

2.5 Carboxylation of organohalides with CO_2

The direct coupling of organohalides with CO_2 represents a powerful approach towards the synthesis of valuable carboxylic acid products. A large amount of work has been done on CO_2 utilization because of the ubiquity and high potential of CO_2 as C1 building block in organic synthesis. The majority of the work done on the carboxylation of organohalides goes through an initial generation of reactive organometallic intermediates such as organomagnesium and lithium reagents. More recently, Pd(0) and Ni(0) catalyzed carboxylation reactions were reported in high efficiencies.[83] Various types of organohalides and alcohol based pseudohalides have been used as substrates in catalytic carboxylation reactions. As depicted in Figure 7A, a general mechanism using Ni catalysis showed several reduction processes were necessary in order to achieve organohalide activation, CO_2 insertion and regeneration of the catalyst.[83] As such, the use of electrochemistry to facilitate carboxylation reactions provides new platforms to enable more selective transformations and enable the use of more sustainable transition metals.

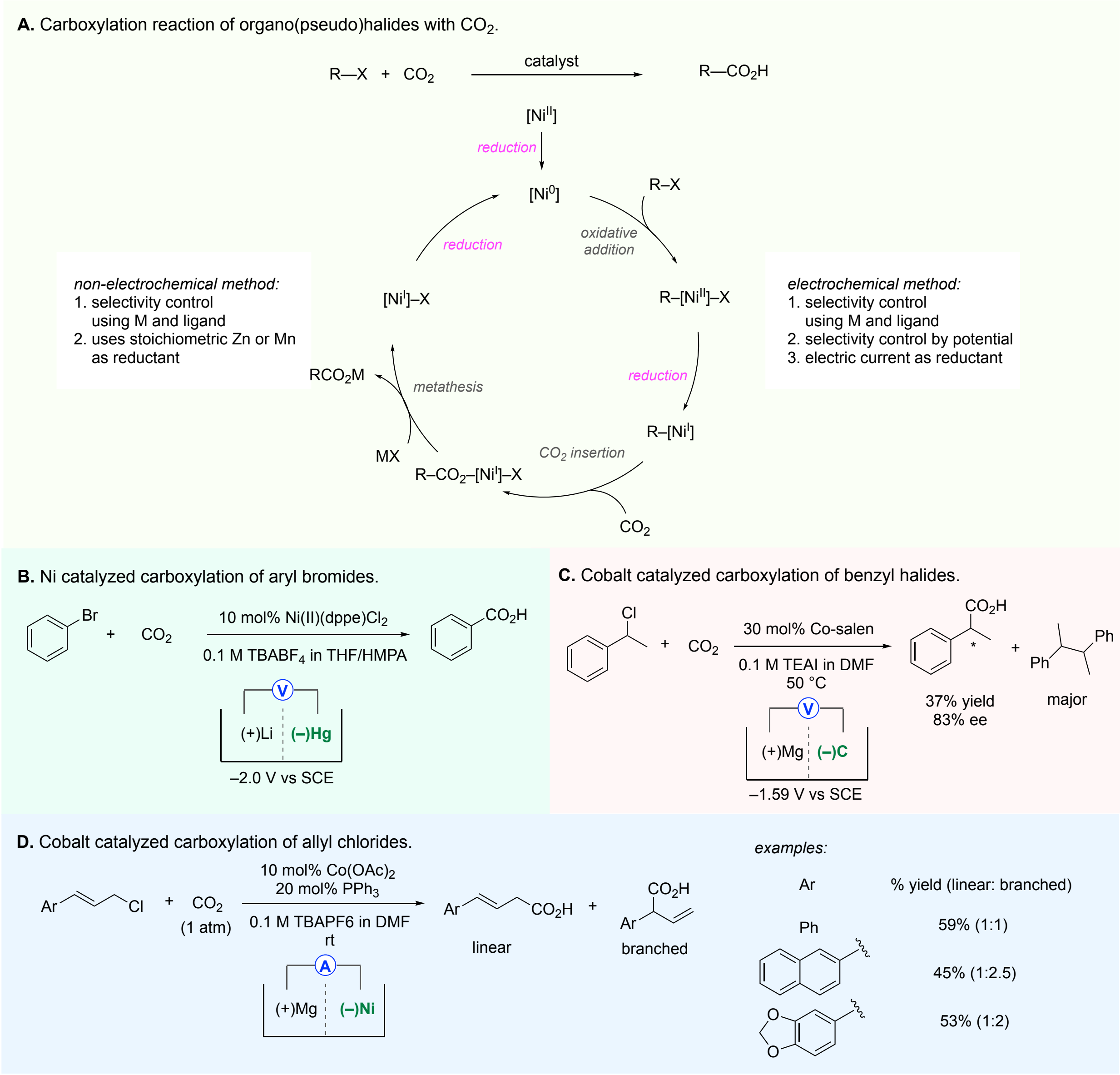


Figure 7. (A) General scheme and proposed mechanism for the metal-catalyzed carboxylation of organohalides with CO_2. (B-D) Examples of electrocatalytic carboxylation of organohalides to generate carboxylic acids.

The electrochemical and metal-catalyzed carboxylation of organohalides have also been reported using cobalt and nickel electrocatalysts.[84] The direct reduction of CO_2 occurs at rather very negative potentials (more negative than –2.0 V vs SCE in most solvents). Depending on the experimental conditions, reduction of CO_2 results in the formation of a mixture of products, including oxalate, formate, carbon monoxide, and others. As such, the search for electrocatalysts able to decrease the relatively high overpotential and to increase the selectivity of the reductive process has become an important challenge. Initial reports of metal-catalyzed electrochemical carboxylation of aryl halides were disclosed by Perichon, Jutand, Amatore and co-workers in 1980s using Ni, Pd and Co catalysts.[85,86]. Amatore and Jutand reported a detailed study on Ni(II)(dppe)Cl_2 electrocatalyzed carboxylation of bromobenzene in 1991 (Figure 7B). This reductive potentiostatic carboxylation at –2.0 V (vs SCE) resulted in a high yield of benzoic acid and a trace amount of biphenyl byproduct. Mechanistic studies implicate initial cathodic reduction of Ni(II) to Ni(0) followed by two-electron oxidative addition to bromobenzene to generate PhNi(II)(dppe)Br intermediate. It was also proposed that CO_2 insertion happens after one-electron reduction of the organometallic intermediate to PhNi(II)-species. While this is an important early report in this area, its synthetic utility is limited by the use of mercury pool working electrode and HMPA as a co-solvent.

Asymmetric carboxylation of 2-chloroethylbenzene was reported by Wang and Lu using chiral cobalt-salen electrocatalysts (Figure 7C).[87] Enantioselectivities up to 83% were obtained; however, the reaction gave rather low yields and required high catalyst loading (38% yield using 30% catalyst loading). The major product in this reaction was found to be the dimerized benzyl chloride and was found as a major challenge in earlier reports on cobalt-catalyzed carboxylation of benzyl halides. The development of electrocatalysts capable of selective and asymmetric carboxylation of organohalides remains to be a challenge in this area, as well as in general metal-catalyzed carboxylation of organohalides. Electrocatalytic carboxylations of organo pseudohalides were also reported. Dunach reported a Ni-catalyzed electrochemical carboxylation of allylic acetates.[88] Fujihara and Tsuji reported a Ni or Co electrocatalyzed carboxylation of aryl/alkenyl triflates and propargyl acetates in good yields.[89,90]

The groups of Mei[91] and Ackerman[92] have developed electrocatalytic carboxylation reactions of allylic esters and halides using Pd and Co electrocatalysts, respectively. Using cobalt and phosphine ligands, Ackerman showed the conversion of allylic chlorides to linear and branched allylic carboxylic acids in good yield under atmospheric CO_2 (Figure 7D). This reaction was performed under constant current electrolysis and required the use of Mg as a sacrificial anode.

2.6 Cross-electrophile couplings of organohalides

Cross-electrophile coupling of two different organohalides (or pseudohalides) is an interesting strategy to obtain various sp^2-sp^2 and sp^2-sp^3 carbon-carbon bonds from readily available materials.[93,94] Two central challenges of cross-electrophile couplings include the carefully chosen scope of electrophiles and cross-selectivity. Recent non-electrochemical synthetic advances and mechanistic studies have shed light on possible methods for overcoming this challenge: (1) employing an excess of one reagent, (2) electronic differentiation of starting materials, and (3) catalyst−substrate steric matching.[94] As depicted in Figure 8A, the reaction mechanism and selectivity in electrophile activation rely on the oxidation number of transition metal to obtain reactivity and selectivity on substrate activate and product formation.[95,96] Importantly, the required reduction steps can be controlled using an appropriate oxidant. Electrocatalysis provides a unique opportunity to access the necessary oxidation states and reactivity and selectivity of the catalyst in cross-electrophile coupling. As such, electrocatalysis has been well adapted to provide selectivity and broaden the scope of cross-electrophile coupling.

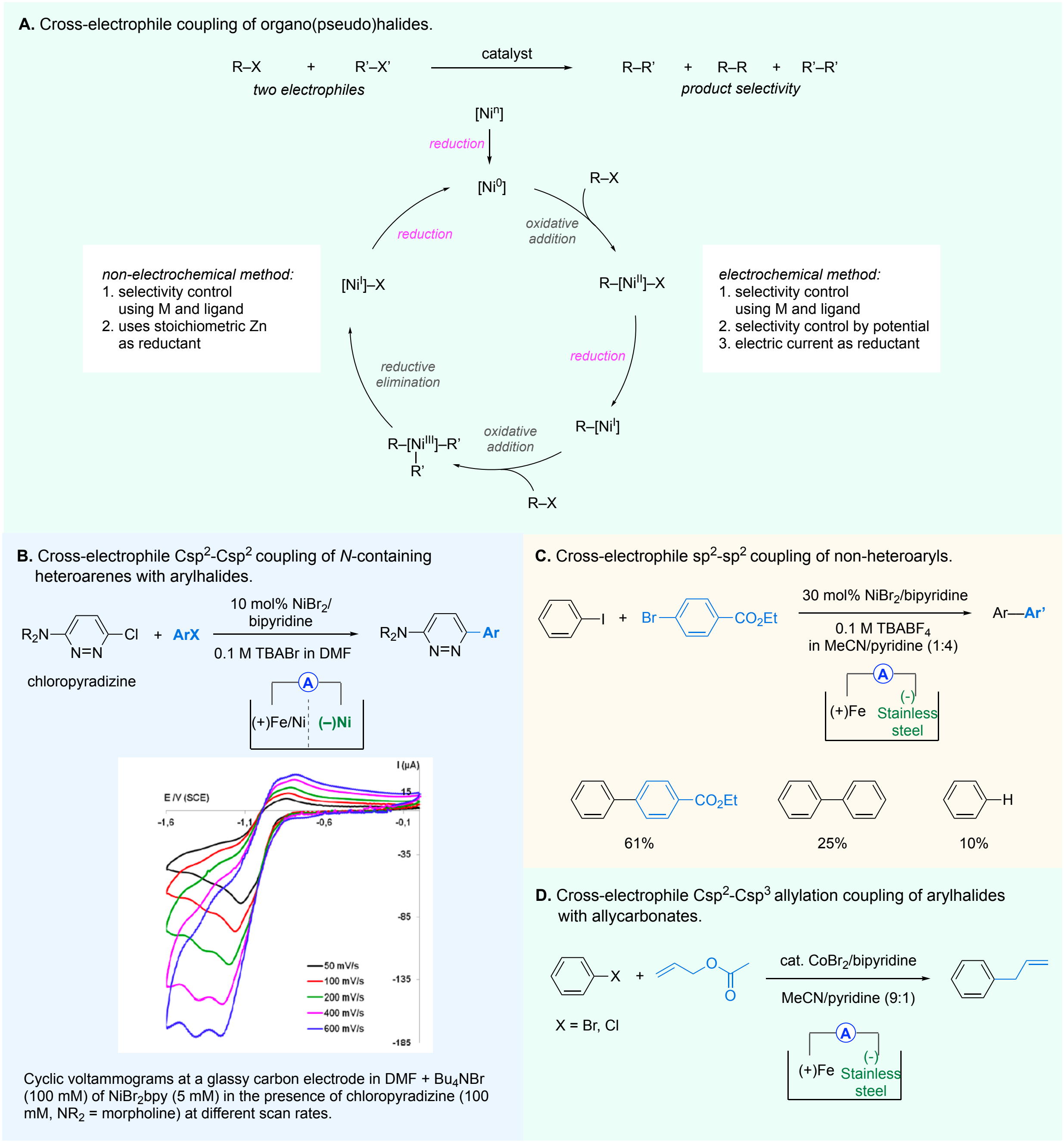


Figure 8. (A) Cross-electrophile coupling reaction of two organo(pseudo)halides and comparison of selectivity control and reduction approach using electrochemical and non-electrochemical approaches. (B-D) Nickel and cobalt catalyzed electrochemical cross-electrophile couplings. Cyclic voltammograms in (B) is reprinted from *J. Org. Chem.* **2013**, *78*, 370–379. Copyright (2013) American Chemical Society.

Gosmini reported the cross-electrophile coupling of 2-halopyridine, 2-chloropyrimidine, 2-chloropyrazine, and 4-chloroquinolines with various functionalized aryl halides by using nickel/bipyridine to generate nitrogen-containing biaryls.[97-99] These reactions use nickel/bipyridine or cobalt electrocatalysts as well as sacrificial anodes (Mg, Zn, or Fe) to generate products in high yields and selectivities. Leonel and co-workers reported a nickel-catalyzed electrochemical arylation of 3-amino-6-chloropyridazines and chloropyrimidines with aryl halides using an iron/nickel as the sacrificial anode (Figure 8B).[100,101] Voltammetric studies show that an electrochemically generated Ni(I) complex activates the chloropyridazine substrate via an EC'-type mechanism.

Unsymmetrical biaryls via the coupling of two non-heteroatom-containing aryl halides (aryl bromide and aryl iodide) were also realized using cobalt catalysis under cathodic reduction (Figure 8C). This reaction is highly promising in the context of biaryl synthesis; however, achieving high product selectivity remains a great challenge due to the high propensity of homocoupling of the aryl iodide. With the proper selection of coupling partners and conditions, the formation of unsymmetrical biaryls can be obtained in good yields. Vinylation of aryl halides using vinyl acetates was also reported by Gosmini using cobalt electrocatalysis to generate functionalized styrenes.[102]

Early reports on the electrochemical cross-electrophile coupling to generate sp^2-sp^3 carbon-carbon bonds were limited to activated alkyl halides. Sibille, Durandetti, and co-workers reported the coupling of aryl halides with various activated organohalides such as alpha-chloro esters and nitriles, as well as benzylic and allylic halides under nickel electrocatalysis.[103,104] An initial electrochemical reduction for Ni(II) to Ni(0) was proposed followed by oxidative addition to the activated organohalide. These reactions necessitate the use of sacrificial anodes such as Fe, Zn, or Al. In some cases, the yields are improved by the slow addition of the more reactive organohalide. Gosmini reported a cobalt-electrocatalyzed coupling of aryl halides with allylic acetates and carbonates to generate allylated arenes in good yields (Figure 8D).[102] The use of pyridine as cosolvent was found critical to prevent catalyst decomposition.

Enantioselective electrocatalytic cross-electrophile couplings are highly desirable transformations in organic synthesis as they deliver chiral products from two abundant and stable organohalide starting materials. DeLano and Reisman reported one of the earliest examples of an enantioselective cross-electrophile couplings under electrocatalysis in 2019 (Figure 9A).[105]

Alkenyl bromides were coupled with benzylic chlorides to generate chiral Csp^2-Csp^3 bonds in high yields and excellent enantioselectivities. Electrocatalysis was performed using RVC working electrodes and Zn as sacrificial anodes under constant current conditions. High enantioselectivities were obtained using the combination of catalytic $NiCl_2$ and chiral bis(oxazoline) ligand **A** as electrocatalysts. Various functionalities, including aryl methylethers, pyridines, free alcohols, alkyl chlorides were tolerated. More recently, Mei and co-workers described an electrocatalytic enantioselective homocoupling of aryl bromides to generate biaryl atropisomers (Figure 9B).[106] Chiral biaryls were generated in good yields and enantioselectivities using catalytic $NiCl_2$ and chiral pyrox ligand B under constant current electrolysis in an undivided cell. Reactions can be performed on gram scale to generate enantioenriched axially chiral biaryls. Moreover, the use of common metal reductants such as Mn or Zn powder resulted in significantly lower yields in the absence of electric current under otherwise identical conditions, underscoring the enhanced reactivity provided by the combination of transition metal catalysis and electrochemistry.

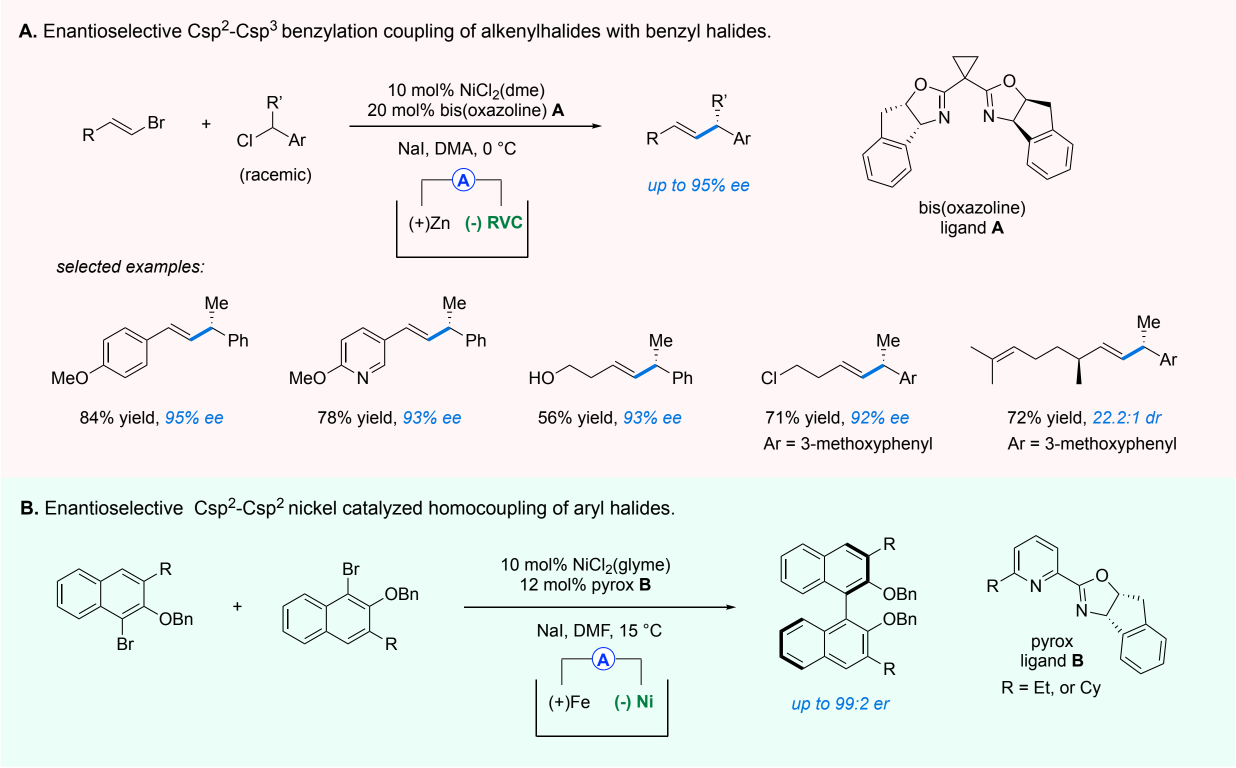
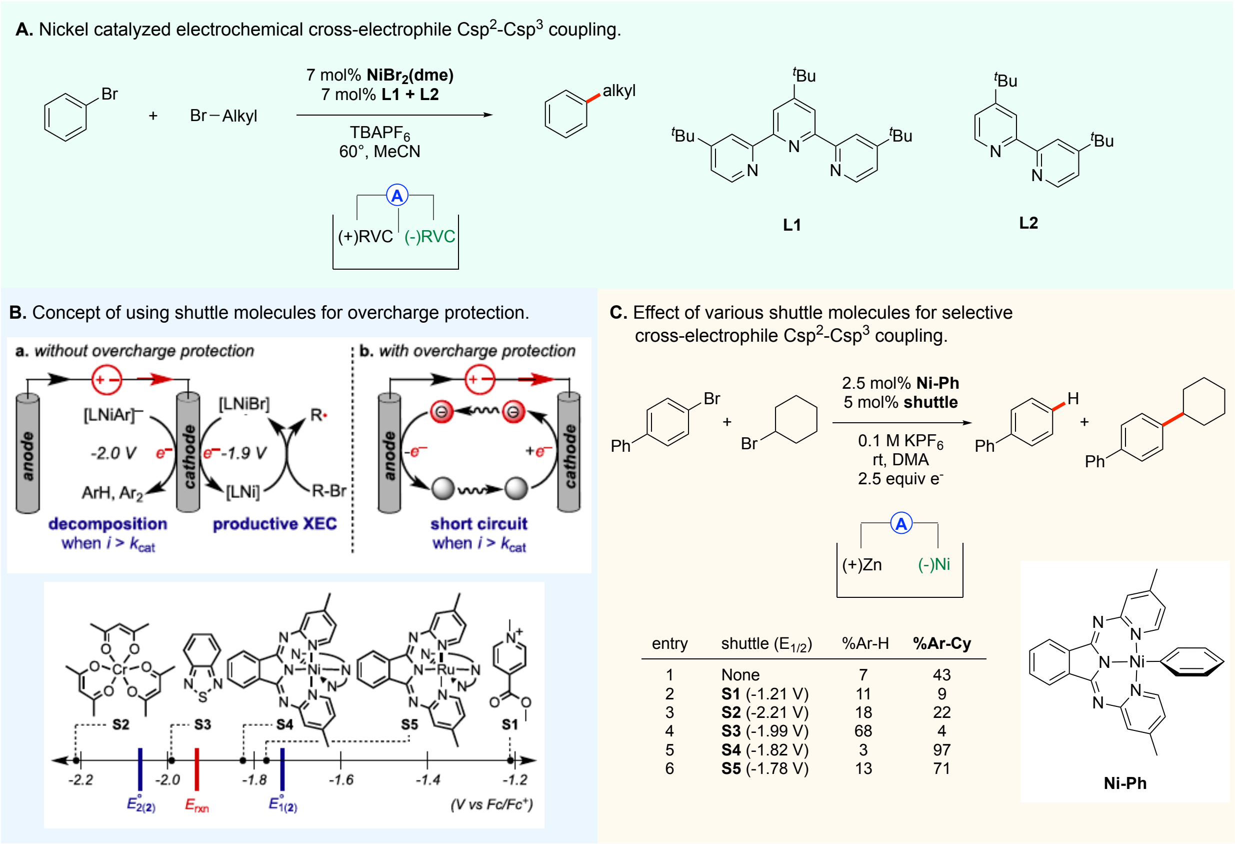


Figure 9. Enantioselective electrocatalytic cross-electrophile couplings of organohalides.

The electrochemical cross-electrophile coupling of aryl halides with unactivated alkyl halides was found very challenging. This is mainly due to competing protodehalogenation of the aryl halides caused by the decomposition of aryl-metal organometallic species from overpotential. The groups of Hansen and Weix developed a multi-ligand system for the nickel catalyzed electrochemical coupling of aryl bromides and alkyl bromides to generate sp^3-sp^2 carbon-carbon bonds with great selectivity (Figure 10A).[107] This electrocatalytic process in an undivided cell provided products in moderate to good yields and was showcased via scale-up.

Sevov recently reported an efficient nickel-catalyzed electrochemical coupling of aryl halides with various primary and secondary unactivated alkyl halides to generate sp^3-sp^2 carbon-carbon bonds (Figure 10B).[108] The protodehalogenation of aryl halides was circumvented by the use of shuttle molecular electrocatalysts as overcharge protectors. This enabling strategy is inspired by the use of overcharge protection molecules in the energy storage industry. Various organic and metal complexes utilized in nonaqueous flow batteries were investigated because of their reversible reduction potentials and high persistence in all redox states. Furthermore, these shuttles were deliberately selected because their potentials bracket the key redox events of the coupling catalyst (red and blue markers). Using shuttle **S4** (Figure 10C), high yields and selectivity of the desired product were observed.



entry	shuttle ($E_{1/2}$)	%Ar-H	%Ar-Cy
1	None	7	43
2	**S1** (-1.21 V)	11	9
3	**S2** (-2.21 V)	18	22
4	**S3** (-1.99 V)	68	4
5	**S4** (-1.82 V)	3	97
6	**S5** (-1.78 V)	13	71

Figure 10. Nickel catalyzed electrochemical cross-electrophile coupling of aryl and alkyl halides. (B-C) Use of shuttle molecules for overcharge protection in nickel catalyzed electrochemical cross-electrophile sp^2-sp^3 couplings. Figure 10A: Reprinted from *J. Am. Chem. Soc.* **2020**, *142*, 5884–5893. Copyright (2020) American Chemical Society.

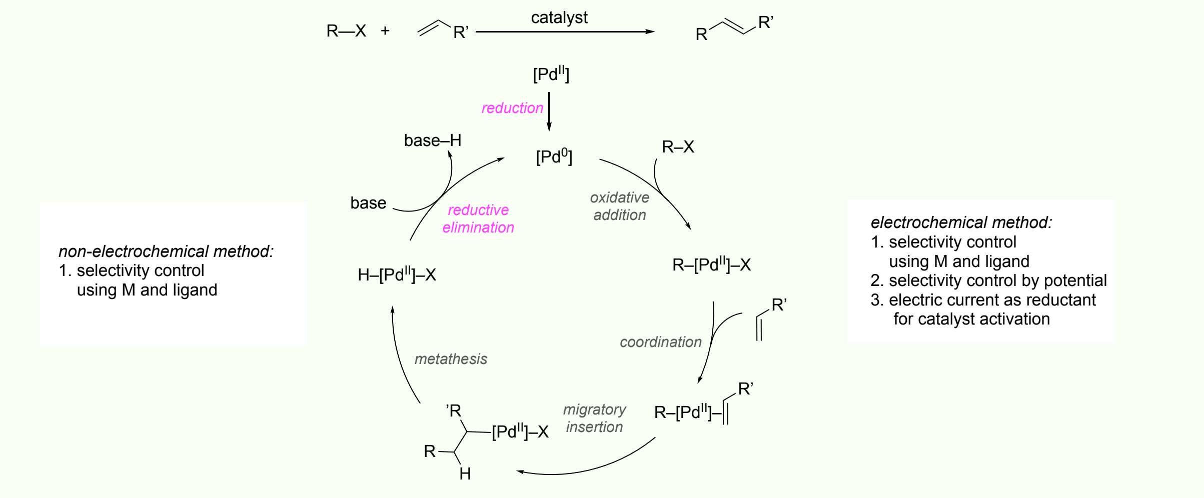
2.7 Cross-coupling with carbon-based nucleophiles

The Heck reaction has been a well-utilized method for the coupling of organohalides with olefins to generate carbon-carbon bonds.[109] Figure 11A summarizes a general Heck coupling reaction and the proposed mechanism. While traditional Heck reactions utilize chemical reductants to generate the active M(0) catalyst, the use of electrochemistry provides electric charge as a benign reductant and could potentially broaden the reaction's scope and functional group tolerance.

Moeller and coworkers developed Pd-catalyzed electrochemical Heck coupling reactions between aryl iodides and activated alkenes (Figure 11B).[110] Their discovery resulted from their initial efforts in developing electrode chip-based Heck reactions. The developed methodology allows Heck reactions to occur at room temperatures and in the absence of ligand. Various aryl iodides were coupled with various activated terminal olefins to give substituted styrenes in good yields. This electrochemical transformation was further utilized in size-selective Pd-catalyzed reactions such as Suzuki and allylation reactions to functionalize a microelectrode array (Figure 11C).[111,112] Microelectrode arrays hold great promise as analytical platforms for detecting ligand-receptor interactions in real-time. Suzuki reactions are faster than the Heck reactions and thus require more careful control of the reactions in order to maintain confinement.

