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Electrochemical strategies for C–H functionalization and C–N bond formation

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Conventional methods for carrying out carbon–hydrogen functionalization and carbon–nitrogen bond formation are typically conducted at elevated temperatures, and rely on expensive catalysts as well as the use of stoichiometric, and perhaps toxic, oxidants. In this regard, electrochemical synthesis has recently been recognized as a sustainable and scalable strategy for the construction of challenging carbon–carbon and carbon–heteroatom bonds. Here, electrosynthesis has proven to be an environmentally benign, highly effective and versatile platform for achieving a wide range of nonclassical bond disconnections *via* generation of radical intermediates under mild reaction conditions. This review provides an overview on the use of anodic electrochemical methods for expediting the development of carbon–hydrogen functionalization and carbon–nitrogen bond formation strategies. Emphasis is placed on methodology development and mechanistic insight and aims to provide inspiration for future synthetic applications in the field of electrosynthesis.

1. Introduction

Synthetic chemists are constantly faced with the challenge of producing molecules, whether it be small-molecule synthesis or accessing increasingly complex target structures, in a selective and efficient manner. The methods and strategies of organic synthesis are continuously being improved and augmented in order to expand the chemical toolbox, thereby enabling new routes to solve ever-increasingly complex problems in chemical research.^{1–6} Over the years, the use of renewable chemical

feedstocks,⁷ biocatalysis⁸ and base-metal catalysis,⁹ in combination with the development of cascade/tandem processes¹⁰ has become paramount for realizing atom-economic and more sustainable reaction platforms.¹¹ Recently, research in the chemical sciences has experienced renewed interest in visible light photocatalysis^{12,13} and electrochemistry.^{14–17} These versatile synthetic platforms have the ability to promote challenging bond constructions under mild reaction conditions.

1.1. Fundamental principles and general considerations of preparative electrochemistry

Electrolysis is carried out in an electrochemical cell, a reactor that is comprised of an electroactive species/substrate, electrolyte, solvent and (at least) two electrodes (an anode and a cathode). The anode is connected to the positive pole of a power source (galvanostat or potentiostat) and is oxidative while the cathode is connected to the negative pole and is reductive. For construction of the cell, two different options exist: undivided cells and divided cells (Fig. 1). In undivided cells the anode and cathode are not separated and are thus placed in the same compartment. This setup is preferred due to its ease of construction and allows for both reduction and oxidation to occur within the same compartment, thereby enabling the substrate to be exposed to all species present in the reaction. When employing this arrangement, it is crucial to consider the possible reactions that may occur at the auxiliary electrode.¹⁸ However, examples exist where a species produced at the auxiliary electrode interferes with the electrochemical process at the working electrode. This issue can be ameliorated using a divided cell. In this arrangement, the two (anodic and cathodic) compartments are physically separated through the use of a small, porous frit. This allows for the transfer

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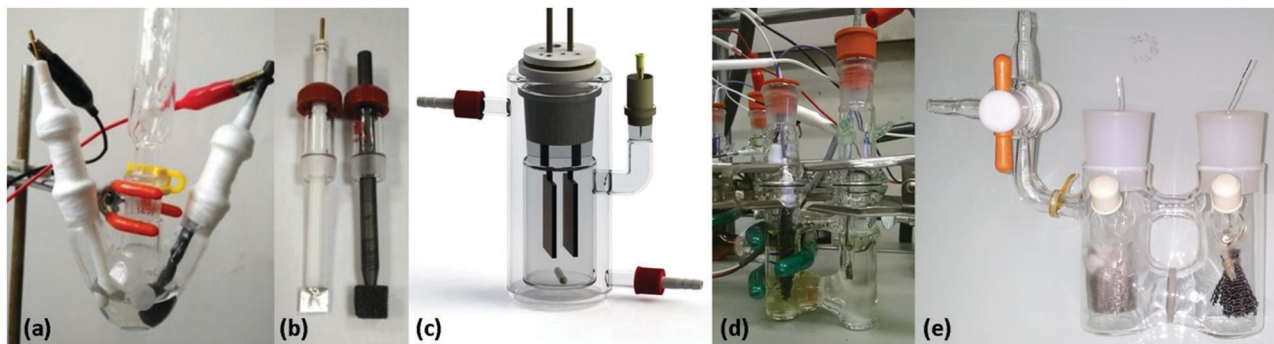


Fig. 1 Selected electrolysis setups. (a) Three-necked round-bottom flask equipped with (b) a reticulated vitreous carbon anode and a platinum plate cathode (Reprinted with permission from ref. 926. Copyright 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim). (c) Undivided beaker-type glass cell equipped with an isostatic graphite anode and a platinum cathode (Reproduced from ref. 918 with permission from The Royal Society of Chemistry). (d) H-Type divided cell equipped with a reticulated vitreous carbon anode and a platinum wire cathode (Reprinted with permission from ref. 398. Copyright 2018 American Chemical Society). (e) H-Type divided cell equipped with a 4G glass filter, an anode made of carbon strings and a platinum plate cathode (Reprinted with permission from ref. 958. Copyright 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim).

of charge and enables the two half-reactions of the electrolysis to occur separately.^{19,20}

In principle, electrodes can be constructed from any inert material that enables electron transfer in solution. Examples of electrodes include carbon-based materials (graphite and glassy carbon), magnesium, platinum and stainless steel. Another appealing electrode material is reticulated vitreous carbon (RVC), a material that combines the properties of carbon with glass, which has a high surface area, high void volume, and chemical resistance. At the end of the reaction, the electrodes can simply be physically removed as long as they are stable to the applied reaction conditions.^{21,22} Acceptable solvents that can be employed in electrochemical processes include, but are not limited to acetonitrile, dichloromethane, methanol, or dimethylformamide. Here, the use of nonconventional organic solvents, such as trifluoroethanol,²³ trifluoroacetic acid,²⁴ ionic liquids²⁵ and supercritical fluids,²⁶ has also received attention. In order for the reaction solution to become conductive, a supporting electrolyte has to be added. These are typically simple salts, such as alkali metal perchlorates and tetraalkyl ammonium salts, and are mainly used for increasing the conductivity of organic systems.

The electron transfer events that occur at the anode or cathode enable one to classify the electrochemical reactions as either oxidations or reductions, respectively. They occur on the surface of the electrodes and are therefore heterogeneous processes. The resulting species that is generated after the initial electron transfer between an electrode and an organic substrate is subsequently diffused into solution, which is followed by a secondary reaction of the initially produced radical species.^{27–31} Here, the potential of the electrode (E)—that is the difference between the potential at the electrode of interest and the selected reference electrode, such as the saturated calomel electrode (SCE)—will determine whether a specific electron transfer process is thermodynamically feasible, and is given by eqn (1):

$$\Delta G = -nFE \quad (1)$$

where ΔG is the free energy change, F is Faraday's constant (96 485 Coulombs mol⁻¹), and n is the number of electrons involved in the overall reaction. An advantage of preparative electrolysis is that an initial electroanalytical evaluation using, for example, cyclic voltammetry (CV) enables convenient assessment of the reaction system. Such simple analyses provide a great deal of vital information with relatively limited experimental effort and insight into which functional groups that may be oxidized or reduced, as well as the magnitude of the free energy that is needed to promote electron transfer in the studied electrochemical process.³²

It is important to note that the electrolysis experiments can be conducted using either a controlled-current or controlled-potential approach. In a controlled-current experiment, the current is held constant while the voltage gradually increases until the potential is reached for the electroactive species. Once depleted, the potential continues to rise until a second electroactive species or solvent molecule is oxidized or reduced. It is thus critical to consider the redox potentials of the substrate as well as all other species in solution in order to assure that the initial redox reaction does not involve participation of the solvent or other additives. However, if the potential needs to be tightly controlled, a controlled-potential experiment where the potential is set to a certain value will allow for a selective redox reaction to occur.³³ With this setup, it is important to have in mind that the decrease in substrate concentration is accompanied by a decrease in the current, and thus the rate of the reaction.

1.2. Historical advances in synthetic electrochemistry

Applying electrical current to affect a chemical reaction can be traced back to the 1830s when Faraday electrolyzed an acetate solution to produce hydrocarbons.³⁴ However, the Kolbe electrolysis constitutes one of the earliest carbon-carbon (C-C) bond forming reactions that was studied in detail.^{35,36} Here, carboxylate anions are oxidized at an anode. The initial electron transfer triggers extrusion of CO₂ to generate carbon-centered free radicals, which subsequently undergo homocoupling to produce the new C-C bond. The reaction



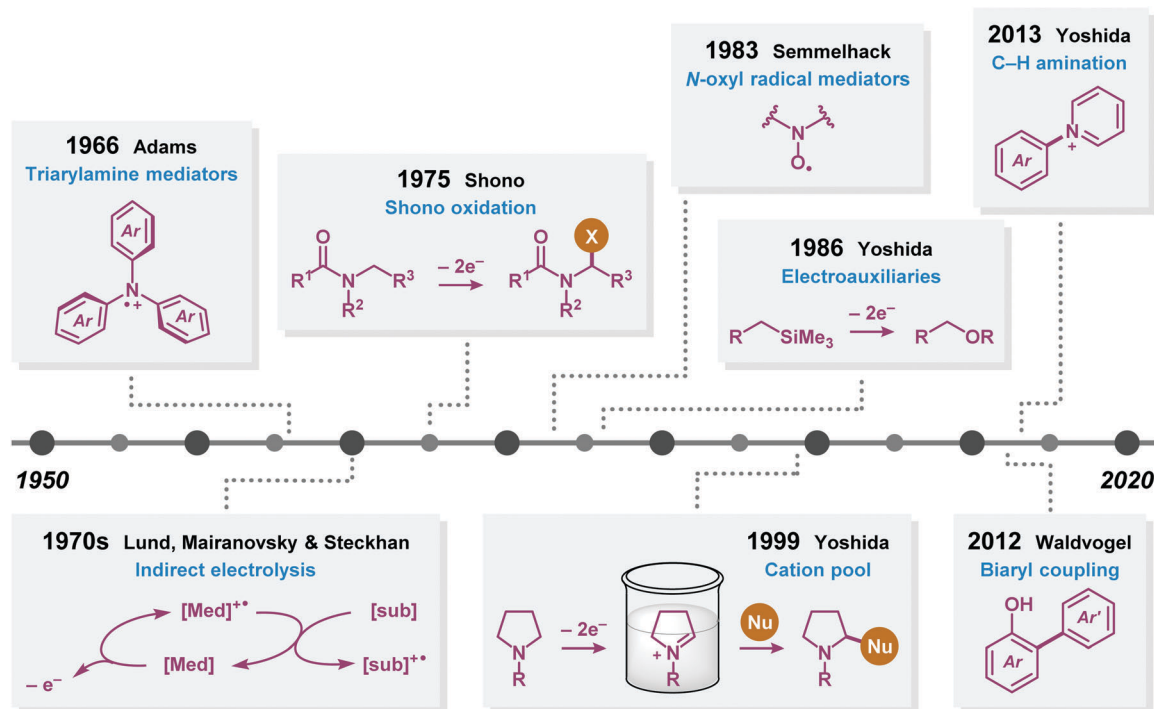


Fig. 2 Advances in organic electrochemistry.

still serves as a versatile method for C–C bond formation in contemporary organic synthesis.³⁷ Preparative electrolysis has also received significant interest from the chemical industry.^{38–40} Classical examples include the chloralkali and the Hall–Héroult processes, as well as production of organic compounds, such as adiponitrile and ethylene glycol.⁴¹

Additional advances in preparative electrolysis include the use of indirect electrolysis in which a redox mediator undergoes electron transfer at an electrode to afford an electrochemically generated reagent that triggers the reaction of interest (Fig. 2).⁴² This approach has a long history⁴³ and one of the earliest industrial applications concerned the oxidation of glucose to calcium gluconate using bromide as mediator.⁴⁴ During the last four decades, commonly employed organic redox mediators for anodic oxidations are triarylamines⁴⁵ and nitroxyl radicals.^{46,47} Since the active species of the mediator is continuously regenerated at the electrode it enables the use of substoichiometric quantities. Advantages of redox-mediated electrolysis (indirect electrolysis) are that problems such as are that problems associated with heterogeneous electron transfer, such as overpotentials,⁴⁸ can be avoided and that electrolysis can be conducted at lower potentials than

the redox potential of the substrate, accelerating the reaction rate while affording higher selectivities by circumventing potential side reactions. It should be noted that there exist several similarities between electrochemically-mediated reactions and visible light photoredox catalysis (Fig. 3). In this visible light-mediated platform a photocatalyst absorbs photonic energy. Upon absorption of visible light, a long-lived redox-active excited state is produced, which can engage in single-electron transfer (SET) events with, for example, organic substrates.

In the late 1980s, Yoshida introduced the concept of using electroauxiliaries.^{49,50} Typical electroauxiliaries include enol ethers,⁵¹ organostannanes,⁵² silyl groups,⁵³ and thioacetals.⁵⁴ The electroauxiliary is functionality appended to a compound in order to aid the oxidation or reduction of the substrate by reducing its oxidation or reduction potential. This facilitates either oxidation or reduction of the starting material in the presence of the desired nucleophile and reduces the likelihood of overoxidation or overreduction of the resultant product by promoting electron transfer in a more selective and predictable fashion. Moreover, noticeable contributions during the 21st century include Waldvogel's work on selective biaryl cross-coupling

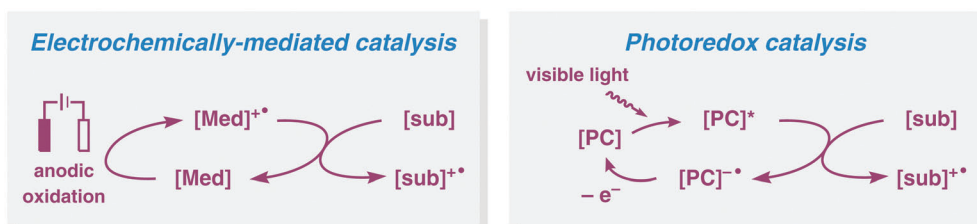


Fig. 3 Comparison of electrochemically-mediated catalysis and visible light photoredox catalysis. PC = photocatalyst.



platforms⁵⁵ and Yoshida's strategy for C–H amination⁵⁶ of aromatic compounds using the “cation pool” method.^{57,58}

1.3. Advantages of applying electrochemical methods in organic synthesis

The use of electrochemistry is considered a “green” and sustainable alternative to traditional, toxic redox-based methods. It has the ability to maximize atom efficiency while replacing stoichiometric redox reagents, such as NaH, OsO₄ and Pb(OAc)₄, with an electrical current, thereby minimizing production of reagent waste. Moreover, since the energy of the electrochemical system can be governed by the applied electrode potential, a majority of the preparative electrochemical reactions, even the ones with high activation energies, can be carried out at ambient temperature. Therefore, the application of electrochemistry in organic synthesis constitutes an appealing strategy for generating reactive radical intermediates under mild conditions.^{59,60}

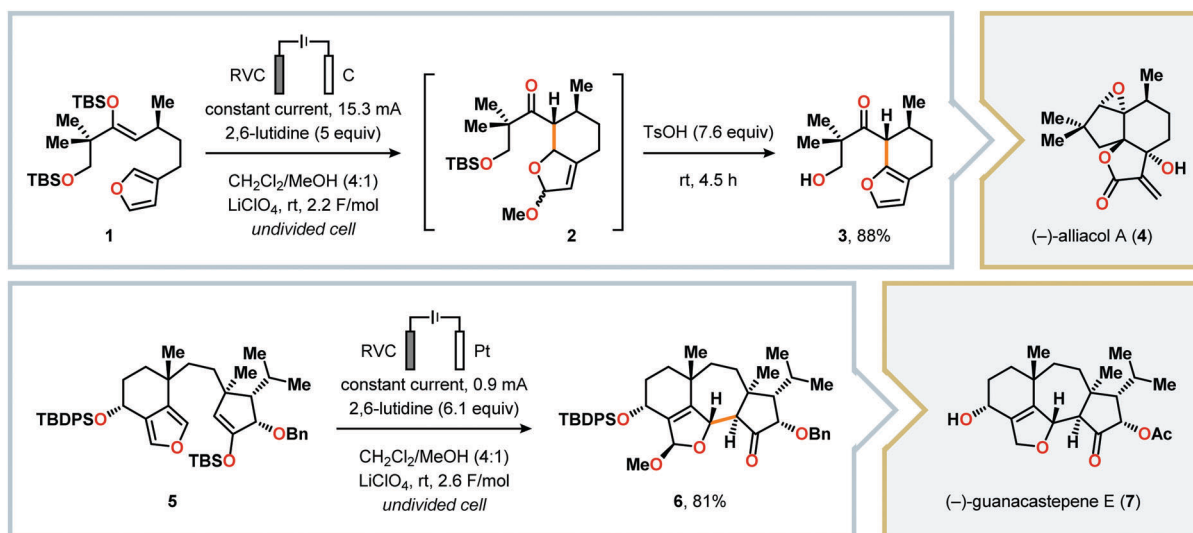
Radical cyclization reactions, for example, have typically been conducted in the presence of stoichiometric quantities of hazardous and toxic reagents, such as tin hydrides and azobis(isobutyronitrile) (AIBN). However, employing electrochemistry allows the development of reagent-free protocols that operate under mild reaction conditions, providing an environmentally friendly alternative.^{32,61} In addition to the aforementioned advantages of applying electrochemistry in organic synthesis, another feature of electrochemistry is that it can also be used to trigger umpolung reactions.^{62–64} Two elegant examples of using such a strategy can be found in Moeller's synthesis of alliacol A (**4**)^{65,66} and Trauner's synthesis of guanacastepene E (**7**)^{67,68} in which silyl enol ethers are coupled with furans *via* intramolecular electrooxidative coupling (Scheme 1).

It is evident that organic electrochemistry represents an enabling technology for the organic chemistry research community for generating reactive but controllable radical intermediates under neutral reaction conditions. However, for the technique to become part of the standard chemical toolbox, the barrier to adoption

needs to be eliminated. The necessity to construct your own home-made electrochemical apparatus has certainly contributed to the general lack of interest in pursuing electrochemistry, for example, as part of a total synthesis. The barrier to adoption becomes even higher if there exist alternative methods for accomplishing the desired transformation. Furthermore, the numerous reaction variables, such as cell type, experiment type, electrode material and electrolyte, might be overwhelming, especially for practicing organic chemists without any prior experience in electrochemistry. Organic electrochemistry would benefit from being presented in a more user-friendly manner. Access to a commercially available standardized device for organic electrochemistry would certainly mitigate this barrier to adoption and allow the field to develop more rapidly.⁶⁹

1.4. 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.⁷⁰ Pioneering reviews include those by Wawzonek⁷¹ and Weinberg.⁷² Anodic oxidation processes have been examined by Adams,⁷³ Ebersson^{27,74} and Shono,⁷⁵ and more recently by Boydston,⁷⁶ Chiba,⁷⁷ Moeller,^{78–81} and Schäfer.^{82,83} Reviews detailing both anodic oxidation and cathodic reduction processes have been summarized by Schäfer,^{84,85} Wright⁸⁶ and Yoshida.⁸⁷ Progress in indirect electrolysis has been reviewed by Nikishin,^{42c} Steckhan,^{42a,b} as well as Francke and Little^{42d} while the synthetic endeavors of using electrochemistry in complex settings have been described by Baran.⁸⁸ In this review an overview of the electrochemical strategies for carrying out carbon–hydrogen (C–H) functionalization as well as carbon–nitrogen (C–N) bond formation is presented with an emphasis on methods development and mechanistic insight.⁸⁹ The review is organized based on the aforementioned reaction types and are grouped according to the electrochemical methods employed. While focus is on representative examples from the past two decades, early pioneering work is also highlighted. The aim of this review is to encourage



Scheme 1 Synthesis of alliacol A and guanacastepene E *via* anodic coupling reactions.



researchers to explore and to adopt organic electrochemistry, a technique with considerable potential, to the general synthetic toolbox.

2. Carbon–hydrogen (C–H) functionalization under oxidative electrochemical control

Over the past decade, transition metal-catalyzed C–H functionalization has enabled the development of a variety of nontraditional and innovative bond constructions in contemporary synthetic organic chemistry. The direct functionalization of C–H bonds represents a powerful strategy for selective C–C and carbon–heteroatom (C–X) bond formation, thereby improving atom- and step economy as well as streamlining chemical synthesis. However, despite intensive efforts and increased understanding of the mechanistic aspects of the C–H functionalization reaction manifolds, the inherent difficulty of activating kinetically inert C–H bonds has limited the development of catalytic platforms that operate efficiently under mild reaction conditions.^{90,91} In this chapter, various electrochemical concepts to expedite the development of C–H functionalization platforms are therefore surveyed.

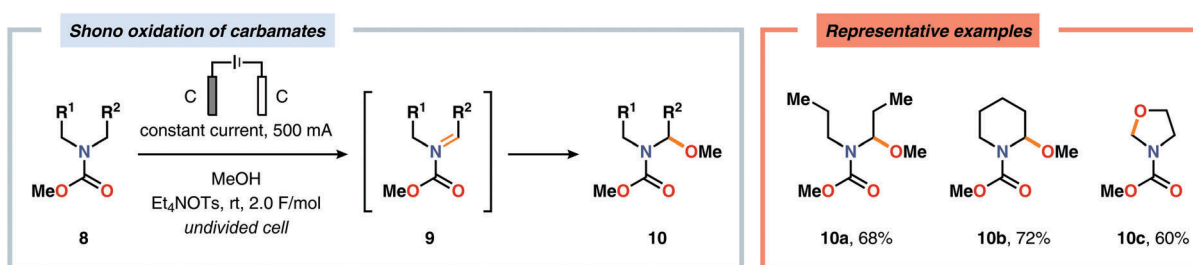
2.1. Shono-type anodic oxidations

Nitrogen-based heterocycles constitute an essential structural motif and are commonly found in natural products. In 1975, Shono and coworkers disclosed an electrochemical method for oxidation of carbamates to *N*-carbamoyl iminium ions.^{92–95} The reaction proceeds through the initial formation of a nitrogen-centered radical (*vide infra*), which is subsequently oxidized to an iminium ion intermediate that can be trapped with an alcoholic solvent molecule.⁹⁶ This allows for functionalization of the α -position adjacent to the nitrogen atom in heterocycles.^{97–110} For example, carrying out the anodic oxidation in methanol gives access to α -methoxylated products **10** (Scheme 2), which are established precursors to *N*-acyl iminium ions. If the substrate contains an alcohol moiety, intramolecular trapping produces oxazoline derivatives, such as **10c**.⁹² Upon treatment with Brønsted or Lewis acids, the generated *N,O*-aminals can be converted back to the iminium ion species, which allows for trapping with allyl silanes,^{111–113} cyanide,^{114–116} fluoride,¹¹⁷ furans,¹¹⁸ isocyanides,¹¹⁹ silyl enol ethers,¹²⁰ and trialkyl phosphites.¹²¹ Alternatively, functionalization can be carried out to yield a diversity of scaffolds as shown

in Scheme 3.¹²² Attempts have also been focused on developing asymmetric versions of the Shono oxidation using chiral cyclic dipeptides,^{123–126} oxazolines,¹²⁷ oxazolidinones¹²⁸ and pyrrolidones^{129–131} as well as ketopinic acid¹³² and carbamate,^{133–136} phosphorus^{137,138} and sulfur-based¹³⁹ chiral auxiliaries to give poor to high stereoselectivities in the alkylation step (Scheme 4).

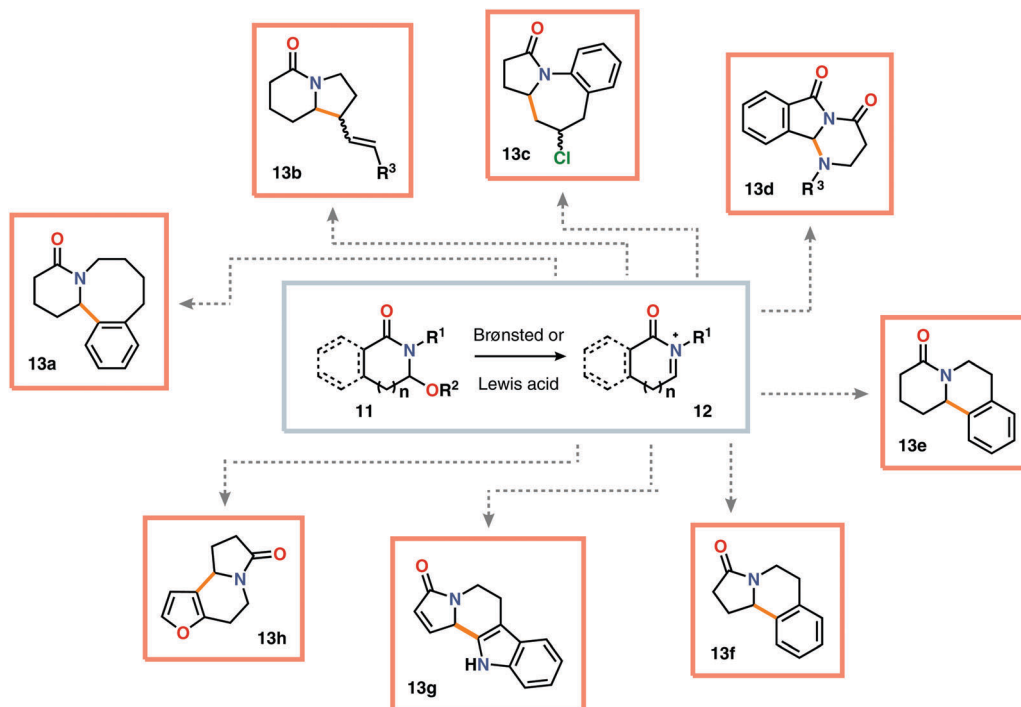
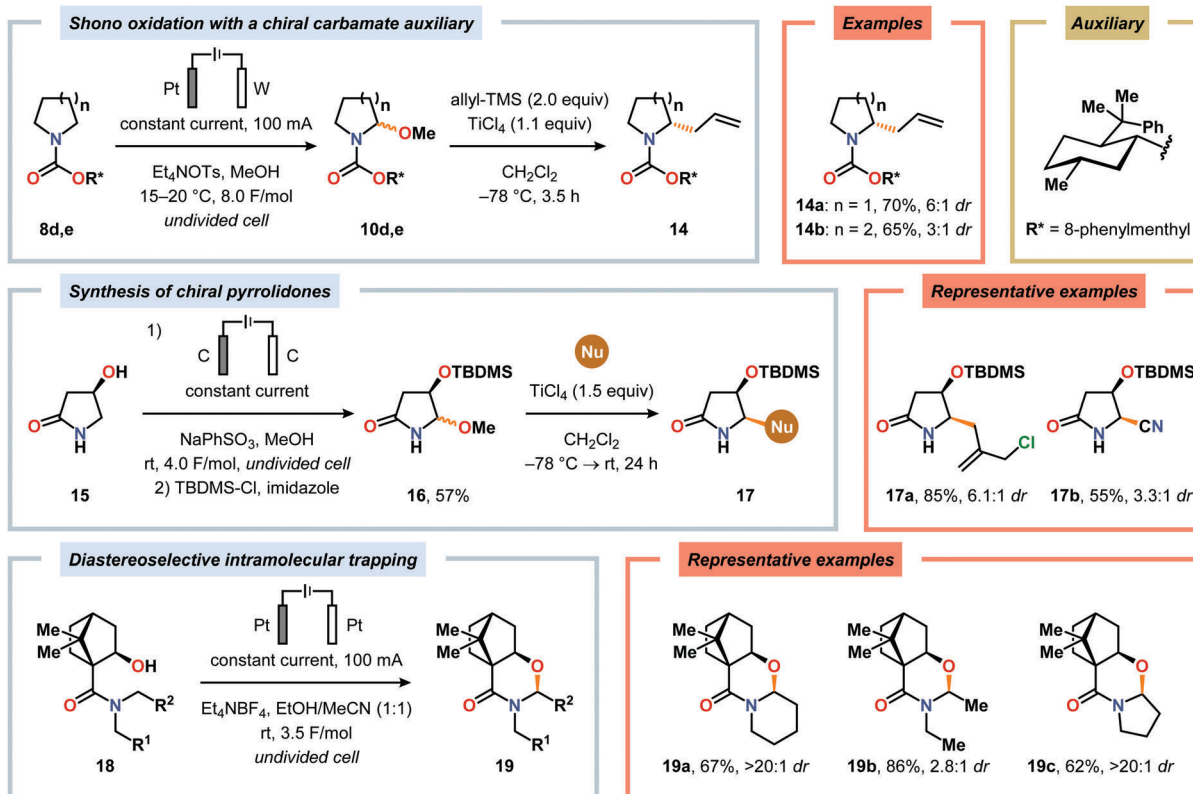
Shono-type anodic oxidations have in general been carried out with substrates and nucleophiles, such as methanol and cyanide, which possess high oxidation potentials. Although amines have lower oxidation potentials, which should facilitate the electrochemical oxidation process, protocols utilizing amines have been employed less frequently compared to their amide and carbamate counterparts. Huang and Gong recently disclosed a method for the electrochemical oxidation of γ -lactams. Direct trapping of the generated electrophilic acyliminium ions with anilines could be accomplished despite their low oxidation potential (Scheme 5).¹⁴⁰ Key to achieving high yields of the substituted γ -lactam products was to carry out the oxidation in a “quasi-divided cell”^{141,142} with a Pt wire anode and a Pt foil cathode in which the large difference in surface areas of the working and counter electrodes provided high current density at the anode, thereby favoring oxidation of the lactam. The protocol was applicable to a wide range of anilines containing electron-withdrawing groups, such as CF₃, CO₂Et, and OCF₃, as well as electron-donating groups, such as Me and OMe. Halogen-containing anilines were also effective substrates for the developed reaction, which provides an opportunity for further synthetic elaborations.¹⁴⁰ Fuchigami and Baba have also demonstrated anodic oxidation of imidates and imines to yield α -methoxylated or α -acetoxyated products (Scheme 6).¹⁴³

Of the limited protocols that exist that rely on using amines as substrates,^{144,145} Gallardo and Vilà reported that hindered secondary alkyl diamines **28** could be produced from anodic oxidation of hindered secondary alkyl amines **27** (Scheme 7).^{146–148} They subsequently demonstrated an electrochemical procedure to afford imidazolium and tetrahydropyrimidinium derivatives **30** from secondary alkyl diamines **29** (Scheme 8).¹⁴⁹ The Matsumura group has also shown that the introduction of a nucleophile to the α -position of an L-prolinol derivative (**31**) upon Shono-type oxidation is viable (Scheme 9).¹⁵⁰ Furthermore, Hurvois and coworkers prepared an α -amino nitrile through anodic oxidation in a synthesis of (+)-myrtine.¹⁵¹ Shono-type oxidation of aliphatic amines can also be extended to the synthesis of sulfonyl amidines.¹⁵² Different tertiary amines (**36**) were initially evaluated and were



Scheme 2 Shono oxidation of carbamates.



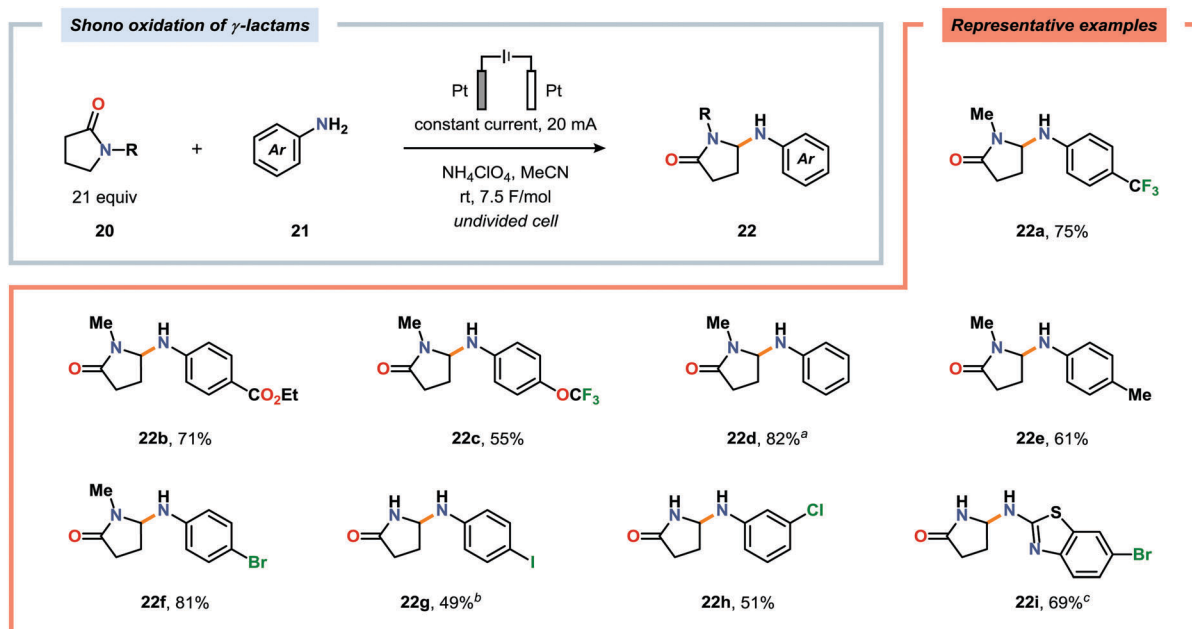
Scheme 3 Scaffold diversity from *N*-acyl iminium ions.

Scheme 4 Selected strategies for stereoselective functionalization of Shono oxidation products.

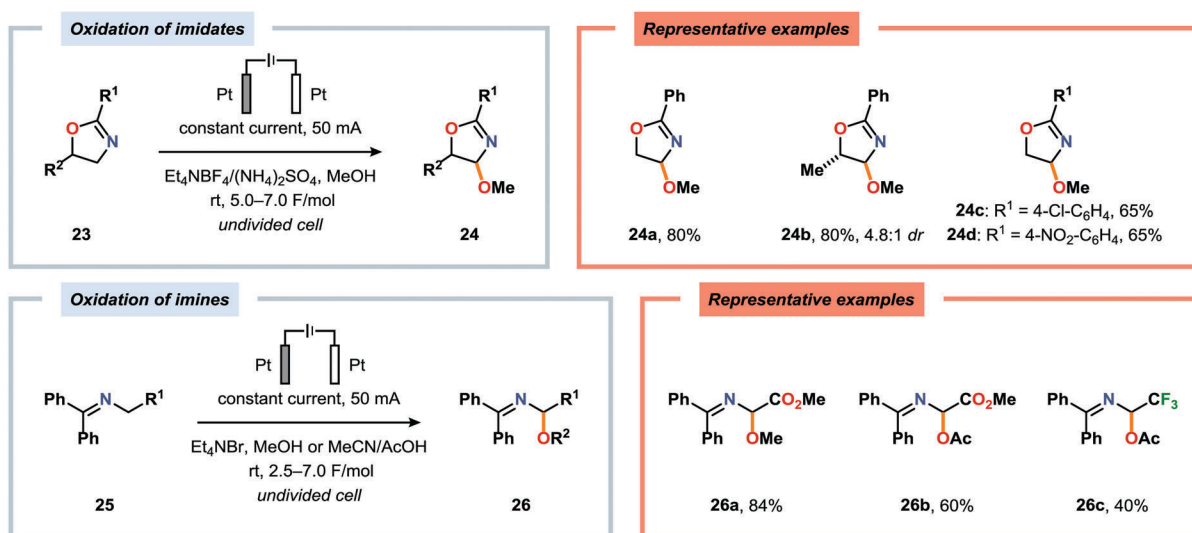
shown to efficiently afford the sulfonyl amidine derivatives **38** upon reaction with sulfonyl azides **37** (Scheme 10). Employing Et_3N as the amine these transformations presumably include

anodic oxidation of the aliphatic amine to produce an iminium intermediate (**39**), which tautomerizes into the corresponding enamine (**40**). Subsequent 1,3-dipolar cycloaddition between the

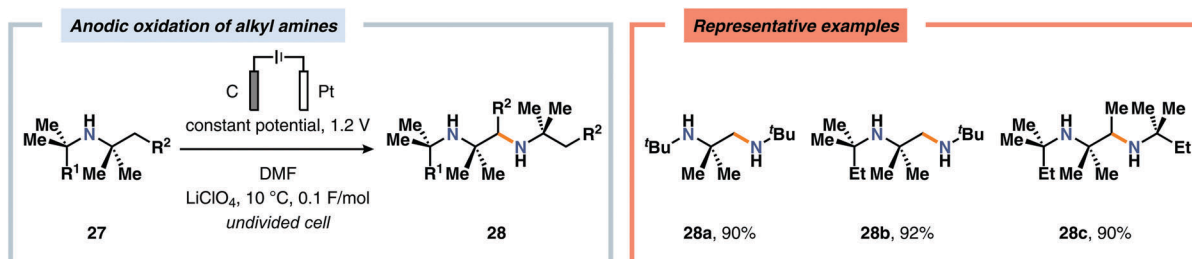




Scheme 5 Shono oxidation of γ -lactams using anilines as the trapping nucleophiles. ^a Carried out in MeCN/EtOAc (3:2), Et₃N (1.7 equiv.), constant current (10 mA) and 10.5 h. ^b After 1.5 h. ^c After 5 h.

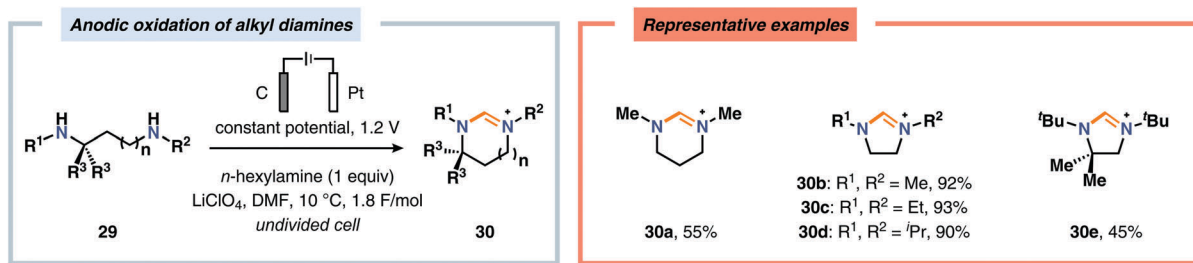


Scheme 6 Anodic oxidation of imidates and imines.

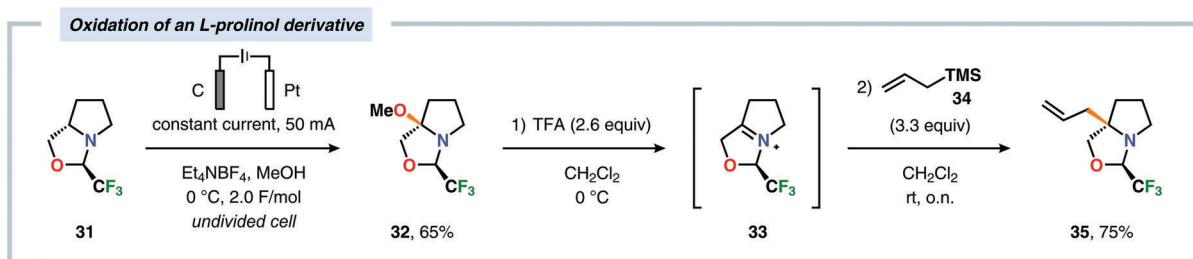


Scheme 7 Shono-type anodic oxidation of hindered secondary alkyl amines.





Scheme 8 Shono-type oxidation of secondary alkyl diamines.



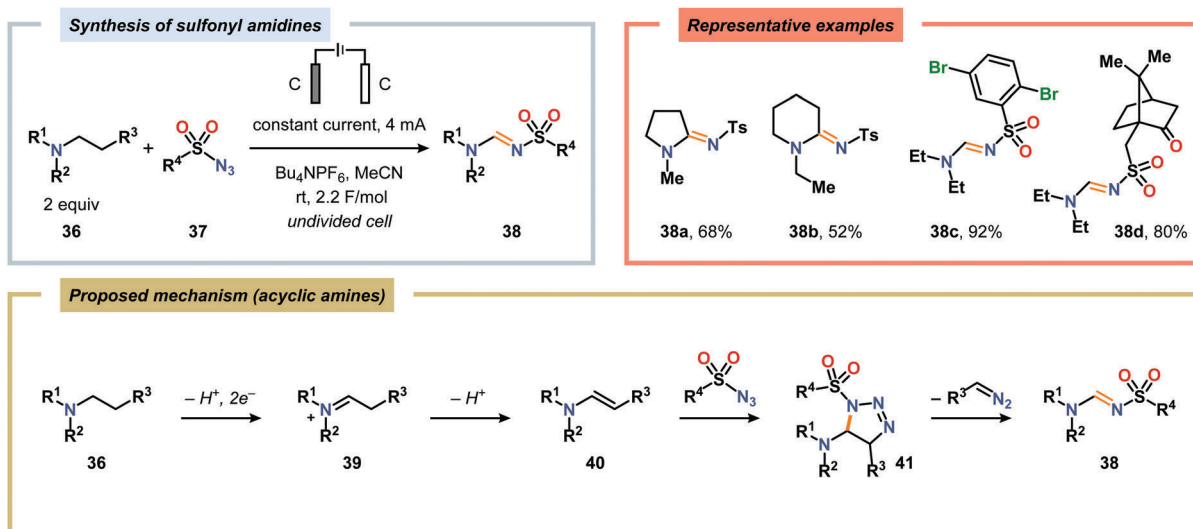
Scheme 9 Electrochemical oxidation of an L-prolinol derivative.

generated enamine and tosyl azide furnishes cycloadduct **41**. Finally, extrusion of CH_2N_2 delivers the desired amidine product **38**. The synthesis of amidine derivatives was also accomplished using secondary and primary aliphatic amines.

Okimoto and coworkers have also demonstrated that Shono-type oxidation of various amine-containing motifs carrying pendant nucleophiles can be employed to access a diverse set of heterocyclic compounds through intramolecular C–C or C–X bond formation processes (Scheme 11).^{153–159} Using a combination of NaOMe and KI as supporting electrolyte in MeOH proved to be the optimal for affecting electrochemical oxidation and subsequent intramolecular cyclization of tetrahydro(iso)quinolines **42** and **44** housing pendant alcohol or amine groups.

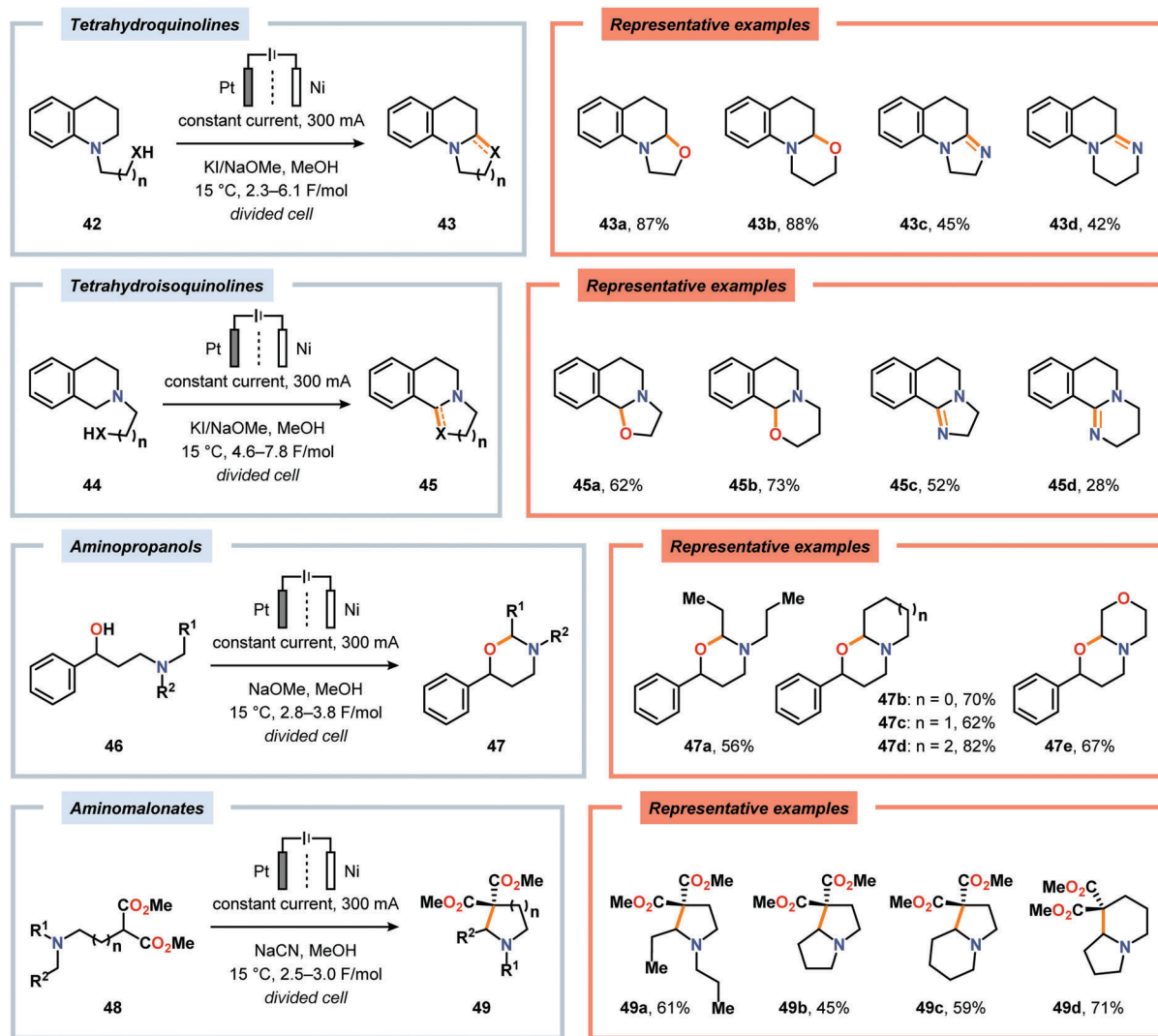
For the tetrahydroisoquinoline-derived substrates **44a** and **44b**, selective oxidation at the benzylic position afforded **45a** and **45b**.¹⁵⁷ The electrochemical oxidation/cyclization strategy could also be applied on 3-dialkylamino-1-phenylpropanols **46** to give the 1,3-oxazinane derivatives **47** in moderate to high yields.¹⁵⁸ Furthermore, the authors also investigated the electrooxidation of dimethyl aminomalonates **48**. Here, the use of NaCN as the supporting electrolyte resulted in the highest yields for the cyclized products **49**.^{157,160}

The Luo laboratory recently reported a visible light-mediated protocol for the enantioselective coupling of tetrahydroisoquinolines and simple alkyl ketones to furnish *syn*-Mannich-type adducts with good to excellent diastereo- and enantioselectivities.



Scheme 10 Electrochemical synthesis of sulfonyl amidines from aliphatic amines and sulfonyl azides.





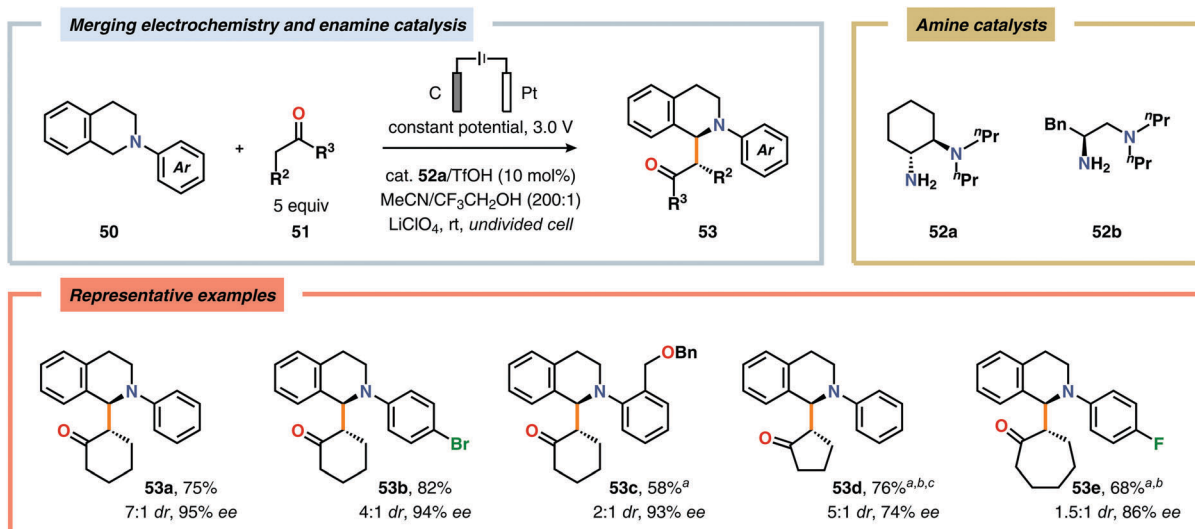
Scheme 11 Electrooxidative cyclizations of amine-containing motifs.

However, the process required the use of substoichiometric amounts of 3-nitrobenzoic acid as sacrificial oxidant.¹⁶¹ In order to improve the utility and eliminate the use of a chemical oxidant, Luo and coworkers developed a protocol based on enamine catalysis and electrochemical C–H oxidation. The authors identified the chiral primary amine **52a** as the optimal catalyst and trifluoroethanol (CF₃CH₂OH) as the ideal additive. The established oxidant-free coupling reaction tolerated an array of *N*-aryl substituted tetrahydroisoquinolines and various simple ketones to provide the asymmetric oxidative coupling products **53** in good yields with good to excellent diastereo- and enantioselectivities (Scheme 12).¹⁶² *N*-Aryl substituted tetrahydroisoquinolines are also susceptible to anodic nitro-Mannich C–C bond formation using nitromethane as the nucleophile.¹⁶³ Furthermore, Shono-type oxidation of tetrahydroisoquinolines has also been used for the oxidative functionalization of benzylic C–H bonds, mediated by a dual bromide ion/2,2,6,6-tetramethylpiperidinyl-*N*-oxyl (TEMPO) redox catalyst system, to produce dihydro-isoquinolinones.^{164,165}

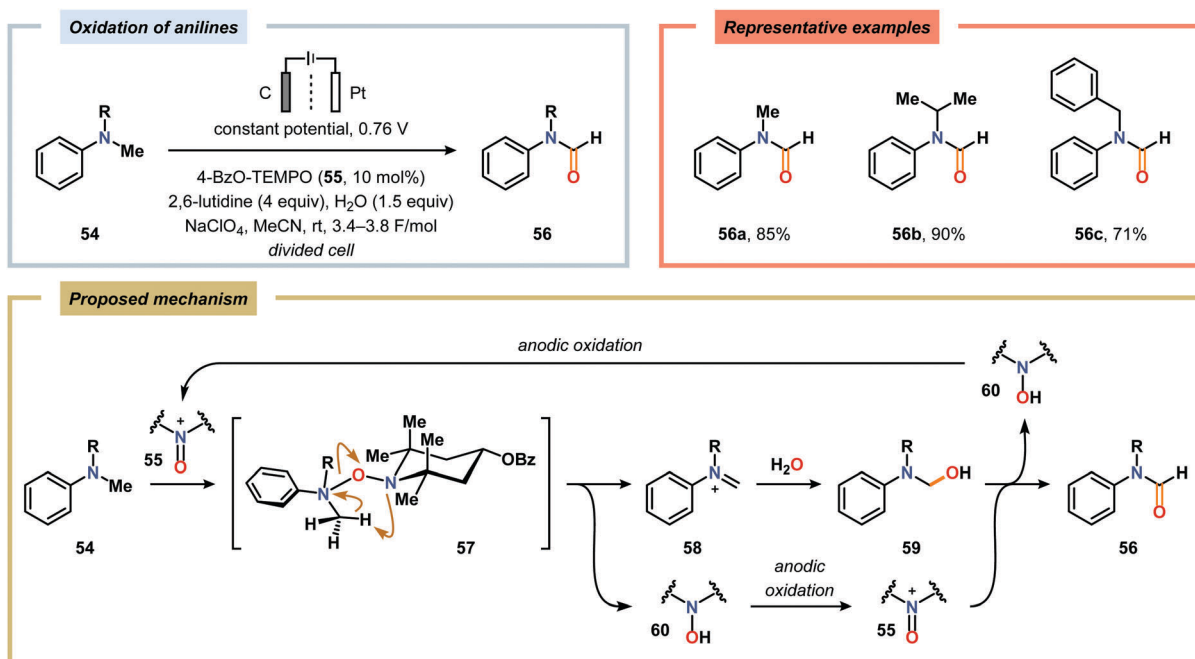
Kashiwagi and Anzai explored the electrochemical oxidation of *N*-alkyl-*N*-methylanilines (**54**) in aqueous media using a nitroxyl-based mediator. *N*-Alkylformanilides (**56**) were the major products and were obtained in 71–90% yield. The mechanism presumably proceeds through an iminium ion intermediate (**58**) which is hydrolyzed to produce hemiaminal **59**. This species undergoes a second oxidation event, mediated by the electrochemically generated oxoammonium species **55**, to furnish the corresponding formanilide **56** (Scheme 13).¹⁶⁶

A potential strategy to expand the scope of the nucleophiles is to employ the “cation pool” method.⁵⁷ The “cation pool” method involves generation and accumulation of cations, such as *N*-acyliminium ions, through electrolysis at low temperatures. The nucleophile is subsequently introduced to the reaction mixture under non-oxidative conditions, which allows for easily oxidized nucleophiles to be used. Early work from Yoshida and coworkers involving the generation of “cation pools” from carbamates by low-temperature electrolysis enabled the use of a collection of carbon nucleophiles, including allyl silanes, enol





Scheme 12 Oxidative coupling of tertiary amines with simple ketones through the merger of electrochemical C–H oxidation and enamine catalysis. ^a Hexafluoroisopropanol (HFIP) as additive. ^b **52b** as amine catalyst. ^c Cell potential of 2.0 V.