Recently, Sevov developed a Heck coupling reaction of aryl halides and a broad range of alkenes that utilizes electrochemistry as a means to promote Ni-catalyzed coupling under mild conditions (Figure 11D).[113] Stoichiometric studies implicate low-valent Ni complexes as key intermediates in route to rapid reactions with even unactivated alkenes. Cyclohexenone was found to be an unreactive substrate but a crucial additive that promotes facile electroreduction of the Ni catalyst and functionalization of other alkenes in high yields.

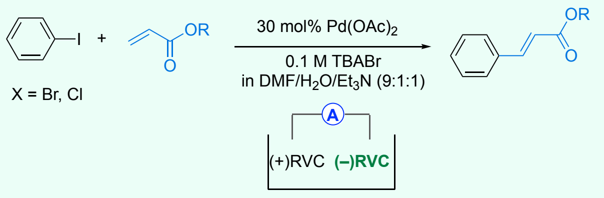
A. Metal catalyzed Heck reaction: coupling of organohalides with alkenes.



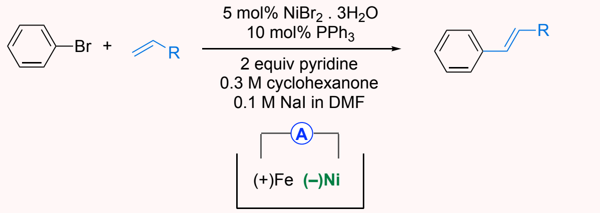
non-electrochemical method:
1. selectivity control using M and ligand

electrochemical method:
1. selectivity control using M and ligand
2. selectivity control by potential
3. electric current as reductant for catalyst activation

B. Pd-catalyzed electrochemical Heck reaction.



D. Ni-catalyzed electrochemical Heck reaction with unactivated alkenes.



C. Pd-mediated electrochemical (a) Heck and (b) Suzuki reactions for site-selective construction of microelectrode arrays.

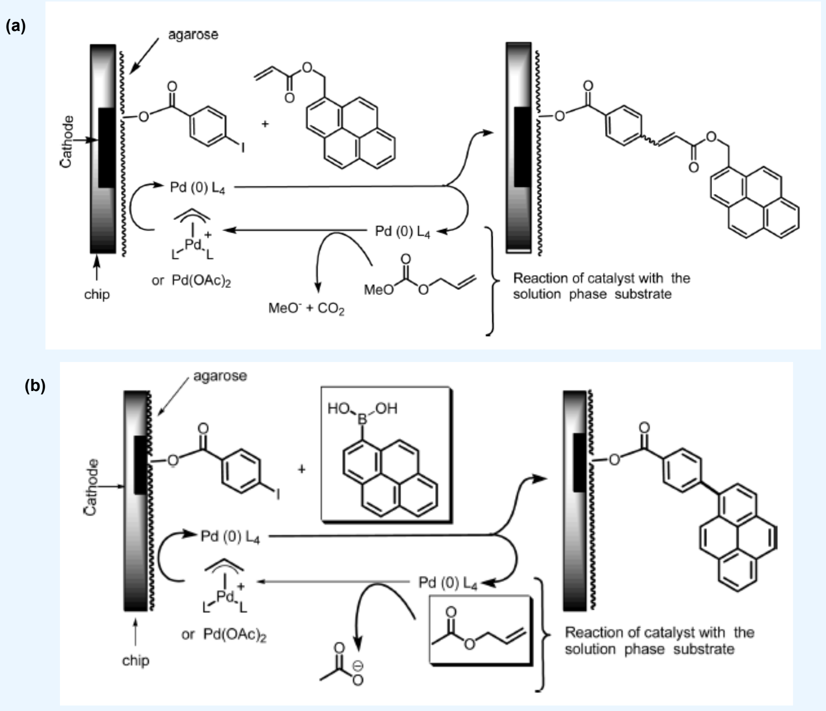


Figure 11. (A) General metal-catalyzed Heck reactions and proposed mechanism. (B-D) Pd and Ni catalyzed electrochemical Heck and Suzuki cross-coupling reactions. Figures in (C) are reprinted from *J. Am. Chem. Soc.* **2010**, *132*, 16610–16616. Copyright (2010) American Chemical Society.

2.8 Cross-coupling with heteroatoms (C-N, C-O, C-S, C-P)

More recently, the development of metal-catalyzed electrochemical cross-coupling of arylhalides to generate aryl amines, thiols, and phosphonates was reported. Baran, Minteer, and Neurock reported a nickel-catalyzed electrochemical amination of aryl halides to generate aryl amines (Figure 12A).[10,11] Mechanistic information from voltammetric studies and DFT calculations informed the development of a highly efficient amination protocol. This reaction proceeds at room temperature using a weak organic base and applicable to a broad range of aryl halides and amine nucleophiles, including: complex examples of oligopeptides, heterocycles, sugars, and natural products. The methodology was also demonstrated in batch and flow scale-ups (up to 100 g scale). The optimized condition was also tested for C-O coupling using alcohols and water as nucleophiles. Aryl ethers and phenol were obtained, however, in low yields.

Very recently, Baran reported an electrochemical approach for the coupling of aryl halides with alkyl alcohols to generate aryl alkyl ethers in good yields (Figure 12B).[114] This scalable process uses a nickel/bipyridine electrocatalyst and has been shown to give exceptionally broad substrate scope and functional group tolerance. To date, the use of phenolic coupling partners in electrochemical etherification to obtain diaryl ethers has been found to be challenging.[11,114]

The groups of Buchwald and Jensen showed a nickel catalyzed electrochemical coupling of aryl bromides and carboxylic acids to form esters.[115] The catalytic C–O bond forming reaction was performed via a microfluidic redox neutral electrochemistry platform where both reactive intermediates of the coupling partners are generated from the cathode and anode and a rapid molecular diffusion across a microfluidic channel outpaces the decomposition of the intermediates.

Mei reported the first examples of nickel-catalyzed electrochemical thiolation of aryl bromides and chlorides in the absence of an external base at room temperature using undivided electrochemical cells (Figure 12C).[116] Conventional transition-metal-catalyzed thiolation of aryl bromides and chlorides typically requires the use of a strong base under elevated reaction temperature. The proposed mechanism involves the oxidative addition of electrochemically generated low-valent Ni to aryl halides followed by the coordination of thiolates generated from cathodic reduction.

Leonel and coworkers disclosed a nickel catalyzed electrochemical phosphonation from the coupling of aryl halides and dimethylphosphonite (Figure 12D).[117] Very mild and simple conditions are employed as the cross-coupling is carried out in galvanostatic mode, in an undivided cell at room temperature, using $NiBr_2bpy$ as the easily available pre-catalyst. Various aryl bromides and iodides as well as vinyl bromides were converted to aryl or vinylphosphonates in good yield.

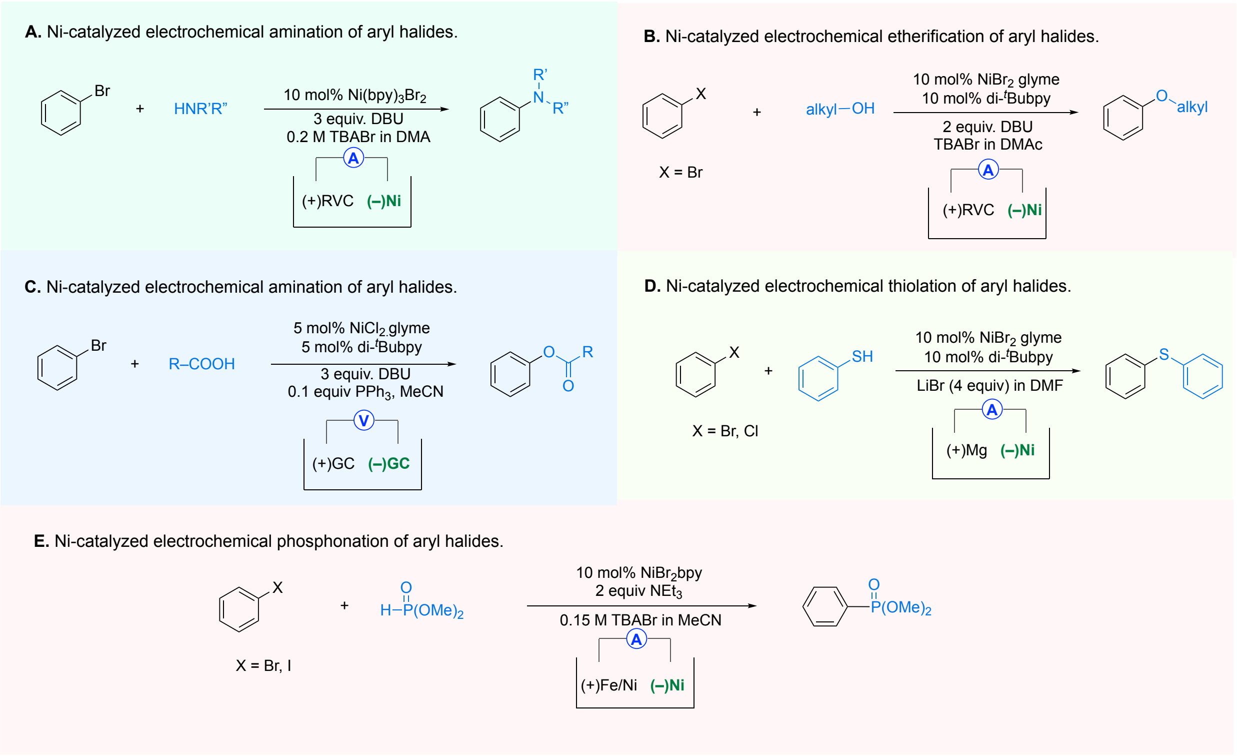


Figure 12. Electrocatalytic cross-coupling reactions of aryl halides to generate carbon-heteroatom bonds.

3. ELECTROCATALYTIC FUNCTIONALIZATIONS OF ALKENES AND ALKYNES

Alkenes and alkynes provide an opportunity for multi-component cross-coupling reactions. Electrocatalytic functionalization methods provide an additional reaction development platform enabling cleaner reaction conditions and/or access to additional reactivity.

3.1 Annulation reactions of alkenes

Lei and coworkers reported the Co-catalyzed [4+2] annulation with alkenes/alkynes and acrylamide/benzamide derivatives (Figure 13A) using quinoline as directing group.[118] Co catalysts have been used in C–H functionalizations for a number of years,[119-121] but these methods required stoichiometric oxidants such as Ag and Mn salts to regenerate the active Co catalyst.[122-124] The authors found that the use of a carbon anode could facilitate the catalyst to turnover. Additionally, the utilization of a Ni cathode (to effect hydrogen reduction) afforded the product in greater yield than other counter-electrodes. The addition of NaOPiv aided in the C–H/N–H functionalization, and the reaction occurred optimally at a constant current. The functional group tolerance included aryl halides, a thiophene derivative, and yields were similar between both alkenes and alkynes.

The same year, Ackerman and coworkers reported the same transformation with allenes, albeit with pyridine *N*-oxide (PyO) as the directing group instead of quinoline (Figure 13B).[125] The authors found similar conditions for this transformation as those utilized by Lei and coworkers above, including the $Co(OAc)_2$ catalyst, NaOPiv base, and methanol solvent. The functional group tolerance was similar, with the requirement of R^1 being an electron-withdrawing group.

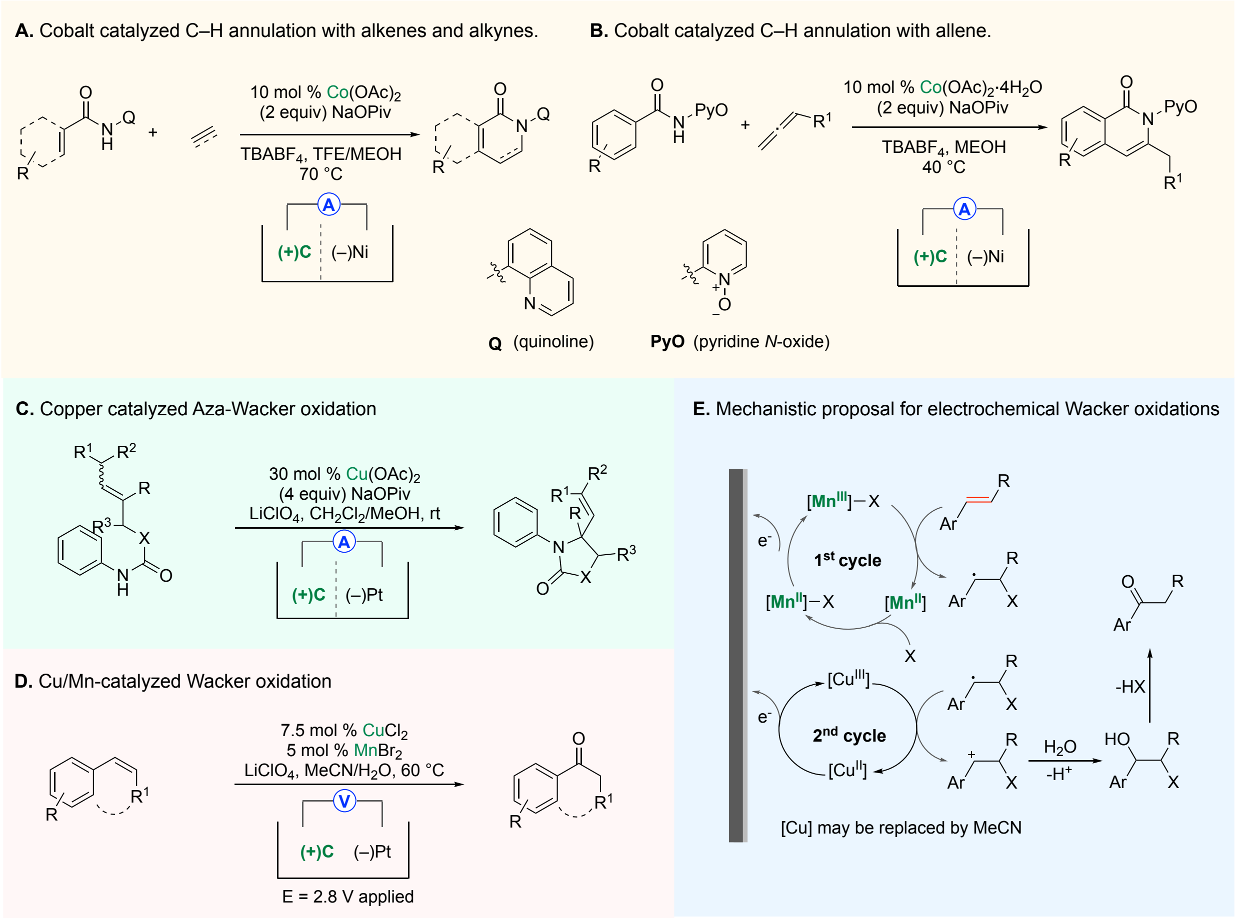


Figure 13. Electrocatalytic annulation reactions of alkenes and allenes and Wacker oxidations of alkenes.

3.2 Wacker oxidations of alkenes

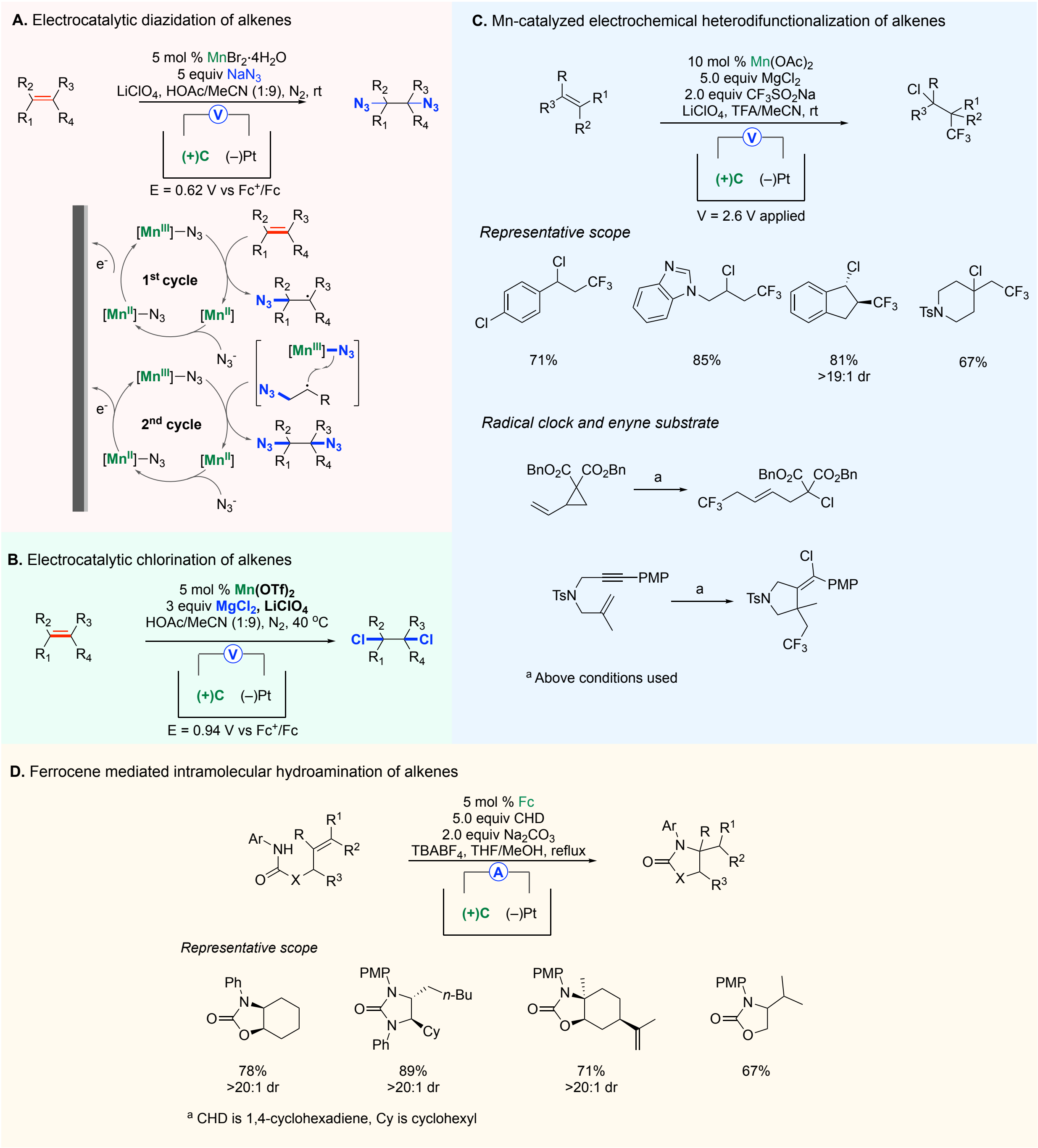
In 2018, Hu and coworkers reported the Cu-catalyzed electrochemical Aza-Wacker cyclization (Figure 13C).[126] Non-electrochemically mediated Aza-Wacker reactions typically use stoichiometric oxidants such as benzoquinone and metal salts to regenerate the active catalyst.[127,128] The byproducts of these oxidants generate significant amounts of waste and can be difficult to remove in some cases. The authors found the use of NaOPiv as an additive to be beneficial to the reaction, with $LiClO_4$ serving as the electrolyte in a DCM/MeOH (1:1) solvent. Constant current electrolysis afforded oxazolidinone derivative products from aryl amide substrates.

Pericàs and coworkers reported a Cu/Mn-catalyzed Wacker-Tsuji-type oxidation of styrene derivatives to obtain acetophenone derivatives (Figure 13D).[129] In general, electron-rich arenes were not well tolerated, but electron-withdrawing groups are common in the reported scope. Endocyclic and acyclic alkenes performed similarly in the reaction. The authors found that an applied voltage of +2.8V afforded the products in the greatest yields, with a carbon anode and platinum cathode. Furthermore, Pericàs and coworkers proposed a mechanism requiring two separate one-electron oxidations, the first one being mediated by Mn, and the second one mediated by either Cu or the acetonitrile (MeCN) solvent (Figure 13E). The addition of water to the carbocation and an elimination affords the product.

3.3 Difunctionalization of alkenes

Lin and coworkers have found that manganese can convert alkenes and sodium azide to vicinal diazides with a single step and high selectivity, which can be seen in Figure 14A.[130] The resulting vicinal diazide products can easily be converted to vicinal diamines via a single step. The substrate and sodium azide were dissolved acetic acid/acetonitrile with graphite as the anodic working electrode and the counter electrode as platinum at an applied potential of 2.3 V. The graphite was used as the working electrode because of the high surface area, easy fabrication, and low cost. Platinum is used as the counter electrode because of its low overpotential for the reduction of protons, only producing hydrogen gas. The acetic acid provided protons to be reduced on the platinum electrode. Sodium azide was utilized as the azide source due to its low toxicity and its high availability. The electrolyte, lithium perchlorate, can be replaced with tetrabutylammonium salts, as its role is simply conducting charge. In general, the scope of the alkene is general, including styrene derivatives, stilbenes, enynes, and tri- and tetrasubstituted alkenes.

It was found that without the redox-active manganese complex, a radical is formed that undergoes many transformations: dimerization, polymerization, oxidation, and reduction because of its reactivity. Thus, the occurrence of many competing reactions resulted in a low yield of the diazide. The redox-active catalyst is to improve selectivity through kinetic control by complexing the azide ion, N_3^- forming a metal azidyl complex, $M–N_3$, which can then undergo direct transfer of the azidyl radical. A second $M–N_3$ can then intercept the resulting carbon-centered radical to afford the diazide product. The proposed mechanism can be seen in Figure 14A. The reaction is irreversible as the azide ion decomposes on the electrode. Under constant current electrolysis, the reactions proceed with a similar yield with a slight increase in voltage, showing that the manganese operates at the potential close to where the azide oxidation occurs at 0.71 V. The faradaic efficiencies were found to be about 70%, suggesting that most of the potential was toward the reaction with a small amount going towards azidyl dimerization. Upon removing the Mn catalyst, and adding TEMPO, an azidooxygenated product was formed. This aided in the elucidation of the proposed mechanism.



A. Electrocatalytic diazidation of alkenes

B. Electrocatalytic chlorination of alkenes

C. Mn-catalyzed electrochemical heterodifunctionalization of alkenes

[a] Above conditions used

D. Ferrocene mediated intramolecular hydroamination of alkenes

[a] CHD is 1,4-cyclohexadiene, Cy is cyclohexyl

Figure 14. Electrocatalytic difunctionalization and heterodifunctionalization of alkenes.

Inspired by the above diazidation, the reaction shows the possibility of performing other types of alkene difunctionalization.[131] Simply, the addition of other anions to the same reaction platform that has been developed could afford a wide array of products. Lin and coworkers have applied this same reaction to halogens, specifically chloride, for alkene dichlorination (Figure 14B). A number of chloride sources were examined. The chlorine salts were chosen as they are readily available. Sodium and calcium chloride were tested as possible reagents but were unsuccessful due to their solubility. Magnesium chloride performed better than LiCl as the chloride source. The reaction operates at a slightly higher temperature because the reaction proceeds at a slower rate with chloride. The reaction is a similar setup as the azide, with the change being a chlorine salt instead of an azide as the nucleophilic source that is being dissolved in the electrolyte solution. This process was able to achieve both chemo- and stereoselectivity from the dichlorination via oxidation of the chlorine radical.

Under the optimal conditions, dichlorination was found to be successful for a range of substrates, especially with cyclic alkenes and β-alkylsytrenes, as they displayed interesting diastereochemistry. The reaction also worked with aliphatic alkenes with a range of substitution patterns. Mono-, di-, and tri- substituted alkene show reactivity towards the product of interest. Tetrasubstituted alkenes would react, but the products were not isolated in significant yields, likely due to product instability and the propensity to form a stabilized chloronium ion. Although they were reactive to tetrasubstituted alkenes, they were hard to isolate. This electrochemical technique has shown wider access to a variety of dichlorinated compounds from alkenes. The catalytic mechanism of the alkene dichlorination is similar to the diazidation with the exception of the reagent used for the difunctionalization.

3.4 Heterodifunctionalization of alkenes

Lin and coworkers developed a heterodifunctionalization of alkenes, installing both a chloride and trifluoromethyl group vicinal to one another (Figure 14C).[132] This reaction utilized the Langlois reagent (CF_3SO_2Na) as a trifluoromethyl source,[133] and $MgCl_2$ as the chloride source utilized previously. A variety of alkenes were compatible with this reaction, with various functional groups, such as amines and aryl chlorides, being well-tolerated. Endocyclic, exocyclic, and acyclic alkenes are reactive under these conditions. A tetrasubstituted alkene also reacts under these conditions, albeit with reduced yield due to the slow reactivity of tetrasubstituted alkenes. Furthermore, the use of a radical clock afforded a ring-opened product, and the use of an enyne generated the cyclized product.

Xu and coworkers reported a ferrocene-mediated, intramolecular hydroamination of alkenes (Figure 14D).[134] Other methods to generate nitrogen-centered radicals include chemical oxidants,[135,136] such as 2-iodoxybenzoic acid (IBX), or direct electrolysis.[137,138] These methods suffer from reduced selectivity or electrode passivation.[139] The authors found that ferrocene could oxidize the anion of an amide in MeOH/THF, but not the amide in basic MeOH. 1,4-cyclohexadiene was used as a hydrogen source to quench the radical and generate the product, and Na_2CO_3 as the base to deprotonate the amide. Both carbamates and ureas were tolerated, as well as endocyclic, acyclic and trisubstituted alkenes. The reaction generally proceeded with high diastereoselectivity.

3.5 Carboxylation and carbonylation reactions of alkynes

In 1988, Perichon and coworkers reported the Ni-catalyzed carboxylation of terminal alkynes with CO_2 to afford the 1,1-disubstituted alkene products and internal alkenes as a mixture of isomers (Figure 15A).[140] This stemmed from their previous carboxylation of alkenes.[141] The authors used a carbon fiber anode and a Mg cathode at a constant current. One limitation of this work was the product selectivity, as substantial amounts of both carboxylated products would be formed. A number of functional groups were tolerated, albeit in reduced selectivity. Following these results, Perichon and coworkers reported the carboxylation of internal alkynes in 1989 to generate carboxylated products using the same conditions as above.[142] Symmetrical alkynes provided the mono-carboxylated product in moderate yields, with low amounts of the di-carboxylated products being obtained. Unsymmetrical internal alkynes suffered from either low yields or poor regioselectivity.

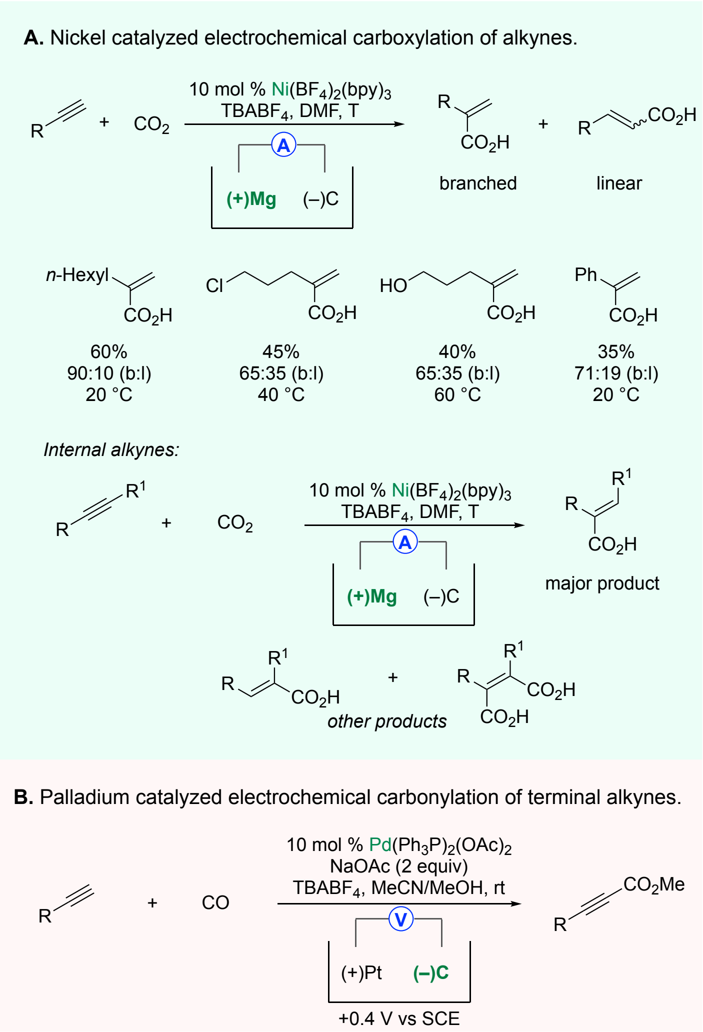


Figure 15. Electrocatalytic carboxylation and carbonylation reactions of alkynes

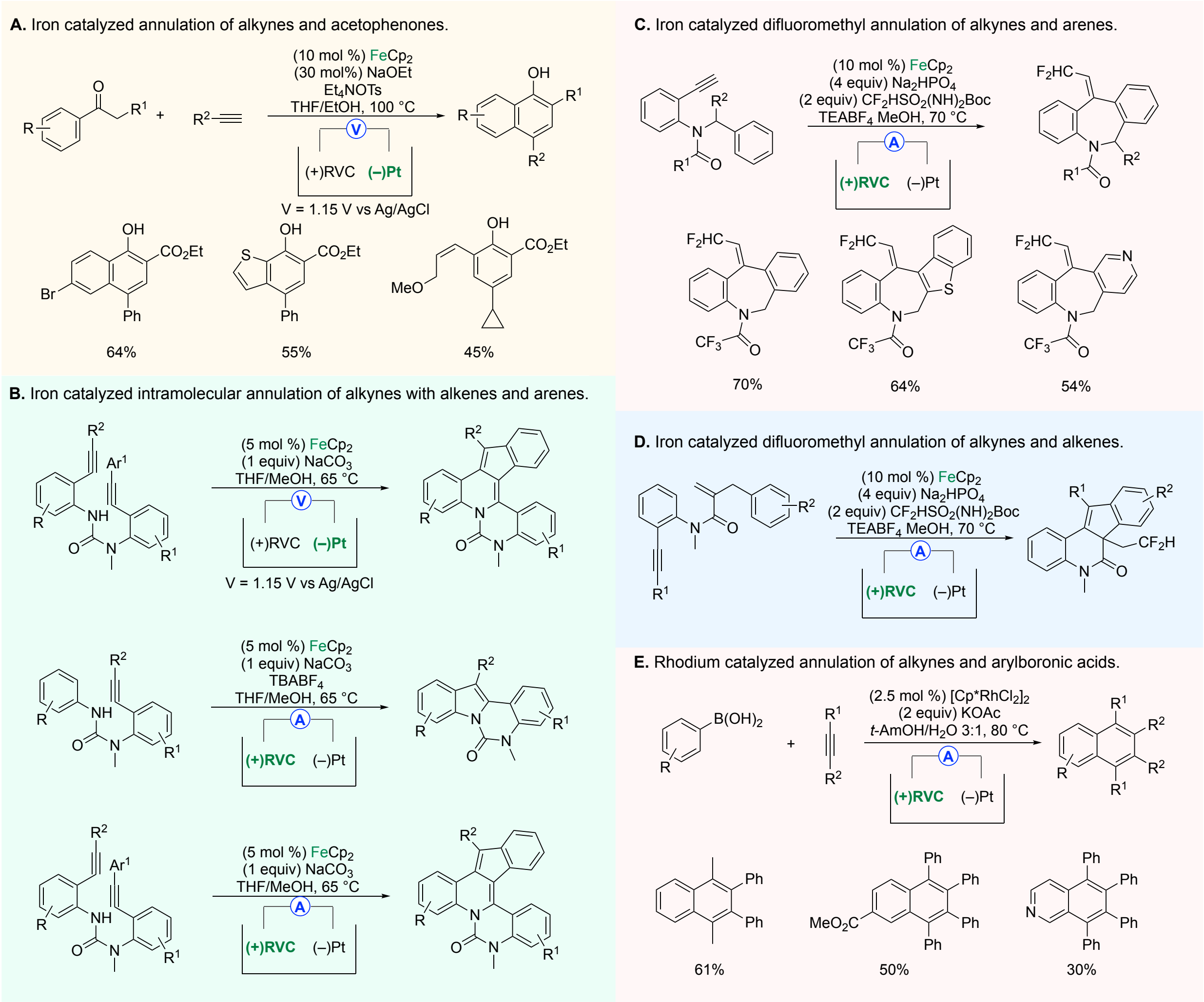
In 2002, Carelli and coworkers published the Pd-catalyzed carboxylation with terminal alkynes and carbon monoxide to afford methyl alkynoates (Figure 15B).[143] The presence of the constant voltage ensures that Pd(0) is oxidized to Pd(II), which is required for the reaction to proceed. Terminal alkynes with aryl and alkyl substituents were well-tolerated and provided the products in moderate yields. The authors found that using triethylamine instead of sodium acetate afforded the product in higher yield.

3.6 Annulation reactions of alkynes

Pan and coworkers reported an intermolecular annulation between acetophenone derivatives and alkynes to obtain 1-naphthalenol derivatives (Figure 16A).[144] Using an undivided cell, with

RVC cathode, Pt anode, and ferrocene as a mediator to facilitate oxidation of the putative enolate intermediate formed in the reaction. An aryl bromide, thiophene, and a cyclopropyl group were all well tolerated to furnish the products.

In 2017, Xu and coworkers reported the intramolecular annulation of alkynes and arenes to obtain polycyclic aromatic hydrocarbon products (Figure 16B).[145] The authors employed ferrocene as a mediator to facilitate oxidation of the substrate and generate a radical intermediate that could then undergo the reaction to form the products. This reaction tolerated aryl halides, and an alkyl group for the substituent, albeit in reduced yield. The authors found that an increase in applied current density caused reduced yield, possibly due to oxidation of the products. Cyclic voltammetric studies showed that the starting material had an oxidation potential of +1.43 V vs SCE, while the product exhibited an oxidation potential of only +0.89 V vs SCE. However, upon deprotonation of the amide, the oxidation potential of the starting material is only +0.53 V vs SCE, much closer to that of ferrocene, 0.49 V vs SCE. In 2016, Xu and coworkers reported the ferrocene-mediated, electrochemical synthesis of indoles via an oxidative process.[146] This work represents an expansion of their previous work with alkenes to include alkynes. Electron-rich and poor arenes were well tolerated, as well as a cyclohexene moiety.



A. Iron catalyzed annulation of alkynes and acetophenones.

B. Iron catalyzed intramolecular annulation of alkynes with alkenes and arenes.

C. Iron catalyzed difluoromethyl annulation of alkynes and arenes.

D. Iron catalyzed difluoromethyl annulation of alkynes and alkenes.

E. Rhodium catalyzed annulation of alkynes and arylboronic acids.

Figure 16. Electrocatalytic annulations of alkynes.

In 2018, Xu and coworkers reported the difluoromethylation of aryl alkynes to form dibenzazipenes (Figure 16C and D).[147] The authors used the precedence by Baran and Blackmond to electrochemically form the difluoromethyl radical from the sulfonamide reagent in the solution.[148] This radical then reacts with the alkyne in an undivided cell, leading to product formation. With respect to the arenes, the scope was rather broad, including benzothiophene and pyridine, among others (not shown). This reaction was ferrocene-mediated, with an RVC cathode and Pt anode under constant current electrolysis. It is important to note that the difluoromethyl radical reacted preferentially with the alkene over the alkyne. This afforded the formation of polycyclic aromatic hydrocarbons bearing a difluoromethyl group.

Ackerman and coworkers reported the generation of polycyclic aromatic hydrocarbons with boronic acids, and internal alkynes in a [2+2+2] cycloaddition (Figure 16E).[149] This was accomplished under constant current conditions of 4mA with an RVC anode and Pt cathode to generate oxidative conditions. Rhodium facilitated the reaction, but its exact role was not elucidated. The model substrate afforded product **3d** in 73% yield, and changes to either the boronic acid or alkyne generally resulted in reduced yield, but functional group tolerance was fairly broad, including electron-donating and withdrawing groups. Protic solvents performed the best, with a mixture of *t*-AmOH/H_2O (3:1) providing the best yield, with KOAc as the additive.

Finn and coworkers reported the electrochemical, Cu(I)-catalyzed azide/alkyne [4+2] cycloaddition in 2008 (Figure 17A).[31] The authors used an RVC anode and a Pt cathode to apply a constant voltage of -0.2V vs Ag/AgCl. This transformation furnished the triazole product in excellent yield. Steckhan and coworkers reported the oxidative functionalization of alkenes and alkynes with α-nitroketones to afford functionalized isoxazole *N*-oxide products.[32] They demonstrated this method with superstoichiometric Mn(III) and electrochemically generated Mn(III). Figure 17B displays the non-electrochemical method. The yields of the products are similar between the two developed methods, with the electrochemical method consuming less Mn catalyst. The authors proposed that the role of Mn(III) is to oxidize the α-nitroketone enolate to generate an α-radical that reacts with the alkene/alkyne.[32]

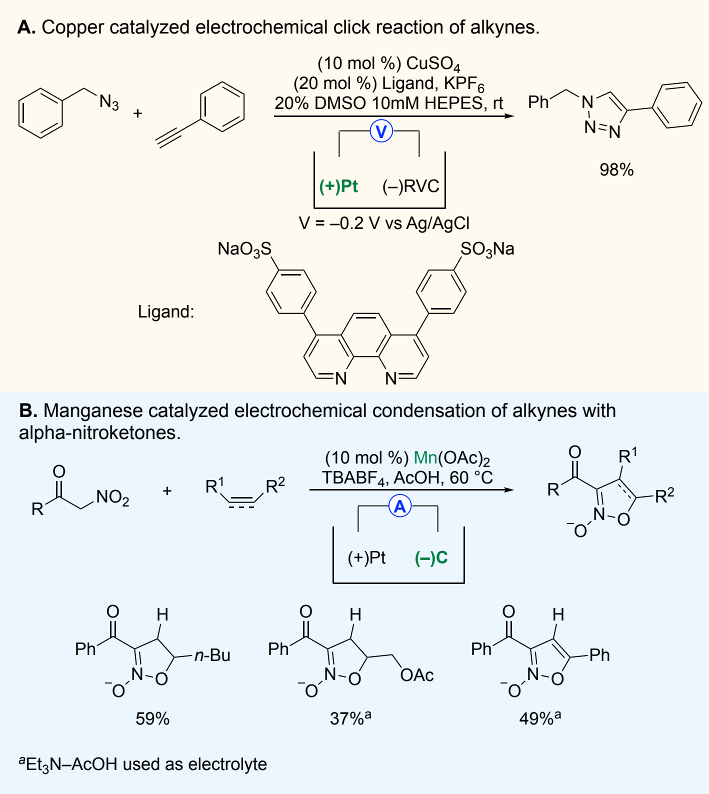


Figure 17. Electrocatalytic cycloaddition reactions of alkynes with azides and alpha-nitroketones.

4. ELECTROCATALYTIC C–H FUNCTIONALIZATION REACTIONS

Selective C–H functionalization reactions on arene cores are crucial to building complexity on aromatic molecules[150,151]. Expanding this class of reactions equips synthetic chemists with more reliable routes to develop new scaffolds that appeal to the pharmaceutical and technological sectors.

4.2 Electrocatalytic Palladium C–H functionalization processes

The catalytic C–H functionalization using Pd catalyst has proven to be highly effective under non-electrochemical conditions. Employing electrochemistry to access necessary oxidation states of Pd intermediate for C–H activation and bond-forming steps will provide reaction selectivity as well as the incorporation of a desired functional group. Traditionally, installing C-C bonds on aromatic molecules relies on the pre-functionalization of the arene core. For instance, in the Heck reaction, coupling arenes with alkenes using palladium requires an aryl halide, crucial for the initial oxidative addition step.[109] Fujiwara-Moritani type reactions represent a more sustainable alternative since no pre-functionalization of the arene partner is required and the functionalization of the aromatic C-H moiety renders a C-C bond[152,153]. In this case, the main challenge relies on the recovery of Pd(II), which is the active intermediate, from Pd(0) that is produced after the reductive elimination step. Traditionally, Heck-type reactions employ stoichiometric amounts of oxidants, including: Ag(I), Cu(II), *t*-BuOOH, and $PhCO_3Bu$[109,154]. Benzoquinone has been used in catalytic amounts for recovering Pd (II) in C-H functionalization reactions, but again it requires toxic co-oxidants[155]. The use of electrochemistry to propel palladium/benzoquinone systems has been established before by Backwall in the oxidation of dienes.[156] Taking this work into account, Amatore and Jutand developed a Fujiwara-Moritani type C-H alkynylation reaction using a catalytic Pd (II/0) manifold and co-catalytic quantities of 1,4-benzoquinone (Figure 18).[157] In this system, the oxidation of [Pd^0] does not take place directly at the electrode but is the 1,4-benzoquinone that plays a shuttle role in transferring the electrons to the anode. This work shows the compatibility of palladium C-H functionalization catalysis with electrosynthesis as well as the significance of merging these two fields in the future evolution of chemical synthesis.

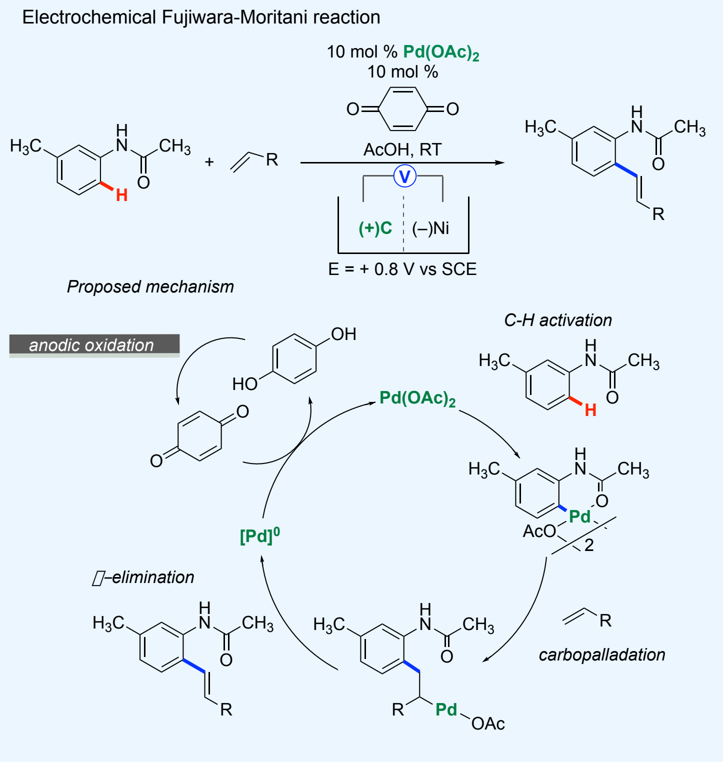


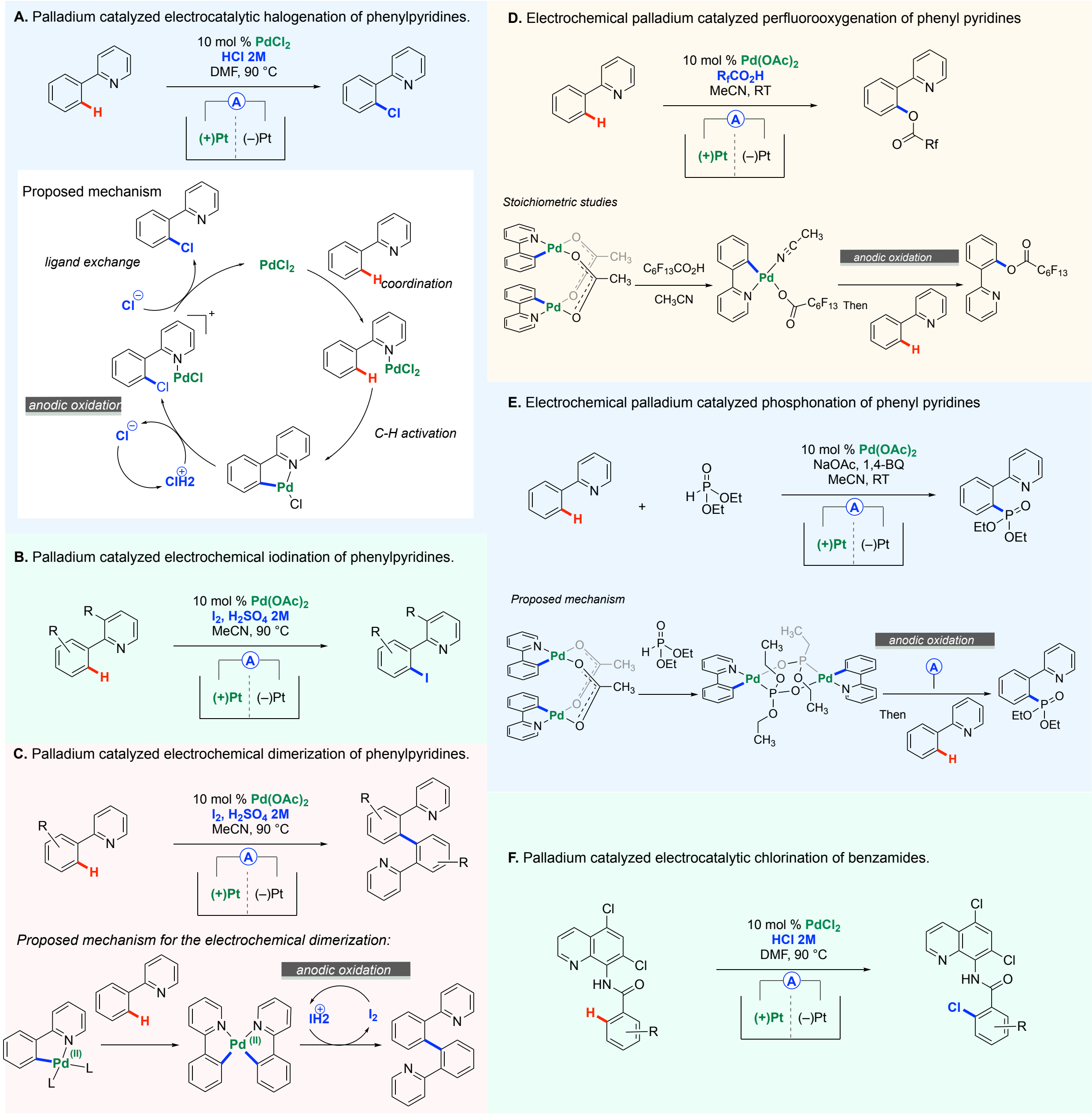
Figure 18. Palladium electrocatalytic Fujiwara-Moritani transformation.

The proposed mechanism is outlined in Figure 18. Initial coordination of $Pd(OAc)_2$ with substrate followed by a based-assisted C-H activation process[158] renders the palladacycle intermediate. This dimeric complex undergoes a carbopalladation process with alkene leading to the formation of the appropriate intermediate that can undergo β-elimination to give the functionalized product and [Pd^0]. Oxidation of the [Pd^0] intermediate is mediated by 1,4-benzoquinone resulting in hydroquinone and the catalytically active Pd (II), which continues with the C-H functionalization cycle. Hydroquinone undergoes an oxidation process at the carbon anode recovering 1,4-benzoquione, while reduction of protons to produce molecular hydrogen takes place at the nickel cathode.

In 2009, Kakiuchi reported an electrocatalytic halogenation process of phenyl pyridine substrates (Figure 19A).[159] This transformation is normally performed using chemical oxidant reagents that are normally in excess and also produce toxic by-products after the reaction is completed, making the purification step rather cumbersome.[160-168] In this example, however, the authors developed an environmentally friendly and selective electrochemical reaction in which the substrate is subjected to constant current electrolysis conditions to produce the halogenating agent required to yield the product in excellent efficiencies. The proposed mechanism of this transformation is illustrated in Figure 19A. Coordination of pyridine substrate to $PdCl_2$ gives an intermediate that undergoes a proximity-driven C-H activation process to form the palladacycle. Reaction of the cyclopalladated intermediate with the anodically generated halonium ion results in the formation of C-X bond at the ortho position. Ligand exchange at the produced cationic intermediate delivers the final halogenated product. Given the importance of iodoarenes in cross-coupling reactions,[169-172] the same research team developed an electrocatalytic palladium halogenation procedure to produce iodo-containing arenes using elemental iodine as iodonium precursor (Figure 19B).[173] This transformation proved to be efficient rendering the iodine-containing products in good yields.

During the development of the electrochemical iodination procedure, the authors were able to isolate a by-product that corresponded to the dimer of the phenyl pyridine substrates.[173,174] The formation of this dimeric species can be rationalized as depicted in Figure 19C. Coordination of phenyl pyridine substrates to $Pd(OAc)_2$ gives a complex intermediate after a C-H activation process. Then, the intermediate undergoes a second C-H activation event with a free phenyl pyridine substrate to afford the bis-(phenylpyridine) palladium complex. Exposure of this intermediate to the anodically generated iodonium species renders the dimer.[175-179] Kakiuchi and coworkers explored further these results seeking to develop efficient catalytic conditions for a C-

C bond-forming reaction while suppressing the iodination pathway.[174] Thus, the authors observed that increasing the concentration of the phenyl pyridine substrate would lead to high amounts of the palladium complex, which is key to favor the dimerization route. Catalytic conditions were developed to afford dimeric products bearing different functional groups in moderate yields. This transformation showed high levels of regioselectivity, which is remarkable since traditional arene homocoupling reactions sometimes give a mixture of products.[169,180-184] Additionally, the Sanford group previously investigated palladium-catalyzed oxidative coupling of arenes using oxone as an oxidant.[185]


A. Palladium catalyzed electrocatalytic halogenation of phenylpyridines.

B. Palladium catalyzed electrochemical iodination of phenylpyridines.

C. Palladium catalyzed electrochemical dimerization of phenylpyridines.

D. Electrochemical palladium catalyzed perfluorooxygenation of phenyl pyridines

E. Electrochemical palladium catalyzed phosphonation of phenyl pyridines

F. Palladium catalyzed electrocatalytic chlorination of benzamides.

Figure 19. Palladium electrocatalytic C-H functionalization of phenyl pyridines and benzamides.

Direct C-H oxygenation transformations[186,187] are also important targets for electrocatalytically-driven transition metal C-H functionalization. Budnikova and coworkers were able to achieve a palladium-catalyzed electrochemical perfluorocarboxylation reaction[188] on phenyl pyridine substrates, giving the desired products (Figure 19D).[189] The electrocatalytic procedure works efficiently for long-chain perfluoro carboxylic acids. Increasing the current resulted in the formation of perfluoroalkylation compound, which is an interesting observation, albeit in low yield. Only traces of trifluoroacetylation product was observed. The same group led by Budnikova reported a catalytic phosphonation reaction by means of electrochemistry coupled with palladium catalysis (Figure 19E).[190-192] The resulting phosphonate-containing pyridines are particularly relevant for their bidentate ability to coordinate metals and potentially used in ligand development.[193-198] Electrolysis of a mixture of phenyl pyridines, phosphonate, and in the presence of catalytic amounts of $Pd(OAc)_2$ renders product in an excellent yield. This reaction is thought to occur via the acetate-bridged palladium complex that breaks in the presence of the phosphonate to form the binuclear phosphonate palladium (II) complex. Electrooxidation of the Pd(II) complex generates a putative Pd(IV) intermediate in the solution that renders the desired product after reductive elimination.

The ability of bidentate coordination to direct C-H activation reactions has been broadly explored in transition metal catalysis.[199-202] In particular, the 8-aminoquinoline directing group (8-AQ) has facilitated a range of palladium-catalyzed C-H functionalization processes.[203-211] Kakiuchi and coworkers engineered an 8-AQ derivative to efficiently guide a selective ortho chlorination reaction (Figure 19F).[212] Substrates bearing different functional groups were tolerated in good efficiencies. An important achievement that demonstrates the practicality of this electrochemical methodology was mirrored by the synthesis of vismodegib, an FDA-approved drug for the treatment of cell carcinoma.[213,214]

While the majority of the Pd-catalyzed electrochemical approaches have been focused on $C(sp^2)$-H transformations, efforts activating $C(sp^3)$-H bonds remain elusive.[215-217] In 2017, electrochemistry appeared in this field in an elegant piece of work led by Mei and co-workers.[218] The authors developed a palladium-based electrocatalytic C-H acetoxylation strategy that allowed aliphatic oxime substrates to give the desired products (Figure 20A). The same group published two electrochemical palladium-catalyzed C-H functionalization reactions by means of methylation and benzoylation of oxime substrates (Figure 20B).[219] Starting from aryl oximes, optimized electrochemical conditions using CH_3BF_3K and catalytic amounts of $Pd(OAc)_2$, ortho methylated products can be obtained. Mechanistically, this reaction is believed to begin with the interaction between $Pd(OAc)_2$ and the substrate to form a complex that undergoes a C-H activation process to give a palladacycle intermediate. Important to note that intermediate was isolated and its structure confirmed by X-ray crystallography. This provided mechanistic evidence on the relevance of high-valent Pd in the C-H functionalization reaction. High valent palladium species $ArPd(III)CH_3$ or $ArPd(IV)CH_3$ are generated under anodic conditions by either a transmetallation process of CH_3BF_3K or the attack of a radical generated from the same reagent to the palladacycle. Desired methylated products are obtained via a reductive elimination process. Moreover, oxime substrates can also undergo a benzoylation reaction using 2-oxo-2-phenylacetic acid as a reaction partner under palladium catalyzed electrochemical conditions. Different benzoylation products can be synthesized in moderate to good yields.