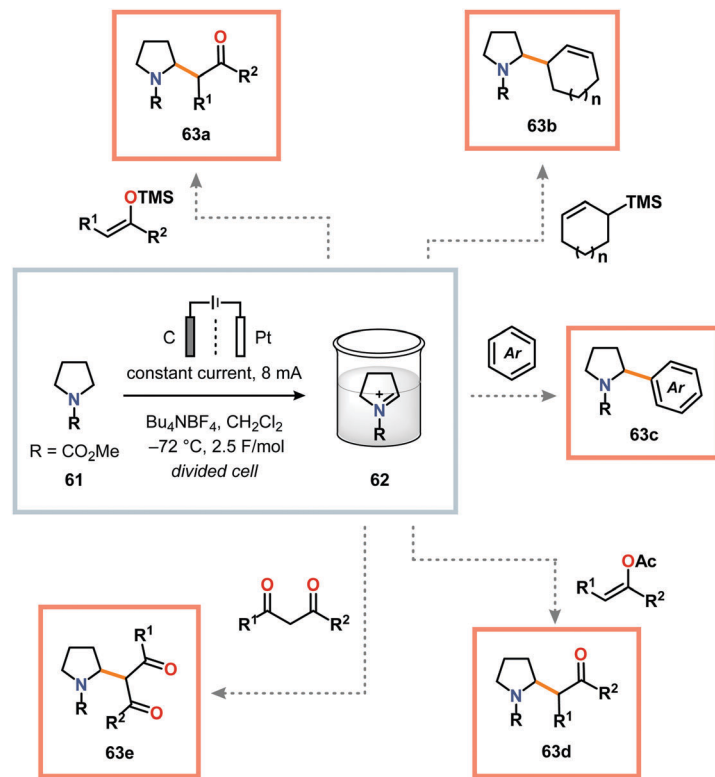
Scheme 13 Electrochemical oxidation of *N*-alkyl-*N*-methylanilines using a nitroxyl mediator.

silyl ethers, enol acetates as well as aromatic and 1,3-dicarbonyl compounds (Scheme 14).¹⁶⁷ Other compatible nucleophiles consist of allyl stannanes, benzyl silanes, Grignard reagents and organoaluminum compounds.^{168–170} These oxidative C–C bond forming reactions can also be carried out in a flow system, thus enabling continuous sequential combinatorial synthesis.^{171–175} The Yoshida group has also highlighted that electrochemical reduction of *N*-acyliminium ions, generated by the “cation pool” method, affords α -amidyl radicals. These radicals can be harnessed to produce homocoupled products or be intercepted with electron-deficient olefins in Giese-type^{176,177} reactions (Scheme 15).^{178,179} The latter transformation serves as a formal addition of C–H bonds

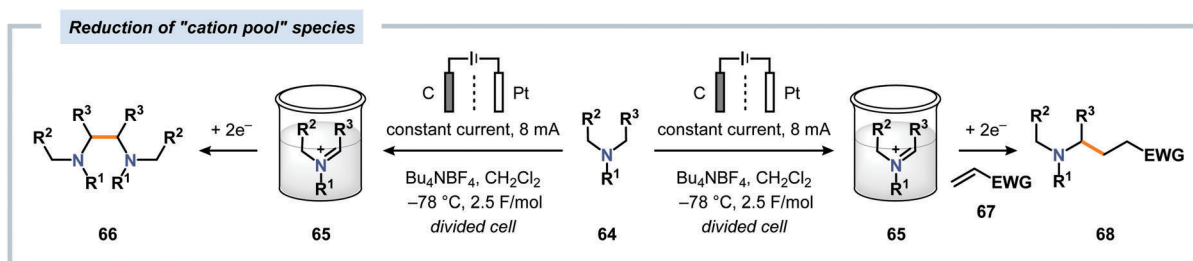
to alkenes and offers new redox-based opportunities to manipulate free radical species.

Additional strategies that allow for direct trapping of electrochemically generated *N*-acyliminium ions include the use of parallel laminar flow in micro-flow reactors,^{180,181} “site isolation”,^{182,183} and acoustic emulsification.^{184–188} The Atobe group has illustrated that the direct allylation of carbamates can be accomplished through the use of micro-flow reactors in which the flow is stable and laminar, thereby enabling a stable liquid–liquid interface and mass transfer between the two streams occurs only through diffusion. This concept affords selective anodic oxidation of substrates without affecting the oxidation of nucleophile and provides effective trapping of





Scheme 14 Carbon-carbon bond formation of carbamates using the "cation pool" method.

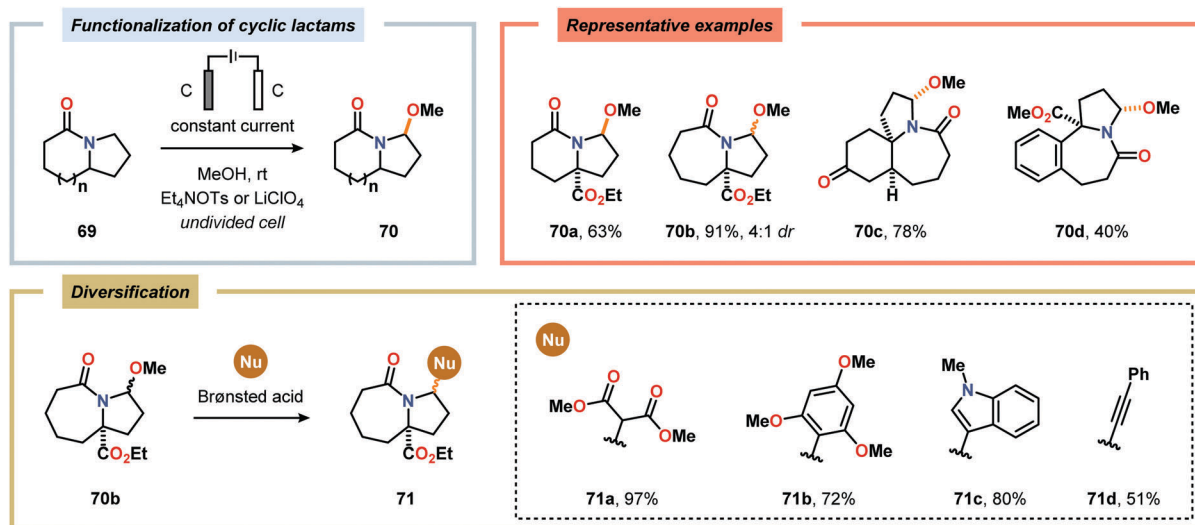


Scheme 15 Electrochemical reduction of "cation pool" generated acyliminium ions.

potentially unstable cationic intermediates.^{180,181} Atobe and co-workers have also established the feasibility of using acoustic emulsification in Shono oxidations. Here, chemoselective anodic oxidation of the substrate is realized by selecting an electrolytic medium in which the nucleophile is insoluble in. Upon ultrasonication, the nucleophile is dispersed as submicrometer range droplets, which react with the electrogenerated carbocations when the two species are in close proximity.^{186,187} The Tajima laboratory has demonstrated the direct oxidative cyanation based on the concept of "site isolation". Using a polystyrene-supported quaternary ammonium cyanide (PS-Me₃N⁺CN⁻) as the heterogeneous cyanating reagent enabled the direct cyanation of anodically produced *N*-acyliminium ions, generated *via* Shono oxidation of carbamates. This highlights that the site isolation between an anode and, for example, the cyanating reagent (PS-Me₃N⁺CN⁻) dramatically suppresses the undesired oxidation of CN⁻ and allows for anodic cyanation of organic compounds, even ones that

have higher oxidation potentials compared to CN⁻.¹⁸² Furthermore, utilizing recyclable solid-supported bases for *in situ* generation of electrolytes enables the development of systems where protic organic solvents serve as both the solvent and the supporting electrolyte.¹⁸⁹⁻¹⁹⁶ This allows for easy separation of the solid-supported base through filtration and provides, for example, the methoxylated Shono-type product, which can be subjected to the subsequent C-C bond forming reaction without having to replace the solvent.^{197,198} A complementary strategy for expanding the scope of Shono-type oxidations consists of using electroauxiliaries.⁵⁰ This concept relies on the inherent properties of the electroauxiliaries to lower the oxidation potential of the substrate, thereby facilitating and providing enhanced control of the anodic oxidation of the substrate. The electroauxiliaries employed in Shono-type oxidations have typically been silyl-based,¹⁹⁹⁻²¹³ although 2,4,6-trimethoxyphenyl²¹⁴ and sulfur-based²¹⁵⁻²¹⁷ electroauxiliaries have also been employed.





Scheme 16 Electrochemical modification and diversification of cyclic lactams.

Considering the versatility of Shono-type oxidation reactions, it is perhaps unsurprising that these reactions have found numerous synthetic applications. The groups of Moeller and Aubé developed a practical two-step protocol for the late-stage functionalization of lactams by combining an intramolecular Schmidt reaction of keto azides followed by electrochemical anodic oxidation. The applicability of the Shono oxidation was exemplified across a range of ring systems. Finally, the versatility of the produced methoxyhemiaminals (**70**) was illustrated by synthesizing an array of functionalized lactam products (**71**) through the addition of various nucleophilic partners to the subsequent *in situ* generated *N*-acyliminium ions (Scheme 16).²¹⁸ Azanucleosides and related analogues have been found to exhibit anticancer and antiviral activity. Furthermore, incorporation of azanucleoside motifs into oligonucleotide sequences results in increased tolerance towards degradation by nucleases.²¹⁹ In this regard, the Matsumura group has exploited the Shono oxidation for preparation of azasugars,²²⁰ and Chiba and coworkers recently applied the Shono oxidation in the development of a synthetic method for accessing azanucleosides. Initial studies revealed that various nucleophiles and nucleobases could be introduced at the α -position upon the anodic modification of *N*-carbamate protected prolinol derivatives.^{221,222} Subsequent work showcased that *N*-acryloyl proline derivatives **72** could also be converted into the corresponding azanucleosides **74** by use of the Shono reaction. Moreover, the presence of the *N*-acryloyl group allowed for substrate postsynthetic modification through thiol conjugate addition or olefin cross-metathesis with a fluorescent dye (Scheme 17).²²³ Electrochemical oxidation has also proven to be a viable strategy towards the synthesis of γ -amino acids²²⁴ and preparing peptidomimetics.^{225–235} Schmalz and coworkers utilized the Shono oxidation in the context of accessing a tricyclic dipeptide mimetic (**80**) starting from *L*-proline (**77**). The anodic oxidation of *L*-proline *tert*-butyl ester **78** afforded gram scale quantities of the desired methoxylated product **79** in virtually quantitative yield (Scheme 18). Building block **79** was subsequently converted into

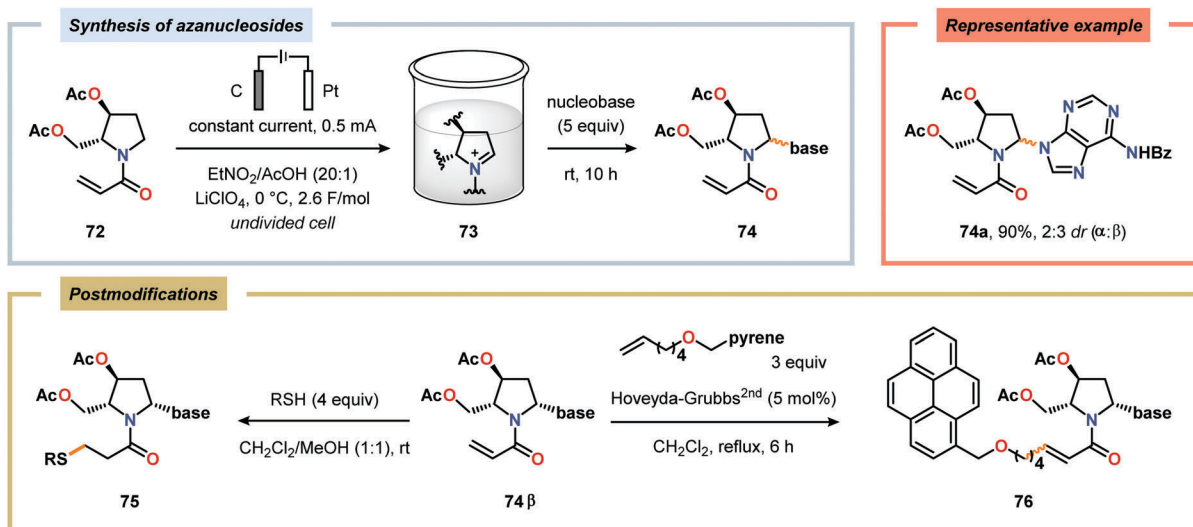
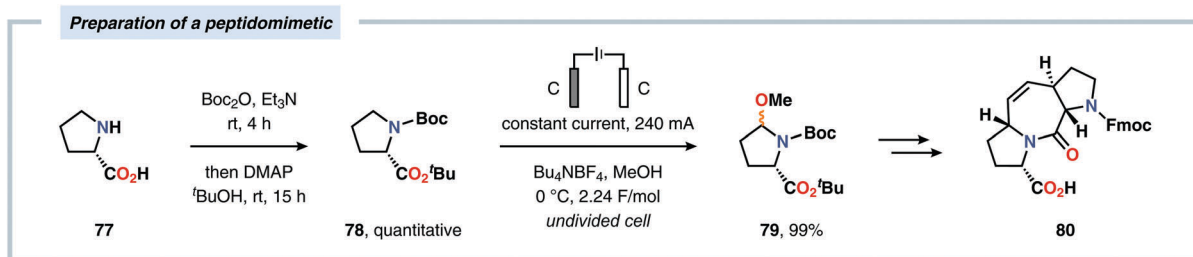
diproline mimetic **80** through peptide coupling, ring-closing metathesis and protecting group adjustment.²³⁶

The Shono oxidation has been exploited as a general synthetic method for accessing β -substituted indoles (Scheme 19). The products derived from the Shono oxidation served as masked aminoaldehydes, which upon treatment with arylhydrazines and ZnCl_2 afforded the corresponding β -substituted indoles through a Fischer indole synthesis pathway.²³⁷ Ley and coworkers identified flow electrochemistry as an enabling technology for the Shono oxidation of various *N*-protected cyclic amines. Here, the Shono oxidation furnished the corresponding cyclic α -methoxyamines in excellent yields. Applying a Pictet–Spengler reaction between the electrosynthesized α -methoxyamines and substituted tryptamines afforded the biologically active indole alkaloid nazlinine (**88c**) and numerous related unnatural congeners (Scheme 20).²³⁸ Other alkaloids that have been prepared include (–)-crispine **A**²³⁹ and (±)-pumiliotoxin **C**.²⁴⁰ Here, anodic cyanation furnished the desired α -amino nitriles, which upon further manipulations furnished the target alkaloids. The Santos laboratory has also demonstrated the utility of the Shono oxidation in total syntheses of ropivacaine²⁴¹ (**93**, Scheme 21), (–)-quinolactacin **B**²⁴² (**96**, Scheme 22) as well as (+)-lennoxamine²⁴³ (**99**, Scheme 23). Finally, the Kam group reported that electrochemical oxidation could be applied to aspidofractinine-type alkaloids for construction of kopsidines **A** and **B** (Scheme 24), thus highlighting the potential of carrying out late-stage functionalization of complex molecules.²⁴⁴ Additional synthetic applications of Shono-type oxidations include the synthesis of an angiotensin-converting enzyme inhibitor,²⁴⁵ preparation of methoxylated analogues of the anticancer drugs ifosfamide and cyclophosphamide,²⁴⁶ as well as dealkylation,^{247–250} deallylation and debenzoylation²⁵¹ of amines and amides.

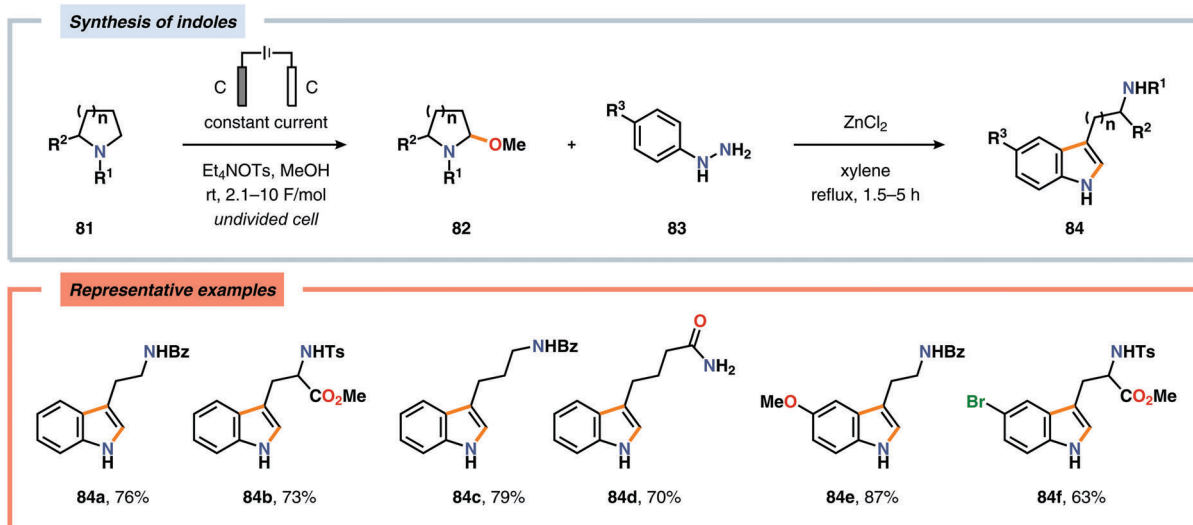
2.2. Anodic halogenation

Incorporation of fluorine into organic compounds has found broad applications in medicinal,^{252–254} agrochemical^{255,256} and material sciences.²⁵⁷ Over the past decade, significant advances



Scheme 17 Electrochemical synthesis and postmodification of *N*-acryloyl azanucleosides.

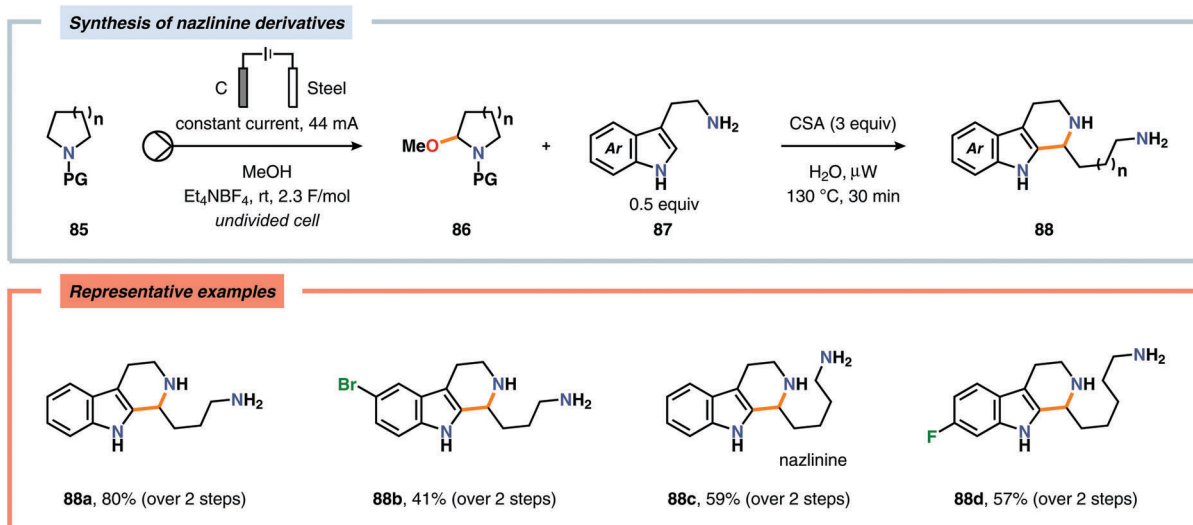
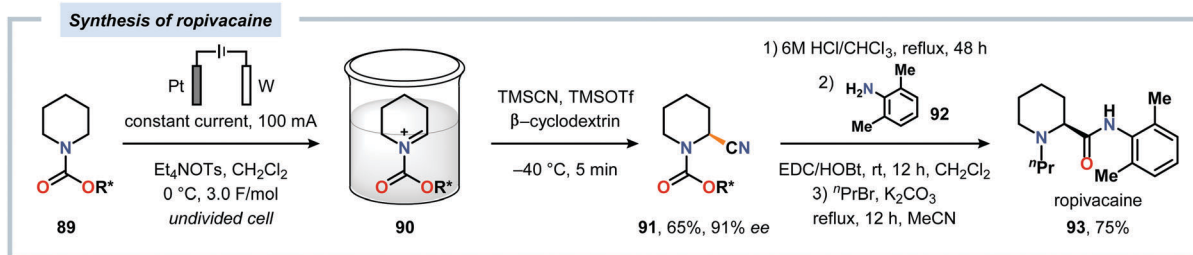
Scheme 18 Application of the Shono oxidation in the preparation of a peptidomimetic.

Scheme 19 Synthesis of β -substituted indoles *via* the Shono oxidation.

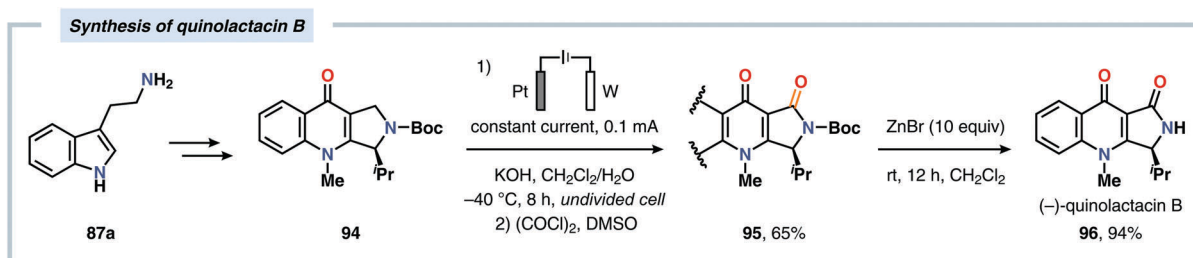
in chemo- and stereoselective fluorination of molecules with high functional and structural complexity have been made. In general, three different strategies exist for synthesis of organofluorine compounds: electrophilic,²⁵⁸ nucleophilic²⁵⁹ and radical²⁶⁰ fluorination.^{261,262}

Seminal studies by Rozhkov and coworkers in 1970 highlighted that selective electrochemical fluorination of arenes could be achieved in MeCN using $\text{Et}_4\text{NF}\cdot 3\text{HF}$ as the ionic liquid, albeit in low yields. These reactions were proposed to proceed *via* arene radical cations, generated at the anode, that

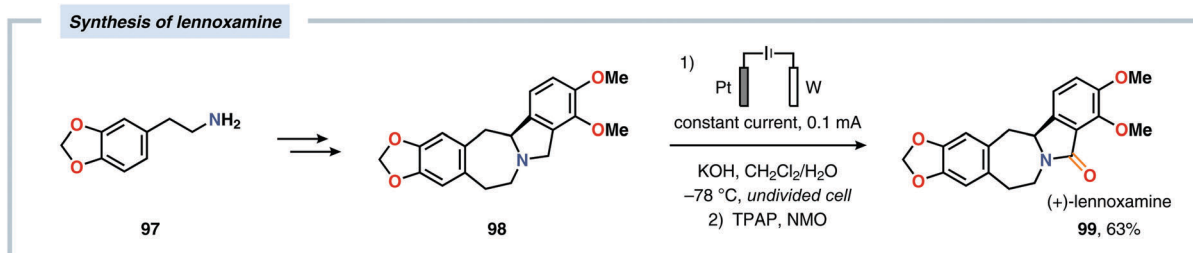


Scheme 20 Synthesis of nazoline and unnatural congeners *via* a two-step method.