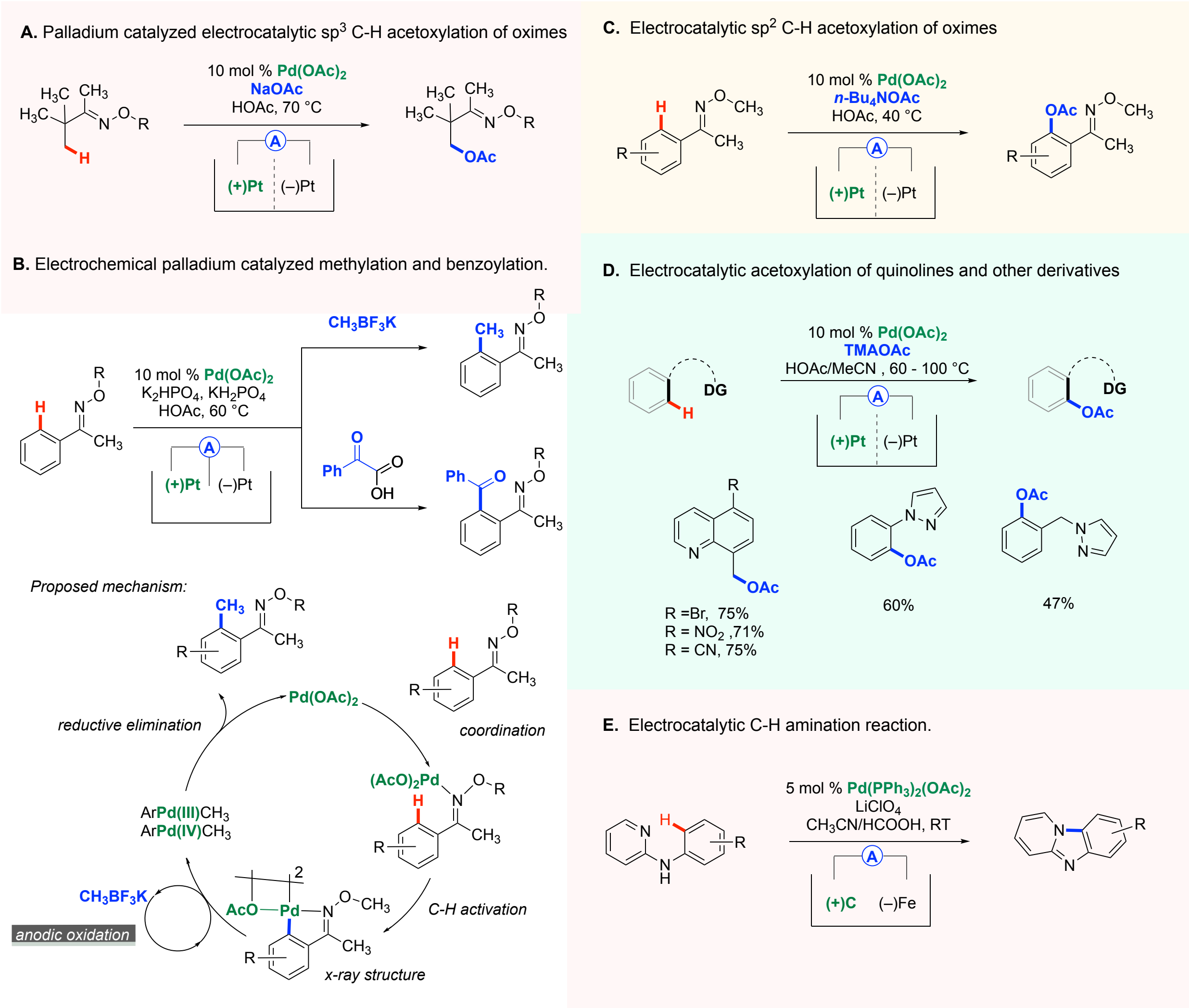


Figure 20. Palladium electrocatalytic C-H functionalization of oximes, quinolines, and other directing groups.

Mei and coworkers also expanded their electrocatalytic acetoxylation strategy to ketoximes,[220] (Figure 20C). Subjection of the ketoxime to palladium-catalyzed electrocatalytic conditions rendered the desired acetoxylated scaffolds. The Sanford group also reported an acetoxylation strategy enabled by palladium catalysis merged with electrochemical oxidation (Figure 20D).[221] Different quinoline substrates and derivatives were subjected to electrocatalytic conditions to produce acetoxylated molecules in high yields. Pyridine and pyrazole analogs were also efficient substrates under the optimized electrocatalytic conditions.

Pyrido[1,2-a]benzimidazole are important motifs present in biologically relevant molecules, including: antimalarial,[222] anticancer[223] and antiviral agents.[224] Several efforts have been published describing methods to access to this privileged class of heterocycles. These approaches rely on an oxidative annulation process, using Cu salts, I_2 or hypervalent iodine reagents.[225-228] Recently, Lei reported an electrocatalytic approach for the synthesis of pyrido[1,2-a]benzimidazole,[229] (Figure 20E). The authors developed electrochemical conditions to transform pyridine-2-amines into the desired scaffolds. Substituents including methyl, methoxy, and halogens were compatible with the optimized electrochemical conditions and gave the heterocycle products in good efficiencies.

Despite the efforts on electrocatalytic palladium C-H activation reactions, examples displaying high levels of enantioselectivity have been poorly explored. In fact, to date, there is only one report by the Ackermann group in which they show an enantioselective electrocatalytic palladium C-H activation reaction (Figure 21).[230] This transformation was achieved with the aid of a transient directing group, a strategy widely used in the C-H functionalization field.

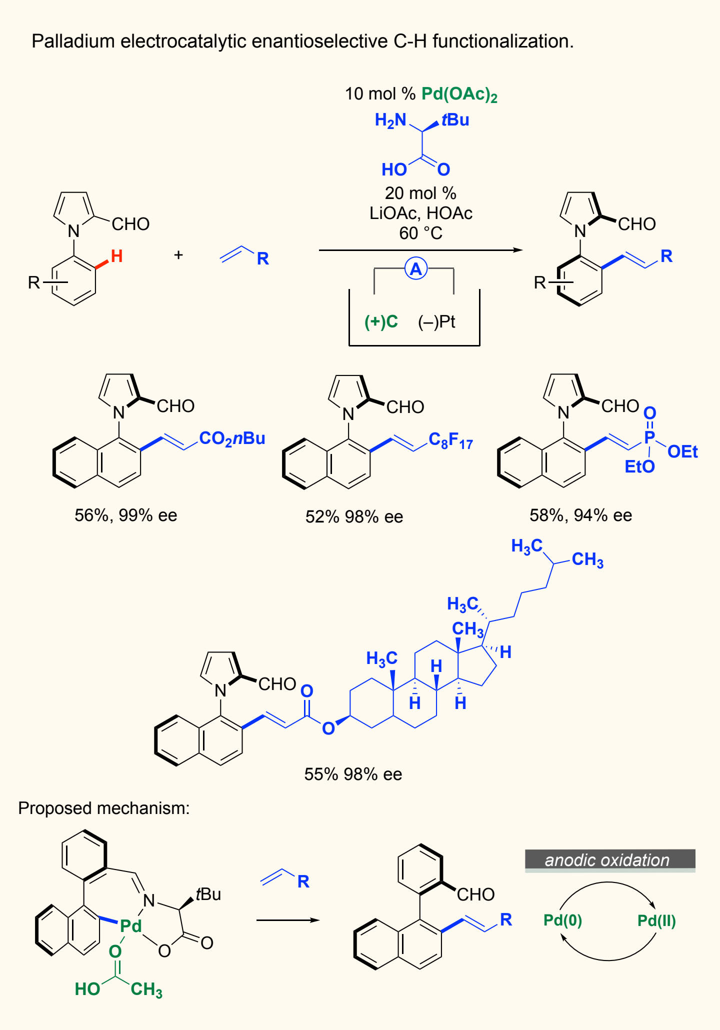


Figure 21. Enantioselective electrocatalytic palladium C-H functionalization by a transient directing group.

Axially chiral biaryls moieties are privileged scaffolds since they have been successfully used as ligands[231-233] in catalysis and are present in biologically privileged natural products.[234,235] A number of efforts have reported atroposelective synthesis of axially chiral biaryls.[236-241] The group led by Ackermann unraveled the first electrocatalytic enantioselective synthesis of axially chiral biaryls using a transient group strategy. As shown in Figure 21, starting materials are subjected to electrochemical conditions in the presence of electron-withdrawing alkenes using L-*tert*-leucine as a transient directing group and catalytic $Pd(OAc)_2$ to render the olefinated product. Different substituents on the arene moiety are compatible with the electrochemical conditions affording the desired products in good yields and excellent enantioselectivities. Acrylates, perfluoroalkenes, vinyl phosphantes, vinyl sulfone, and even a cholesterol derivative worked well under optimized conditions, showing the versatility and robustness of this methodology. This reaction proceeds via the formation of the palladacycle that, in the presence of an electron-withdrawing alkene, undergoes coordination and insertion followed by a reductive elimination event to give the final product. The resulting Pd(0) is oxidized in the anode, restoring the catalytically active Pd(II).

The field of electrocatalytic C–H functionalization using Pd catalyst has proven to be effective in electrochemically generating active Pd species necessary for C–H˙ activation step. Moreover, the field has advanced to functionalize sp^2 and sp^3 C–H bonds and generate carbon-carbon and carbon-heteroatom bonds. Their application towards asymmetric synthesis of biaryls was also demonstrated. With the rich chemistry being developed in Pd C–H functionalization, we expect this area to soon expand in selective non-directed C–H activation strategies.

4.2 Electrocatalytic rhodium C-H functionalization reactions

Rhodium (III) catalysis has proven to be contributory in the development of C-H functionalization processes,[242,243] with an emphasis on oxidative C-H reactions. While unassailable progress has been made,[244-249] rhodium (III) catalyzed oxidative C-H transformations require stoichiometric amounts of harmful and/or costly copper (II) or silver (I) salts. The integration of electrochemistry in this area is expected to not only provide selective formation of active Rh catalysts toward C–H activation but also in eliminating the necessity of using stoichiometric metal salts as oxidants or reductants.

The group led by Ackermann has reported a seminal work in which rhodium (III) catalyzes a cross-dehydrogenative alkenylation of arenes using carboxylic acid as weak coordinating directing group and electricity as sole oxidant,[250] (Figure 22A). The versatility of this transformation is given by the number of substrates that produced the desired products in synthetically useful yields. The proposed working mechanism of this electrochemical rhodium-catalyzed alkenylation reaction is shown in Figure 22. The catalytically active rhodium complex **22-I**, which is formed in the reaction mixture, undergoes coordination followed by a C-H activation step with the substrate rendering the rhodacycle **22-II**. Coordination of alkene followed by migratory insertion process provides the seven-membered ring species **22-III**. The rhodium complex **22-III** undergoes a β-hydride elimination followed by a reductive elimination and anodic oxidation gives the final product and the catalytically active rhodium species **22-I**.

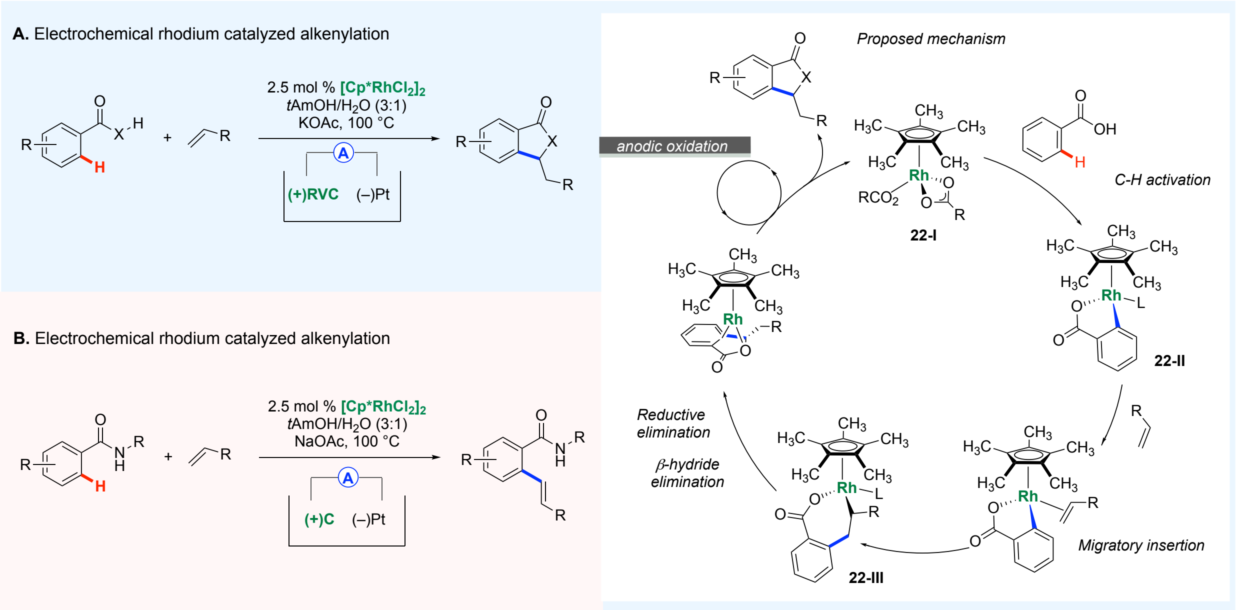


Figure 22. Electrocatalytic rhodium cross-dehydrogenative alkenylation and alkenylation reaction.

Selective C-H alkenylation of arene cores, enabled by chelation assistance, is a powerful strategy to form C-C bonds.[158,251,252] Despite the significant efforts on merging electrochemistry with transition metal C-H functionalization during recent years, there is only one example of a metal-catalyzed C-H olefination reaction propelled by electricity. This example, reported by Jutand and Amatore in 2007, shows few examples of a catalytic Fujiwara-Moritani type reaction, using a palladium-benzoquinone system.[157] Given the importance of developing electrooxidative C-H olefination reactions, the Ackermann group has recently unraveled a novel rhodium-catalyzed C-H alkenylation transformation using electricity as oxidant (Figure 22B).[253] Different styrene substrates displaying a range of substituents were compatible with the electrooxidative rhodium C-H alkenylation reaction.

Performing electrosynthesis in a flow[254,255] fashion renders a number of benefits, including improvements on electrode surface area/volume ratio as well as mass and heat transfer. The scaling-up process is also facilitated and the electrolyte footprint can be reduced.[28,30] Despite all these advantages, the use of flow systems in electrochemical-assisted metal C-H functionalization has been scarcely studied. A recent report released by the Ackermann group shows the implementation of a flow system for the development of an electro-catalyzed alkyne annulation via a rhodium C-H functionalization (Figure 23A).[256] Electrochemical conditions were optimized to enable the intermolecular annulation of imidate substrates and unsymmetrical alkynes affording the corresponding isoquinoline products. Different substituents were tolerated, including methoxy, bromo and thiophene groups yielding the final products in good yields. Moreover, an intramolecular version was also implemented, as depicted in Figure 23B. Starting from the appropriate substrate containing the reacting alkyne and imidate functionalities, a range of azo-tetracycles were also synthetized. Mechanistically, this reaction is believed to proceed via a chelation-assisted C-H activation between the catalytically active rhodium complex **23-I** and the substrate to afford the rhodacycle **23-II**. Coordination of the alkyne to the **23-II** complex gives rise to the intermediate **23-III**. Anodic oxidation and a subsequent migratory insertion event produce the high valent rhodium (IV) species **23-IV**. Reductive elimination followed by anodic oxidation provides the desired product and regeneration of the active catalyst.

Polycyclic aromatic hydrocarbons (PAHs) are a class of molecules with a wide range of applications, including: catalysis, optoelectronics, and bioimaging.[257-261] The physicochemical behavior of PAHs can be tuned by manipulating variables such as edge topology, shape, and π-extension. Thus, the development of a synthetic tool to ensemble PAHs at atom-level precision has gained attention in the chemistry community. Chemical methods to access PAHs, have relied on cross-couplings, Diels-Alder cycloadditions, and cyclotrimerization strategies.[262-265] Metal catalyzed C-H functionalization approaches, which heavily rely on stoichiometric amounts of oxidants, have also been developed for the synthesis of these aromatic materials.[266-278] However, the Ackermann group has designed an electrocatalytic platform to access PAHs combining two distinct processes (Figure 23C): (1) unprecedented annulative [2+2+2] cycloaddition via a rhodium electro-catalyzed C-H activation process, using boronic acid as starting materials, and (2) electrocatalytic dehydrogenation reaction, using DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) as redox mediator, to allow the formation of the final PAHs.[149]

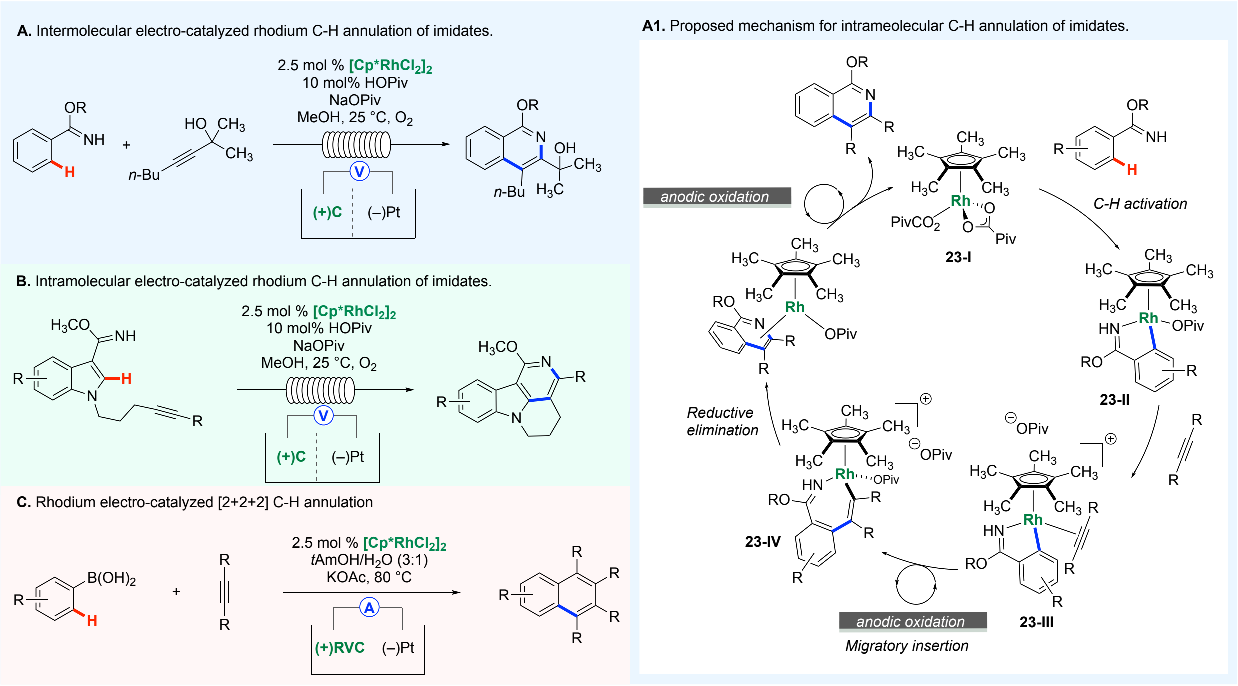


Figure 23. Electrochemical Rh catalyzed C-H annulations.

The optimized rhodium-catalyzed electrochemical conditions enabled the C-H annulation process between boronic acids and alkynes, yielding the desired products in high efficiencies. Different substrates were also tested in the alkyne reaction partner giving the annulated product in reasonable yields. The role of electrochemistry in this reaction is thought to restore the catalytically active rhodium (III) species by anodic oxidation. The incorporation of heteroatoms into PAHs scaffolds can considerably alter the physicochemical properties of these relevant materials.[279-284] Thus, aza-PAHs are important targets for the synthetic community and existing strategies to access these scaffolds remain difficult, relying on laborious multi-step procedures.[262-264,285,286] Recently, however, the same group has developed a rhoda-electrocatalyzed alkyne annulation protocol to access aza-PAHs.[287]

Organophosphorus compounds play a central role in catalysis, material science and chemical biology.[288-293] The use of metal-catalyzed approaches to synthesize these types of compounds can be difficult due to the intrinsic coordinating ability of phosphorous reacting partners, potentially leading to catalyst poison.[294-296] However, the Xu group has developed an electrochemical rhodium-catalyzed platform to access aryl phosphine oxides (Figure 24).[297] Different phosphine structures displaying a range of electronically as well as sterically different substituents were evaluated, resulting in the desired products in high efficiencies. The proposed mechanism involves rhodium (III) complex to undergo an ortho C-H activation event with the substrate producing a rhodacycle intermediate. Ligand exchange with phosphine oxide gives rise to an intermediate that goes through anodic oxidation to form high valent rhodium species. This facilitates the reductive elimination process, releasing the final product as well as the catalytically relevant rhodium (III) complex.

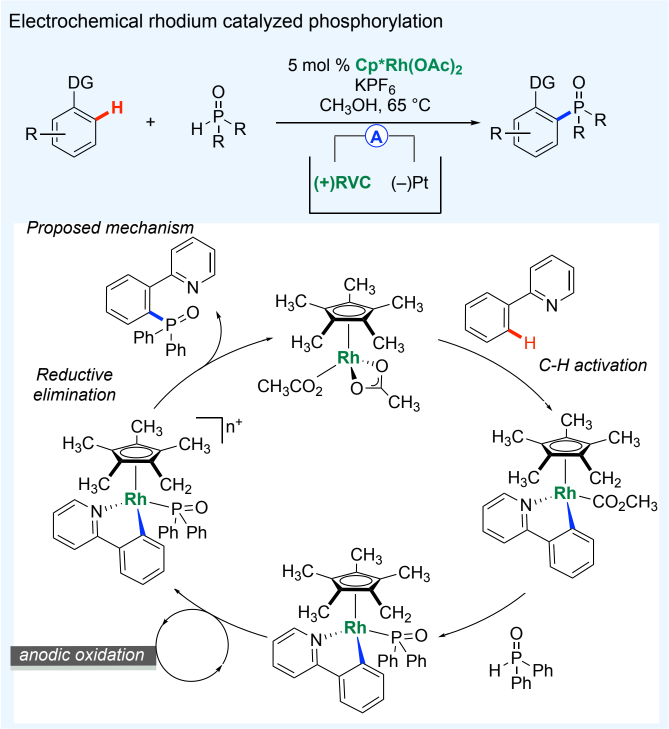


Figure 24. Electrocatalytic rhodium C-H phosphorylation.

The past decade has shown the effective utility of electrochemistry in Rh-catalyzed directed C–H functionalization to generate carbon-carbon and carbon-heteroatom bonds. More importantly, they have been found useful in annulation reactions involving arene C–H bonds with saturated systems. These reactions provide useful nitrogen and oxygen-containing heterocycles as products and we expect their utility in to provide a general construction of heterocycles as well as bicyclic compounds.

4.3 Electrocatalytic ruthenium C–H functionalization processes

Ruthenium catalysis has proven to be instrumental in the development of a myriad of chemoselective C–H activation processes.[298-312] Initial efforts merging electrochemistry with ruthenium-catalyzed C–H activation processes have been reported by Xu and coworkers. In this case, the authors showed an electrochemical annulation process driven by ruthenium catalysis (Figure 25A).[313] Subjecting aniline and alkyne substrates under electrochemical ruthenium-catalyzed conditions delivered indole scaffolds. While this reaction has been previously reported using chemical oxidants,[314] the work developed by Xu has proven to be efficient with a broad scope using electricity as sole oxidant. Different aniline substrates bearing electron-donating and withdrawing substituents were tolerated in high yields. The authors believe this reaction proceeds via an initial C-H activation process promoted via the *in situ* generated Ru(II) catalyst and substrate to give a ruthenacycle. Coordination to alkyne substrate and migratory insertion event delivers the desired product and Ru (0), after reductive elimination. Anodic oxidation recovers the catalytically active Ru (II) intermediate.

Almost simultaneously, the Ackermann group released an electrochemical annulation process driven by ruthenium catalysis to produce isocoumarins, as shown in Figure 25B.[315] Benzoic acids and alkynes were subjected to electrochemical conditions and catalytic amounts of ruthenium salts, delivering the desired heterocycles products.

The group led by He also reported the use of electrochemical conditions to promote a [4 + 2] annulation process between arylglyoxylic acids and alkynes producing substituted isocoumarines (Figure 25C).[316] Symmetrical alkynes bearing fluoroarene groups as well as unsymmetrical substrates containing a cyclopropyl moiety were well tolerated. Isocoumarines substituted with the biologically relevant estrone unit were also synthesized by this methodology. The same research team also reported an electrocatalytic annulation process between benzylic alcohols and alkynes to produce isocoumarine products.[317]

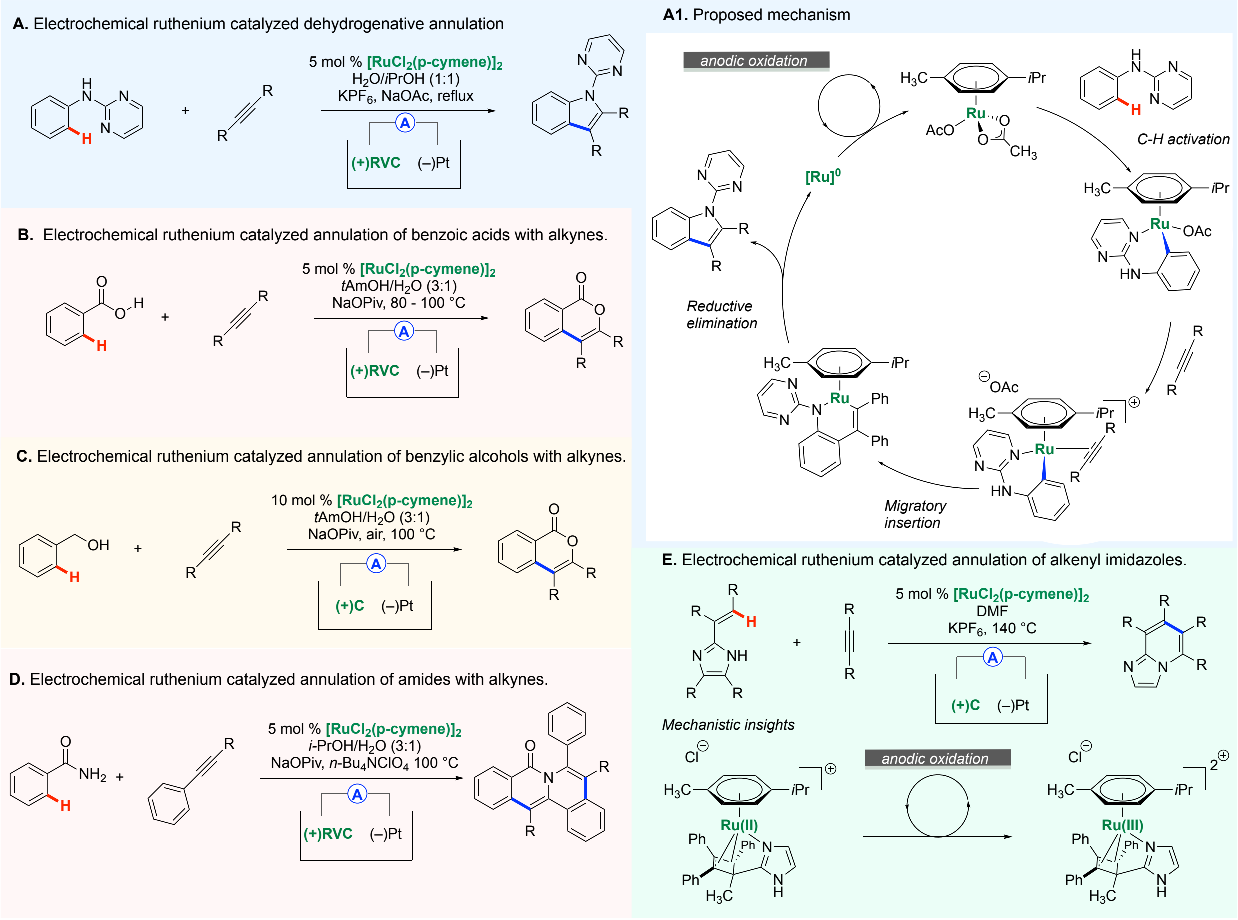


Figure 25. Electrochemical ruthenium catalyzed annulation arene C-H annulation with alkynes.

The Ackermann group disclosed another electrocatalytic annulation process involving alkynes, but in this case, with aryl carbamates as reaction partners to afford pyridine derivatives (Figure 25E).[318] Different symmetrical alkynes substrates containing arene and alkyl substituents worked well under the electrochemical conditions. A range of functionalities installed on the aryl carbamate reaction partner was also explored, producing the desired pyridine derivatives in high yields. This transformation also proceeds with the *in situ* formation of the catalytically active Ru(II) complex.

Electrocatalytic ruthenium annulation strategies to produce isoquinoline derivatives from amides and alkynes have also been reported.[319] Ackermann also reported that alkenyl imidazoles are also effective to undergo an electrocatalytic annulation process with alkynes to produce N-fused bicyclic heteroarenes.[320]

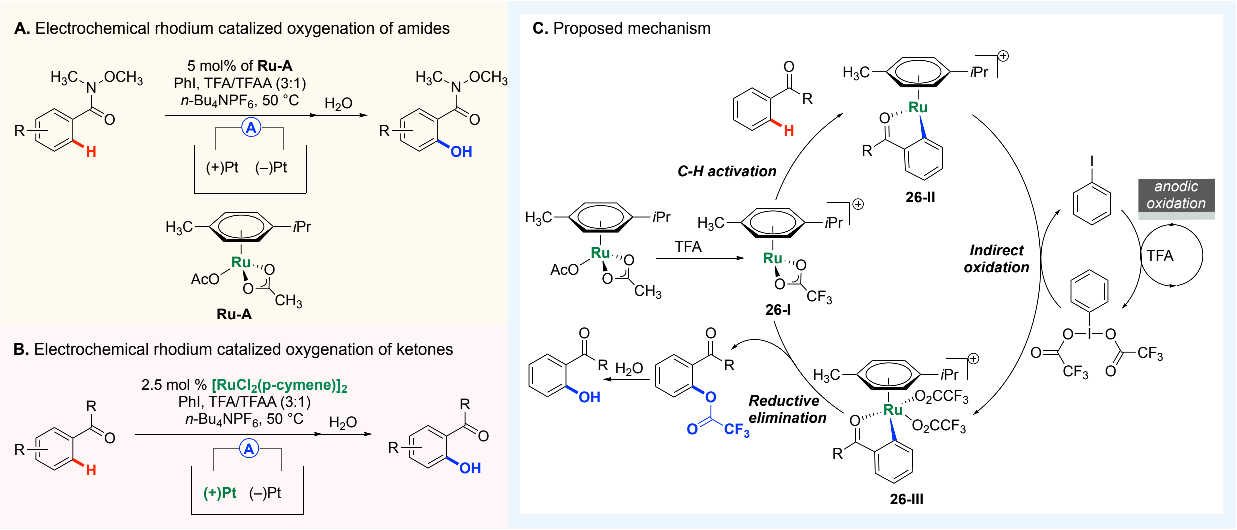


Figure 26. Electrochemical ruthenium catalyzed arene C–H oxidation aryl amides and ketones.

A novel electrocatalyzed oxygenation transformation enabled by weak coordination has recently been reported by Ackermann and coworkers (Figure 26A, 26B).[321] Catalytic amounts of iodoarenes together with catalytic amounts of ruthenium (II) complexes facilitate this reaction to occur broadly and efficiently. Different amides were subjected to this dual electrocatalytic setup and rendered synthetically useful hydroxylated Weinreb analogs in high yields and selectivity. Ketones were also successful substrates for this transformation, not only tolerating variations on the carbonyl group, but also on the arene scaffold. The working mechanism of this reaction is depicted in Figure 26C. Ligand exchange of complex **Ru-A** with TFA generates the highly electrophilic ruthenium intermediate **26-I**, which undergoes a C–H activation process with carbonyl substrates, producing a ruthenacycle intermediate **26-II**. This intermediate is then oxidized by a hypervalent iodine reagent, giving rise to the Ru(IV) complex **26-III**. Reductive elimination of this intermediate releases the product that readily hydrolyses to give the final phenolic product.

4.4 Electrocatalytic Cobalt C–H functionalizations

While outstanding developments in the field of C–H activation have been achieved by precious 4d and 5d transition metals, cost-effective earth-abundant base metals represent a more sustainable alternative to the field.[121,130,131,199,200,322-335] Recently, efforts showing the efficacy of electrochemical protocols to achieve C–H activation processes using cobalt catalysis is a growing area. In 2017, the Ackermann group reported the first electrocatalytic cobalt C–H activation process (Figure 27A).[336] After screening different directing groups, the authors found pyridine N-oxides to be the most efficient scaffolds for the C–H activation process of benzamide substrates in the presence of alcohols. Electrocatalytic cobalt conditions delivered the desired oxygenated products in good efficiencies. The same group explored this reactivity further by developing a C–H/N–H activation process using the same class of substrates.[337] Subjection of benzamides in the presence of alkynes under cobalt catalyzed electrochemical conditions delivered the final annulated products (Figure 27B). The Lei group also explored this chemistry by developing [4 + 2] annulation reactions using the *N*-(quinoline-8-yl)benzamides and ethylene or ethyne (Figure 27B).[118]

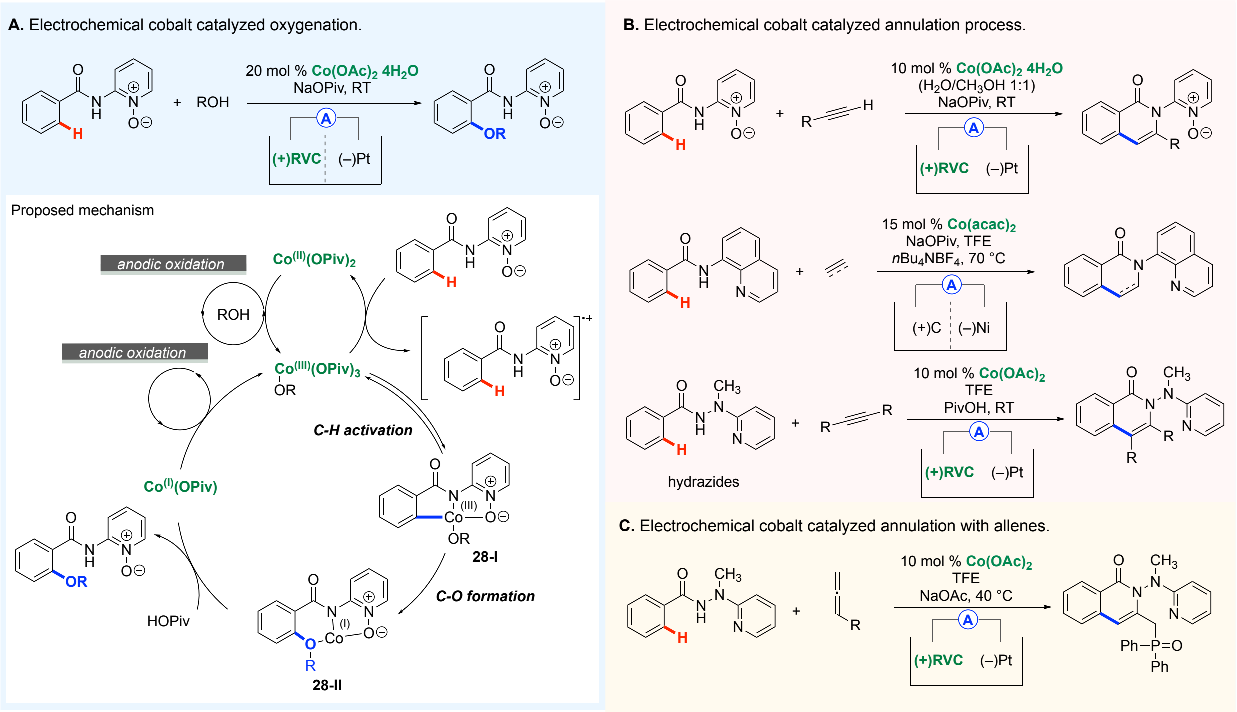


Figure 27. Electrochemical cobalt catalyzed arene C–H oxygenation and annulation.

Ackermann developed an electrocatalytic cobalt C–H activation process on aromatic C–H bonds using hydrazides as directing groups (Figure 27B).[338] Hydrazides react with alkynes under electrocatalytic cobalt conditions to give the annulated products**.** Symmetrical and unsymmetrical alkynes were tolerated in this transformation affording the desired products in decent efficiencies. Substituents on the aromatic core were also investigated, producing the annulated outcomes in good yields. The same reactivity was explored with other reaction partners, including diynes and allenes, giving products in excellent yields (Figure 27C).

Amination reactions can also be achieved by this reactivity mode.[339] Figure 28A shows the electrochemical conditions by which benzamides react with free amines to form aniline derivatives. A range of piperidines proved to be efficient substrates for this transformation, and scope studies on the benzamide core also revealed a good set of working substrates. Lei explored further this electrosynthetic methodology and developed conditions for an amination process based on benzamide substrates.[340] Different arene and heteroarenes were tolerated in the benzamide core. Carbonylation reactions can also be achieved on benzamides by electrochemical cobalt catalysis (Figure 28B).[341] Intramolecular carbonylation products were obtained in excellent yields on different substrates. Moreover, intermolecular carbonylation in the presence of an external amine was also possible.

Ackermann and coworkers have also implemented a C-H allylation method using benzamides and unactivated alkenes as reaction partners (Figure 28C).[342] Substitutions on the benzamide core were compatible with the electrochemical conditions delivering the desired products in good efficiencies. Also, different chemicals anchored to the alkenes were tolerated. The mechanism of the reaction is depicted in Figure 28D. Selective C–H activation after substrate coordination and an anodic oxidation process affords the Co(III) metallacycle **28-I**. This reacts with the incoming alkene to render the seven-membered ring intermediate **28-II**. Beta-hydride elimination generates the desired product and Co(I) species, which undergoes an anodic oxidation to regenerate the active catalyst.

The use of non-precious metals for C–H functionalization reactions has been an active research area in this field. The integration of electrochemistry to access reactive intermediates such as low and high valent cobalt species will help advance this field. We expect the development of various electrocatalytic cobalt C–H functionalization reactions using various directing groups and coupling partners.

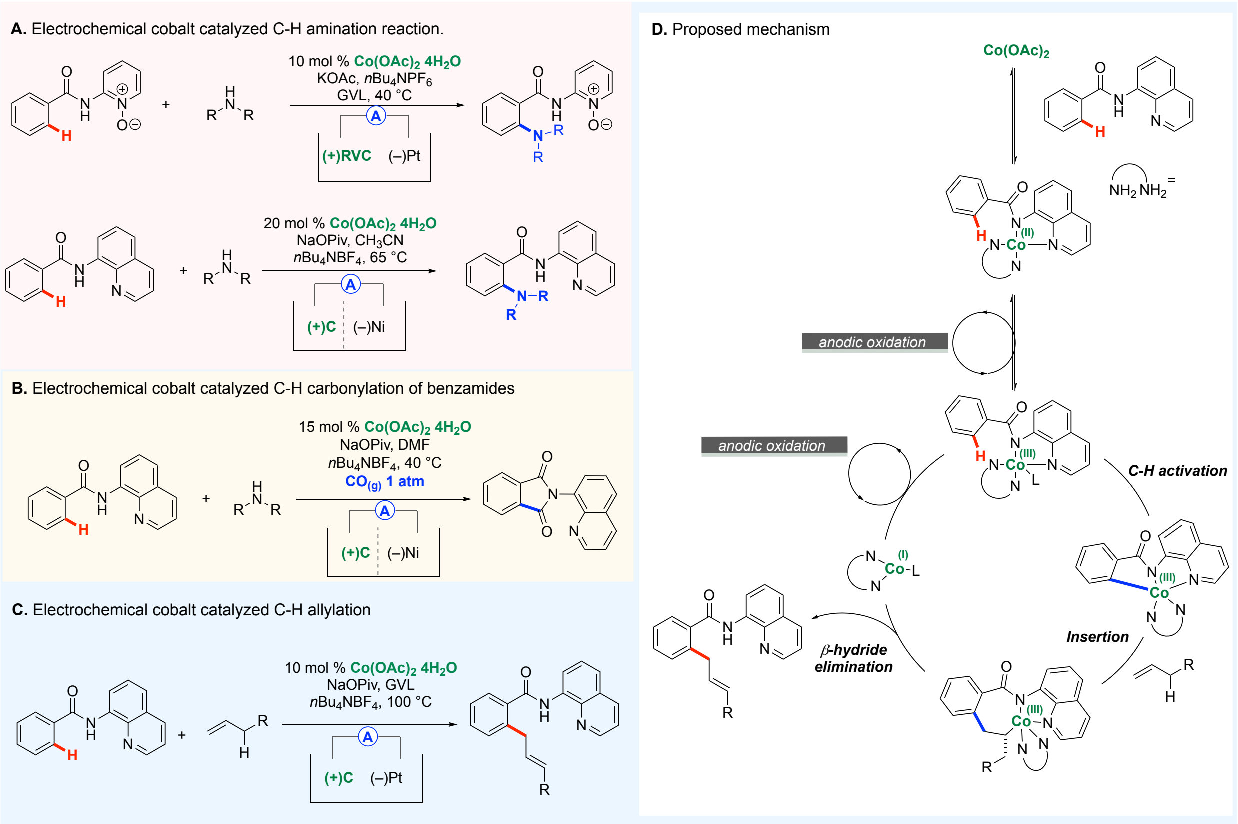


Figure 28. Electrochemical cobalt catalyzed arene C-H functionalization.

5. ELECTROCATALYTIC OXIDATION OF ALCOHOLS

The electrochemical oxidation of alcohols is one of the key fundamental chemical transformations, and often requires complexes of noble-metal catalysts.[343-347] Accordingly, the past decade has seen considerable efforts in developing electrocatalytic alcohol oxidations employing non-precious metals as catalysts. Attempts in this regard include the application of homogeneous nickel diphosphine complexes[348,349] and organic *N*-oxyls.[350] For example, Weiss et al. reported that the incorporation of pendant amines to the phosphine ligand could facilitate the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones. While this method is effective, the reactivity was poor, especially towards methanol and ethanol.[348] In contrast, organic nitroxyls often exhibit good reactivity with a turnover rate of 1-2 s^{-1}. Particularly, TEMPO (2,2,6,6-tetramethyl-1-piperidine *N*-oxyl) has been extensively studied for electrocatalytic alcohol oxidation.[350,351] Typically, TEMPO is electrochemically oxidized to generate the oxidant oxoammonium species ($TEMPO^+$), followed by the formation of $TEMPO^+$/alkoxide adduct, which yields aldehyde or ketone products *via* intramolecular hydrogen transfer (Figure 28A). This electrochemical generation of $TEMPO^+$ by one-electron oxidation of TEMPO is simple and clean as compared to chemical oxidation. Nevertheless, the high electrode potentials required for the $TEMPO/TEMPO^+$ are not desirable for energy transformations.

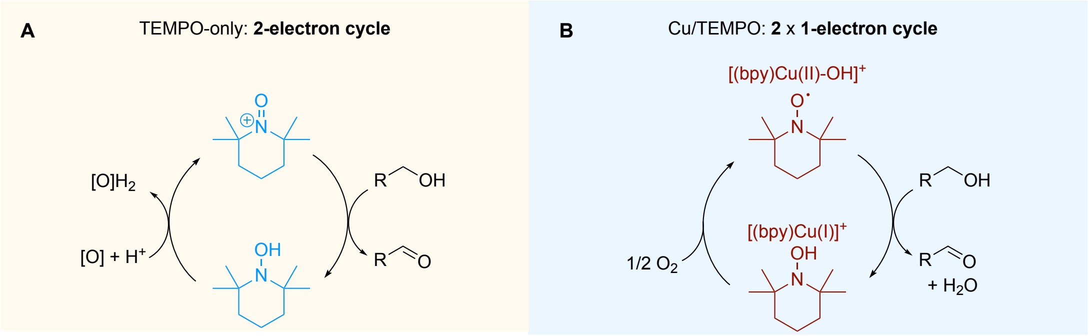


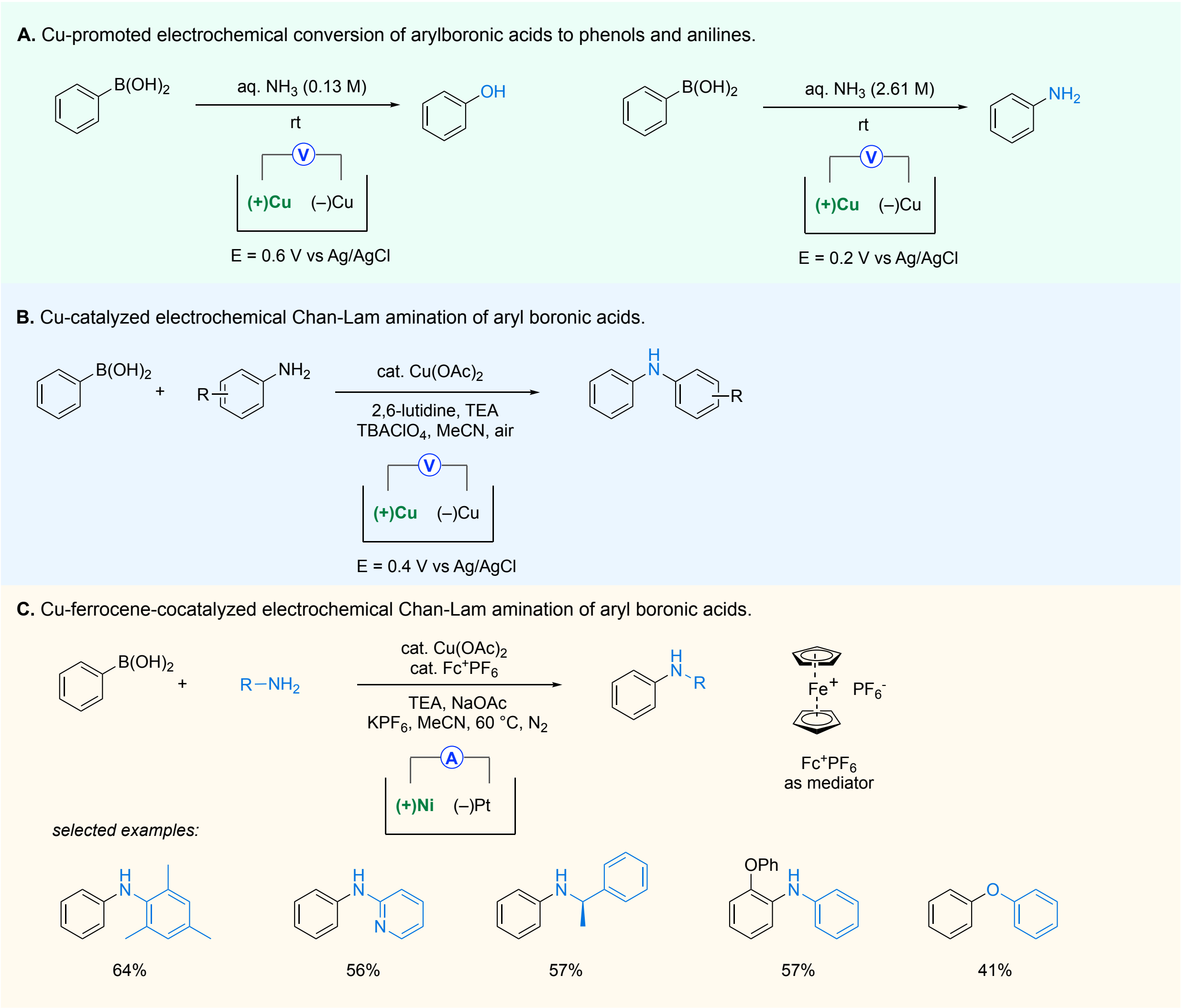
Figure 29. Copper/TEMPO electrocatalyzed oxidation of alcohols.

To resolve this dilemma, Stahl reported a (bpy)Cu/TEMPO co-catalyst system (where bpy is 2,2′-bipyridine) for electrochemical alcohol oxidation.[352] Using this system, the reaction rate for benzyl alcohol as substrate (k_{obs}) was improved to 11.6 s^{-1}, while the TEMPO-only system only showed a rate of 2.3 s^{-1}. Additionally, this fast turnover rate was achieved at an applied potential of - 0.14 V – a half-volt lower than what used in the TEMPO-only regime (0.36 V). To gain more insights into the Cu/TEMPO system, kinetic isotope effects and Hammett studies were performed. Very interestingly, the Hammett plot showed the opposite electronic trends in comparison to the TEMPO-only process: electron-deficient alcohols are instead oxidized more easily than electron-rich alcohols. These differences indicated that the rate-limiting step for the Cu/TEMPO system is the Cu(II)/alkoxide formation, while in the TEMPO-only system, it is the hydrogen transfer from the alcohol to $TEMPO^+$ within the $TEMPO^+$/alkoxide adduct. As a result, the Cu/TEMPO system affords a unique catalytic path: Cu(II) acts as a one-electron oxidant, while TEMPO only serves as an electron-proton acceptor (Figure 29). This observation is non-trivial as it implies the synergy effect of cooperating electron-proton-transfer mediators with transition metals to increase the reactivity for proton-coupled two-electron reactions. As two-electron redox reactions are widely present, developing cooperative electrocatalysts are poised to play a critical role in energy conversions.

6. ELECTROCATALYTIC TRANSFORMATIONS OF ORGANOBORON REAGENTS

Organoboron reagents are highly attractive starting materials in organic synthesis due to their abundance, stability, and ease of preparation. Electrochemical methods for their coupling with organohalides via Suzuki-type reactions have been reported (see Section 2.7).[112] The direct functionalization of organoboron reagents to generate phenols, anilines, and other functional groups has been realized more recently. Huang reported an electrochemical conversion of aryl boronic acids to anilines and phenols using copper as both the cathode and anode materials using aqueous ammonia under undivided cell electrolysis (Figure 30A).[353] By simply changing the concentration of aqueous ammonia and the anode potential, good yields of phenols and anilines can be obtained chemoselectively with high reaction rates. It is believed that the reaction is mediated by copper species generated during the electrolysis. Recently, Gale-Day and coworkers reported an electrocatalytic coupling of arylboronic acids with anilines using a copper catalyst and a dual copper electrode system (Figure 30B).[354] In their work, they enabled the coupling of anilines that are found challenging under the conditions previously reported by Huang. The coupling reaction was enabled by the use of base additives such as 2,6-lutidine and triethyl amine under constant potential electrolysis and aerobic conditions to give desired aniline products in good to high yields.

Despite the success of electrochemical amination of boronic acids, electrooxidative reactions with ligandless copper catalysts are known to be plagued by slow electron-transfer kinetics, irreversible copper plating, and competitive substrate oxidation. Sevov reported an electrochemical Chan−Lam coupling of aryl-, heteroaryl-, and alkylamines with arylboronic acids with higher yields and shorter reaction times than conventional reactions in air and provided complementary substrate reactivity (Figure 30C).[355] This was enabled by the implementation of substoichiometric quantities of redox mediators to address limitations to Cu-catalyzed electrosynthesis. Mechanistic studies reveal that mediators serve multiple roles by (i) rapidly oxidizing low-valent Cu intermediates, (ii) stripping Cu metal from the cathode to regenerate the catalyst and reveal the active Pt surface for proton reduction, and (iii) providing anodic overcharge protection to prevent substrate oxidation. Under similar conditions, when phenol was used as the coupling partner, diaryl ether was obtained, albeit in lower yield.



A. Cu-promoted electrochemical conversion of arylboronic acids to phenols and anilines.

B. Cu-catalyzed electrochemical Chan-Lam amination of aryl boronic acids.

C. Cu-ferrocene-cocatalyzed electrochemical Chan-Lam amination of aryl boronic acids.

Figure 30. Electrocatalytic functionalization and cross-coupling of organoboron reagents.

7. CONCLUSIONS AND FUTURE DIRECTIONS

In the past two decades, there have been significant advancements made towards the development of molecular transition metal electrocatalysis for organic synthesis. These advancements were made possible by the increased recognition of electrochemistry as a highly effective benign reagent in electron transfer processes to generate highly reactive intermediates. In addition, the rapidly growing developments in transition metal catalysis and ligand design as potential electrocatalysts to mediate electron transfer and facilitate bond-forming and bond-breaking events led to the development of new, highly efficient, and selective electrochemical transformations. This review demonstrates that electrocatalysis, through the merger of homogenous transition metal catalyst and electrochemistry, has greatly expanded the scope and improved the selectivity and reaction conditions in many important and challenging transformations, including cross-coupling of organohalides to form various carbon-carbon and carbon-heteroatom bonds, functionalization of alkene and alkynes, and C-H functionalizations.

We expect that transition metal electrocatalysis will continue to expand towards reaction discovery and address challenges in organic synthesis, especially in the context of sustainable, selective and efficient transformations. In the coming years, we anticipate several emerging research directions of synthetic organic electrocatalysis, such as:

(a) Development of new chemical spaces especially those that involve challenging bond-breaking and bond-forming reactions to enable the utility of abundant reagents towards organic synthesis.

(b) Enabling abundant and non-toxic transition metals in place of precious and rare transition metals as electrocatalysts for sustainable organic synthesis.

(c) Development of highly selective transformations including stereo and regioselectivity.

(d) Applications towards synthesis and functionalization of complex molecules that will allow electrosynthesis to be part of a medicinal chemist's toolbox through late-stage functionalization and diversification.

(e) Integration of synthetic organic electrochemistry with well-developed and advancing technologies including: flow chemistry for scale-up processes; material science for heterogenous catalysis and electrode design; high-throughput screening for rapid reaction development; and photocatalysis and biocatalysis towards efficiency and sustainability, and the upgrading of chemical feedstock.

(f) Adoption of electrochemical and analytical techniques together with organometallic chemistry, physical organic chemistry, and data science to understand reaction mechanisms and predict reactivity. This will streamline the tedious process of reaction discovery and development, and aid in the discovery of new chemical spaces.

Overall, we anticipate that transition metal electrocatalysis will drive the discovery of new reactivities and help solve key challenges in contemporary organic synthesis. The advancement of transition metal catalysis and ligand design, and the innovative application of fundamental and applied electrochemistry will catalyze future developments in organic synthesis. Moreover, the integration of transition metal electrocatalysis with multidisciplinary fields such as material science, data science, and medicinal chemistry through academic and industry collaborations will provide a strong foundation for the utility and advancement of electrosynthesis in modern synthesis.

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REFERENCES

(1) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic organic electrochemical methods since 2000: on the verge of a renaissance. *Chem. Rev.* **2017,** *117*, 13230-13319.
(2) Moeller, K. D. Using physical organic chemistry to shape the course of electrochemical reactions. *Chem. Rev.* **2018,** *118*, 4817-4833.
(3) Moeller, K. D. *Intramolecular carbon-carbon bond forming reactions at the anode. In: Steckhan E. (eds) Electrochemistry VI electroorganic synthesis: bond formation at anode and cathode*; Springer: Berlin, Heidelberg, 1997, 1-100.
(4) Francke, R.; Little, R. D. Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **2014,** *43*, 2492-2521.
(5) Shono, T. H., H.; Matsumura, Y. Electroorganic chemistry. XX. Anodic oxidation of carbamates. *J. Am. Chem. Soc* **1975,** *97*, 4264-4268.
(6) Shono, T. Electroorganic chemistry in organic synthesis. *Tetrahedron* **1984,** *40*, 811-850.
(7) Hartwig, J. F. *Organotransition metal chemistry*; University Science Books: Sausalito, CA, 2010, pages.

(8) Forero-Cortés, P. A.; Haydl, A. M. The 25th anniversary of the Buchwald–Hartwig amination: development, applications, and outlook. *Org. Process Res. Dev.* **2019,** *23*, 1478-1483.

(9) Ruiz-Castillo, P.; Buchwald, S. L. Applications of palladium-catalyzed C-N cross-coupling reactions. *Chem. Rev.* **2016,** *116*, 12564-12649.

(10) Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.et al. Electrochemically enabled, nickel-catalyzed amination. *Angew Chem Int Ed Engl* **2017,** *56*, 13088-13093.

(11) Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.et al. Electrochemically driven, Ni-catalyzed aryl amination: scope, mechanism, and applications. *J. Am. Chem. Soc.* **2019,** *141*, 6392-6402.

(12) Barman, K.; Edwards, M. A.; Hickey, D. P.; Sandford, C.; Qiu, Y.; Gao, R.; Minteer, S. D.; White, H. S. Electrochemical reduction of $[\mathrm{Ni(Mebpy)_3}]^{2+}$: elucidation of the redox mechanism by cyclic voltammetry and steady-state voltammetry in low ionic strength solutions. *ChemElectroChem* **2020,** *7*, 1473-1479.

(13) N. L. Weinberg, H. R. W. Electrochemical oxidation of organic compounds. *Chem. Rev.* **1968,** *68*, 449-523.