Scheme 21 Synthesis of ropivacaine employing the “cation pool” strategy. R* = 8-phenylmenthyl.

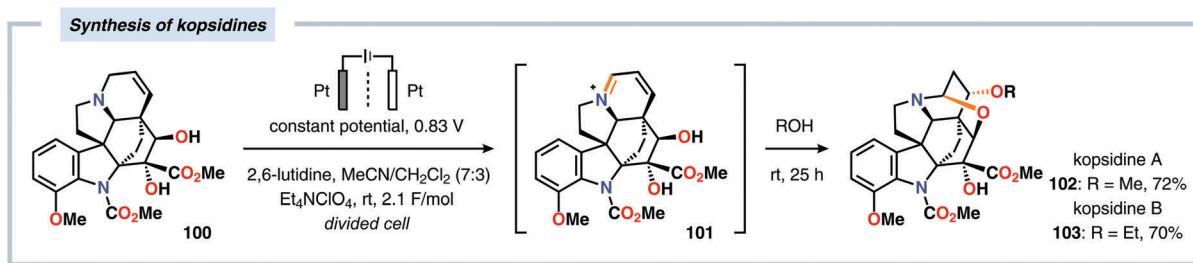


Scheme 22 Application of a late-stage Shono oxidation in the synthesis of (-)-quinolactacin B.



Scheme 23 Application of a late-stage Shono oxidation in the synthesis of (+)-lennoxamine.



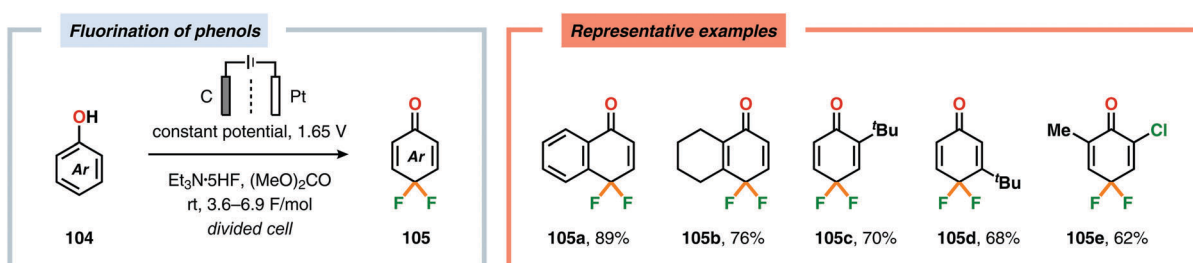


Scheme 24 Shono-type oxidation of aspidofractinine-type alkaloids.

subsequently were trapped by fluoride to produce the carbon-fluorine (C-F) bond.^{263–265} More recently, attempts to achieve selective fluorination of simple aromatic compounds include the work by Matsuda and coworkers. However, the yields of the fluorobenzenes were typically low.^{266–269} Unlike unsubstituted arenes, such as benzene and naphthalene, electrochemical fluorination of toluene and related derivatives remains a challenge, as mixtures of products are formed originating from aromatic substitution, side chain substitution and addition reactions.^{270–275} Heteroaromatics^{276–283} and nitrogen-containing heterocycles^{284–286} have also been reported to react in a similar manner. Anodic oxidation of phenols using $\text{Et}_3\text{N}\cdot 5\text{HF}$ as the electrolyte was examined by the groups of Hara and Yoneda, and selectively afforded the corresponding 4,4-difluorocyclohexadienone derivatives in good yields (Scheme 25).^{287–291} Furthermore, trifluoromethanesulfinate (CF_3SO_2^-) has recently been exploited as a source for electrochemical generation of trifluoromethyl radicals (CF_3^\bullet) in the presence of electron-rich aromatics²⁹² and heterocycles.²⁹³ In this regard, the Baran and Blackmond groups demonstrated that electrochemical oxidation of zinc trifluoromethanesulfinate $\{\text{Zn}(\text{SO}_2\text{CF}_3)_2\}$ in DMSO in the presence of heterocycles, such as pyrazoles, pyrroles and benzothiazoles, afforded the corresponding trifluoromethylated products (Scheme 26). Moreover, the authors successfully highlighted that the developed electrochemical protocol was able to provide the functionalized heterocyclic products more effectively than conventional peroxide radical-initiated protocols for a majority of the screened substrates.²⁹³

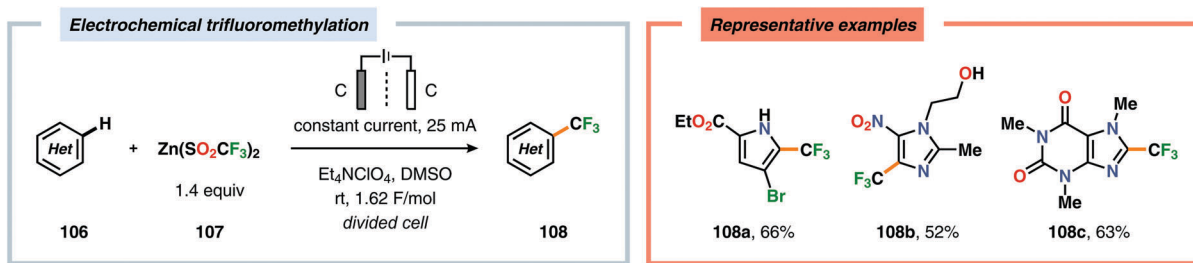
Electrochemical fluorination of arylsulfides constitutes another transformation that has been extensively studied by several research groups. Early work during the 1990s from the Fuchigami^{294–302} (Scheme 27) and Laurent^{303,304} (Scheme 28) laboratories demonstrated that the introduction of an electron-withdrawing group at the α -position to sulfur had a dramatic

influence on the reactions. These α -fluorination transformations were believed to proceed through a Pummerer-type mechanism where the electron-withdrawing group facilitates deprotonation of the α -carbon to produce intermediate **110**, thereby promoting fluorination.³⁰⁵ The same effect could also be achieved using aromatics containing strongly electron-withdrawing groups, such as *p*-CN, *p*-NO₂ and *p*-SO₂Ph, as demonstrated by Simonet and coworkers.^{306,307} These seminal studies constitute the first examples of selective electrochemical fluorination of chalcogen compounds. Since then, a variety of distinct sulfide-based motifs, such as 2*H*-benzo[*b*][1,4]-thiazin-3(4*H*)-one (**114j**),³⁰⁸ benzothiazole (**114o**),^{309–311} 2,3-dihydrothiochroman-4-one (**114k**),³¹² 1,3-dithiolan-4-one (**114c**),³¹³ lactam (**114a**),³⁰⁸ 1,3,4-oxadiazole (**114l**),^{311,314} 1,3-oxathiolan-5-one (**114b**),³¹⁵ pyrimidin-4(3*H*)-one (**114h**),³¹⁶ phosphonate (**114d**),^{317,318} pyridine (**114e**),^{310,319} pyrimidine (**114g**),^{310,311,319,320} quinazolin-4(3*H*)-one (**114i**),³¹⁹ quinoline (**114f**),³¹⁰ 1,3,4-thiadiazole (**114m**),^{311,314} and 1,2,4-triazole (**114n**),³¹⁴ have been shown to be amenable to regioselective monofluorination (Scheme 29). Because of their good conductivity, non-flammability, non-volatility and thermal stability, ionic liquids, such as $\text{Et}_3\text{N}\cdot n\text{HF}$, have found widespread use as solvents in electrochemical fluorination reactions.^{321–326} Recently, Fuchigami and coworkers demonstrated miscellaneous approaches to improve the electrochemical fluorination. One approach makes use of ultrasonication to promote the mass transport of the substrate due to the high viscosity associated with the ionic liquids. This was shown to increase the current efficiencies, selectivities and yields in the anodic fluorination of a variety of organosulfur compounds.³²⁷ The authors have also developed an electrochemical system based on the cation-exchange reaction between alkali-metal fluorides and solid-supported acids. In the presence of 2,6-lutidine, the exchange reaction results in the *in situ* generation of 2,6-lutidine-HF, which functions as the fluorinating agent and supporting electrolyte, thus

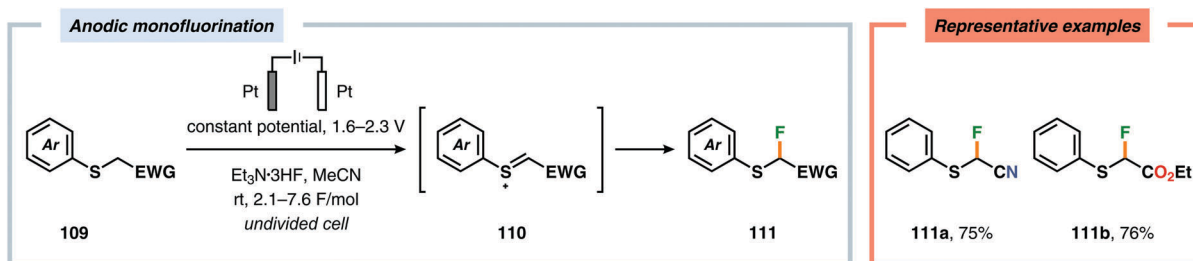


Scheme 25 Synthesis of difluorocyclohexadienones through electrochemical oxidation of phenols.

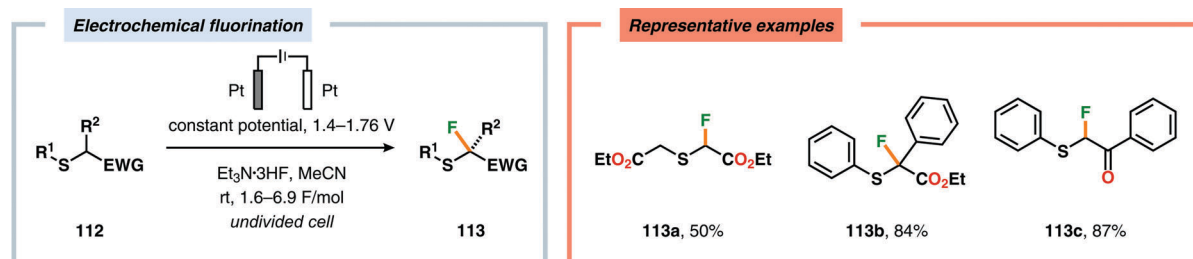




Scheme 26 Electrochemical trifluoromethylation of heterocycles.



Scheme 27 Anodic monofluorination of organosulfur compounds.



Scheme 28 Electrochemical fluorination of organosulfur compounds.

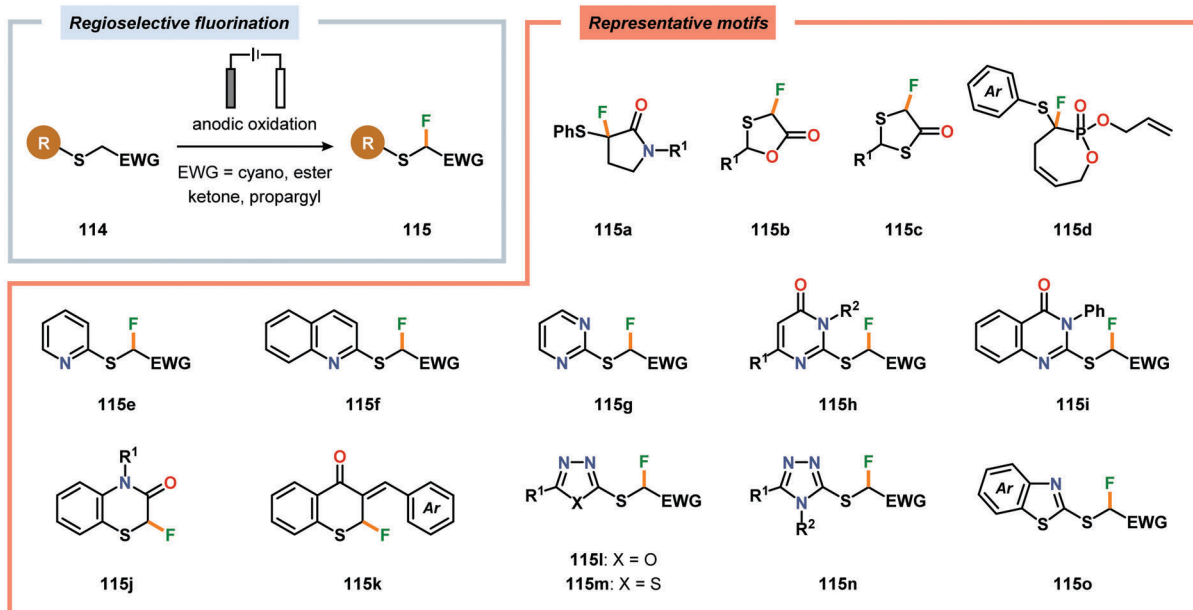
obviating the need to handle hazardous HF.³²⁸ The Fuchigami group has also shown that indirect anodic fluorination can be realized using a hypervalent iodoarene difluoride (ArIF_2) mediator, which can be anodically produced from the corresponding iodoarene species and a HF-based ionic liquid ($\text{Et}_3\text{N}\cdot 3\text{HF}$). Here, indirect reaction with the hypervalent iodoarene mediator proceeded efficiently to furnish the desired monofluorinated product, thus limiting anode passivation (the formation of a nonconducting polymer film on the electrode surface that suppresses faradaic current), a drawback that is often encountered when carrying out direct electrochemical fluorination.³²⁹ Attempts to develop diastereoselective fluorination protocols have also been reported using chiral auxiliaries derived from camphorsulfonic acid,³³⁰ (*R*)-(-)-3-chloro-1,2-propanediol,³³¹ L-cysteine³³² and menthol,³³³ providing the monofluorinated products in modest to good diastereoselectivities.

Recently, electrochemical fluorination of adamantane derivatives has been studied by Hara and coworkers. By controlling the oxidation potential, the authors were able to guide the fluorination process to selectively yield the mono-, di-, tri- or tetrafluorinated adamantane derivatives (Scheme 30).^{334,335}

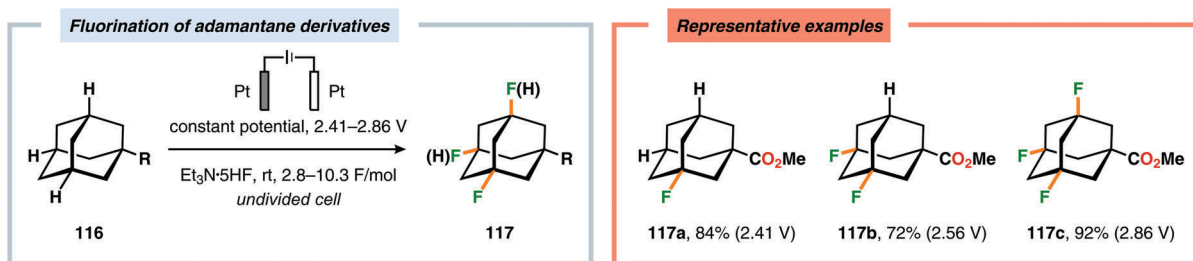
Moreover, regioselective electrochemical monofluorination has also been reported for a collection of oxygen-containing heterocycles, including carbonates,^{336,337} chroman-4-ones,^{338–340} esters,³³⁷ ethers^{336,337} and lactones.^{336,337} Additionally, electrochemical protocols for accomplishing fluorodesulfurization,^{341–349} difluorination,^{350,351} fluoro-selenylation,³⁵² iodofluorination³⁵³ and thiofluorination³⁵⁴ of electron-deficient olefins as well as partial fluorination of conjugated dienes³⁵⁵ have been devised.³⁵⁶

In contrast to the electrochemical fluorination strategies, the anodic oxidation protocols involving chlorides, bromides and iodides typically proceed *via* generation of the corresponding electrophilic molecular counterpart (X_2) due to the relatively low oxidation potentials of these halogen ions.^{357–367} Due to the limited solubility of alkali metal halide salts in organic solvents, a biphasic system consisting of an aqueous phase and a halogenated organic solvent is commonly employed to affect chlorination of aromatics^{368,369} and heterocycles³⁷⁰ as well as bromination of toluene derivatives.³⁷¹ The electrodes are placed in the upper layer of the aqueous phase, thus enabling selective oxidation of the halide. The electrochemically produced X_2 or hypohalite subsequently reacts with the organic substrate at the aqueous/organic





Scheme 29 Electrochemical regioselective fluorination of organosulfur compounds.

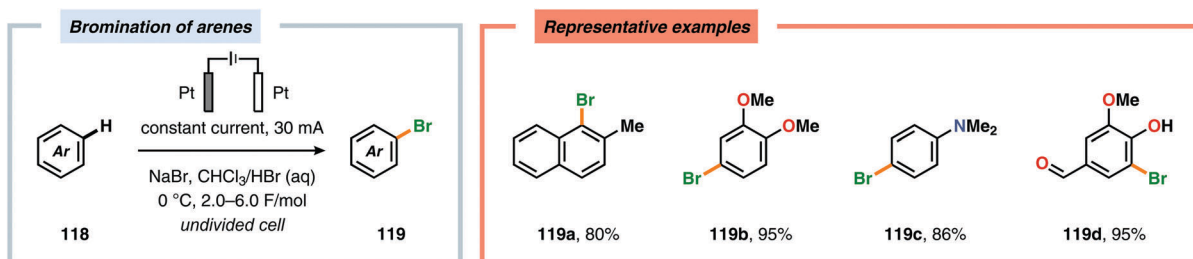


Scheme 30 Selective electrochemical fluorination of adamantane derivatives.

interface to ultimately produce the desired halogenated product. However, this can to some extent be circumvented using poly(ethylene glycol) as an additive, which enhances the solubility of the inorganic salts in aprotic organic solvents.³⁷² By employing a biphasic system, bromination of various arenes³⁷³ (Scheme 31) as well as benzylic mono-³⁷⁴ (Scheme 32) and dibromination³⁷⁵ (Scheme 33) of alkyl aromatics has been achieved. In addition to these examples, electrochemical chlorination of 1,3-dicarbonyl compounds using Cu catalysis,³⁷⁶ azulene derivatives,^{377,378} olefins,^{379–384} phenols³⁸⁵ and pyrazolecarboxylic acids,³⁸⁶ as well

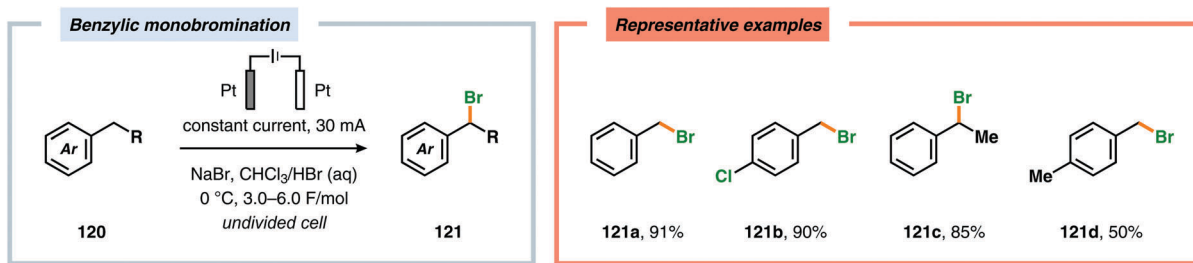
as bromination of heterocycles³⁸⁷ and olefins^{388–391} have been reported.

By employing a similar electrochemical strategy as used for the chlorination of pyrazolecarboxylic acids,³⁸⁶ Petrosyan and coworkers developed an electrochemical protocol for iodination of pyrazole and derivatives thereof. The iodination was carried out in a biphasic system consisting of water and chloroform using KI as the iodine source. As expected, the presence of electron-donating groups was found to facilitate the electrochemical iodination.^{392,393} The Yoshida group has elegantly

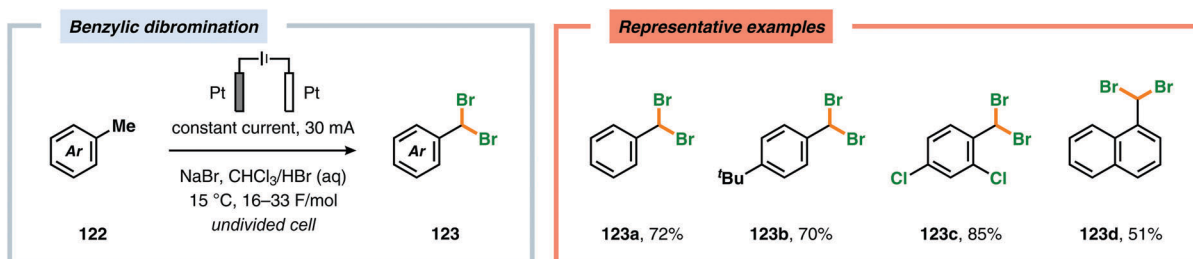


Scheme 31 Electrochemical bromination of arenes.

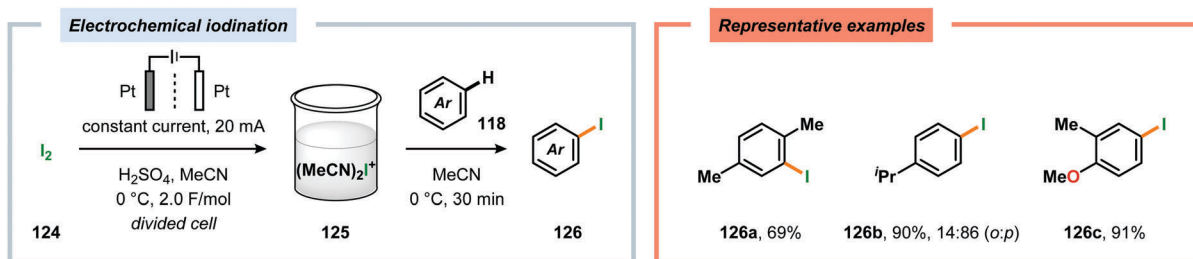




Scheme 32 Benzylic monobromination of alkyl aromatics.



Scheme 33 Benzylic dibromination of alkyl aromatics.

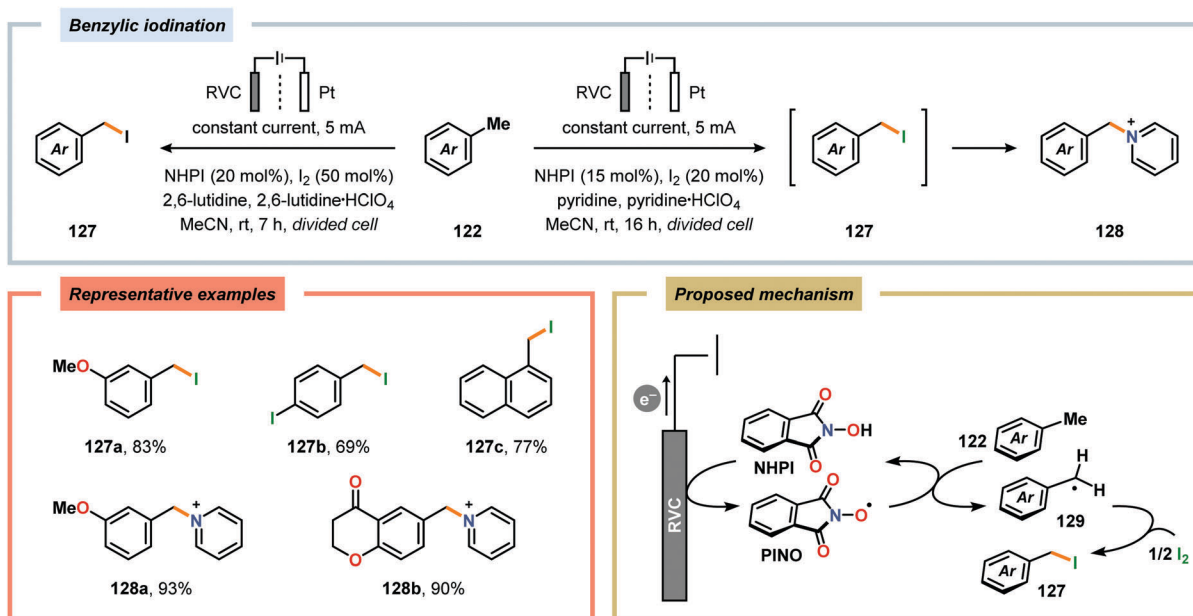


Scheme 34 Electrochemical iodination of aromatic compounds.

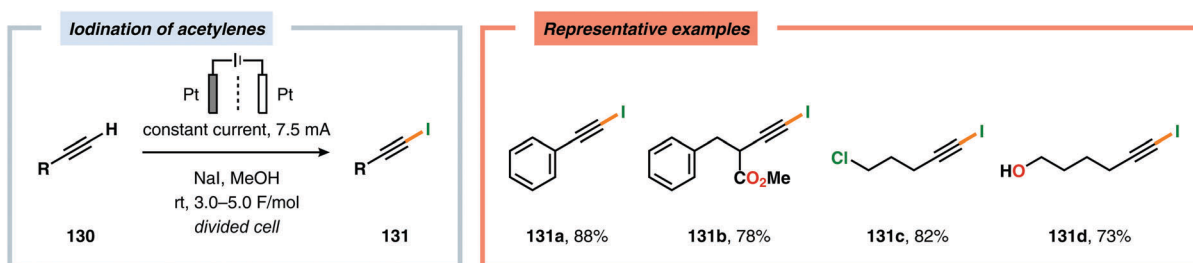
demonstrated iodination of aromatic compounds using electroaccumulated I⁺ (Scheme 34). Initially, a “cation pool” approach was employed in which an MeCN solution containing iodine (I₂) was electrolyzed for generation of the electrophilic iodination agent, which was proposed to involve (MeCN)₂I⁺. Subsequently, the anodic solution was added to a solution containing the arene. Alternatively, running the reactions in flow was shown to both increase the selectivity for the monoiodo compound and the yields compared to a batch reactor. Furthermore, the flow rate had a dramatic influence on the product selectivity where lower flow rates dramatically decreased the selectivity of the monoiodo compound due to less efficient mixing.^{394,395} In addition, Hilt and coworkers recently revealed that electrochemical synthesis of aryl iodides can be achieved through anodic iododesilylation.³⁹⁶ Anodic oxidation of arenes containing alkyl side chains provides aryl radical cations, which can subsequently be further oxidized to afford benzylic cations upon release of a proton, thus presenting a strategy for carrying out benzylic functionalization.³⁹⁷ Recently, the Stahl group disclosed an alternative approach to benzylic C–H functionalization (Scheme 35).^{398,399} The developed

concept consisted of employing *N*-hydroxyphthalimide (NHPI) as a mediator.^{400–402} Here, NHPI undergoes proton-coupled electron transfer at the anode to give phthalimido-*N*-oxyl (PINO), which subsequently mediates hydrogen atom transfer (HAT) from weak C–H bonds.⁴⁰³ Using toluene derivatives and in the presence of a base, such as 2,6-lutidine, Stahl and coworkers were able to generate benzylic radicals at relatively modest oxidation potentials. I₂ was shown to be an effective radical trapping agent, thereby providing the corresponding benzyl iodide. The authors had to use a divided cell configuration in order to avoid reduction of the trap at the cathode. The developed benzylic C–H iodination method tolerated several functional groups, including esters, ethers, halides and ketones. *In situ* nucleophilic substitution using pyridine/pyridinium as the electrolyte proved to lead to efficient displacement of iodide by pyridine, leading to the corresponding benzylpyridinium product under electrochemical control. Iodide is produced in the nucleophilic displacement step, which can be reoxidized to iodine at the anode, allowing these reactions to be performed with substoichiometric amounts of iodine (20 mol%). Finally, using the *in situ* functionalization protocol enabled the authors to prepare three vital pharmaceutical building blocks,





Scheme 35 Electrochemical iodination of toluene derivatives using NHPI as mediator.



Scheme 36 Electrochemical iodination of terminal acetylenes.

highlighting the concept of using toluene derivatives as alkylating agents.³⁹⁸ Moreover, Nishiguchi and coworkers exploited the electrochemical oxidation of terminal acetylenes using a divided cell in the presence of NaI as the supporting electrolyte. The electrochemical method efficiently provided the desired 1-iodoacetylenes in good to excellent yields (Scheme 36).⁴⁰⁴

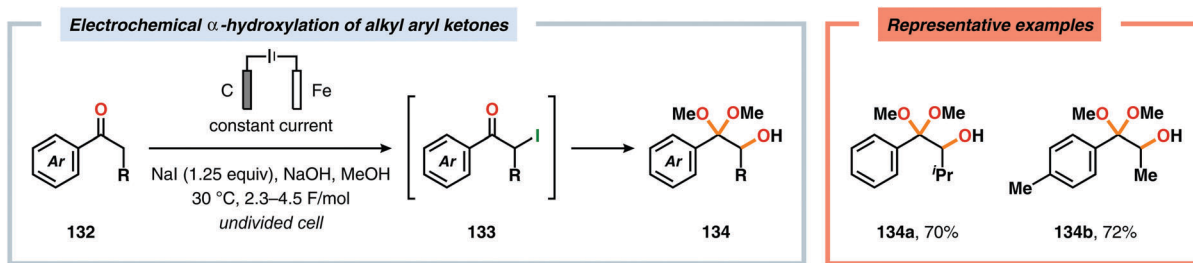
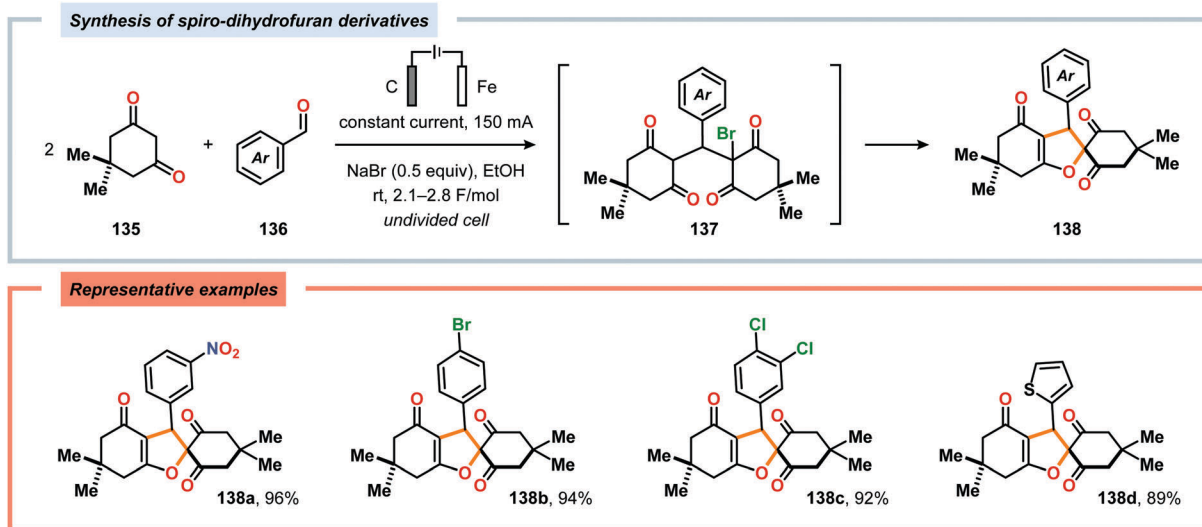
2.3. Electrochemical C–H bond oxygenation

α -Oxygenation of carbonyl compounds can be accomplished using alkali metal halide salts. These halide salts can undergo anodic oxidation, generating α -halo compounds or carbon-centered α -radicals. Seminal work by Shono and coworkers demonstrated that iodide-mediated α -oxidation of aldehydes and ketones delivered the corresponding α -hydroxylated acetals or ketals.⁴⁰⁵ More recently, Elinson and coworkers have also studied the sodium halide/sodium hydroxide system for indirect electrochemical α -oxidation of carbonyl compounds.^{406,407} Based on these results, the authors employed the mediatory system NaI/NaOH for converting alkyl aryl ketones into the corresponding α -hydroxy ketals (Scheme 37). These reactions were proposed to proceed *via* α -iodoketone **133**.⁴⁰⁸ The iodide-mediated oxidation system was subsequently employed for α -hydroxylation of

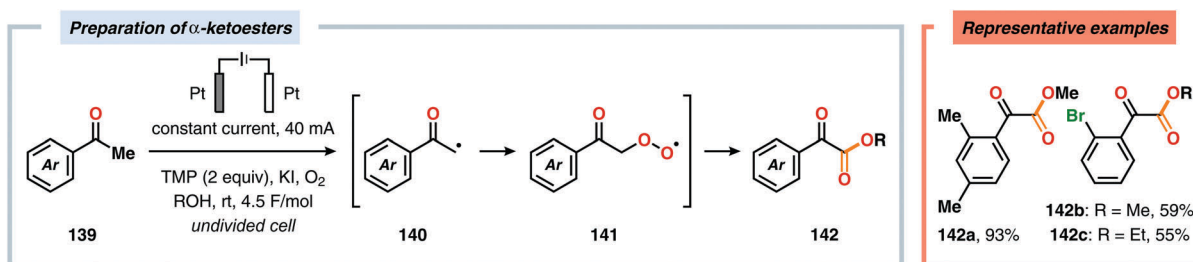
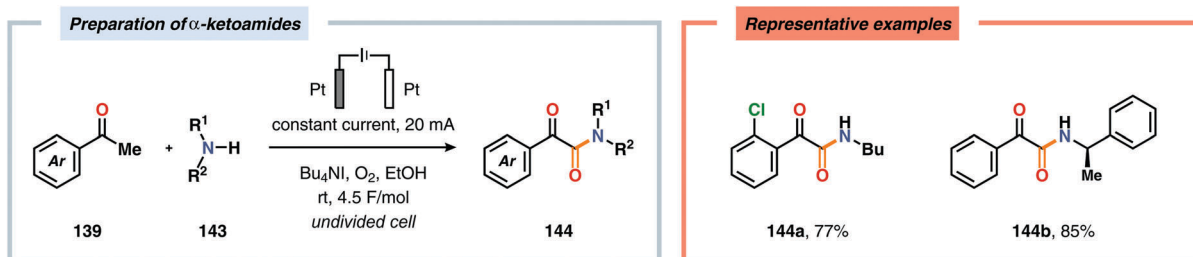
cyclohexanones⁴⁰⁹ and piperidin-4-ones.⁴¹⁰ Bromide-mediated α -oxidation has also been used for accessing spiro-dihydrofuran derivatives from dimedone and aldehydes (Scheme 38).⁴¹¹ Furthermore, both intermolecular⁴¹² and intramolecular^{413–428} protocols for C–C bond formation based on halide-mediated anodic oxidation of carbonyl compounds and related derivatives have also been disclosed.

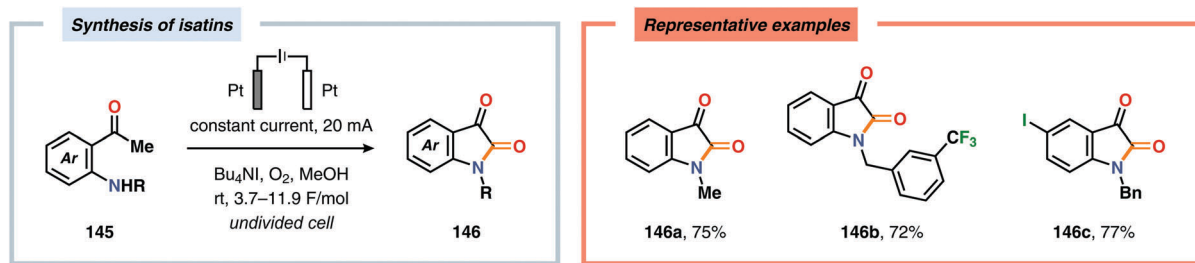
The Wang group has shown that iodide-mediated anodic oxidation of aryl methyl ketones can be exploited for synthesis of α -ketoesters (Scheme 39),^{429–431} α -ketoamides (Scheme 40)⁴³² and isatins (Scheme 41).⁴³³ Here, a radical-based pathway in which an iodine radical (I^\bullet) is proposed to undergo a HAT event with the aryl methyl ketone to deliver hydrogen iodide and an α -carbon-centered radical (**140**). The intermediate radical can subsequently be trapped with dioxygen to afford peroxy radical **141**, which is readily converted to the corresponding ketoaldehyde compound. Finally, nucleophilic addition to this intermediate and a further oxidation event yields the desired product. α -Oxygenation of aliphatic aldehydes has been accomplished through a dual electrochemical/organocatalytic strategy (Scheme 42).⁴³⁴ In this transformation, the generated α -iminyl radical cation is intercepted with TEMPO to afford the α -oxygenated product **148** upon



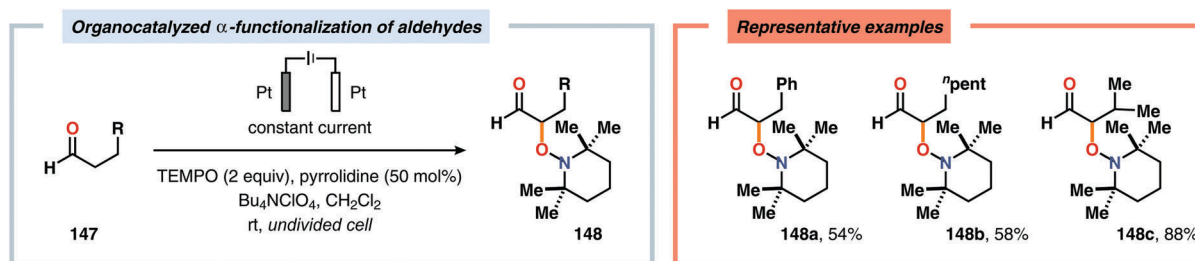
Scheme 37 Indirect electrochemical α -hydroxylation of alkyl aryl ketones.

Scheme 38 Electrochemical synthesis of spiro-dihydrofuran derivatives.

Scheme 39 Electrochemical preparation of α -ketoesters. TMP = 2,2,6,6-tetramethylpiperidine.Scheme 40 Preparation of α -ketoamides through anodic oxidation.

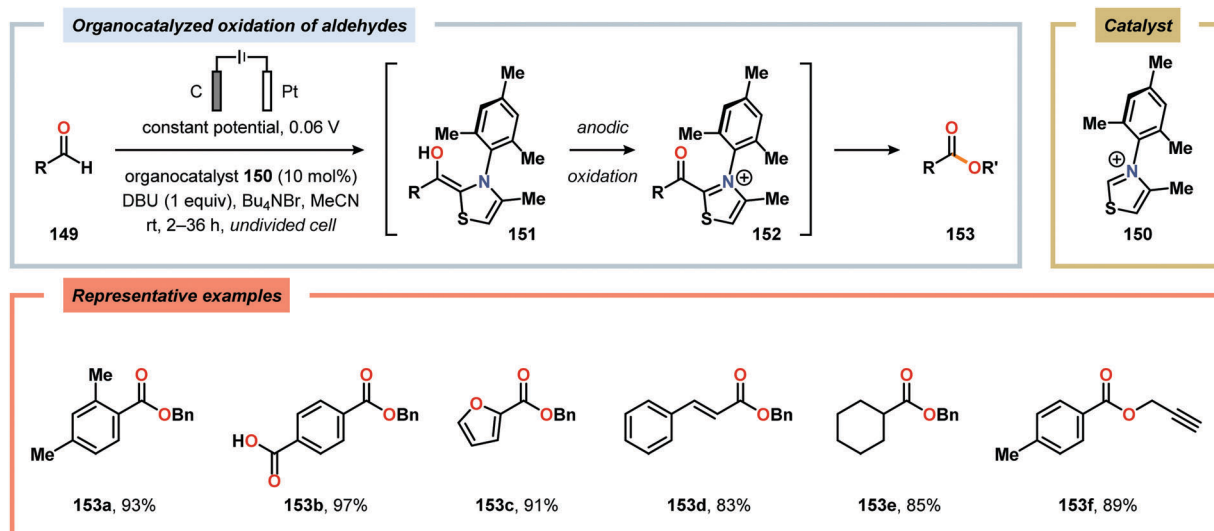


Scheme 41 Iodide-mediated synthesis of isatins.

Scheme 42 Dual electrochemical/organocatalyzed α -oxygenation of aldehydes.

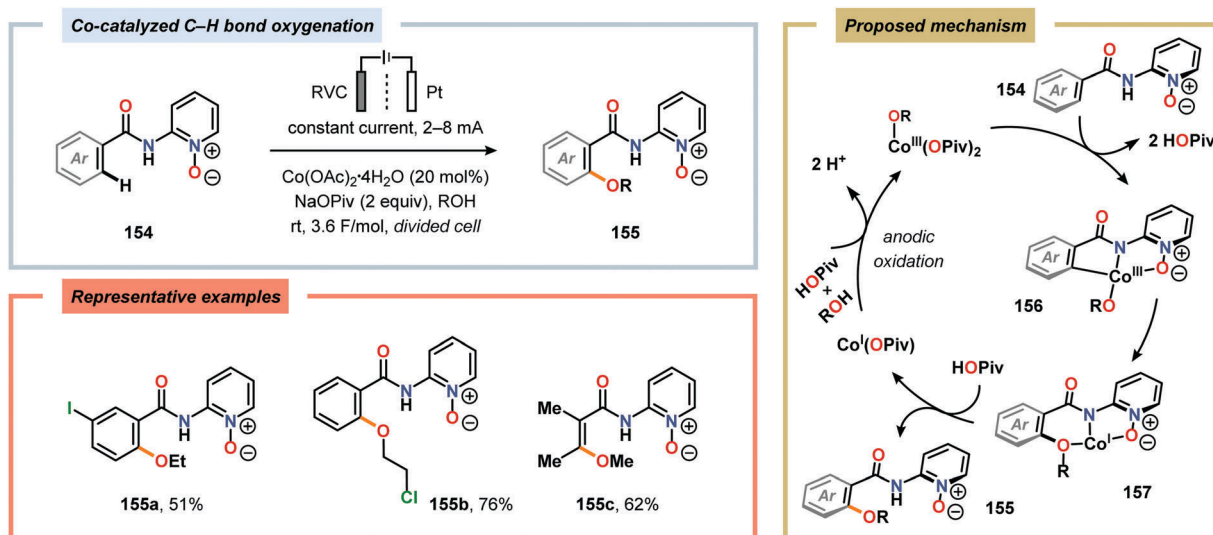
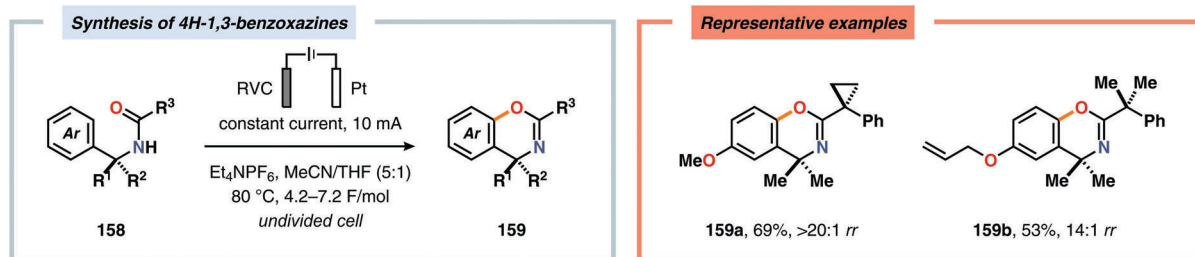
hydrolysis of the resultant iminium ion. In addition, various chiral *sec*-amines were evaluated in order to develop an enantioselective protocol. However, only moderate enantioselectivities were obtained using the Hayashi-Jørgensen catalyst.^{435,436} The merger of electrochemistry with other organocatalytic activation modes was utilized by Boydston and coworkers for conversion of aldehydes to esters (Scheme 43). The method interfaced N-heterocyclic carbene-based organocatalysis with anodic oxidation for achieving efficient two-electron oxidation of the *in situ* generated Breslow intermediate (151) to produce an electrophilic 2-acylazolium species (152).⁴³⁷⁻⁴³⁹ Subsequently, the authors disclosed a method for the direct conversion of aldehydes to thioesters *via* integration of organocatalysis and electrosynthesis.⁴⁴⁰ Based on this dual catalytic activation mode,

Brown and coworkers successfully demonstrated that the oxidative esterification of aldehydes⁴⁴¹ as well as amidation of aldehydes⁴⁴² could be conducted in an undivided electrochemical flow cell. Recently, the Ackermann laboratory exploited the powerful nature of dual catalytic methods for achieving C(sp²)-H oxygenation of aromatic and alkene moieties.⁴⁴³ Here, the combination of cobalt catalysis and electrochemical oxidation enabled C-H alkoxylation under mild reaction conditions at ambient temperature (Scheme 44). Employing electrical current as an oxidant obviated the need of stoichiometric amounts of Ag(I) salts through the use of an earth-abundant cobalt redox manifold. Furthermore, the developed protocol exhibited high levels of chemo-, regio- and diastereoselectivity. Electrooxidative C-H



Scheme 43 Organocatalyzed anodic oxidation of aldehydes.



Scheme 44 Electrochemical cobalt-catalyzed C(sp²)-H alkoxylation.

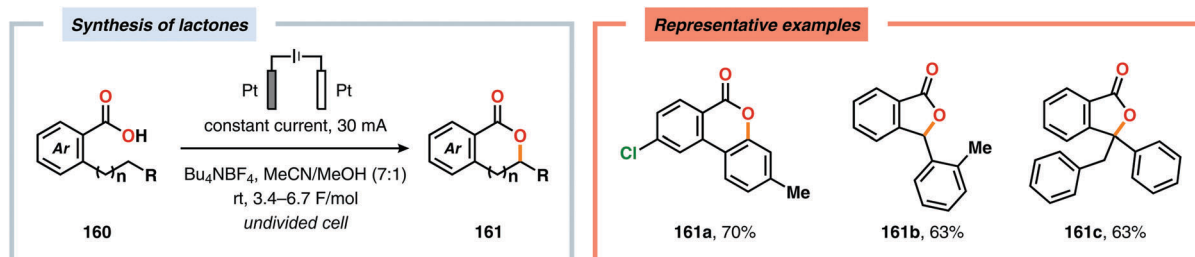
Scheme 45 Synthesis of 4H-1,3-benzoxazines through electrochemical C-H oxygenation.

activation with weakly coordinating benzoic acids has also been accomplished using rhodium-⁴⁴⁴ or ruthenium catalysis.⁴⁴⁵

Electrochemical aromatic C(sp²)-H oxygenation has also been utilized for carrying out oxidative annulations. Xu and coworkers disclosed an electrochemical method featuring the direct electrolysis of *N*-benzylamides for preparing a range of substituted 4H-1,3-benzoxazines (Scheme 45). The electrolysis was proposed to facilitate anodic oxidation of the electron-rich aromatic nucleus, triggering regioselective cyclization to afford a cyclohexadienyl radical. Finally, rearomatization is realized upon abstraction of an electron and a proton, furnishing the desired benzoxazine **159**.⁴⁴⁶ The Zeng group demonstrated that carboxylic acids can be anodically oxidized to generate the

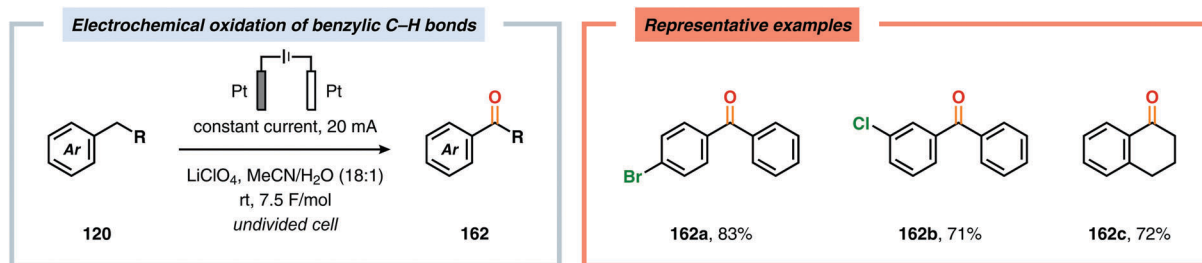
corresponding carboxylate radical. The generated radical could subsequently undergo intramolecular addition to electron-rich aromatic rings to produce the C-O coupled lactone product (Scheme 46).⁴⁴⁷⁻⁴⁵⁰ In addition to these examples, electrochemical oxygenation of furan derivatives⁴⁵¹⁻⁴⁵³ has also been reported and has, for example, been utilized for oxygenation of hispanolone⁴⁵⁴ as well as preparation of dideoxynucleoside analogues.⁴⁵⁵

Development of strategies for oxygenation of C(sp³)-H bonds constitutes a compelling approach for delivering alcohol and carbonyl derivatives. Historically, chemists have confided to using stoichiometric, and often toxic, oxidants for carrying out these transformations, resulting in the formation of considerable



Scheme 46 Electrochemical lactonization of C-H bonds.





Scheme 47 Electrolysis of ketones through anodic oxidation of benzylic methylenes.