(14) Ogawa, K. A.; Boydston, A. J. Recent developments in organocatalyzed electroorganic chemistry. *Chem. Lett.* **2015,** *44*, 10-16.

(15) Yuan, Y.; Lei, A. Electrochemical oxidative cross-coupling with hydrogen evolution reactions. *Acc. Chem. Res.* **2019,** *52*, 3309-3324.

(16) Feng, R.; Smith, J. A.; Moeller, K. D. Anodic cyclization reactions and the mechanistic strategies that enable optimization. *Acc. Chem. Res.* **2017,** *50*, 2346-2352.

(17) Schäfer, H. J. Carbon-carbon bond formation via electron transfer: anodic coupling. *ChemCatChem* **2014,** *6*, 2792-2795.

(18) Sperry, J. B.; Wright, D. L. The application of cathodic reductions and anodic oxidations in the synthesis of complex molecules. *Chem. Soc. Rev.* **2006,** *35*, 605-621.

(19) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern strategies in electroorganic synthesis. *Chem. Rev.* **2008,** *108*, 2265-2299.

(20) Wang, F.; Stahl, S. S. Electrochemical oxidation of organic molecules at lower overpotential: accessing broader functional group compatibility with electron-proton transfer mediators. *Acc. Chem. Res.* **2020,** *53*, 561-574.

(21) Novaes, L. F. T.; Liu, J.; Shen, Y.; Lu, L.; Meinhardt, J. M.; Lin, S. Electrocatalysis as an enabling technology for organic synthesis. *Chem. Soc. Rev.* **2021**, DOI:10.1039/d1cs00223f 10.1039/d1cs00223f.

(22) Horn, E. J.; Rosen, B. R.; Baran, P. S. Synthetic organic electrochemistry: an enabling and innately sustainable method. *ACS Cent. Sci.* **2016,** *2*, 302-308.

(23) Freguia, S.; Virdis, B.; Harnisch, F.; Keller, J. Bioelectrochemical systems: microbial versus enzymatic catalysis. *Electrochim. Acta* **2012,** *82*, 165-174.

(24) Wu, R.; Ma, C.; Zhu, Z. Enzymatic electrosynthesis as an emerging electrochemical synthesis platform. *Curr. Opin. Electrochem.* **2020,** *19*, 1-7.

(25) Chen, H.; Simoska, O.; Lim, K.; Grattieri, M.; Yuan, M.; Dong, F.; Lee, Y. S.; Beaver, K.; Weliwatte, S.; Gaffney, E. M.et al. Fundamentals, applications, and future directions of bioelectrocatalysis. *Chem. Rev.* **2020,** *120*, 12903-12993.

(26) Hickey, D. P. M., R. D.; Rasmussen, M.; Abdellaoui, S.; Nguyen, K.; Minteer, S. D. *Fundamentals and applications of bioelectrocatalysis. Electrochemistry: Vol 13.*; The Royal Society of Chemistry: Cambridge, 2015, pages.

(27) Rodrigo, S.; Gunasekera, D.; Mahajan, J. P.; Luo, L. Alternating current electrolysis for organic synthesis. *Curr. Opin. Electrochem.* **2021,** *28*.

(28) Atobe, M.; Tateno, H.; Matsumura, Y. Applications of flow microreactors in electrosynthetic processes. *Chem. Rev.* **2018,** *118*, 4541-4572.

(29) Noel, T.; Cao, Y.; Laudadio, G. The fundamentals behind the use of flow reactors in electrochemistry. *Acc. Chem. Res.* **2019,** *52*, 2858-2869.

(30) Pletcher, D.; Green, R. A.; Brown, R. C. D. Flow electrolysis cells for the synthetic organic chemistry laboratory. *Chem. Rev.* **2018,** *118*, 4573-4591.

(31) Ackermann, L. Metalla-electrocatalyzed C-H activation by earth-abundant 3d metals and beyond. *Acc. Chem. Res.* **2020,** *53*, 84-104.

(32) Karkas, M. D. Electrochemical strategies for C-H functionalization and C-N bond formation. *Chem. Soc. Rev.* **2018,** *47*, 5786-5865.

(33) Jiao, K. J.; Xing, Y. K.; Yang, Q. L.; Qiu, H.; Mei, T. S. Site-selective C-H functionalization via synergistic use of electrochemistry and transition metal catalysis. *Acc. Chem. Res.* **2020,** *53*, 300-310.

(34) Jiang, Y.; Xu, K.; Zeng, C. Use of electrochemistry in the synthesis of heterocyclic structures. *Chem. Rev.* **2018,** *118*, 4485-4540.

(35) Yamamoto, K.; Kuriyama, M.; Onomura, O. Anodic oxidation for the stereoselective synthesis of heterocycles. *Acc. Chem. Res.* **2020,** *53*, 105-120.

(36) Fuchigami, T.; Inagi, S. Recent advances in electrochemical systems for selective fluorination of organic compounds. *Acc. Chem. Res.* **2020,** *53*, 322-334.

(37) Rockl, J. L.; Pollok, D.; Franke, R.; Waldvogel, S. R. A decade of electrochemical dehydrogenative C,C-coupling of aryls. *Acc. Chem. Res.* **2020,** *53*, 45-61.

(38) Xiong, P.; Xu, H. C. Chemistry with electrochemically generated *N*-centered radicals. *Acc. Chem. Res.* **2019,** *52*, 3339-3350.

(39) Yoshida, J. I.; Shimizu, A.; Hayashi, R. Electrogenerated cationic reactive intermediates: the pool method and further advances. *Chem. Rev.* **2018,** *118*, 4702-4730.

(40) Chen, N.; Ye, Z.; Zhang, F. Recent progress on electrochemical synthesis involving carboxylic acids. *Org. Biomol. Chem.* **2021,** *19*, 5501-5520.

(41) Leech, M. C.; Lam, K. Electrosynthesis using carboxylic acid derivatives: new tricks for old reactions. *Acc. Chem. Res.* **2020,** *53*, 121-134.

(42) Martins, G. M.; Shirinfar, B.; Hardwick, T.; Ahmed, N. A Green Approach: Vicinal Oxidative Electrochemical Alkene Difunctionalization. *ChemElectroChem* **2018,** *6*, 1300-1315.

(43) Martins, G. M.; Shirinfar, B.; Hardwick, T.; Murtaza, A.; Ahmed, N. Organic electrosynthesis: electrochemical alkyne functionalization. *Catal. Sci. Technol.* **2019,** *9*, 5868-5881.

(44) Mei, H.; Yin, Z.; Liu, J.; Sun, H.; Han, J. Recent advances on the electrochemical difunctionalization of alkenes/alkynes. *Chin. J. Chem.* **2019**, DOI:10.1002/cjoc.201800529 10.1002/cjoc.201800529.

(45) Sauer, G. S.; Lin, S. An electrocatalytic approach to the radical difunctionalization of alkenes. *ACS Catal.* **2018,** *8*, 5175-5187.

(46) Siu, J. C.; Fu, N.; Lin, S. Catalyzing electrosynthesis: a homogeneous electrocatalytic approach to reaction discovery. *Acc. Chem. Res.* **2020,** *53*, 547-560.

(47) Jutand, A. Contribution of electrochemistry to organometallic catalysis. *Chem. Rev.* **2008,** *108*, 2300-2347.

(48) Francke, R.; Schille, B.; Roemelt, M. Homogeneously catalyzed electroreduction of carbon dioxide-methods, mechanisms, and catalysts. *Chem. Rev.* **2018,** *118*, 4631-4701.

(49) Mellah, M.; Gmouh, S.; Vaultier, M.; Jouikov, V. Electrocatalytic dimerisation of PhBr and $PhCH_2Br$ in [BMIM]+NTf_2− ionic liquid. *Electrochem. Commun.* **2003,** *5*, 591-593.

(50) Magdesieva, T. V.; Graczyk, M.; Vallat, A.; Nikitin, O. M.; Demyanov, P. I.; Butin, K. P.; Vorotyntsev, M. A. Electrochemically reduced titanocene dichloride as a catalyst of reductive dehalogenation of organic halides. *Electrochim. Acta* **2006,** *52*, 1265-1280.

(51) Shen, Y.; Inagi, S.; Atobe, M.; Fuchigami, T. Electrocatalytic debromination of open-chain and cyclic dibromides in ionic liquids with cobalt(II)salen complex as mediator. *Res. Chem. Intermed.* **2012,** *39*, 89-99.

(52) Hickey, D. P.; Sandford, C.; Rhodes, Z.; Gensch, T.; Fries, L. R.; Sigman, M. S.; Minteer, S. D. Investigating the role of ligand electronics on stabilizing electrocatalytically relevant low-valent Co(I) intermediates. *J. Am. Chem. Soc.* **2019,** *141*, 1382-1392.

(53) Sandford, C.; Fries, L. R.; Ball, T. E.; Minteer, S. D.; Sigman, M. S. Mechanistic studies into the oxidative addition of Co(I) complexes: combining electroanalytical techniques with parameterization. *J. Am. Chem. Soc.* **2019,** *141*, 18877-18889.

(54) Fry, A. J. S., A. H. Cobalt(salen)-electrocatalyzed reduction of benzal chloride. Dependence of products upon electrolysis potential. *J. Org. Chem.* **1994,** *59*, 8172-8177.

(55) Tang, T.; Sandford, C.; Minteer, S. D.; Sigman, M. S. Analyzing mechanisms in Co(I) redox catalysis using a pattern recognition platform. *Chem. Sci.* **2021,** *12*, 4771-4778.

(56) Lin, Q.; Fu, Y.; Liu, P.; Diao, T. Monovalent nickel-mediated radical formation: a concerted halogen-atom dissociation pathway determined by electroanalytical studies. *J. Am. Chem. Soc.* **2021,** *143*, 14196-14206.

(57) Wuttig, A.; Derrick, J. S.; Loipersberger, M.; Snider, A.; Head-Gordon, M.; Chang, C. J.; Toste, F. D. Controlled single-electron transfer via metal-ligand cooperativity drives divergent nickel-Eeectrocatalyzed radical pathways. *J. Am. Chem. Soc.* **2021,** *143*, 6990-7001.

(58) Gosmini, C. R., Y.; Nedelec, J.-Y.; Perichon, J. New efficient preparation of arylzinc compounds from aryl halides using cobalt catalysis and sacrificial anode process. *J. Org. Chem.* **2000,** *65*, 6024-6026.

(59) Le Gall, E. G., C.; Nedelec, J.-Y.; Perichon, J. Synthesis of functionalized 4-phenyl-pyridines via electrochemically prepared organozinc reagents. *Tetrahedron* **2001,** *57*, 1923-1927.

(60) Fillon, H.; Gosmini, C.; Périchon, J. A convenient method for the preparation of aromatic ketones from acyl chlorides and arylzinc bromides using a cobalt catalysis. *Tetrahedron* **2003,** *59*, 8199-8202.

(61) Lai, Y. L.; Huang, J. M. Palladium-catalyzed electrochemical allylic alkylation between alkyl and allylic halides in aqueous solution. *Org. Lett.* **2017,** *19*, 2022-2025.

(62) Boyd, J. D. F., C. S.; Imagawa, D. K. Carbon-carbon bond formation catalyzed by vitamin B12 and a vitamin B12 model compound. Electrosynthesis of bicyclic ketones by 1,4 addition. *J. Am. Chem. Soc* **1980,** *102*, 2342.

(63) Scheffold, R., et. al. Vitamin B12-mediated electrochemical reactions in the synthesis of natural products. *Pure Appl. Chem.* **1987,** *59*, 363-372.

(64) Takasu, K. O., H.; Kuroyanagi, J.-I.; Ihara, M. Novel intramolecular [4 + 1] and [4 + 2] annulation reactions employing cascade radical cyclizations. *J. Org. Chem.* **2002,** *67*, 6001-6007.

(65) Gomes, P. G., C.; Nedelec, J.-Y.; Perichon, J. Cobalt bromide as catalyst in electrochemical addition of aryl halides onto activated olefins. *Tetrahedron Lett* **2000,** *41*, 3385-3388.

(66) Condon, S. D., D.; Falgayrac, G.; Nedelec, J.-Y. Nickel-catalyzed electrochemical arylation of activated olefins. *Eur J Org Chem* **2002**, 105-111.

(67) Esteves, A. P. G., D. M.; Klein, L. J.; Lemos, M. A.; Medeiros, M. J.; Peters, D. G. Electroreductive intramolecular cyclization of a bromo propargyloxy ester catalyzed by Nickel(I) tetramethylcyclam electrogenerated at carbon cathodes in dimethylformamide. *J. Org. Chem.* **2002,** *68*, 1024-1029.

(68) Ischay, M. A. M., M. S.; Peters, D. G. Catalytic reduction and intramolecular cyclization of haloalkynes in the presence of nickel(I) salen electrogenerated at carbon cathodes in dimethylformamide. *J. Org. Chem.* **2006,** *71*, 623-628.

(69) Toyota, M. I., A.; Kashiwagi, Y.; Ihara, M. One-pot assembly of tricyclo[6.2.1.01,6]undecan-4-one and related polycyclic compounds by tandem electroreductive cyclization. *Org. Lett.* **2004,** *6*, 3629-3632.

(70) Mikhaylov, D.; Gryaznova, T.; Dudkina, Y.; Khrizanphorov, M.; Latypov, S.; Kataeva, O.; Vicic, D. A.; Sinyashin, O. G.; Budnikova, Y. Electrochemical nickel-induced fluoroalkylation: synthetic, structural and mechanistic study. *Dalton Trans.* **2012,** *41*, 165-172.

(71) S. Sengmany, E. L., J. P. Paugam, J.-Y. Nedelec. Cyclopropane formation by copper-catalysed indirect electroreductive coupling of activated olefins and activated a,a,a-trichloro or gem-dichloro compounds. *Synthesis* **2002,** *4*, 533-537.

(72) Hilt, G. S., K. I. Electrochemical regeneration of low-valent indium(I) species as catalysts for C–C bond formations. *Angew. Chem., Int. Ed.* **2001,** *40*, 3399-3402.

(73) Hilt, G. S., K. I.; Waloch, C. Indium-catalyzed allylation of imines with electrochemically assisted catalyst regeneration. *Tetrahedron Lett* **2002,** *43*, 1437-1439.

(74) Huang, J. M.; Dong, Y. Zn-mediated electrochemical allylation of aldehydes in aqueous ammonia. *Chem. Commun.* **2009**, DOI:10.1039/b905553c 10.1039/b905553c, 3943-3945.

(75) Huang, J. M.; Wang, X. X.; Dong, Y. Electrochemical allylation reactions of simple imines in aqueous solution mediated by nanoscale zinc architectures. *Angew Chem Int Ed Engl* **2011,** *50*, 924-927.

(76) Durandetti, M. M., C.; Perichon, J. Iron-catalyzed electrochemical allylation of carbonyl compounds by allylic acetates. *J. Org. Chem.* **2002,** *68*, 3121-3124.

(77) Durandetti, M. M., C.; Perichon, J. Iron-mediated electrochemical reaction of alpha-chloroesters with carbonyl compounds. *Org. Lett.* **2003,** *5*, 317-320.

(78) Durandetti, M. P., J.; Nédélec, J.-Y. . Nickel- and chromium-catalysed electrochemical coupling of aryl halides with arenecarboxaldehydes. *Tetrahedron Lett* **1999,** *40*, 9009-9013.

(79) Durandetti, M. N., J.-Y.; Périchon, J. An electrochemical coupling of organic halide with aldehydes, catalytic in chromium and nickel salts. The Nozaki–Hiyama–Kishi reaction. *Org. Lett.* **2001,** *3*, 2073-2076.

(80) Gao, Y.; Hill, D. E.; Hao, W.; McNicholas, B. J.; Vantourout, J. C.; Hadt, R. G.; Reisman, S. E.; Blackmond, D. G.; Baran, P. S. Electrochemical Nozaki-Hiyama-Kishi coupling: scope, applications, and mechanism. *J. Am. Chem. Soc.* **2021,** *143*, 9478-9488.

(81) Grigg, R. P., B.; Urch, C. J. Electrochemically driven catalytic Pd(0)/Cr(II) mediated coupling of organic halides with aldehydes. The Nozaki-Hiyama–Kishi reaction. *Tetrahedron Lett* **1997,** *38*, 6307-6308.

(82) Kuroboshi, M. T., M.; Kishimoto, S.; Tanaka, H.; Torii, S. Electrochemical regeneration of chromium(II). Alkenylation of carbonyl compounds. *Synlett* **1999,** *1999*, 67-90.

(83) Borjesson, M.; Moragas, T.; Gallego, D.; Martin, R. Metal-catalyzed carboxylation of organic (pseudo)halides with CO_2. *ACS Catal.* **2016,** *6*, 6739-6749.

(84) Senboku, H.; Katayama, A. Electrochemical carboxylation with carbon dioxide. *Curr. Opin. Green Sustain. Chem.* **2017,** *3*, 50-54.

(85) Amatore, C. J., A. Activation of carbon dioxide by electron transfer and transition metals. Mechanism of nickel catalyzed electrocarboxylation of aromatic halides. *J. Am. Chem. Soc.* **1991,** *113*, 2819-2825.

(86) Amatore, C. J., A.; Khalil, F.; Nielsen, M. F. Carbon dioxide as a C1 building block. Mechanism of palladium-catalyzed carboxylation of aromatic halides. *J. Am. Chem. Soc.* **1992,** *114*, 7076-7085.

(87) Chen, B.-L.; Zhu, H.-W.; Xiao, Y.; Sun, Q.-L.; Wang, H.; Lu, J.-X. Asymmetric electrocarboxylation of 1-phenylethyl chloride catalyzed by electrogenerated chiral [CoI(salen)]− complex. *Electrochem. Commun.* **2014,** *42*, 55-59.

(88) Medeiros, M. J.; Pintaric, C.; Olivero, S.; Dunach, E. Nickel-catalysed electrochemical carboxylation of allylic acetates and carbonates. *Electrochim. Acta* **2011,** *56*, 4384-4389.

(89) Nogi, K.; Fujihara, T.; Terao, J.; Tsuji, Y. Cobalt-catalyzed carboxylation of propargyl acetates with carbon dioxide. *Chem. Commun.* **2014,** *50*, 13052-13055.

(90) Nogi, K.; Fujihara, T.; Terao, J.; Tsuji, Y. Cobalt- and nickel-catalyzed carboxylation of alkenyl and sterically hindered aryl triflates utilizing CO_2. *J. Org. Chem.* **2015,** *80*, 11618-11623.

(91) Jiao, K.-J.; Li, Z.-M.; Xu, X.-T.; Zhang, L.-P.; Li, Y.-Q.; Zhang, K.; Mei, T.-S. Palladium-catalyzed reductive electrocarboxylation of allyl esters with carbon dioxide. *Org. Chem. Front.* **2018,** *5*, 2244-2248.

(92) Ang, N. W. J.; Oliveira, J. C. A.; Ackermann, L. Electroreductive cobalt-catalyzed carboxylation: cross-clectrophile clectrocoupling with atmospheric CO_2. *Angew Chem Int Ed Engl* **2020,** *59*, 12842-12847.

(93) Everson, D. A.; Weix, D. J. Cross-electrophile coupling: principles of reactivity and selectivity. *J. Org. Chem.* **2014,** *79*, 4793-4798.

(94) Weix, D. J. Methods and mechanisms for cross-electrophile coupling of C(sp^2) halides with alkyl electrophiles. *Acc. Chem. Res.* **2015,** *48*, 1767-1775.

(95) Biswas, S.; Weix, D. J. Mechanism and selectivity in nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides. *J. Am. Chem. Soc.* **2013,** *135*, 16192-16197.

(96) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing conventional carbon nucleophiles with electrophiles: nickel-catalyzed reductive alkylation of aryl bromides and chlorides. *J. Am. Chem. Soc.* **2012,** *134*, 6146-6159.

(97) Gomes, P. F., H.; Gosmini, C.; Labbe, E.; Perichon, J. Synthesis of unsymmetrical biaryls by electroreductive cobalt-catalyzed cross-coupling of aryl halides. *Tetrahedron* **2002,** *58*, 8417-8424.

(98) Gosmini, C. N., J. Y.; Perichon, J. Electrochemical cross-coupling between functionalized aryl halides and 2-chloropyrimidine or 2-chloropyrazine catalyzed by nickel 2,2'-bipyridine complex. *Tetrahedron Lett* **2000,** *41*, 201-203.
(99) Le Gall, E. G., C.; Nedelec, J.-Y.; Perichon, J. Cobalt-catalyzed electrochemical cross-coupling of functionalized phenyl halides with 4-chloroquinoline derivatives. *Tetrahedron Lett* **2001,** *42*, 267-269.
(100) Sengmany, S.; Vasseur, S.; Lajnef, A.; Le Gall, E.; Léonel, E. Beneficial effects of electrochemistry in cross-coupling reactions: electroreductive synthesis of 4-aryl- or 4-heteroaryl-6-pyrrolylpyrimidines. *Eur. J. Org. Chem.* **2016,** *2016*, 4865-4871.
(101) Sengmany, S.; Vitu-Thiebaud, A.; Le Gall, E.; Condon, S.; Leonel, E.; Thobie-Gautier, C.; Pipelier, M.; Lebreton, J.; Dubreuil, D. An electrochemical nickel-catalyzed arylation of 3-amino-6-chloropyridazines. *J. Org. Chem.* **2013,** *78*, 370-379.
(102) Gomes, P. G., C.; Perichon, J. Cobalt-catalyzed direct electrochemical cross-coupling between aryl or heteroaryl halides and allylic acetates or carbonates. *J. Org. Chem.* **2003,** *68*, 1142-1145.
(103) Durandetti, M. N., J.-Y.; Perichon, J. Nickel-catalyzed direct electrochemical cross-coupling between cryl halides and activated alkyl halides. *J. Org. Chem.* **1996,** *61*, 1748-1755.
(104) Durandetti, M. P., J.; Nedelec, J.-Y. Nickel-catalysed electrochemical coupling of 2- and 3-bromothiophene with alkyl and llkenyl halides. *Tetrahedron Lett* **1997,** *38*, 8683-8686.
(105) DeLano, T. J.; Reisman, S. E. Enantioselective electroreductive coupling of alkenyl and benzyl halides via nickel catalysis. *ACS Catal.* **2019,** *9*, 6751-6754.
(106) Qiu, H.; Shuai, B.; Wang, Y. Z.; Liu, D.; Chen, Y. G.; Gao, P. S.; Ma, H. X.; Chen, S.; Mei, T. S. Enantioselective Ni-catalyzed electrochemical synthesis of biaryl atropisomers. *J. Am. Chem. Soc.* **2020,** *142*, 9872-9878.
(107) Perkins, R. J.; Hughes, A. J.; Weix, D. J.; Hansen, E. C. Metal-reductant-free electrochemical nickel-catalyzed couplings of aryl and alkyl bromides in acetonitrile. *Org. Process Res. Dev.* **2019,** *23*, 1746-1751.
(108) Truesdell, B. L.; Hamby, T. B.; Sevov, C. S. General C(sp^2)-C(sp^3) cross-electrophile coupling reactions enabled by overcharge protection of homogeneous electrocatalysts. *J. Am. Chem. Soc.* **2020,** *142*, 5884-5893.
(109) Beletskaya, I. P.; Cheprakov, A. V. The Heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.* **2000,** *100*, 3009-3066.
(110) Tian, J. M., K. D. Electrochemically assisted Heck reactions. *Org. Lett.* **2005,** *7*, 5381-5383.
(111) Yeh, N.-H. Z., Y.; Moeller, K. D. Electroorganic synthesis and the construction of addressable molecular surfaces. *ChemElectroChem* **2019,** *6*, 4134-4143.
(112) Hu, L. S., M.; Tian, J.; Maurer, K.; Moeller, K. D. Building addressable libraries: site-selective use of Pd(0) catalysts on microelectrode arrays. *J. Am. Chem. Soc.* **2010,** *132*, 16610-16616.
(113) Walker, B. R.; Sevov, C. S. An electrochemically promoted, nickel-catalyzed Mizoroki–Heck reaction. *ACS Catal.* **2019,** *9*, 7197-7203.
(114) Zhang, H. J.; Chen, L.; Oderinde, M. S.; Edwards, J. T.; Kawamata, Y.; Baran, P. S. Chemoselective, scalable nickel-electrocatalytic *O*-arylation of alcohols. *Angew Chem Int Ed Engl* **2021,** *60*, 20700-20705.

(115) Mo, Y. L., Z.; Rughoobur, G.; Patil, P.; Gershenfeld, N.; Akinwande, A. I.; Buchwald, S. L.; Jensen, K. F. Microfluidic electrochemistry for single-electron transfer redox-neutral reactions. *Science* **2020,** *368*, 1352-1357.
(116) Liu, D.; Ma, H. X.; Fang, P.; Mei, T. S. Nickel-catalyzed thiolation of aryl halides and heteroaryl halides through electrochemistry. *Angew Chem Int Ed Engl* **2019,** *58*, 5033-5037.
(117) Sengmany, S.; Ollivier, A.; Le Gall, E.; Leonel, E. A mild electroassisted synthesis of (hetero)arylphosphonates. *Org. Biomol. Chem.* **2018,** *16*, 4495-4500.
(118) Tang, S.; Wang, D.; Liu, Y.; Zeng, L.; Lei, A. Cobalt-catalyzed electrooxidative C-H/N-H [4+2] annulation with ethylene or ethyne. *Nat. Commun.* **2018,** *9*, 798.
(119) Ackermann, L. Cobalt-Catalyzed C–H Arylations, Benzylations, and Alkylations with Organic Electrophiles and Beyond. *J. Org. Chem.* **2014,** *79*, 8948-8954.
(120) Gao, K.; Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C–H Functionalization. *Acc. Chem. Res.* **2014,** *47*, 1208-1219.
(121) Moselage, M.; Li, J.; Ackermann, L. Cobalt-catalyzed C–H activation. *ACS Catal.* **2016,** *6*, 498-525.
(122) Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed Direct Carbonylation of Aminoquinoline Benzamides. *Org. Lett.* **2014,** *16*, 4688-4690.
(123) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. Cobalt-Catalyzed Cyclization of Aliphatic Amides and Terminal Alkynes with Silver-Cocatalyst. *J. Am. Chem. Soc.* **2015,** *137*, 12990-12996.
(124) Tan, G.; He, S.; Huang, X.; Liao, X.; Cheng, Y.; You, J. Cobalt-Catalyzed Oxidative C−H/C−H Cross-Coupling between Two Heteroarenes. *Angew. Chem. Int. Ed.* **2016,** *55*, 10414-10418.
(125) Meyer, T. H.; Oliveira, J. C. A.; Sau, S. C.; Ang, N. W. J.; Ackermann, L. Electrooxidative Allene Annulations by Mild Cobalt-Catalyzed C–H Activation. *ACS Catalysis* **2018,** *8*, 9140-9147.
(126) Yi, X.; Hu, X. Formal Aza-Wacker Cyclization by Tandem Electrochemical Oxidation and Copper Catalysis. *Angew. Chem. Int. Ed.* **2019,** *58*, 4700-4704.
(127) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. Palladium(II)-catalyzed amidation of alkenes. *Tetrahedron Lett.* **1992,** *33*, 6643-6646.
(128) Allen, J. R.; Bahamonde, A.; Furukawa, Y.; Sigman, M. S. Enantioselective N-Alkylation of Indoles via an Intermolecular Aza-Wacker-Type Reaction. *J. Am. Chem. Soc.* **2019,** *141*, 8670-8674.
(129) Lai, J.; Pericàs, M. A. Manganese/Copper Co-catalyzed Electrochemical Wacker–Tsuji-Type Oxidation of Aryl-Substituted Alkenes. *Org. Lett.* **2020,** *22*, 7338-7342.
(130) Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. Metal-catalyzed electrochemical diazidation of alkenes. *Science* **2017,** *357*, 575-579.
(131) Fu, N.; Sauer, G. S.; Lin, S. Electrocatalytic radical dichlorination of alkenes with nucleophilic chlorine sources. *J. Am. Chem. Soc.* **2017,** *139*, 15548-15553.
(132) Ye, K.-Y.; Pombar, G.; Fu, N.; Sauer, G. S.; Keresztes, I.; Lin, S. Anodically Coupled Electrolysis for the Heterodifunctionalization of Alkenes. *J. Am. Chem. Soc.* **2018,** *140*, 2438-2441.
(133) Langlois, B. R.; Laurent, E.; Roidot, N. Trifluoromethylation of aromatic compounds with sodium trifluoromethanesulfinate under oxidative conditions. *Tetrahedron Lett.* **1991,** *32*, 7525-7528.

(134) Xiong, P. X., F.; Qian, X.-Y.; Yohannes, Y.; Song, J.; Lu, X.; Xu, H.-C. Copper-catalyzed intramolecular oxidative amination of unactivated internal alkenes. *Chem. Eur. J.* **2016,** *22*, 4379-4383.

(135) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. *Chem. Rev.* **2015,** *115*, 2596-2697.

(136) Bernoud, E.; Lepori, C.; Mellah, M.; Schulz, E.; Hannedouche, J. Recent advances in metal free- and late transition metal-catalysed hydroamination of unactivated alkenes. *Catalysis Science & Technology* **2015,** *5*, 2017-2037.

(137) Xu, H.-C.; Moeller, K. D. Intramolecular Anodic Olefin Coupling Reactions: The Use of a Nitrogen Trapping Group. *J. Am. Chem. Soc.* **2008,** *130*, 13542-13543.

(138) Xu, H.-C.; Campbell, J. M.; Moeller, K. D. Cyclization Reactions of Anode-Generated Amidyl Radicals. *J. Org. Chem.* **2014,** *79*, 379-391.

(139) Francke, R.; Little, R. D. Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **2014,** *43*, 2492-2521.

(140) Duñach, E.; Périchon, J. Electrochemical carboxylation of terminal alkynes catalyzed by nickel complexes: unusual regioselectivity. *J. Organomet. Chem.* **1988,** *352*, 239-246.

(141) Dérien, S.; Clinet, J.-C.; Duñach, E.; Périchon, J. Electrochemical incorporation of carbon dioxide into alkenes by nickel complexes. *Tetrahedron* **1992,** *48*, 5235-5248.

(142) Duñach, E.; Dérien, S.; Périchon, J. Nickel-catalyzed reductive electrocarboxylation of disubstituted alkynes. *J. Organomet. Chem.* **1989,** *364*, C33-C36.

(143) Chiarotto, I.; Carelli, I. PALLADIUM-CATALYZED ELECTROCHEMICAL CARBONYLATION OF ALKYNES UNDER VERY MILD CONDITIONS. *Synth. Commun.* **2002,** *32*, 881-886.

(144) He, M.-X.; Mo, Z.-Y.; Wang, Z.-Q.; Cheng, S.-Y.; Xie, R.-R.; Tang, H.-T.; Pan, Y.-M. Electrochemical Synthesis of 1-Naphthols by Intermolecular Annulation of Alkynes with 1,3-Dicarbonyl Compounds. *Org. Lett.* **2020,** *22*, 724-728.

(145) Hou, Z.-W.; Mao, Z.-Y.; Song, J.; Xu, H.-C. Electrochemical Synthesis of Polycyclic N-Heteroaromatics through Cascade Radical Cyclization of Diynes. *ACS Catalysis* **2017,** *7*, 5810-5813.

(146) Hou, Z.-W.; Mao, Z.-Y.; Zhao, H.-B.; Melcamu, Y. Y.; Lu, X.; Song, J.; Xu, H.-C. Electrochemical C−H/N−H Functionalization for the Synthesis of Highly Functionalized (Aza)indoles. *Angew. Chem. Int. Ed.* **2016,** *55*, 9168-9172.

(147) Xiong, P.; Xu, H.-H.; Song, J.; Xu, H.-C. Electrochemical Difluoromethylarylation of Alkynes. *J. Am. Chem. Soc.* **2018,** *140*, 2460-2464.

(148) O'Brien, A. G.; Maruyama, A.; Inokuma, Y.; Fujita, M.; Baran, P. S.; Blackmond, D. G. Radical C H Functionalization of Heteroarenes under Electrochemical Control. *Angew. Chem. Int. Ed.* **2014,** *53*, 11868-11871.

(149) Kong, W.-J.; Finger, L. H.; Oliveira, J. C. A.; Ackermann, L. Rhodaelectrocatalysis for annulative C−H activation: polycyclic aromatic hydrocarbons through versatile double electrocatalysis. *Angew. Chem., Int. Ed.* **2019,** *58*, 6342-6346.

(150) Lyons, T. W.; Sanford, M. S. Palladium-catalyzed ligand-directed C−H functionalization reactions. *Chem. Rev.* **2010,** *110*, 1147-1169.

(151) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C–H bond activation. *Chem. Soc. Rev.* **2011,** *40*, 4740-4761.

(152) Moritanl, I.; Fujiwara, Y. Aromatic substitution of styrene-palladium chloride complex. *Tetrahedron Lett.* **1967,** *8*, 1119-1122.

(153) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. Aromatic substitution of styrene-palladium chloride complex. II effect of metal acetate. *Tetrahedron Lett.* **1968,** *9*, 633-636.

(154) Jia, C.; Kitamura, T.; Fujiwara, Y. Catalytic functionalization of arenes and alkanes via C−H bond activation. *Acc. Chem. Res.* **2001,** *34*, 633-639.

(155) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. Highly efficient Pd-catalyzed coupling of arenes with olefins in the presence of tert-butyl hydroperoxide as oxidant. *Org. Lett.* **1999,** *1*, 2097-2100.

(156) Bäckvall, J.-E.; Gogoll, A. Palladium–hydroquinone catalysed electrochemical 1,4-oxidation of conjugated dienes. *J. Chem. Soc., Chem. Commun.* **1987**, DOI:10.1039/C39870001236 10.1039/C39870001236, 1236-1238.

(157) Amatore, C.; Cammoun, C.; Jutand, A. Electrochemical recycling of benzoquinone in the Pd/benzoquinone-catalyzed Heck-type reactions from arenes. *Adv. Synth. Catal.* **2007,** *349*, 292-296.

(158) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C−H Bond Functionalizations: Mechanism and Scope. *Chemical Reviews* **2011,** *111*, 1315-1345.

(159) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. Palladium-catalyzed aromatic C−H halogenation with hydrogen halides by means of electrochemical oxidation. *J. Am. Chem. Soc.* **2009,** *131*, 11310-11311.

(160) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. Cu(II)-catalyzed functionalizations of aryl C−H bonds using O_2 as an oxidant. *J. Am. Chem. Soc.* **2006,** *128*, 6790-6791.

(161) Dick, A. R.; Hull, K. L.; Sanford, M. S. A highly selective catalytic method for the oxidative functionalization of C−H bonds. *J. Am. Chem. Soc.* **2004,** *126*, 2300-2301.

(162) Giri, R.; Chen, X.; Yu, J.-Q. Palladium-catalyzed asymmetric iodination of unactivated C–H bonds under mild conditions. *Angew. Chem., Int. Ed.* **2005,** *44*, 2112-2115.

(163) Hull, K. L.; Anani, W. Q.; Sanford, M. S. Palladium-catalyzed fluorination of carbon−hydrogen bonds. *J. Am. Chem. Soc.* **2006,** *128*, 7134-7135.

(164) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. Scope and selectivity in palladium-catalyzed directed C–H bond halogenation reactions. *Tetrahedron* **2006,** *62*, 11483-11498.

(165) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. A simple catalytic method for the regioselective halogenation of arenes. *Org. Lett.* **2006,** *8*, 2523-2526.

(166) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. Pd(II)-catalyzed monoselective ortho halogenation of C–H bonds assisted by counter cations: a complementary method to directed ortho lithiation. *Angew. Chem., Int. Ed.* **2008,** *47*, 5215-5219.

(167) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. Highly selective C−H functionalization/halogenation of acetanilide. *J. Am. Chem. Soc.* **2006,** *128*, 7416-7417.

(168) Zhao, X.; Dimitrijević, E.; Dong, V. M. Palladium-catalyzed C−H bond functionalization with arylsulfonyl chlorides. *J. Am. Chem. Soc.* **2009,** *131*, 3466-3467.

(169) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl−aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **2002,** *102*, 1359-1470.

(170) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chemical Reviews* **2011,** *111*, 1417-1492.

(171) Molnár, Á. Efficient, selective, and recyclable palladium catalysts in carbon−carbon coupling reactions. *Chem. Rev.* **2011,** *111*, 2251-2320.

(172) Yin; Liebscher, J. Carbon−carbon coupling reactions catalyzed by heterogeneous palladium catalysts. *Chem. Rev.* **2007,** *107*, 133-173.

(173) Aiso, H.; Kochi, T.; Mutsutani, H.; Tanabe, T.; Nishiyama, S.; Kakiuchi, F. Catalytic electrochemical C–H iodination and one-pot arylation by on/off switching of electric current. *J. Org. Chem.* **2012,** *77*, 7718-7724.

(174) Saito, F.; Aiso, H.; Kochi, T.; Kakiuchi, F. Palladium-catalyzed regioselective homocoupling of arenes using anodic oxidation: formal electrolysis of aromatic carbon–hydrogen bonds. *Organometallics* **2014,** *33*, 6704-6707.

(175) Miller, L. L.; Kujawa, E. P.; Campbell, C. B. Iodination with electrolytically generated iodine(I). *J. Am. Chem. Soc.* **1970,** *92*, 2821-2825.

(176) Miller, L. L.; Watkins, B. F. Scope and mechanism of aromatic iodination with electrochemically generated iodine(I). *J. Am. Chem. Soc.* **1976,** *98*, 1515-1519.

(177) Shono, T.; Matsumura, Y.; Katoh, S.; Ikeda, K.; Kamada, T. Aromatic iodination by positive iodine active species generated by anodic oxidation in trimethyl orthoformate. *Tetrahedron Lett.* **1989,** *30*, 1649-1650.

(178) Whitfield, S. R.; Sanford, M. S. Reactivity of Pd(II) complexes with electrophilic chlorinating reagents: isolation of Pd(IV) products and observation of C−Cl bond-forming reductive elimination. *J. Am. Chem. Soc.* **2007,** *129*, 15142-15143.

(179) Kataoka, K.; Hagiwara, Y.; Midorikawa, K.; Suga, S.; Yoshida, J.-I. Practical electrochemical iodination of aromatic compounds. *Org. Process Res. Dev.* **2008,** *12*, 1130-1136.

(180) Shilov, A. E.; Shul'pin, G. B. Activation of C−H Bonds by metal complexes. *Chem. Rev.* **1997,** *97*, 2879-2932.

(181) Burton, H. A.; Kozhevnikov, I. V. Biphasic oxidation of arenes with oxygen catalysed by Pd(II)—heteropoly acid system: oxidative coupling versus hydroxylation. *J. Mol. Catal. A: Chem.* **2002,** *185*, 285-290.

(182) Yokota, T.; Sakaguchi, S.; Ishii, Y. Aerobic oxidation of benzene to biphenyl using a Pd(II)/molybdovanadophosphoric acid catalytic system. *Adv. Synth. Catal.* **2002,** *344*, 849-854.

(183) Ackerman, L. J.; Sadighi, J. P.; Kurtz, D. M.; Labinger, J. A.; Bercaw, J. E. Arene C−H Bond Activation and Arene Oxidative Coupling by Cationic Palladium(II) Complexes. *Organometallics* **2003,** *22*, 3884-3890.

(184) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. Palladium-catalyzed C−H homocoupling of bromothiophene derivatives and synthetic application to well-defined oligothiophenes. *J. Am. Chem. Soc.* **2006,** *128*, 10930-10933.

(185) Hull, K. L.; Lanni, E. L.; Sanford, M. S. Highly Regioselective Catalytic Oxidative Coupling Reactions: Synthetic and Mechanistic Investigations. *Journal of the American Chemical Society* **2006,** *128*, 14047-14049.

(186) Dick, A. R.; Sanford, M. S. Transition metal catalyzed oxidative functionalization of carbon–hydrogen bonds. *Tetrahedron* **2006,** *62*, 2439-2463.

(187) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. C–H nitrogenation and oxygenation by ruthenium catalysis. *Chem. Commun.* **2014,** *50*, 29-39.

(188) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. Perfluoroalkylation reactions of (hetero)arenes. *RSC Adv.* **2015,** *5*, 62498-62518.

(189) Dudkina, Y. B.; Mikhaylov, D. Y.; Gryaznova, T. V.; Tufatullin, A. I.; Kataeva, O. N.; Vicic, D. A.; Budnikova, Y. H. Electrochemical ortho functionalization of 2-phenylpyridine with fefluorocarboxylic acids catalyzed by palladium in higher oxidation states. *Organometallics* **2013,** *32*, 4785-4792.

(190) Grayaznova, T. V.; Dudkina, Y. B.; Islamov, D. R.; Kataeva, O. N.; Sinyashin, O. G.; Vicic, D. A.; Budnikova, Y. H. Pyridine-directed palladium-catalyzed electrochemical phosphonation of C(sp2)–H bond. *J. Organomet. Chem.* **2015,** *785*, 68-71.

(191) Gryaznova, T.; Dudkina, Y.; Khrizanforov, M.; Sinyashin, O.; Kataeva, O.; Budnikova, Y. Electrochemical properties of diphosphonate-bridged palladacycles and their reactivity in arene phosphonation. *J. Solid State Electrochem.* **2015,** *19*, 2665-2672.

(192) Gryaznova, T. V.; Khrizanforov, M. N.; Levitskaya, A. I.; Kh.Rizvanov, I.; Balakina, M. Y.; Ivshin, K. A.; Kataeva, O. N.; Budnikova, Y. H. Electrochemically driven and acid-driven pyridine-directed ortho-phosphorylation of C(sp^2)–H bonds. *Organometallics* **2020,** *39*, 2446-2454.

(193) Cabrera-Pardo, J. R.; Chai, D. I.; Liu, S.; Mrksich, M.; Kozmin, S. A. Label-assisted mass spectrometry for the acceleration of reaction discovery and optimization. *Nat. Chem.* **2013,** *5*, 423-427.

(194) Cabrera-Pardo, J. R.; Trowbridge, A.; Nappi, M.; Ozaki, K.; Gaunt, M. J. Selective palladium(II)-catalyzed carbonylation of methylene β-C−H bonds in aliphatic amines. *Angew. Chem., Int. Ed.* **2017,** *56*, 11958-11962.

(195) Durand, D. J.; Fey, N. Computational ligand descriptors for catalyst design. *Chem. Rev.* **2019,** *119*, 6561-6594.

(196) Grushin, V. V. Mixed phosphine−phosphine oxide ligands. *Chem. Rev.* **2004,** *104*, 1629-1662.

(197) Montavon, T. J.; Li, J.; Cabrera-Pardo, J. R.; Mrksich, M.; Kozmin, S. A. Three-component reaction discovery enabled by mass spectrometry of self-assembled monolayers. *Nat. Chem.* **2012,** *4*, 45-51.

(198) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. Ligand bite angle effects in metal-catalyzed C−C bond formation. *Chem. Rev.* **2000,** *100*, 2741-2770.

(199) Castro, L. C. M.; Chatani, N. Nickel Catalysts/N,N′-Bidentate Directing Groups: An Excellent Partnership in Directed C–H Activation Reactions. *Chemistry Letters* **2015,** *44*, 410-421.

(200) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Accounts of Chemical Research* **2015,** *48*, 1053-1064.

(201) Kommagalla, Y.; Chatani, N. Cobalt(II)-catalyzed CH functionalization using an *N,N′*-bidentate directing group. *Coord. Chem. Rev.* **2017,** *350*, 117-135.

(202) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. Highly regioselective arylation of sp^3 C−H bonds catalyzed by palladium acetate. *J. Am. Chem. Soc.* **2005,** *127*, 13154-13155.

(203) Ano, Y.; Tobisu, M.; Chatani, N. Palladium-catalyzed direct ethynylation of C(sp^3)–H bonds in aliphatic carboxylic acid derivatives. *J. Am. Chem. Soc.* **2011,** *133*, 12984-12986.

(204) Ano, Y.; Tobisu, M.; Chatani, N. Palladium-catalyzed direct ortho-alkynylation of aromatic carboxylic acid derivatives. *Org. Lett.* **2012,** *14*, 354-357.

(205) Feng, Y.; Chen, G. Total synthesis of celogentin C by stereoselective C–H activation. *Angew. Chem., Int. Ed.* **2010,** *49*, 958-961.

(206) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. Facile benzo-ring construction via palladium-catalyzed functionalization of unactivated sp^3 C−H bonds under mild reaction conditions. *Org. Lett.* **2010,** *12*, 3414-3417.

(207) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. Palladium-catalyzed aryl C−H bonds activation/acetoxylation utilizing a bidentate system. *Org. Lett.* **2009,** *11*, 5726-5729.

(208) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. Sequential C–H arylation and olefination: total synthesis of the proposed structure of pipercyclobutanamide A. *Angew. Chem., Int. Ed.* **2012,** *51*, 7507-7510.

(209) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. Novel acetoxylation and C−C coupling reactions at unactivated positions in alpha-amino acid derivatives. *Org. Lett.* **2006,** *8*, 3391-3394.

(210) Shabashov, D.; Daugulis, O. Auxiliary-assisted palladium-catalyzed arylation and alkylation of sp^2 and sp^3 carbon−hydrogen bonds. *J. Am. Chem. Soc.* **2010,** *132*, 3965-3972.

(211) Tran, L. D.; Daugulis, O. Nonnatural amino acid synthesis by using carbon–hydrogen bond functionalization methodology. *Angew. Chem., Int. Ed.* **2012,** *51*, 5188-5191.

(212) Konishi, M.; Tsuchida, K.; Sano, K.; Kochi, T.; Kakiuchi, F. Palladium-catalyzed ortho-selective C–H chlorination of benzamide derivatives under anodic oxidation conditions. *J. Org. Chem.* **2017,** *82*, 8716-8724.

(213) Robarge, K. D.; Brunton, S. A.; Castanedo, G. M.; Cui, Y.; Dina, M. S.; Goldsmith, R.; Gould, S. E.; Guichert, O.; Gunzner, J. L.; Halladay, J.et al. GDC-0449—a potent inhibitor of the hedgehog pathway. *Bioorg. Med. Chem. Lett.* **2009,** *19*, 5576-5581.

(214) Rudin, C. M.; Hann, C. L.; Laterra, J.; Yauch, R. L.; Callahan, C. A.; Fu, L.; Holcomb, T.; Stinson, J.; Gould, S. E.; Coleman, B.et al. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. *N. Engl. J. Med.* **2009,** *361*, 1173-1178.

(215) Newhouse, T.; Baran, P. S. If C–H bonds could talk: selective C–H bond oxidation. *Angew. Chem., Int. Ed.* **2011,** *50*, 3362-3374.

(216) White, M. C. Adding aliphatic C–H bond oxidations to synthesis. *Science* **2012,** *335*, 807-809.

(217) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C–H bond functionalization: emerging synthetic tools for natural products and pharmaceuticals. *Angew. Chem., Int. Ed.* **2012,** *51*, 8960-9009.

(218) Yang, Q.-L.; Li, Y.-Q.; Ma, C.; Fang, P.; Zhang, X.-J.; Mei, T.-S. Palladium-catalyzed $C(sp^3)$–H oxygenation via electrochemical oxidation. *J. Am. Chem. Soc.* **2017,** *139*, 3293-3298.

(219) Ma, C.; Zhao, C.-Q.; Li, Y.-Q.; Zhang, L.-P.; Xu, X.-T.; Zhang, K.; Mei, T.-S. Palladium-catalyzed C–H activation/C–C cross-coupling reactions via electrochemistry. *Chem. Commun.* **2017,** *53*, 12189-12192.

(220) Li, Y.-Q.; Yang, Q.-L.; Fang, P.; Mei, T.-S.; Zhang, D. Palladium-catalyzed $C(sp^2)$–H acetoxylation via electrochemical oxidation. *Org. Lett.* **2017,** *19*, 2905-2908.

(221) Shrestha, A.; Lee, M.; Dunn, A. L.; Sanford, M. S. Palladium-catalyzed C-H bond acetoxylation via electrochemical oxidation. *Org. Lett.* **2018,** *20*, 204-207.

(222) Ndakala, A. J.; Gessner, R. K.; Gitari, P. W.; October, N.; White, K. L.; Hudson, A.; Fakorede, F.; Shackleford, D. M.; Kaiser, M.; Yeates, C.et al. Antimalarial pyrido[1,2-a]benzimidazoles. *J. Med. Chem.* **2011,** *54*, 4581-4589.

(223) Perin, N.; Nhili, R.; Ester, K.; Laine, W.; Karminski-Zamola, G.; Kralj, M.; David-Cordonnier, M.-H.; Hranjec, M. Synthesis, antiproliferative activity and DNA binding properties of novel 5-aminobenzimidazo[1,2-a]quinoline-6-carbonitriles. *Eur. J. Med. Chem.* **2014,** *80*, 218-227.

(224) Kotovskaya, S. K.; Baskakova, Z. M.; Charushin, V. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Balakhnin, S. M.; Serova, O. A. Synthesis and antiviral activity of fluorinated pyrido[1,2-a]benzimidazoles. *Pharm. Chem. J.* **2005,** *39*, 574-578.

(225) Kutsumura, N.; Kunimatsu, S.; Kagawa, K.; Otani, T.; Saito, T. Synthesis of benzimidazole-fused heterocycles by intramolecular oxidative C-N bond formation using hypervalent iodine reagents. *Synthesis* **2011,** *2011*, 3235-3240.

(226) Lv, Z.; Liu, J.; Wei, W.; Wu, J.; Yu, W.; Chang, J. Iodine-mediated aryl C−H amination for the synthesis of benzimidazoles and pyrido[1,2-a]benzimidazoles. *Adv. Synth. Catal.* **2016,** *358*, 2759-2766.

(227) Qian, G.; Liu, B.; Tan, Q.; Zhang, S.; Xu, B. Hypervalent iodine(III) promoted direct synthesis of imidazo[1,2-a]pyrimidines. *Eur. J. Org. Chem.* **2014,** *2014*, 4837-4843.

(228) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. A direct intramolecular C−H amination reaction cocatalyzed by copper(II) and iron(III) as part of an efficient route for the synthesis of pyrido[1,2-a]benzimidazoles from *N*-aryl-2-aminopyridines. *J. Am. Chem. Soc.* **2010,** *132*, 13217-13219.

(229) Duan, Z.; Zhang, L.; Zhang, W.; Lu, L.; Zeng, L.; Shi, R.; Lei, A. Palladium-catalyzed electro-oxidative C–H amination toward the synthesis of pyrido[1,2-a]benzimidazoles with hydrogen evolution. *ACS Catal.* **2020,** *10*, 3828-3831.

(230) Dhawa, U.; Tian, C.; Wdowik, T.; Oliveira, J. C. A.; Hao, J.; Ackermann, L. Enantioselective pallada-electrocatalyzed C−H activation by transient directing groups: expedient access to helicenes. *Angew. Chem., Int. Ed.* **2020,** *59*, 13451-13457.

(231) Brunel, J. M. BINOL: a versatile chiral reagent. *Chem. Rev.* **2005,** *105*, 857-898.

(232) Min, C.; Seidel, D. Asymmetric Brønsted acid catalysis with chiral carboxylic acids. *Chem. Soc. Rev.* **2017,** *46*, 5889-5902.

(233) Yu, J.; Shi, F.; Gong, L.-Z. Brønsted-acid-catalyzed asymmetric multicomponent reactions for the facile synthesis of highly enantioenriched structurally diverse nitrogenous heterocycles. *Acc. Chem. Res.* **2011,** *44*, 1156-1171.

(234) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective total synthesis of axially chiral biaryl natural products. *Chem. Rev.* **2011,** *111*, 563-639.

(235) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. Total synthesis of chiral biaryl natural products by asymmetric biaryl coupling. *Chem. Soc. Rev.* **2009,** *38*, 3193-3207.

(236) Dherbassy, Q.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. Two stereoinduction events in one C−H activation step: a route towards terphenyl ligands with two atropisomeric axes. *Angew. Chem., Int. Ed.* **2018,** *57*, 4668-4672.

(237) Jin, L.; Yao, Q.-J.; Xie, P.-P.; Li, Y.; Zhan, B.-B.; Han, Y.-Q.; Hong, X.; Shi, B.-F. Atroposelective synthesis of axially chiral styrenes via an asymmetric C–H functionalization strategy. *Chem* **2020,** *6*, 497-511.

(238) Liao, G.; Yao, Q.-J.; Zhang, Z.-Z.; Wu, Y.-J.; Huang, D.-Y.; Shi, B.-F. Scalable, stereocontrolled formal syntheses of (+)-isoschizandrin and (+)-steganone: development

and applications of palladium(II)-catalyzed atroposelective C−H alkynylation. *Angew. Chem., Int. Ed.* **2018,** *57*, 3661-3665.

(239) Yamaguchi, K.; Kondo, H.; Yamaguchi, J.; Itami, K. Aromatic C–H coupling with hindered arylboronic acids by Pd/Fe dual catalysts. *Chem. Sci.* **2013,** *4*, 3753-3757.

(240) Yamaguchi, K.; Yamaguchi, J.; Studer, A.; Itami, K. Hindered biaryls by C–H coupling: bisoxazoline-Pd catalysis leading to enantioselective C–H coupling. *Chem. Sci.* **2012,** *3*, 2165-2169.

(241) Zhang, S.; Yao, Q.-J.; Liao, G.; Li, X.; Li, H.; Chen, H.-M.; Hong, X.; Shi, B.-F. Enantioselective synthesis of atropisomers featuring pentatomic heteroaromatics by Pd-catalyzed C–H alkynylation. *ACS Catal.* **2019,** *9*, 1956-1961.

(242) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-catalyzed C−C bond formation via heteroatom-directed C−H bond activation. *Chem. Rev.* **2010,** *110*, 624-655.

(243) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Rhodium catalyzed chelation-assisted C–H bond functionalization reactions. *Acc. Chem. Res.* **2012,** *45*, 814-825.

(244) Archambeau, A.; Rovis, T. Rhodium(III)-catalyzed allylic C(sp^3)–H activation of alkenyl sulfonamides: unexpected formation of azabicycles. *Angew. Chem., Int. Ed.* **2015,** *54*, 13337-13340.

(245) Lu, Y.; Wang, H.-W.; Spangler, J. E.; Chen, K.; Cui, P.-P.; Zhao, Y.; Sun, W.-Y.; Yu, J.-Q. Rh(III)-catalyzed C–H olefination of *N*-pentafluoroaryl benzamides using air as the sole oxidant. *Chem. Sci.* **2015,** *6*, 1923-1927.

(246) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. Rhodium(III)-catalyzed arene and alkene C−H bond functionalization leading to indoles and pyrroles. *J. Am. Chem. Soc.* **2010,** *132*, 18326-18339.

(247) Yu, D.-G.; Suri, M.; Glorius, F. RhIII/CuII-cocatalyzed synthesis of 1H-indazoles through C–H amidation and N–N bond formation. *J. Am. Chem. Soc.* **2013,** *135*, 8802-8805.

(248) Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. An efficient Rh/O_2 catalytic system for oxidative C–H activation/annulation: evidence for Rh(I) to Rh(III) oxidation by molecular oxygen. *J. Am. Chem. Soc.* **2013,** *135*, 8850-8853.

(249) Zhang, G.; Yu, H.; Qin, G.; Huang, H. Rh-Catalyzed oxidative C–H activation/annulation: converting anilines to indoles using molecular oxygen as the sole oxidant. *Chem. Commun.* **2014,** *50*, 4331-4334.