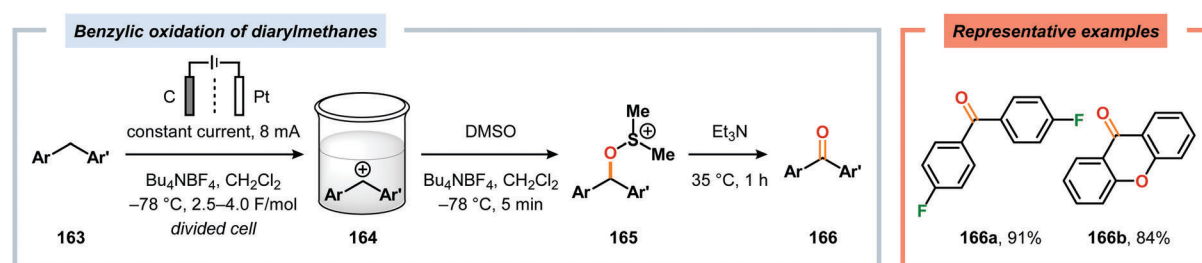
amounts of waste. However, the demand for more sustainable and atom economical methodologies has gained significant attention among the scientific community.⁴⁵⁶ Electrochemical activation of toluene derivatives through initial oxidation of the aromatic core is an appealing platform for realizing C(sp³)-H oxygenation of benzylic carbons. The aryl radical cation that is generated under these reaction manifolds can subsequently undergo deprotonation and a further oxidation to furnish a benzylic cation which can be trapped with various oxygen-based nucleophiles. Such an approach was implemented by the Wang group in which the benzylic cation was intercepted with water to furnish the benzylic alcohol, which underwent additional oxidation to give the corresponding ketone (Scheme 47).⁴⁵⁷ Diarylcarbenium ions can successfully be generated and accumulated by low-temperature electrochemical oxidation using the “cation pool” method.^{458–466} In the presence of DMSO, alkoxy-sulfonium ions serve as the key intermediates. Treatment with a base, such as Et₃N, or hydrolysis selectively affords the corresponding ketone⁴⁶⁷ (Scheme 48) or alcohol⁴⁶⁸ (Scheme 49). The fact that the initial electrochemical oxidation and the product-forming steps are separated implies that the products are not exposed to the electrolysis conditions, thereby limiting overoxidation. An electrochemical protocol for anodic acyloxylation based on the acid–base reactions between acetic acid or trifluoroacetic acid and a solid-supported base has also been reported (Scheme 50).^{469,470} It was found that the silica gel supported base was stable under the electrochemical conditions, permitting easy recovery and reuse of the solid-supported base. Indirect electrolysis using various mediators, such as TEMPO/Br[−],¹⁶⁴ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)^{471,472} and NHPI (Scheme 51),⁴⁷³ can also be harnessed for facilitating oxygenation of benzylic methylenes. In addition, Little and coworkers demonstrated that the use of triarylimidazoles^{474–477}

as redox mediators allowed for selective benzylic oxygenation of unsymmetrical benzyl ethers (Scheme 52).^{478–480}

The oxidation of unactivated C–H bonds typically requires high redox potentials, thus limiting the functional group compatibility and necessitates the use of inert solvents. Allylic oxidations are generally based on the use of toxic reagents, such as chromium and selenium, or scarce transition metal catalysts, such as Pd and Rh, which causes complications in industrial settings. The Baran group has addressed the issue of oxidizing unactivated C–H bonds through indirect electrolysis. After careful evaluation of potential mediators, a NHPI derivative (Cl₄NHPI) was demonstrated to be the optimal mediator for the allylic oxidation of a range of natural product inspired compounds, including sesquiterpene- and steroid-based substrates (Scheme 53).^{481–483} The described protocol exhibited broad substrate scope, operational simplicity and high chemoselectivity, and could even be conducted on a 100 g scale. The reaction is believed to involve hydrogen atom abstraction from the olefinic substrate to the electrochemically generated *N*-oxyl radical species, resulting in regeneration of Cl₄NHPI (178) and an allylic radical (179). Interception of the allylic radical with electrochemically produced ^tBuOO[•] furnishes allylic peroxide 180, providing enone 181 upon elimination of ^tBuOH. Furthermore, direct electrochemical oxidation of cholesterol at the allylic position has been demonstrated by Sobkowiak and coworkers.^{484–489} Baran and coworkers subsequently reported a method for selective functionalization of unactivated methylene and methine moieties utilizing quinuclidine (183) as redox mediator (Scheme 54). Here, an assortment of functional groups were demonstrated to be compatible with the developed chemoselective process.^{490,491}

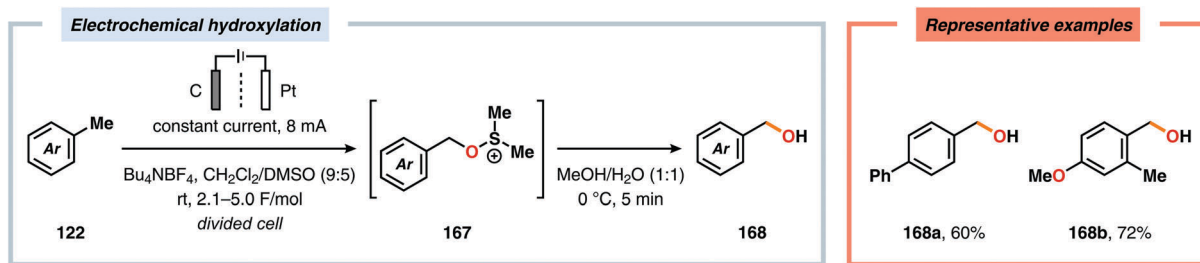
2.4. Palladium-catalyzed anodic C–H functionalization strategies

Palladium-catalyzed cross-coupling reactions have revolutionized C–C bond forming processes. Over the years, a variety

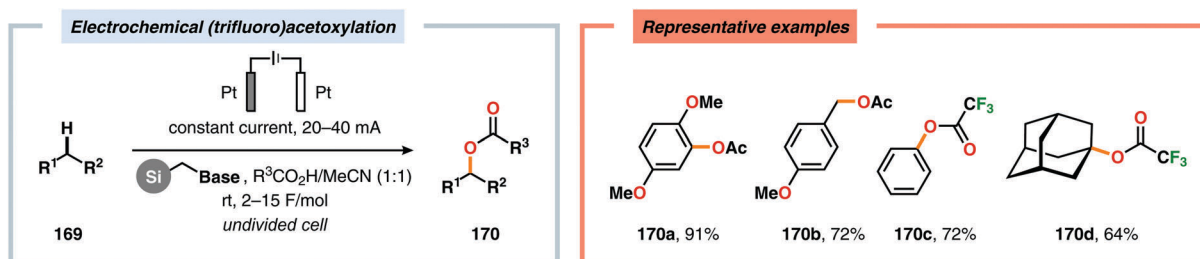
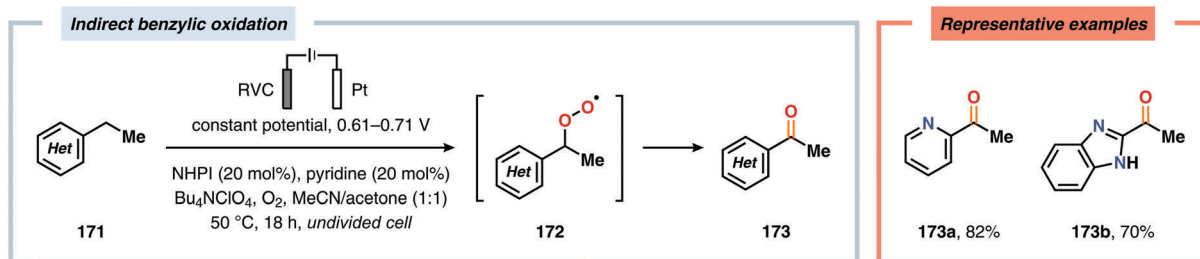


Scheme 48 Electrochemical oxygenation using alkoxy-sulfonium ions.

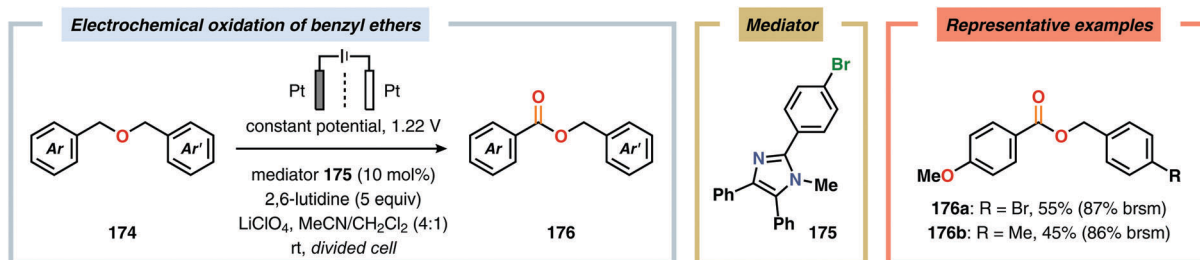




Scheme 49 Electrochemical hydroxylation using alkoxy-sulfonium ions.

Scheme 50 Electrochemical (trifluoro)acetoxylation of C(sp²)-H and C(sp³)-H bonds. Base = morpholine.

Scheme 51 Indirect electrochemical oxygenation using NHPI as mediator.

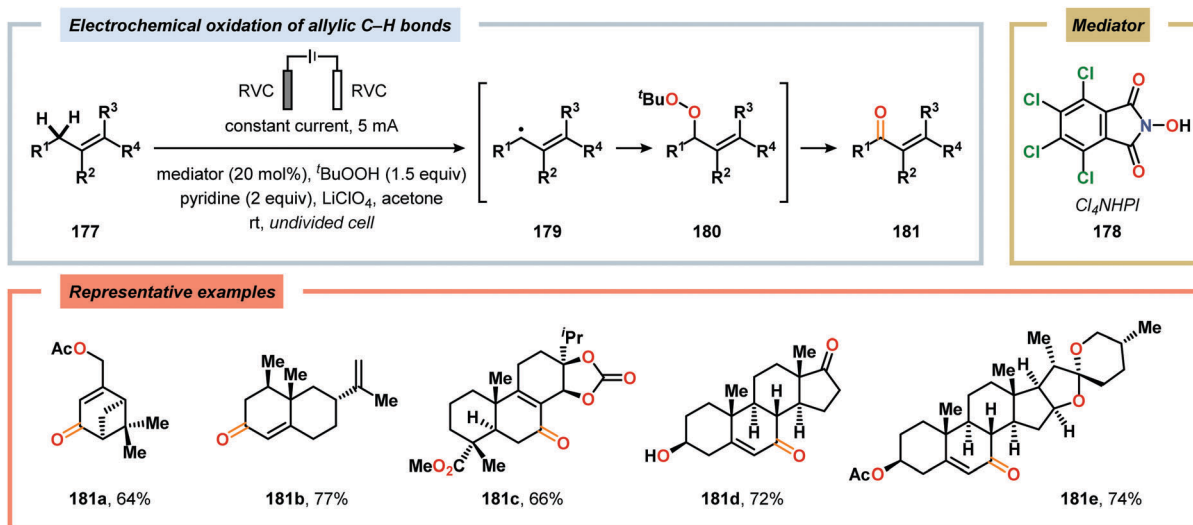


Scheme 52 Benzylic oxygenation using a triarylimidazole mediator.

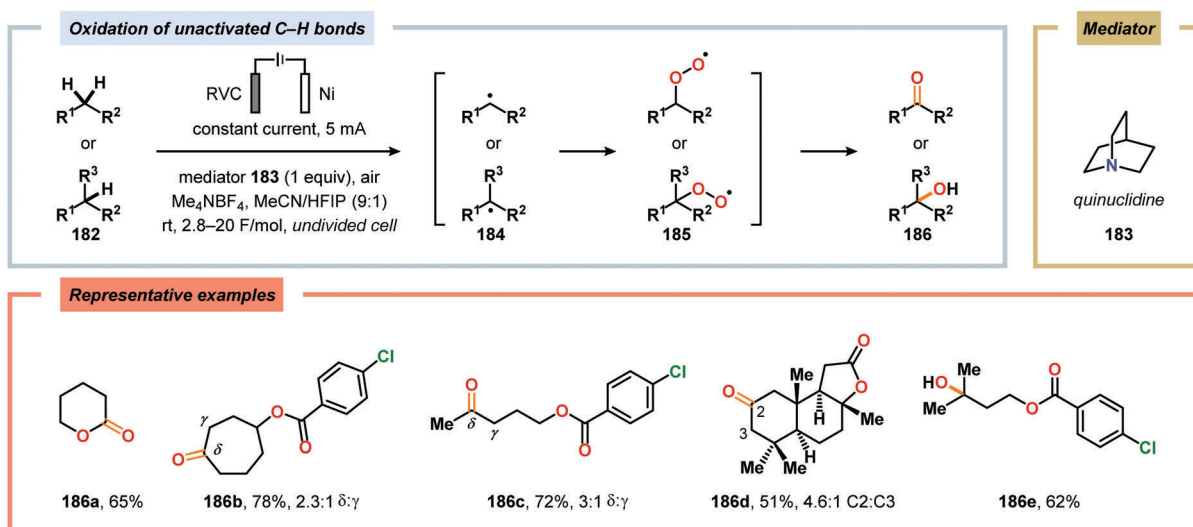
of catalytic platforms, such as carbon–heteroatom coupling, α -arylation and decarboxylative coupling, based on Pd have been designed.⁴⁹² It is therefore not surprising that the synergistic merger of electrochemistry and Pd catalysis has been the subject of keen interest by the synthetic community.^{70,493–497} Pioneering studies by Tsuji and Minato demonstrated a variant of the Wacker oxidation of terminal olefins by combining Pd-catalysis and electrochemical oxidation. In this system, benzoquinone is regenerated at the anode, which subsequently triggers the turnover-limiting reoxidation of Pd⁰ to Pd^{II}.^{498,499}

More recently, related approaches have also been employed for carrying out Heck-type reactions (Scheme 55),^{500,501} Glaser–Hay coupling⁵⁰² as well as homocoupling of arylboronic acids and derivatives thereof,⁵⁰³ and oxidation of alcohols under anaerobic conditions.⁵⁰⁴ Dual catalytic platforms based on Pd/TEMPO have been reported for electrooxidative synthesis of biaryls from arylboronic acids,^{505–507} cross-coupling between terminal alkynes and arylboronic acids⁵⁰⁸ as well as Wacker-type reactions⁵⁰⁹ and cyclizations.⁵¹⁰ Furthermore, Moeller and coworkers have demonstrated that triaryl amines are also effective mediators and have

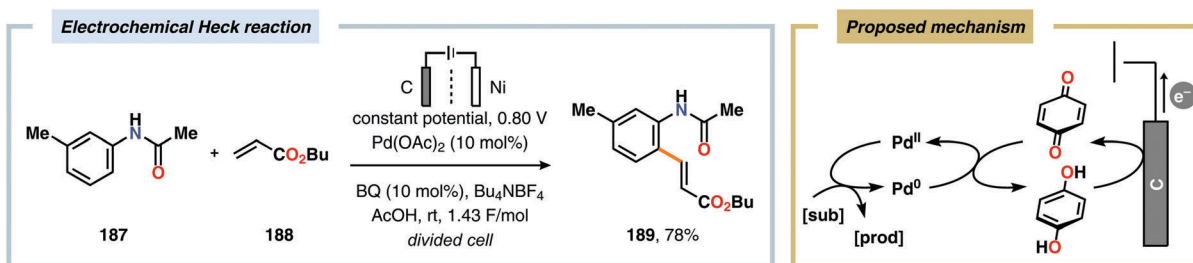




Scheme 53 Indirect electrochemical allylic C–H oxidation.



Scheme 54 Indirect electrochemical oxidation of unactivated C–H bonds.



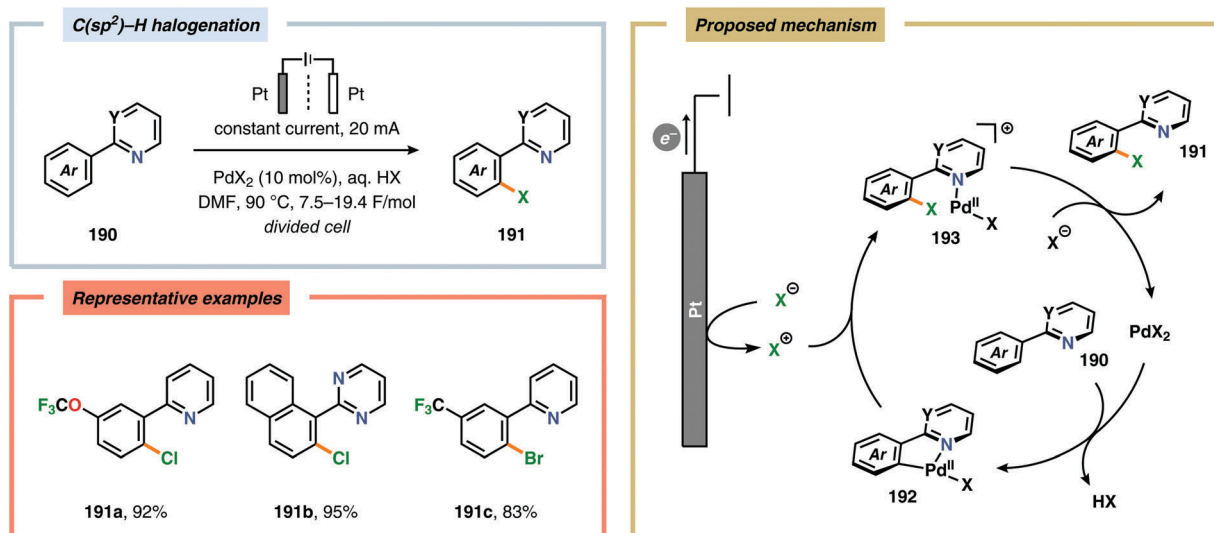
Scheme 55 Electrochemical Heck reaction using benzoquinone as mediator.

utilized this concept for site-selective functionalization of semi-conducting chips.^{511–516}

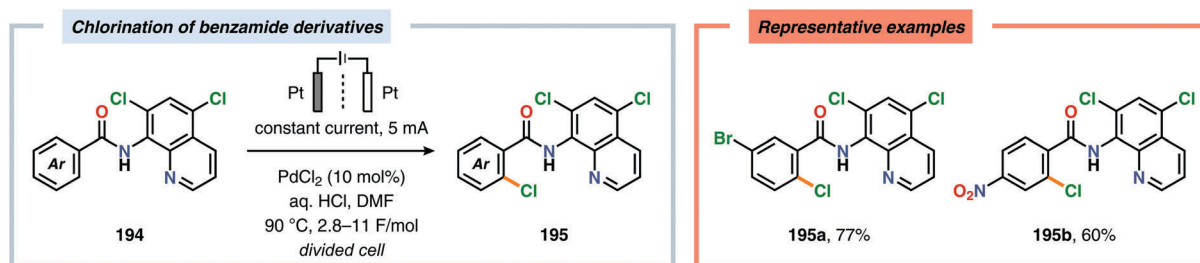
A variety of approaches have been reported for the C–H functionalization of arylpyridine derivatives *via* dual activation by transition-metal catalysis and electrochemical oxidation.

In this regard, the Kakiuchi group has demonstrated that C(sp²)-H halogenation of aromatics using hydrogen halides can be accomplished (Schemes 56 and 57). It was proposed that anodic oxidation of the halide ion produces a halonium ion, which subsequently reacts with the generated palladacycle to





Scheme 56 Regioselective halogenation of arenes through dual Pd catalysis and electrochemical oxidation.

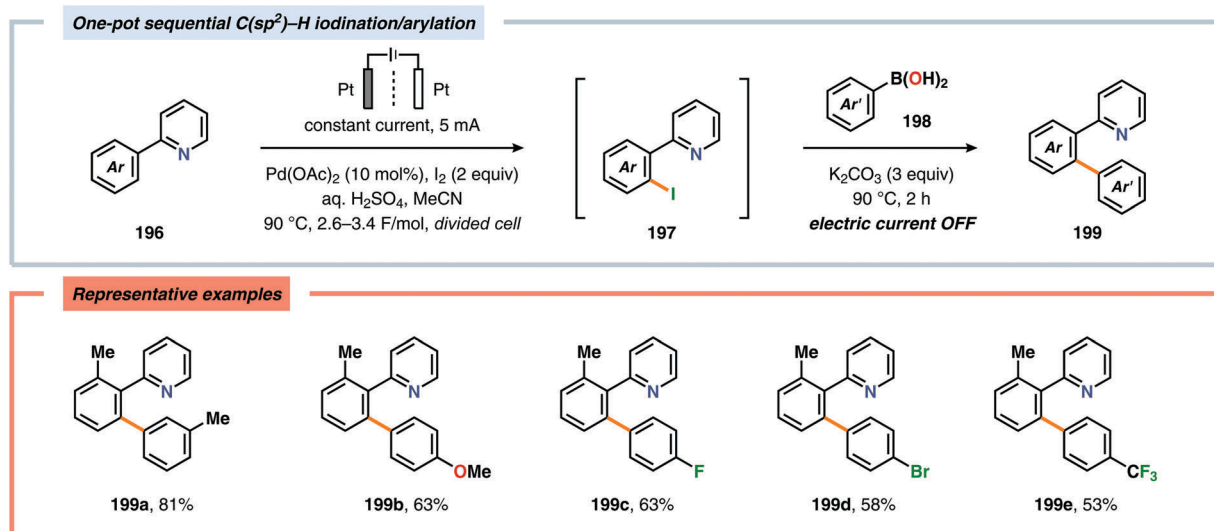
Scheme 57 Electrochemical C(sp²)-H chlorination of benzamide derivatives.

provide the halogenated product while regenerating the Pd^{II} catalyst.^{517–520} Expanding on this concept, the Kakiuchi group disclosed a method for regioselective homocoupling of arylpyridines in the presence of I₂ employing electrooxidative Pd catalysis.⁵²¹ Additionally, protocols for perfluoroacetoxylation,⁵²² perfluoroalkylation^{523,524} and phosphorylation^{525,526} of arylpyridines have been established by the Budnikova group. A procedure for sequential electrochemical C–H iodination followed by a Suzuki–Miyaura coupling has also been developed by Kakiuchi and coworkers. Here, I₂ was employed as the iodine source for the electrochemical C–H iodination. Upon completion of the iodination reaction, the electric current was simply switched off whereupon the arylboronic acid was introduced to the reaction mixture to furnish the corresponding cross-coupled product (Scheme 58).⁵²⁷ Along similar lines, Suga and coworkers reported a dual Pd-mediated electrooxidative homocoupling of *p*-bromophenylacetylene with a subsequent Suzuki–Miyaura coupling. Discrimination between the two reaction sites, the terminal alkyne and the Br group, was realized by the mere on/off application of electricity.⁵²⁸ Furthermore, the Sanford group recently disclosed a Pd-catalyzed electrochemical method for acetoxylation of C(sp³)-H and C(sp²)-H bonds (Scheme 59). It was noted that differences in the relative rates of competing oxidation reactions could prevail under chemical *versus* electrochemical oxidation conditions, thereby resulting in the formation

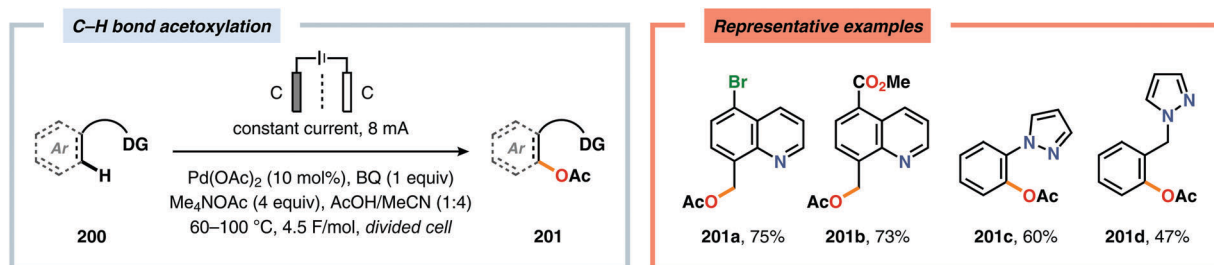
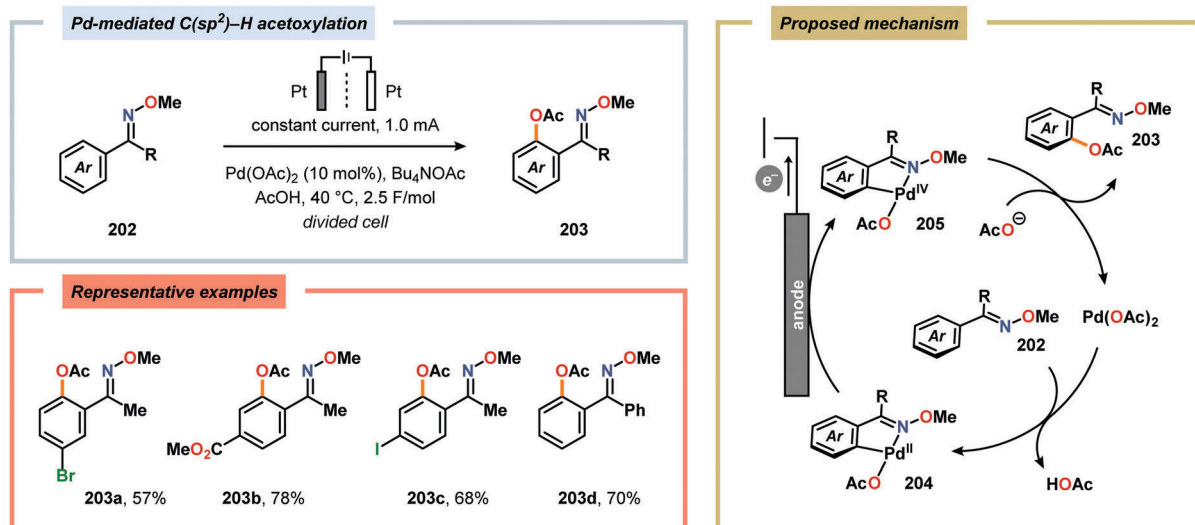
of complementary products. Additionally, the differences in reaction conditions for the chemical and electrochemical reactions, such as solvents as well as the addition of a supporting electrolyte, can translate to fundamental changes in catalyst performance and/or reaction outcomes, and will be imperative when designing new electrochemical platforms.⁵²⁹

Merging Pd catalysis and electrochemical oxidation has also proven to be a successful concept for carrying out C–H functionalization on oxime-based motifs. In this regard, Mei and coworkers have examined the Pd-catalyzed oxime-directed C(sp²)-H acetoxylation employing an anodic oxidation strategy (Scheme 60). In this transformation, it was proposed that the rate-determining oxime-assisted C–H activation generates the desired palladacycle. This Pd^{II} species is subsequently oxidized at the anode to produce the corresponding Pd^{IV} intermediate, which can undergo reductive elimination to deliver the acetoxylation product, thus regenerating Pd^{II} to close the catalytic cycle.⁵³⁰ Shortly thereafter, the authors reported a dual Pd/electrochemical strategy to achieve C(sp²)-H methylation and acylation (Scheme 61). Here, reductive elimination was suggested to occur from a high-valent Pd intermediate, presumably Pd^{III} or Pd^{IV}.⁵³¹ Finally, functionalization of unactivated C(sp³)-H bonds has also been reported using oximes as directing groups. Along similar lines, C–H activation furnishes a Pd^{II} palladacycle, which subsequently is oxidized at the anode to





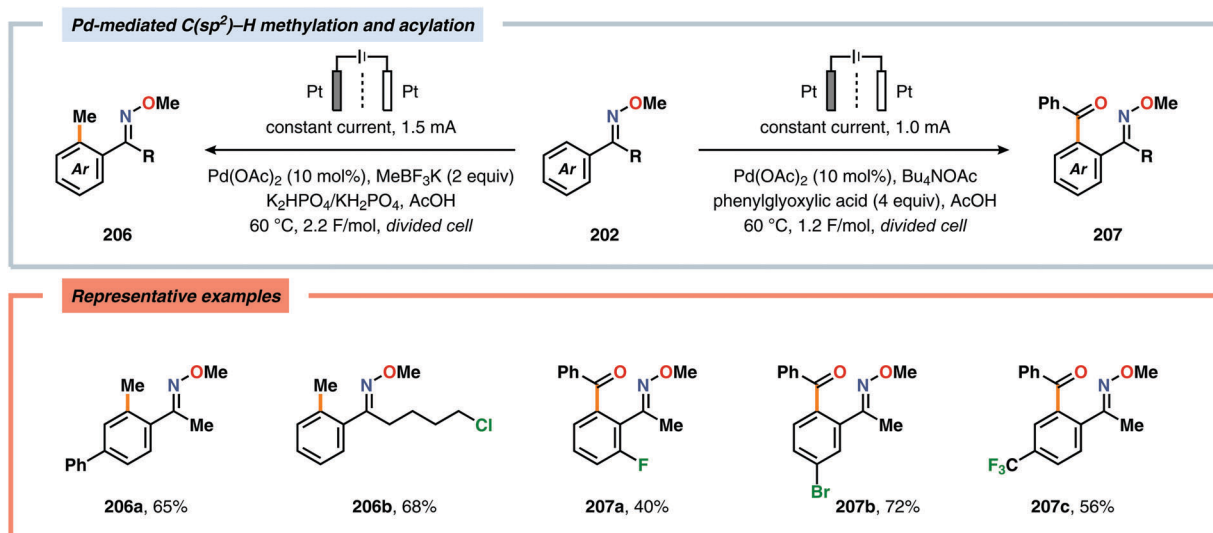
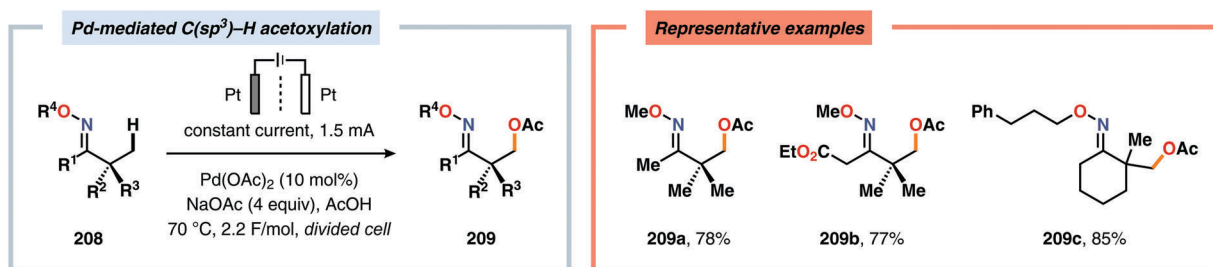
Scheme 58 One-pot C–H iodination/arylation of arylpyridines.