(250) Qiu, Y.; Kong, W.-J.; Struwe, J.; Sauermann, N.; Rogge, T.; Scheremetjew, A.; Ackermann, L. Electrooxidative rhodium-catalyzed C−H/C−H activation: electricity as oxidant for cross-dehydrogenative alkenylation. *Angew. Chem., Int. Ed.* **2018,** *57*, 5828-5832.

(251) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-catalyzed C–H bond activation and functionalization. *Chem. Rev.* **2012,** *112*, 5879-5918.

(252) Yeung, C. S.; Dong, V. M. Catalytic dehydrogenative cross-coupling: forming carbon−carbon bonds by oxidizing two carbon−hydrogen bonds. *Chem. Rev.* **2011,** *111*, 1215-1292.

(253) Zhang, Y.; Struwe, J.; Ackermann, L. Rhodium-catalyzed electrooxidative C−H olefination of benzamides. *Angew. Chem., Int. Ed.* **2020,** *59*, 15076-15080.

(254) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's guide to flow chemistry. *Chem. Rev.* **2017,** *117*, 11796-11893.

(255) Santoro, S.; Ferlin, F.; Ackermann, L.; Vaccaro, L. C–H functionalization reactions under flow conditions. *Chem. Soc. Rev.* **2019,** *48*, 2767-2782.

(256) Kong, W.-J.; Finger, L. H.; Messinis, A. M.; Kuniyil, R.; Oliveira, J. C. A.; Ackermann, L. Flow rhodaelectro-catalyzed alkyne annulations by versatile C–H activation: mechanistic support for rhodium(III/IV). *J. Am. Chem. Soc.* **2019,** *141*, 17198-17206.

(257) Anthony, J. E. Functionalized acenes and heteroacenes for organic electronics. *Chem. Rev.* **2006,** *106*, 5028-5048.

(258) Brasholz, M. "Super-reducing" photocatalysis: consecutive energy and electron transfers with polycyclic aromatic hydrocarbons. *Angew. Chem., Int. Ed.* **2017,** *56*, 10280-10281.

(259) Ponomarenko, L. A.; Schedin, F.; Katsnelson, M. I.; Yang, R.; Hill, E. W.; Novoselov, K. S.; Geim, A. K. Chaotic dirac billiard in graphene quantum dots. *Science* **2008,** *320*, 356-358.

(260) Wu, J.; Pisula, W.; Müllen, K. Graphenes as potential material for electronics. *Chem. Rev.* **2007,** *107*, 718-747.

(261) Ye, Q.; Chi, C. Recent highlights and perspectives on acene based molecules and materials. *Chem. Mater.* **2014,** *26*, 4046-4056.

(262) Ball, M.; Zhong, Y.; Wu, Y.; Schenck, C.; Ng, F.; Steigerwald, M.; Xiao, S.; Nuckolls, C. Contorted polycyclic aromatics. *Acc. Chem. Res.* **2015,** *48*, 267-276.

(263) Ito, H.; Ozaki, K.; Itami, K. Annulative π-extension (APEX): rapid access to fused arenes, heteroarenes, and nanographenes. *Angew. Chem., Int. Ed.* **2017,** *56*, 11144-11164.

(264) Narita, A.; Wang, X.-Y.; Feng, X.; Müllen, K. New advances in nanographene chemistry. *Chem. Soc. Rev.* **2015,** *44*, 6616-6643.

(265) Sun, Z.; Ye, Q.; Chi, C.; Wu, J. Low band gap polycyclic hydrocarbons: from closed-shell near infrared dyes and semiconductors to open-shell radicals. *Chem. Soc. Rev.* **2012,** *41*, 7857-7889.

(266) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. Rhodium or ruthenium-catalyzed oxidative C–H/C–H cross-coupling: direct access to extended π-conjugated systems. *Angew. Chem., Int. Ed.* **2013,** *52*, 580-584.

(267) Fu, W. C.; Wang, Z.; Chan, W. T. K.; Lin, Z.; Kwong, F. Y. Regioselective synthesis of polycyclic and heptagon-embedded aromatic compounds through a versatile π-extension of aryl halides. *Angew. Chem., Int. Ed.* **2017,** *56*, 7166-7170.

(268) Fujikawa, T.; Segawa, Y.; Itami, K. Synthesis, structures, and properties of π-extended double helicene: a combination of planar and nonplanar π-systems. *J. Am. Chem. Soc.* **2015,** *137*, 7763-7768.

(269) Huang, H.; Xu, Z.; Ji, X.; Li, B.; Deng, G.-J. Thiophene-fused heteroaromatic systems enabled by internal oxidant-induced cascade bis-heteroannulation. *Org. Lett.* **2018,** *20*, 4917-4920.

(270) Ito, H.; Segawa, Y.; Murakami, K.; Itami, K. Polycyclic arene synthesis by annulative π-extension. *J. Am. Chem. Soc.* **2019,** *141*, 3-10.

(271) Kadam, V. D.; Feng, B.; Chen, X.; Liang, W.; Zhou, F.; Liu, Y.; Gao, G.; You, J. Cascade C–H annulation reaction of benzaldehydes, anilines, and alkynes toward dibenzo[a,f]quinolizinium salts: discovery of photostable mitochondrial trackers at the nanomolar level. *Org. Lett.* **2018,** *20*, 7071-7075.

(272) Kitano, H.; Matsuoka, W.; Ito, H.; Itami, K. Annulative π-extension of indoles and pyrroles with diiodobiaryls by Pd catalysis: rapid synthesis of nitrogen-containing polycyclic aromatic compounds. *Chem. Sci.* **2018,** *9*, 7556-7561.

(273) Koga, Y.; Kaneda, T.; Saito, Y.; Murakami, K.; Itami, K. Synthesis of partially and fully fused polyaromatics by annulative chlorophenylene dimerization. *Science* **2018,** *359*, 435-439.

(274) Matsuoka, W.; Ito, H.; Itami, K. Rapid access to nanographenes and fused heteroaromatics by palladium-catalyzed annulative π-extension reaction of unfunctionalized aromatics with diiodobiaryls. *Angew. Chem., Int. Ed.* **2017,** *56*, 12224-12228.

(275) Ozaki, K.; Kawasumi, K.; Shibata, M.; Ito, H.; Itami, K. One-shot K-region-selective annulative π-extension for nanographene synthesis and functionalization. *Nat. Commun.* **2015,** *6*, 6251.

(276) She, Z.; Wang, Y.; Wang, D.; Zhao, Y.; Wang, T.; Zheng, X.; Yu, Z.-X.; Gao, G.; You, J. Two-fold C−H/C−H cross-coupling using $RhCl_3 \cdot 3H_2O$ as the catalyst: direct fusion of *N*-(hetero)arylimidazolium salts and (hetero)arenes. *J. Am. Chem. Soc.* **2018,** *140*, 12566-12573.

(277) Yin, J.; You, J. Concise synthesis of polysubstituted carbohelicenes by a C−H activation/radical reaction/C−H activation sequence. *Angew. Chem., Int. Ed.* **2019,** *58*, 302-306.

(278) Zhu, C.; Wang, D.; Wang, D.; Zhao, Y.; Sun, W.-Y.; Shi, Z. Bottom-up construction of π-extended arenes by a palladium-catalyzed annulative dimerization of *o*-iodobiaryl compounds. *Angew. Chem., Int. Ed.* **2018,** *57*, 8848-8853.

(279) Ito, S.; Tokimaru, Y.; Nozaki, K. Benzene-Fused Azacorannulene Bearing an Internal Nitrogen Atom. *Angewandte Chemie International Edition* **2015,** *54*, 7256-7260.

(280) Matsui, K.; Oda, S.; Yoshiura, K.; Nakajima, K.; Yasuda, N.; Hatakeyama, T. One-shot multiple borylation toward BN-doped nanographenes. *J. Am. Chem. Soc.* **2018,** *140*, 1195-1198.

(281) Oki, K.; Takase, M.; Mori, S.; Shiotari, A.; Sugimoto, Y.; Ohara, K.; Okujima, T.; Uno, H. Synthesis, structures, and properties of core-expanded azacoronene analogue: a twisted π-system with two *N*-doped heptagons. *J. Am. Chem. Soc.* **2018,** *140*, 10430-10434.

(282) Tan, Q.; Higashibayashi, S.; Karanjit, S.; Sakurai, H. Enantioselective synthesis of a chiral nitrogen-doped buckybowl. *Nat. Commun.* **2012,** *3*, 891.

(283) Yokoi, H.; Hiraoka, Y.; Hiroto, S.; Sakamaki, D.; Seki, S.; Shinokubo, H. Nitrogen-embedded buckybowl and its assembly with C60. *Nat. Commun.* **2015,** *6*, 8215.

(284) Hirai, M.; Tanaka, N.; Sakai, M.; Yamaguchi, S. Structurally constrained boron-, nitrogen-, silicon-, and phosphorus-centered polycyclic π-conjugated systems. *Chem. Rev.* **2019,** *119*, 8291-8331.

(285) Jayakumar, J.; Parthasarathy, K.; Chen, Y.-H.; Lee, T.-H.; Chuang, S.-C.; Cheng, C.-H. One-pot synthesis of highly substituted polyheteroaromatic compounds by rhodium(III)-catalyzed multiple C–H activation and annulation. *Angew. Chem., Int. Ed.* **2014,** *53*, 9889-9892.

(286) Liu, B.; Hu, F.; Shi, B.-F. Synthesis of sterically congested polycyclic aromatic hydrocarbons: rhodium(III)-catalyzed cascade oxidative annulation of aryl ketoximes with kiphenylacetylene by sequential cleavage of multiple C–H bonds. *Adv. Synth. Catal.* **2014,** *356*, 2688-2696.

(287) Kong, W.-J.; Shen, Z.; Finger, L. H.; Ackermann, L. Electrochemical access to aza-polycyclic aromatic hydrocarbons: rhoda-electrocatalyzed domino alkyne annulations. *Angew. Chem., Int. Ed.* **2020,** *59*, 5551-5556.
(288) Baguley, T. D.; Xu, H.-C.; Chatterjee, M.; Nairn, A. C.; Lombroso, P. J.; Ellman, J. A. Substrate-based fragment identification for the development of selective, nonpeptidic inhibitors of striatal-enriched protein tyrosine phosphatase. *J. Med. Chem.* **2013,** *56*, 7636-7650.
(289) Carroll, M. P.; Guiry, P. J. *P*,*N* ligands in asymmetric catalysis. *Chem. Soc. Rev.* **2014,** *43*, 819-833.
(290) Demmer, C. S.; Krogsgaard-Larsen, N.; Bunch, L. Review on modern advances of chemical methods for the introduction of a phosphonic acid group. *Chem. Rev.* **2011,** *111*, 7981-8006.
(291) Gagnon, K. J.; Perry, H. P.; Clearfield, A. Conventional and unconventional metal–organic frameworks based on phosphonate ligands: MOFs and UMOFs. *Chem. Rev.* **2012,** *112*, 1034-1054.
(292) Queffélec, C.; Petit, M.; Janvier, P.; Knight, D. A.; Bujoli, B. Surface modification using phosphonic acids and esters. *Chem. Rev.* **2012,** *112*, 3777-3807.
(293) Tang, W.; Zhang, X. New chiral phosphorus ligands for enantioselective hydrogenation. *Chem. Rev.* **2003,** *103*, 3029-3070.
(294) Kuninobu, Y.; Yoshida, T.; Takai, K. Palladium-catalyzed synthesis of dibenzophosphole oxides via intramolecular dehydrogenative cyclization. *J. Org. Chem.* **2011,** *76*, 7370-7376.
(295) Sokolov, V. I.; Troitskaya, L. L.; Reutov, O. A. Alternative synthesis of enantiomeric 1-diphenylphosphino-2-dimethylaminomethylferrocene (Kumada's ligand). *J. Organomet. Chem.* **1980,** *202*, C58-C60.
(296) Stepanova, V. A.; Dunina, V. V.; Smoliakova, I. P. Reactions of cyclopalladated complexes with lithium diphenylphosphide. *Organometallics* **2009,** *28*, 6546-6558.
(297) Wu, Z.-J.; Su, F.; Lin, W.; Song, J.; Wen, T.-B.; Zhang, H.-J.; Xu, H.-C. Scalable rhodium(III)-catalyzed aryl C−H phosphorylation enabled by anodic oxidation induced reductive elimination. *Angew. Chem., Int. Ed.* **2019,** *58*, 16770-16774.
(298) Ackermann, L. Catalytic Arylations with Challenging Substrates: From Air-Stable HASPO Preligands to Indole Syntheses and C-H Bond Functionalizations. *Synlett* **2007,** *2007*, 0507-0526.
(299) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. Ruthenium-catalyzed regioselective direct alkylation of arenes with unactivated alkyl halides through C–H bond cleavage. *Angew. Chem., Int. Ed.* **2009,** *48*, 6045-6048.
(300) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. Weakly coordinating directing groups for ruthenium(II)-catalyzed C–H activation. *Adv. Synth. Catal.* **2014,** *356*, 1461-1479.
(301) Fumagalli, F.; Warratz, S.; Zhang, S.-K.; Rogge, T.; Zhu, C.; Stückl, A. C.; Ackermann, L. Arene-ligand-free ruthenium(II/III) manifold for meta-C−H alkylation: remote purine diversification. *Chem. Eur. J.* **2018,** *24*, 3984-3988.
(302) Hofmann, N.; Ackermann, L. Meta-selective C–H bond alkylation with secondary alkyl halides. *J. Am. Chem. Soc.* **2013,** *135*, 5877-5884.
(303) Kozhushkov, S. I.; Ackermann, L. Ruthenium-catalyzed direct oxidative alkenylation of arenes through twofold C–H bond functionalization. *Chem. Sci.* **2013,** *4*, 886-896.

(304) Kumar, N. Y. P.; Bechtoldt, A.; Raghuvanshi, K.; Ackermann, L. Ruthenium(II)-catalyzed decarboxylative C−H activation: versatile routes to meta-alkenylated arenes. *Angew. Chem., Int. Ed.* **2016,** *55*, 6929-6932.

(305) Leitch, J. A.; McMullin, C. L.; Paterson, A. J.; Mahon, M. F.; Bhonoah, Y.; Frost, C. G. Ruthenium-catalyzed para-selective C−H alkylation of aniline derivatives. *Angew. Chem., Int. Ed.* **2017,** *56*, 15131-15135.

(306) Li, J.; Korvorapun, K.; De Sarkar, S.; Rogge, T.; Burns, D. J.; Warratz, S.; Ackermann, L. Ruthenium(II)-catalysed remote C–H alkylations as a versatile platform to meta-decorated arenes. *Nat. Commun.* **2017,** *8*, 15430.

(307) Paterson, A. J.; Heron, C. J.; McMullin, C. L.; Mahon, M. F.; Press, N. J.; Frost, C. G. α-Halo carbonyls enable meta selective primary, secondary and tertiary C–H alkylations by ruthenium catalysis. *Org. Biomol. Chem.* **2017,** *15*, 5993-6000.

(308) Ruan, Z.; Zhang, S.-K.; Zhu, C.; Ruth, P. N.; Stalke, D.; Ackermann, L. Ruthenium(II)-catalyzed meta C−H mono- and difluoromethylations by phosphine/carboxylate cooperation. *Angew. Chem., Int. Ed.* **2017,** *56*, 2045-2049.

(309) Warratz, S.; Burns, D. J.; Zhu, C.; Korvorapun, K.; Rogge, T.; Scholz, J.; Jooss, C.; Gelman, D.; Ackermann, L. *meta*-C−H bromination on purine bases by heterogeneous ruthenium catalysis. *Angew. Chem., Int. Ed.* **2017,** *56*, 1557-1560.

(310) Yang, F.; Rauch, K.; Kettelhoit, K.; Ackermann, L. Aldehyde-assisted ruthenium(II)-catalyzed C–H oxygenations. *Angew. Chem., Int. Ed.* **2014,** *53*, 11285-11288.

(311) Paterson, A. J.; St John-Campbell, S.; Mahon, M. F.; Press, N. J.; Frost, C. G. Catalytic meta-selective C–H functionalization to construct quaternary carbon centres. *Chem. Commun.* **2015,** *51*, 12807-12810.

(312) Korvorapun, K.; Kaplaneris, N.; Rogge, T.; Warratz, S.; Stückl, A. C.; Ackermann, L. Sequential meta-/ortho-C–H functionalizations by one-pot ruthenium(II/III) catalysis. *ACS Catal.* **2018,** *8*, 886-892.

(313) Xu, F.; Li, Y.-J.; Huang, C.; Xu, H.-C. Ruthenium-catalyzed electrochemical dehydrogenative alkyne annulation. *ACS Catal.* **2018,** *8*, 3820-3824.

(314) Ackermann, L.; Lygin, A. V. Cationic ruthenium(II) catalysts for oxidative C–H/N–H bond functionalizations of anilines with removable directing group: synthesis of indoles in water. *Org. Lett.* **2012,** *14*, 764-767.

(315) Qiu, Y.; Tian, C.; Massignan, L.; Rogge, T.; Ackermann, L. Electrooxidative ruthenium-catalyzed C−H/O−H annulation by weak *O*-coordination. *Angew. Chem., Int. Ed.* **2018,** *57*, 5818-5822.

(316) Luo, M.-J.; Zhang, T.-T.; Cai, F.-J.; Li, J.-H.; He, D.-L. Decarboxylative [4+2] annulation of arylglyoxylic acids with internal alkynes using the anodic ruthenium catalysis. *Chem. Commun.* **2019,** *55*, 7251-7254.

(317) Luo, M.-J.; Hu, M.; Song, R.-J.; He, D.-L.; Li, J.-H. Ruthenium(II)-catalyzed electrooxidative [4+2] annulation of benzylic alcohols with internal alkynes: entry to isocoumarins. *Chem. Commun.* **2019,** *55*, 1124-1127.

(318) Mei, R.; Koeller, J.; Ackermann, L. Electrochemical ruthenium-catalyzed alkyne annulations by C–H/Het–H activation of aryl carbamates or phenols in protic media. *Chem. Commun.* **2018,** *54*, 12879-12882.

(319) Wang, Z.-Q.; Hou, C.; Zhong, Y.-F.; Lu, Y.-X.; Mo, Z.-Y.; Pan, Y.-M.; Tang, H.-T. Electrochemically enabled double C–H activation of amides: chemoselective synthesis of polycyclic isoquinolinones. *Org. Lett.* **2019,** *21*, 9841-9845.

(320) Yang, L.; Steinbock, R.; Scheremetjew, A.; Kuniyil, R.; Finger, L. H.; Messinis, A. M.; Ackermann, L. Azaruthena(II)-bicyclo[3.2.0]heptadiene: key intermediate for ruthenaelectro(II/III/I)-catalyzed alkyne annulations. *Angew. Chem., Int. Ed.* **2020,** *59*, 11130-11135.

(321) Massignan, L.; Tan, X.; Meyer, T. H.; Kuniyil, R.; Messinis, A. M.; Ackermann, L. C−H oxygenation reactions enabled by dual catalysis with electrogenerated hypervalent iodine species and ruthenium complexes. *Angew. Chem., Int. Ed.* **2020,** *59*, 3184-3189.

(322) Hu, Y.; Zhou, B.; Wang, C. Inert C–H bond transformations enabled by organometallic manganese catalysis. *Acc. Chem. Res.* **2018,** *51*, 816-827.

(323) Yoshino, T.; Matsunaga, S. (Pentamethylcyclopentadienyl)cobalt(III)-catalyzed C–H bond functionalization: from discovery to unique reactivity and selectivity. *Adv. Synth. Catal.* **2017,** *359*, 1245-1262.

(324) Yamaguchi, J.; Muto, K.; Itami, K. Nickel-catalyzed aromatic C–H functionalization. *Top. Curr. Chem.* **2016,** *374*, 55.

(325) Wei, D.; Zhu, X.; Niu, J.-L.; Song, M.-P. High-valent cobalt-catalyzed C−H functionalization based on concerted metalation–deprotonation and single-electron-transfer mechanisms. *ChemCatChem* **2016,** *8*, 1242-1263.

(326) Liu, W.; Ackermann, L. Manganese-catalyzed C–H activation. *ACS Catal.* **2016,** *6*, 3743-3752.

(327) Cera, G.; Ackermann, L. Iron-catalyzed C–H functionalization processes. *Top. Curr. Chem.* **2016,** *374*, 57.

(328) Hirano, K.; Miura, M. Recent advances in copper-mediated direct biaryl coupling. *Chem. Lett.* **2015,** *44*, 868-873.

(329) Kulkarni, A. A.; Daugulis, O. Direct conversion of carbon-hydrogen into carbon-carbon bonds by first-row transition-metal catalysis. *Synthesis* **2009,** *2009*, 4087-4109.

(330) Gomes, P.; Gosmini, C.; Nédélec, J.-Y.; Périchon, J. Electrochemical vinylation of aryl and vinyl halides with acrylate esters catalyzed by cobalt bromide. *Tetrahedron Lett.* **2002,** *43*, 5901-5903.

(331) Gomes, P.; Gosmini, C.; Nédélec, J.-Y.; Périchon, J. Cobalt bromide as catalyst in electrochemical addition of aryl halides onto activated olefins. *Tetrahedron Lett.* **2000,** *41*, 3385-3388.

(332) Gomes, P.; Gosmini, C.; Périchon, J. Cobalt-catalyzed direct electrochemical cross-coupling between aryl or heteroaryl halides and allylic acetates or carbonates. *J. Org. Chem.* **2003,** *68*, 1142-1145.

(333) Gomes, P.; Gosmini, C.; Périchon, J. Cobalt-catalyzed electrochemical vinylation of aryl halides using vinylic acetates. *Tetrahedron* **2003,** *59*, 2999-3002.

(334) Le Gall, E.; Gosmini, C.; Nédélec, J.-Y.; Périchon, J. Cobalt-catalyzed electrochemical cross-coupling of functionalized phenyl halides with 4-chloroquinoline derivatives. *Tetrahedron Lett.* **2001,** *42*, 267-269.

(335) Gosmini, C.; Nédélec, J. Y.; Périchon, J. Electrochemical cross-coupling between functionalized aryl halides and 2-chloropyrimidine or 2-chloropyrazine catalyzed by nickel 2,2′-bipyridine complex. *Tetrahedron Lett.* **2000,** *41*, 201-203.

(336) Sauermann, N.; Meyer, T. H.; Tian, C.; Ackermann, L. Electrochemical cobalt-catalyzed C–H oxygenation at room temperature. *J. Am. Chem. Soc.* **2017,** *139*, 18452-18455.

(337) Tian, C.; Massignan, L.; Meyer, T. H.; Ackermann, L. Electrochemical C−H/N−H activation by water-tolerant cobalt catalysis at room temperature. *Angew. Chem., Int. Ed.* **2018,** *57*, 2383-2387.
(338) Mei, R.; Sauermann, N.; Oliveira, J. C. A.; Ackermann, L. Electroremovable traceless hydrazides for cobalt-catalyzed electro-oxidative C–H/N–H activation with internal alkynes. *J. Am. Chem. Soc.* **2018,** *140*, 7913-7921.
(339) Sauermann, N.; Mei, R.; Ackermann, L. Electrochemical C−H amination by cobalt catalysis in a renewable colvent. *Angew. Chem., Int. Ed.* **2018,** *57*, 5090-5094.
(340) Gao, X.; Wang, P.; Zeng, L.; Tang, S.; Lei, A. Cobalt(II)-catalyzed electrooxidative C–H amination of arenes with alkylamines. *J. Am. Chem. Soc.* **2018,** *140*, 4195-4199.
(341) Zeng, L.; Li, H.; Tang, S.; Gao, X.; Deng, Y.; Zhang, G.; Pao, C.-W.; Chen, J.-L.; Lee, J.-F.; Lei, A. Cobalt-catalyzed electrochemical oxidative C–H/N–H carbonylation with hydrogen evolution. *ACS Catal.* **2018,** *8*, 5448-5453.
(342) Dhawa, U.; Tian, C.; Li, W.; Ackermann, L. Cobalta-electrocatalyzed C–H allylation with unactivated alkenes. *ACS Catal.* **2020,** *10*, 6457-6462.
(343) Serra, D. C., M. C.; McElwee-White, L. Iron and ruthenium heterobimetallic carbonyl complexes as electrocatalysts for alcohol oxidation: electrochemical and mechanistic studies. *Organometallics* **2011,** *30*, 5568-5577.
(344) Bellini, M.; Bevilacqua, M.; Filippi, J.; Lavacchi, A.; Marchionni, A.; Miller, H. A.; Oberhauser, W.; Vizza, F.; Annen, S. P.; Grutzmacher, H. Energy and chemicals from the selective electrooxidation of renewable diols by organometallic fuel cells. *ChemSusChem* **2014,** *7*, 2432-2435.
(345) Brownell, K. R.; McCrory, C. C.; Chidsey, C. E.; Perry, R. H.; Zare, R. N.; Waymouth, R. M. Electrooxidation of alcohols catalyzed by amino alcohol ligated ruthenium complexes. *J. Am. Chem. Soc.* **2013,** *135*, 14299-14305.
(346) Vannucci, A. K.; Hull, J. F.; Chen, Z.; Binstead, R. A.; Concepcion, J. J.; Meyer, T. J. Water oxidation intermediates applied to catalysis: benzyl alcohol oxidation. *J. Am. Chem. Soc.* **2012,** *134*, 3972-3975.
(347) Yamazaki, S.; Yao, M.; Fujiwara, N.; Siroma, Z.; Yasuda, K.; Ioroi, T. Electrocatalytic oxidation of alcohols by a carbon-supported Rh porphyrin. *Chem. Commun.* **2012,** *48*, 4353-4355.
(348) Weiss, C. J.; Das, P.; Miller, D. L.; Helm, M. L.; Appel, A. M. Catalytic Oxidation of Alcohol via Nickel Phosphine Complexes with Pendant Amines. *Acs Catalysis* **2014,** *4*, 2951-2958.
(349) Weiss, C. J.; Wiedner, E. S.; Roberts, J. A.; Appel, A. M. Nickel phosphine catalysts with pendant amines for electrocatalytic oxidation of alcohols. *Chem Commun* **2015,** *51*, 6172-6174.
(350) Nutting, J. E.; Rafiee, M.; Stahl, S. S. Tetramethylpiperidine N-Oxyl (TEMPO), Phthalimide N-Oxyl (PINO), and Related N-Oxyl Species: Electrochemical Properties and Their Use in Electrocatalytic Reactions. *Chem Rev* **2018,** *118*, 4834-4885.
(351) Li, M.; Klunder, K.; Blumenthal, E.; Prater, M. B.; Lee, J.; Matthiesen, J. E.; Minteer, S. D. Ionic Liquid Stabilized 2,2,6,6-Tetramethylpiperidine 1-Oxyl Catalysis for Alcohol Oxidation. *Acs Sustain Chem Eng* **2020,** *8*, 4489-4498.
(352) Badalyan, A.; Stahl, S. S. Cooperative electrocatalytic alcohol oxidation with electron-proton-transfer mediators. *Nature* **2016,** *535*, 406-410.

(353) Qi, H. L.; Chen, D. S.; Ye, J. S.; Huang, J. M. Electrochemical technique and copper-promoted transformations: selective hydroxylation and amination of arylboronic acids. *J Org Chem* **2013,** *78*, 7482-7487.
(354) Wexler, R. P.; Nuhant, P.; Senter, T. J.; Gale-Day, Z. J. Electrochemically enabled Chan-Lam couplings of aryl boronic acids and anilines. *Org. Lett.* **2019,** *21*, 4540-4543.
(355) Walker, B. R.; Manabe, S.; Brusoe, A. T.; Sevov, C. S. Mediator-enabled electrocatalysis with ligandless copper for anaerobic Chan-Lam coupling reactions. *J. Am. Chem. Soc.* **2021,** *143*, 6257-6265.