Scheme 59 Pd-catalyzed electrochemical method for acetoxylation of C(sp³)-H and C(sp²)-H bonds.Scheme 60 Pd-catalyzed C(sp²)-H acetoxylation via anodic oxidation.

give a high-valent Pd species, presumably a Pd^{IV} intermediate. Generation of the high-valent Pd center promotes the otherwise challenging C–O reductive elimination event to deliver the oxygenated product while regenerating Pd^{II}. In addition to

carrying out C(sp³)-H acetoxylation (Scheme 62), the dual Pd/electrochemical strategy could also be conducted with a variety of oxyanion coupling partners, such as methoxide, tosylate and trifluoroacetate.⁵³² The catalytic protocols described here



Scheme 61 Pd-mediated C(sp²)-H methylation and acylation.Scheme 62 Dual Pd/electrochemical C(sp³)-H functionalization.

proceed under mild reaction conditions and in the absence of exogenous ligands, representing sustainable alternatives to conventional platforms for C-H functionalization that rely on stoichiometric chemical oxidants.

2.5. Electrochemical oxidative cross-couplings

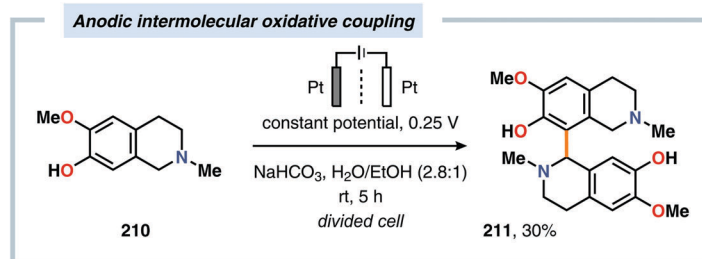
Transition metal-catalyzed cross-coupling reactions serve as an integral part of contemporary synthetic chemistry for the rapid and selective construction of complex architectures from simple building blocks. However, these catalytic bond forming platforms require the use of prefunctionalized substrates, which adds additional preceding synthetic steps. This inevitably culminates in the generation of undesired stoichiometric amounts of waste. In recent years, constructing C-C bonds through the direct coupling of two C-H coupling fragments has emerged as a highly appealing concept. This effective and straightforward strategy not only circumvents the need for using prefunctionalized reagents but also considerably enhances the atom- and step-economy. In principle, dihydrogen (H₂) is the sole (by)product resulting from forging the two C-H bonds; however, typically a sacrificial oxidant is required to accept the H₂, hence the name oxidative cross-coupling or cross-dehydrogenative coupling (CDC). Oxidative cross-coupling is undoubtedly an attractive catalytic platform, yet conceptually and practically challenging due to, for example,

the low reactivity of the C-H bonds in combination with overcoming the limitations in site-selective functionalization.⁵³³⁻⁵³⁶ Moreover, the development of radical-mediated oxidative coupling strategies has also gained significant attention from the scientific community.⁵³⁷

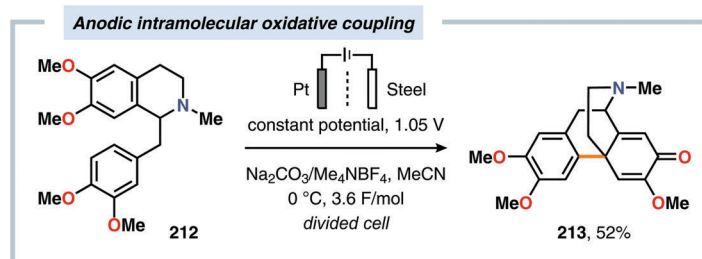
Despite the relatively simple motif, the synthesis of biphenols through oxidative cross-coupling of unprotected phenols has proven to be challenging and often relies on protocols involving expensive catalyst systems or reagents. In addition to producing the desired cross-coupled biphenolic product,⁵³⁸ the reaction is also accompanied by products derived from oxidative dimerization, higher molecular weight polymers as well as compounds housing C-O coupling motifs.⁵³⁹⁻⁵⁴³ Seminal work on the intermolecular anodic oxidative coupling of phenols demonstrated that corypalline (**210**) could be electrochemically oxidized to the corresponding dimer (**211**, Scheme 63).⁵⁴⁴⁻⁵⁴⁸ However, attempts to carry out the related intramolecular C-C coupling on laudanosine (**212**) resulted in oxidative dearomatization of one of the phenolic moieties and furnished *O*-methylflavinantine (**213**, Scheme 64).⁵⁴⁹⁻⁵⁵³ Similar reactivity has also been observed for the related alkaloids amurine, oxocrinine, oxomaritidine and pallidine.⁵⁵⁴⁻⁵⁵⁶

Pioneering studies by the Waldvogel group demonstrated that the direct anodic oxidation of 2,4-dimethylphenol (**214a**) produced the *ortho,ortho*-coupled biphenol **215a**, albeit in





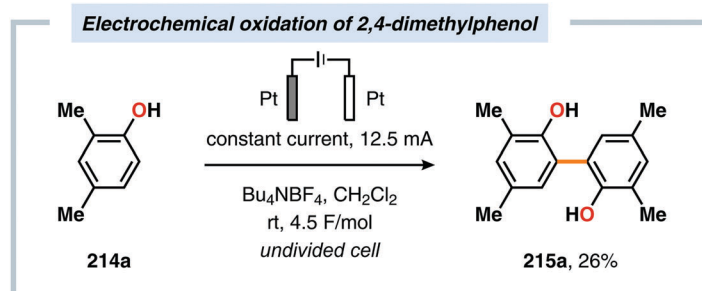
Scheme 63 Anodic intermolecular oxidative coupling of corypalline.



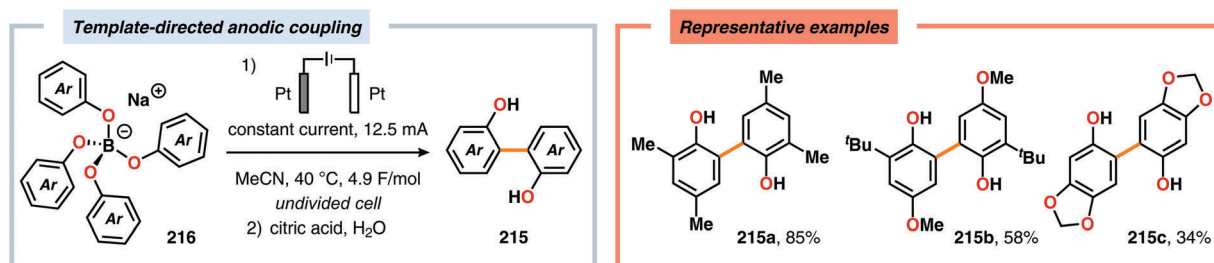
Scheme 64 Anodic intramolecular coupling of laudanoline.

rather poor yield (Scheme 65).⁵⁵⁷ The authors subsequently devised a template-directed method for the anodic coupling of substituted phenols to the corresponding 2,2'-biphenols using tetraphenoxo borate derivatives (Scheme 66). Although the developed protocol was limited to electron-rich substrates, the electrochemical synthesis could be conducted on a kilogram scale.^{558,559} In addition to generating the desired biphenol product, several additional

coupling motifs can also be produced.^{560–565} To circumvent the lack of selectivity, Waldvogel and coworkers realized that boron-doped diamond (BDD) electrodes²² gave almost exclusive selectivity for the *ortho*-coupling product (Scheme 67).^{566,567} It was rationalized that the observed selectivity originated from the high chemical and electrochemical stability of the BDD electrodes in combination with the high overpotential for oxygen evolution in aqueous media and

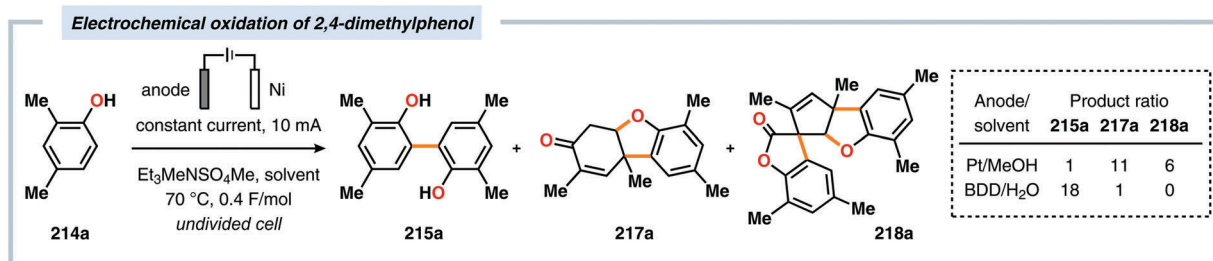


Scheme 65 Electrochemical oxidation of 2,4-dimethylphenol.

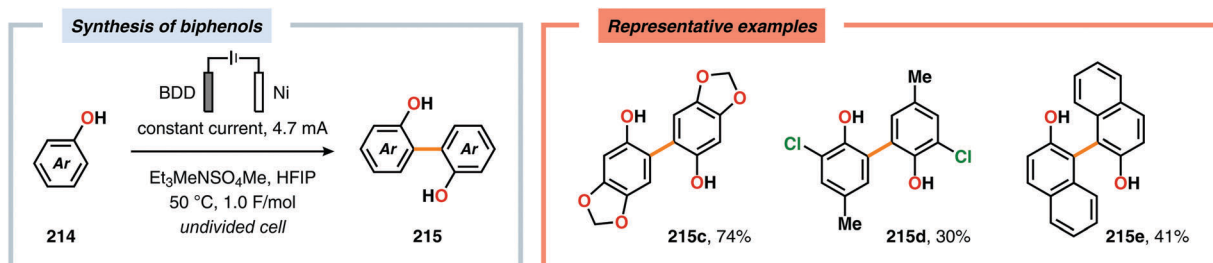


Scheme 66 Template-directed anodic coupling of phenols.





Scheme 67 Product diversity from the electrochemical oxidation of 2,4-dimethylphenol.

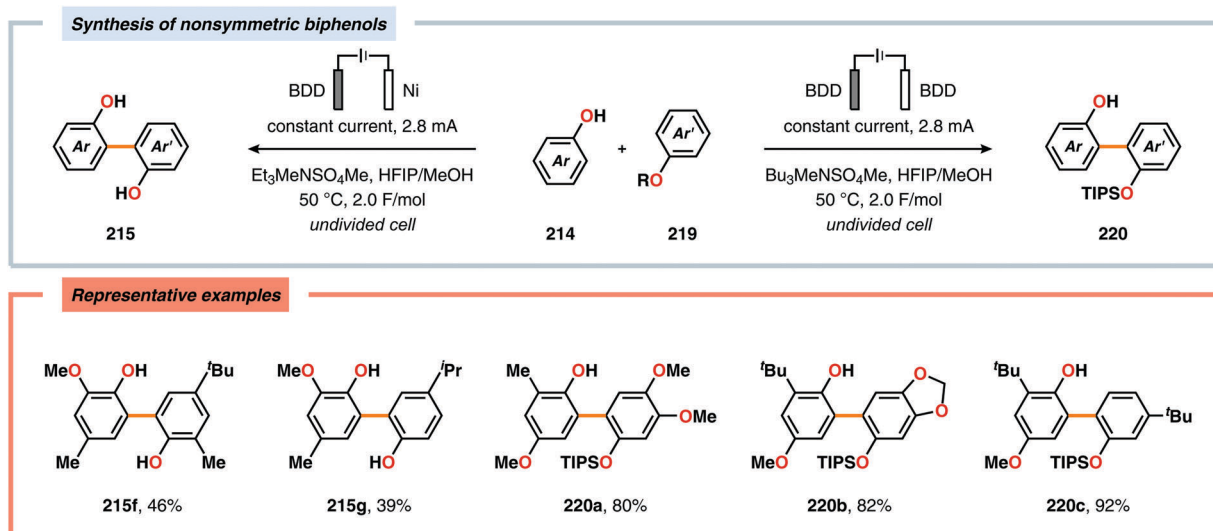


Scheme 68 Electrochemical synthesis of biphenols using a BDD anode.

efficient formation of reactive alkoxy or hydroxyl radicals at the anode that can serve as mediators.^{568–570} Interestingly, by simply switching to fluorinated solvents/mediators, such as hexafluoroisopropanol (HFIP), allowed for the creation of a powerful electrolyte system and significantly expanded the scope and efficiency for the anodic coupling of simple phenols⁵⁷¹ (Scheme 68) as well as guaiacol derivatives^{572–574} on BDD electrodes. Protocols for synthesis of nonsymmetric biphenols (Scheme 69),^{575–577} and anodic cross-coupling of phenols with naphthols⁵⁷⁸ (Scheme 70) as well as aniline derivatives⁵⁷⁹ (Scheme 71) have also been addressed.^{580,581}

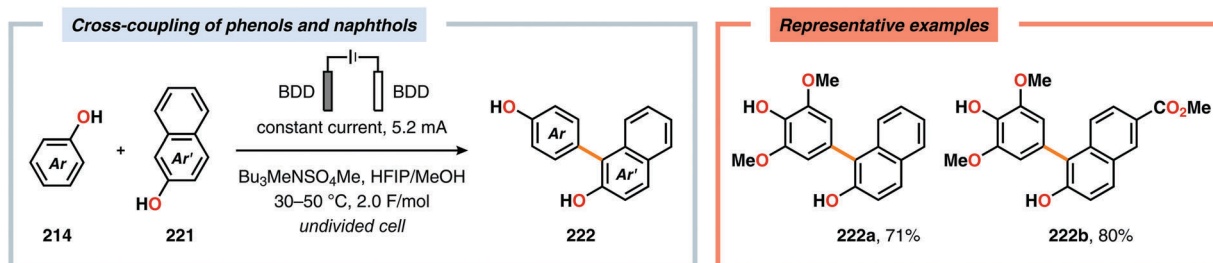
Metal-free electrochemical methodologies that facilitate anodic cross-coupling between phenols and electron-rich arenes have also been developed. The Waldvogel group discovered that

this reaction could be accomplished employing a BDD anode in the presence of HFIP. It was established that HFIP had a crucial role in the reaction as no conversion was observed in the absence of HFIP but were able to rule out the possibility of HFIP acting as a redox mediator.^{55,582} Since the phenol and arene components have similar oxidation potentials, the high level of chemoselectivity was rationalized by oxyl–HFIP hydrogen bonding interactions, which stabilize the produced spin centers.^{583–585} The hydrogen-bond stabilized spin center undergoes HAT with the phenol (214), which produces the more easily oxidized phenoxyl radical 227. Radical 227 is subsequently trapped by the electron-rich arene (118), which gives intermediate 228 upon deprotonation. This is followed by a second HAT event, resulting

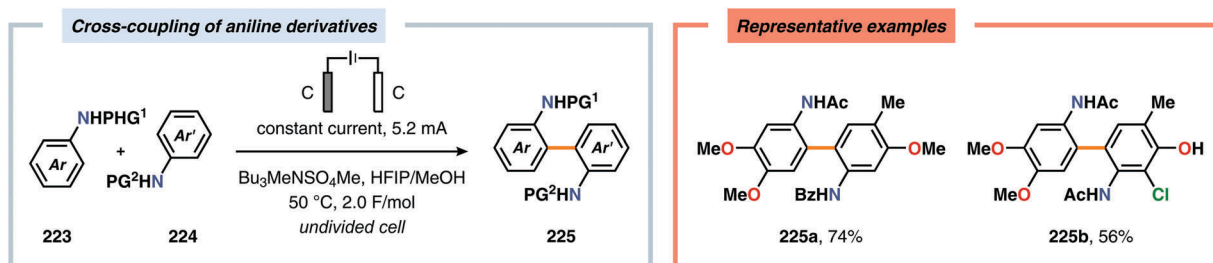


Scheme 69 Synthesis of nonsymmetric biphenols through anodic cross-coupling.





Scheme 70 Anodic cross-coupling of phenols and naphthols.

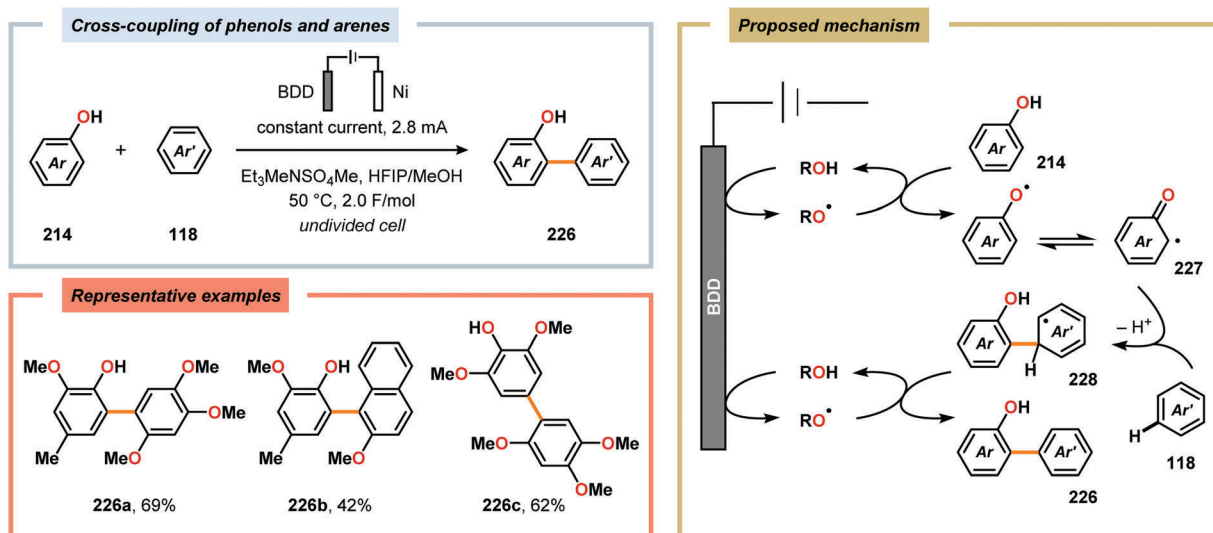


Scheme 71 Anodic cross-coupling of aniline derivatives. PG = protecting group.

in rearomatization and furnishes the cross-coupled biaryl **226** (Scheme 72).^{55,582} This strategy was subsequently extended to enable the development of anodic cross-coupling protocols for synthesis of *meta*-terphenyl-2,2''-diols (Scheme 73),^{586,587} 2,5-bis(2-hydroxyphenyl)thiophenes⁵⁸⁸ (Scheme 74) and dibenzofurans.^{589,590}

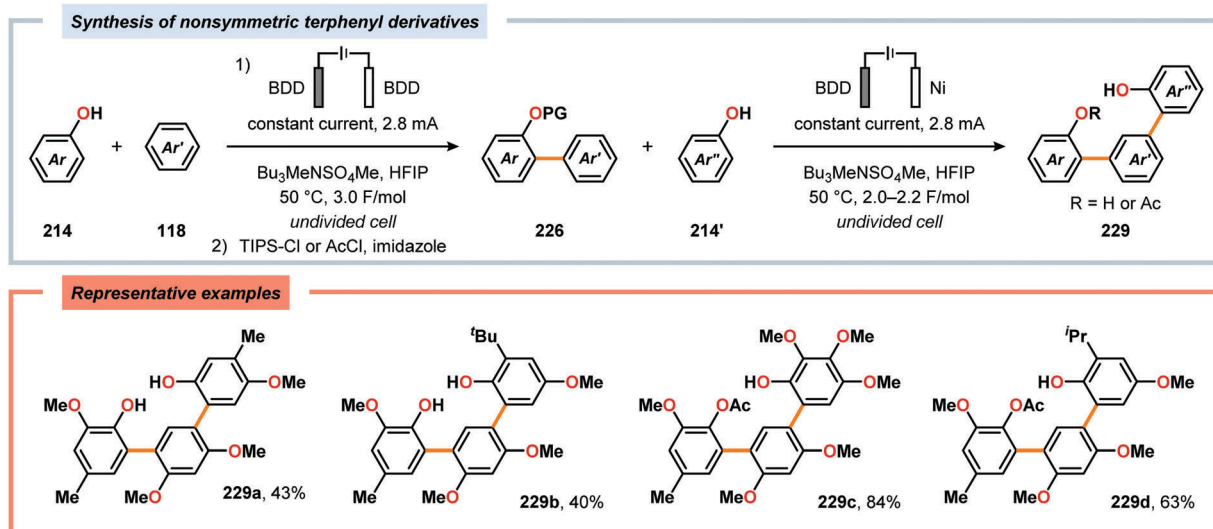
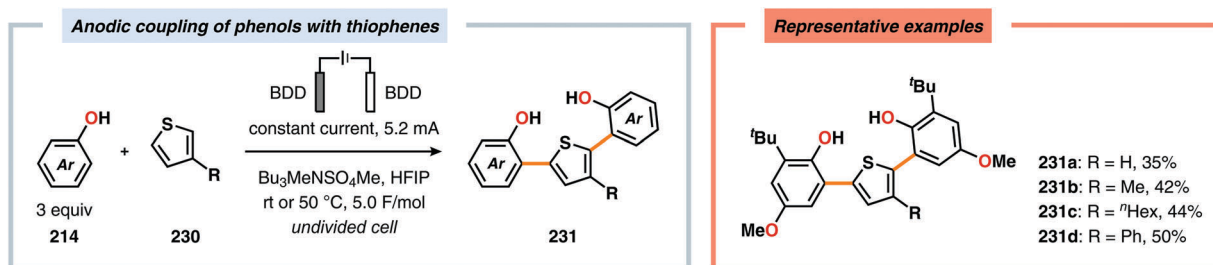
Since the high oxidation potential of electron-deficient arenes, such as nitroarenes, limits direct anodic oxidation of these species, anodic cross-coupling reactions between electron-deficient arenes and nucleophiles engage in a nucleophilic aromatic substitution (S_NAr) type pathway. This two-step process can follow two mechanistically discrete pathways (Scheme 75). The first step involves nucleophilic addition to the electron-deficient arene unit, resulting in either a σ^H or σ^X adduct (Meisenheimer complex).

For the σ^H intermediate (**233**), the second step follows a two-electron mechanism in which formal loss of a hydride occurs and is referred to as nucleophilic aromatic substitution of hydrogen (NASH, S_N^H). However, rearomatization of the σ^X adduct (**235**), generated from attack of the *ipso* carbon, involves an initial single-electron oxidation, which triggers radical elimination of the heteroatom (X^*) and is hence called nucleophilic aromatic substitution of a heteroatom (NASX, S_N^X).⁵⁹¹⁻⁵⁹³ A range of nucleophiles, including acetate,⁵⁹⁴ alkoxides,^{594,595} alkyl lithium or Grignard reagents,⁵⁹⁶ amides,⁵⁹⁷ amines,^{594,595,597} enolates,^{594,598} fluoride,⁵⁹⁵ cyanide,^{594,599} organophosphorus compounds,⁶⁰⁰ tetraalkylborate salts⁶⁰¹ and thiolates,⁵⁹⁵ have been utilized to affect nucleophilic aromatic substitution through electrochemical

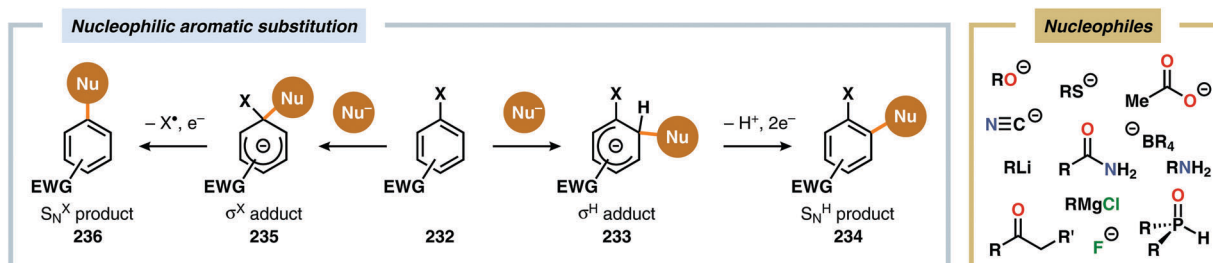


Scheme 72 Direct anodic cross-coupling of phenols and electron-rich arenes.



Scheme 73 Synthesis of nonsymmetric *meta*-terphenyl-2,2''-diols. PG = protecting group.

Scheme 74 Electrochemical synthesis of 2,5-bis(2-hydroxyphenyl)thiophenes.



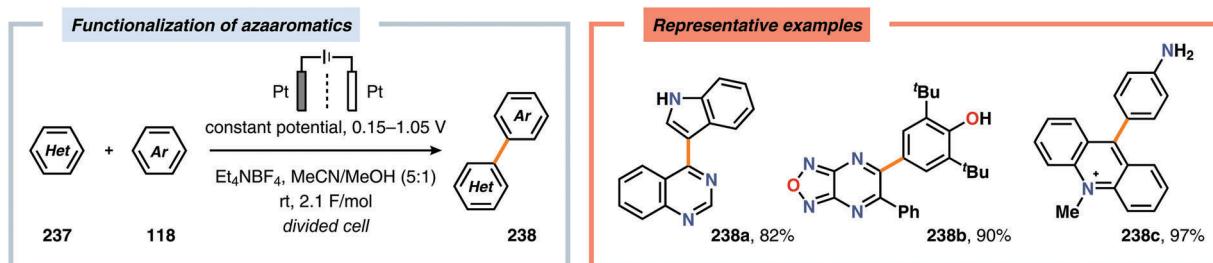
Scheme 75 Nucleophilic aromatic substitution via electrochemical oxidation.

oxidation of the intermediate σ adducts. This concept was recently applied on azaaromatic scaffolds for the synthesis of asymmetrical bi(hetero)aryl motifs (Scheme 76).^{602,603}

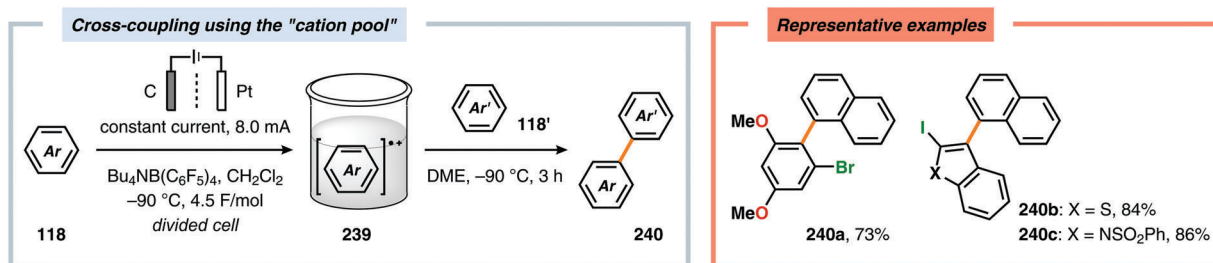
Although oxidative coupling between electron-deficient and electron-rich arenes, two moieties with distinctly different π -electronic properties, generally provides high chemoselectivity of the cross-coupled products over homocoupling as a result of the “electronic differential principle”, anodic cross-coupling of unactivated electron-rich arenes has been achieved. Recently, the Yoshida group highlighted that employing the “cation pool” method allowed the merging of two unactivated aromatic

compounds in a straightforward fashion. Here, initial anodic oxidation at $-78\text{ }^\circ\text{C}$ of the less electron-rich arene component (naphthalene) resulted in accumulation of the corresponding radical cation species. Subsequent introduction of the other aromatic moiety under non-oxidative conditions at $-90\text{ }^\circ\text{C}$ avoided nonselective oxidation of the starting material and overoxidation of the biaryl product (Scheme 77). Notably, the high regioselectivity of the developed cross-coupling method can be estimated based on the spin density of the radical cation and the highest occupied molecular orbital (HOMO) coefficients of the nucleophilic aromatic partner.^{604,605} The use of parallel





Scheme 76 Electrochemical functionalization of azaaromatics through nucleophilic aromatic substitution.



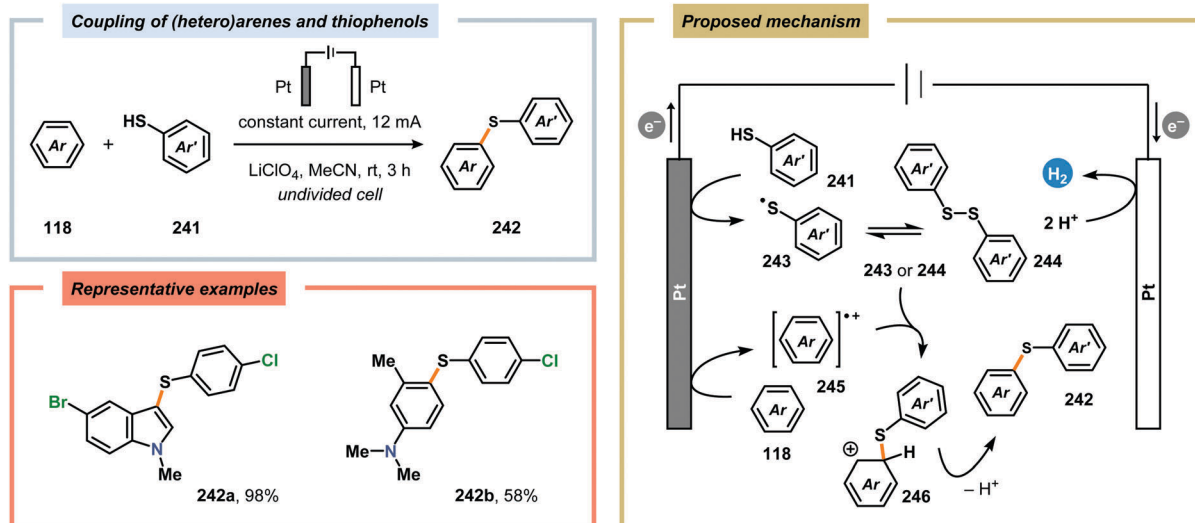
Scheme 77 Cross-coupling of aromatic compounds using the "cation pool" method.

laminar flow also serves as a convenient method for preparing nonsymmetrical biaryl scaffolds as demonstrated by Atobe and coworkers.⁶⁰⁶ An electrochemical method for constructing carbon–sulfur (C–S) bonds was recently reported by the Lei group. The electrochemical reactions were conducted in an undivided cell and allowed a wide range of electron-rich arenes and heteroarenes, such as indole, pyrrole and thiophene, to be coupled with various substituted thiophenols. Mechanistic studies indicated that performing the reaction in the presence of the persistent radical TEMPO did not produce any of the desired C–S coupling product. Furthermore, the involvement of disulfides, generated from dimerization of the thiophenols, was also observed.

Therefore, two mechanistically distinct pathways could explain the noted reaction outcome. Thus, product formation can occur either through direct radical–radical coupling between the arene cation radical intermediate (245) and the thiyl radical (243). Alternatively, C–S bond formation can proceed *via* arene radical addition to the produced disulfide (244) as depicted in Scheme 78.^{607,608}

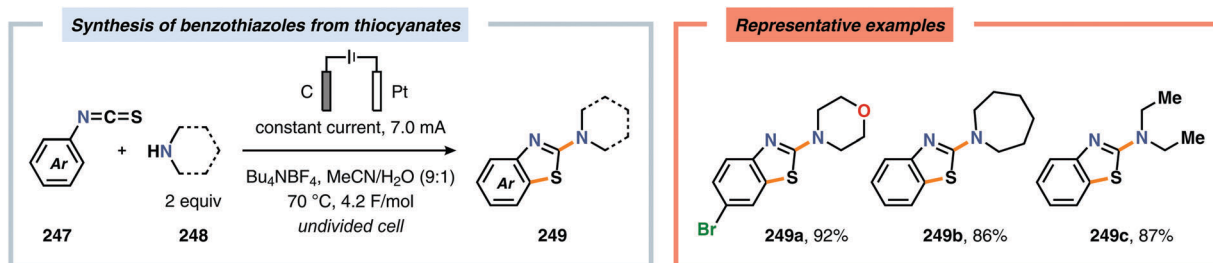
2.6. Oxidative annulations involving (hetero)arenes

Electrochemical approaches for intramolecular C–H thiolations have been reported by the Lei⁶⁰⁹ and Xu⁶¹⁰ groups.⁶¹¹ Lei and coworkers' protocol utilized aryl isothiocyanates, which were

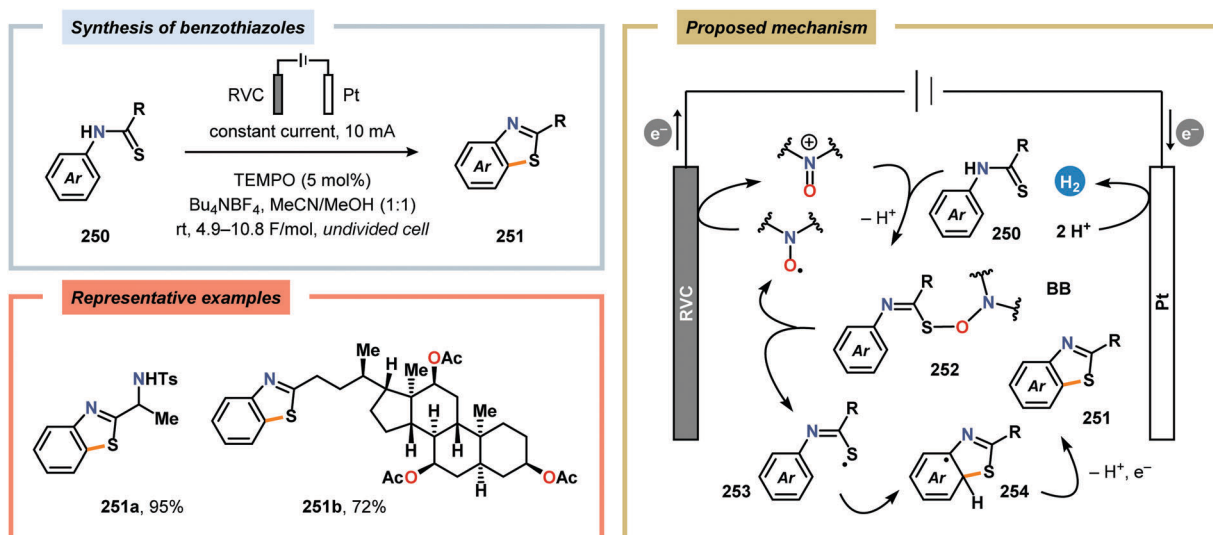


Scheme 78 Direct anodic cross-dehydrogenative coupling of (hetero)arenes and thiophenols.





Scheme 79 Electrochemical synthesis of benzothiazoles from aryl isothiocyanates and amines.



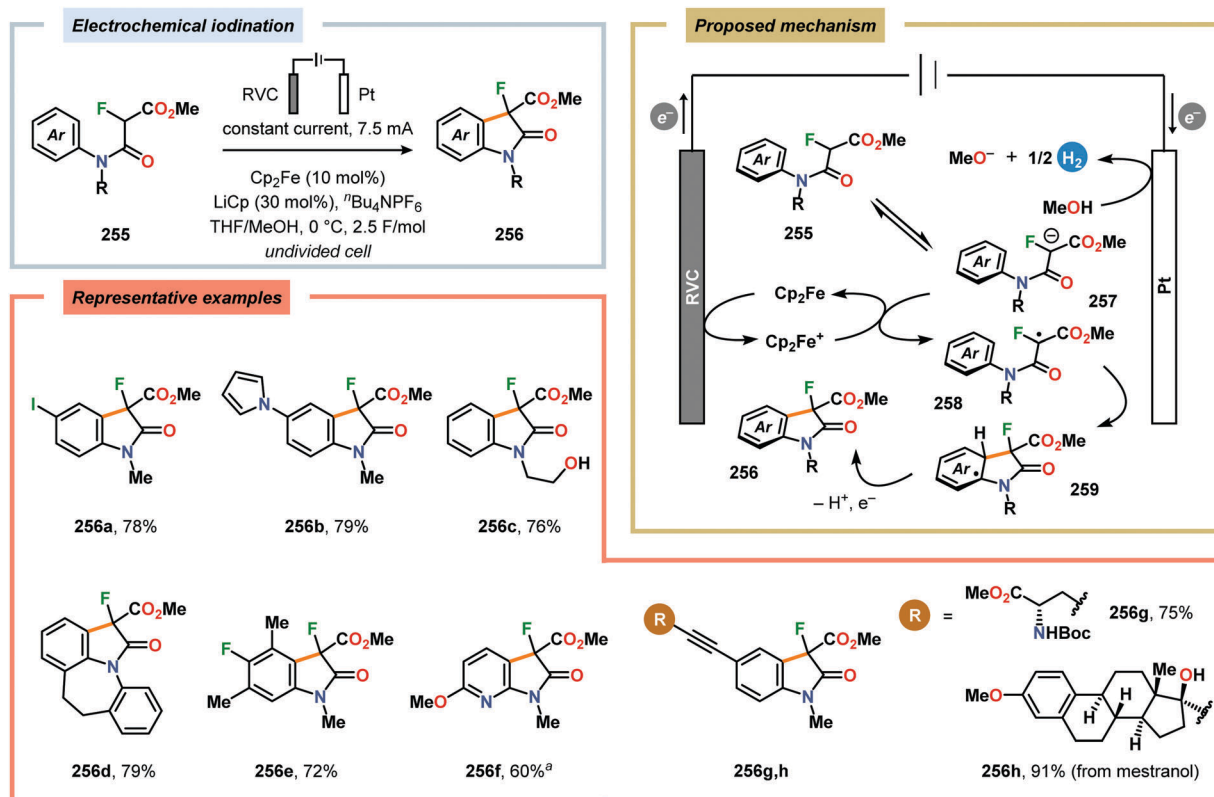
Scheme 80 Electrochemical synthesis of benzothiazoles using TEMPO as redox mediator.

treated with amines to produce the corresponding thioamides. The *in situ* generated thioamides were subsequently electrolyzed at 70 °C in an undivided cell to furnish the desired benzothiazoles (Scheme 79).⁶⁰⁹ On the contrary, Xu and coworkers strategy employed TEMPO as a mild redox-mediator to enable selective C–H thiolation of a variety of N-(hetero)arylthioamides with diverse electronic properties (Scheme 80).^{610,612} Both C–H thiolation strategies are believed to proceed *via* thioamidyl radicals with concomitant formation of H₂ at the cathode. Expanding on the C–H thiolation strategy, the Xu group has recently demonstrated that 3-fluorooxindoles could be accessed through cross-dehydrogenative coupling.^{613,614} Here, ferrocene (Cp₂Fe) was selected as a redox mediator due to earlier literature precedents highlighting its capability of promoting oxidative radical cyclizations.^{615–618} The reactions were carried out in an undivided cell and tolerated a multitude of functional groups, including alcohols, alkynes, aminoesters, halogens, silyl ethers as well as redox-sensitive carbazole, *N*-phenyl carbamate and pyrrole groups (Scheme 81). However, products containing electron-withdrawing groups, such as CF₃, OCF₃ and CO₂Me, were prone to base-induced decomposition and therefore had to be performed at –30 °C for optimal yields. The mechanism is presumed to involve formation of H₂ at the cathode from MeOH, which results in production of MeO[–]. The electrochemically

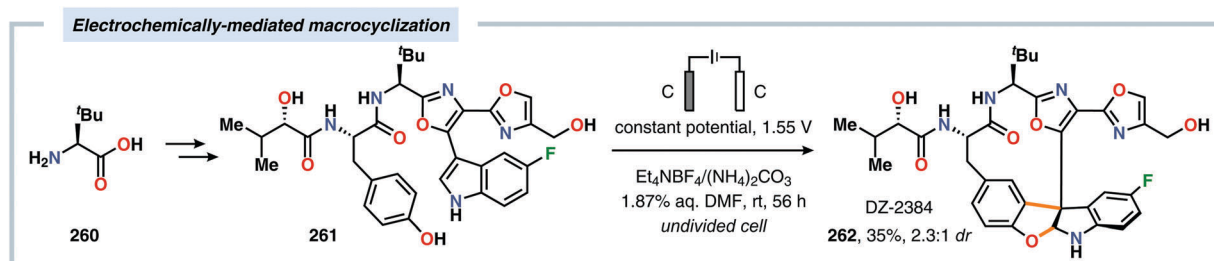
generated base facilitates deprotonation of the substrate (255) to furnish the corresponding enolate (257), which is subsequently oxidized by the anodically generated Cp₂Fe⁺ to produce α -carbon radical intermediate 258. Finally, radical cyclization and rearomatization afford oxindole 256.^{613,619,620}

Harran and coworkers recently showcased electrochemistry as a powerful strategy in organic synthesis, enabling a scalable preparation of DZ-2384 (262), a diazomide-based drug candidate for treatment of cancer.⁶²¹ Initial attempts were aimed at using PhI(OAc)₂ for mediating the dehydrogenative macrocyclization between the phenol and indole components. However, this approach afforded comparable amounts of a spirocyclohexadienone, which severely limited the yield of the desired macrocyclized product and complicated its purification.⁶²² To circumvent formation of this byproduct, an alternative method was pursued. In this regard, the use of an electrochemical method was explored as it would employ substrates derived from common amino acids. In the refined route towards DZ-2384 (262), the anodic oxidation could be performed in the final step at ambient temperature in aqueous DMF in an undivided cell open to air (Scheme 82), highlighting the practicality of the developed electrochemical macrocyclization approach.⁶²¹ A related macrocyclization approach was also explored in the synthesis of azonazine.⁶²³ Subsequently, the Lei group reported a related





Scheme 81 Synthesis of 3-fluorooxindoles through electrochemical cross-dehydrogenative coupling using ferrocene (Cp_2Fe) as redox mediator. ^a Reaction was performed at -30°C .



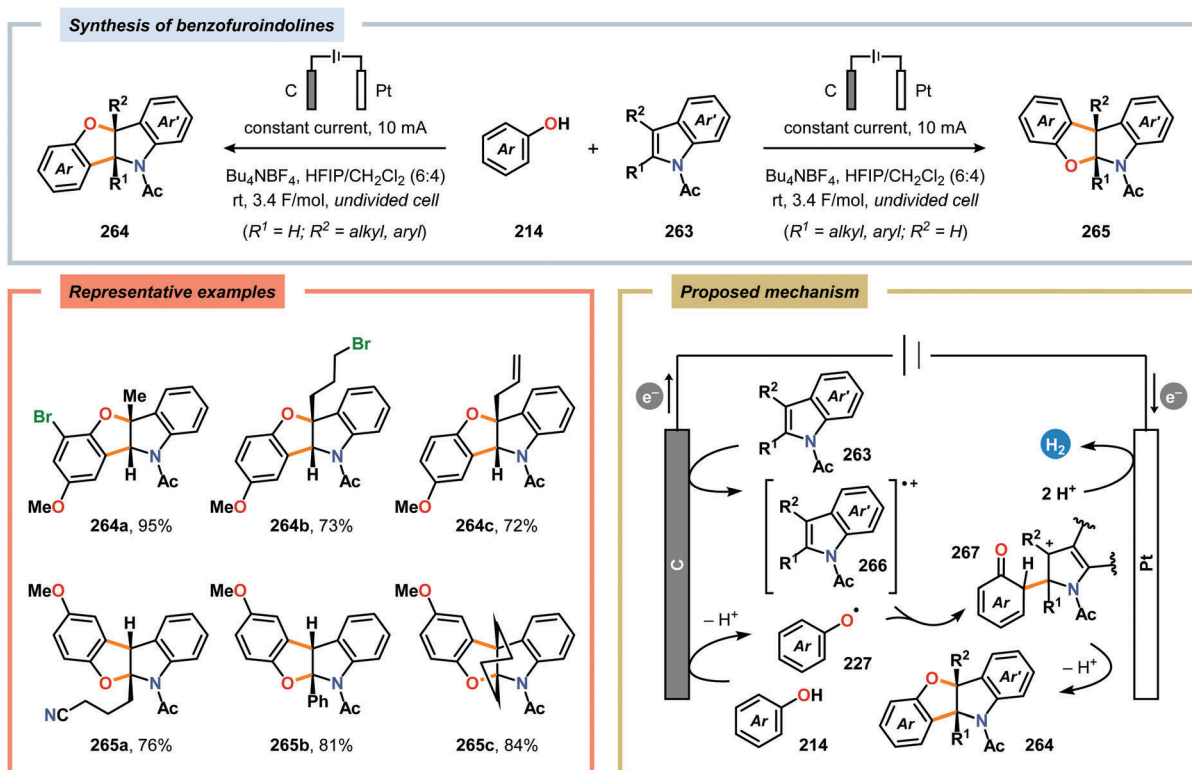
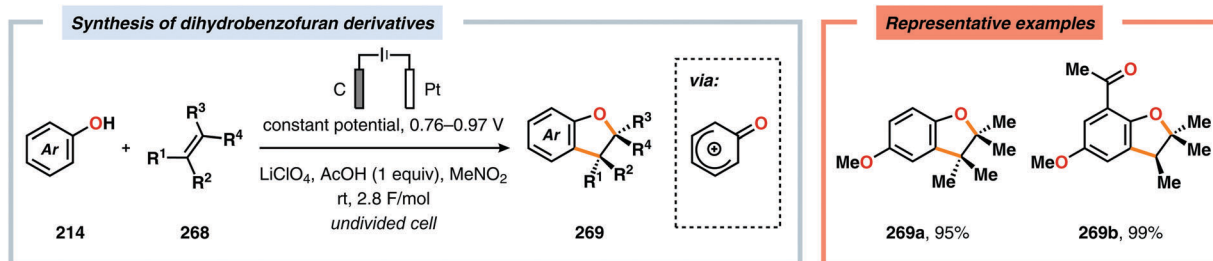
Scheme 82 Preparation of a diazonamide-based drug development candidate by employing a dehydrogenative macrocyclization approach.

dehydrogenative [3+2] annulation between phenol and indole derivatives for accessing benzofuroindolines using an undivided cell (Scheme 83). Here, various *N*-acetylindoles bearing different C-3 substituents were compatible with the electrochemical annulation and afforded the corresponding benzofuro[3,2-*b*]indolines (**264**) in high to excellent yields. However, applying 2-substituted *N*-acetylindoles resulted in a switch in selectivity and instead produced the corresponding benzofuro[2,3-*b*]indoline core (**265**). CV experiments of *p*-methoxyphenol and various *N*-acetylindoles revealed that the oxidation potentials were quite similar, suggesting that anodic oxidation of both coupling components might occur under the electrolytic conditions. Radical coupling between the indolyl cation radical (**266**) and phenoxy radical (**227**) furnishes cation **267**. Finally, intramolecular cyclization and

deprotonation gives the target benzofuroindoline with concomitant formation of H_2 at the cathode. However, a mechanism involving nucleophilic attack of the phenol moiety onto the indolyl cation radical cannot be excluded.⁶²⁴

Anodic oxidation of phenols can result in generation of phenoxonium ions upon removal of two electrons and a proton, which can react with simple nucleophiles, such as MeOH or H_2O , to afford 4-substituted cyclohexa-2,5-dienones.^{625–630} Chiba and coworkers highlighted that the anodically generated phenoxonium ions could engage in intermolecular [3+2] cycloaddition with unactivated alkenes to afford dihydrobenzofuran derivatives (Scheme 84).^{631–635} The reaction has also been conducted using a temperature-controlled multiphase solution consisting of cyclohexane and $\text{LiClO}_4/\text{MeNO}_2$,⁶³⁶ which was



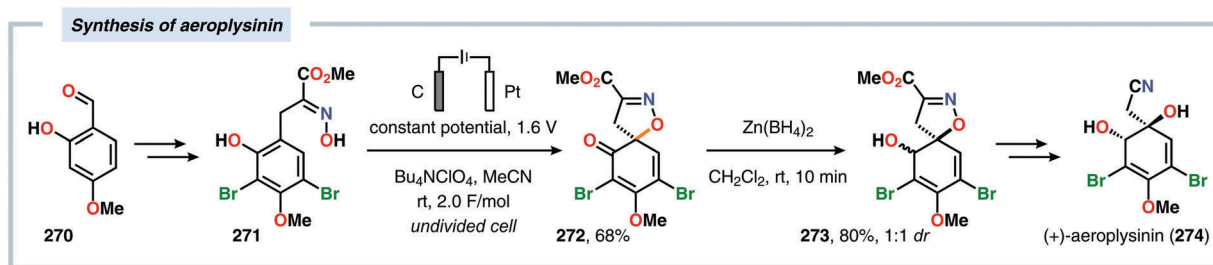
Scheme 83 Electrochemical synthesis of benzofuro[2,3-*b*]indolines and benzofuro[3,2-*b*]indolines.Scheme 84 Synthesis of dihydrobenzofuran derivatives *via* anodic intermolecular cycloaddition of phenols and unactivated alkenes.

shown to significantly enhance the interaction between the hydrophobic aliphatic alkenes and the polar unstable cation intermediates, thereby accelerating the desired [3+2] cycloaddition while avoiding overoxidation of the products.⁶³⁷ Some of these dihydrobenzofuran derivatives display fluorescent properties,^{638,639} a feature which has been exploited for fluorescent labeling of amino acid derivatives⁶⁴⁰ as well as homonucleosides.⁶⁴¹ In addition, the electrochemically produced cyclohexadienone derivatives have also been reported to engage in [4+2]^{642–648} and [5+2]^{649–652} cycloadditions.⁶⁵³ Alternatively, incorporation of a pending nucleophile into the phenol unit allows the design of various types of intramolecular reaction manifolds for construction of spirodienone derivatives.^{654–661} This feature has been leveraged in the synthesis of aeroplysinin (Scheme 85),^{662–665} discorhabdin C (Scheme 86),^{666–669} gymnastatin A (Scheme 87)⁶⁷⁰

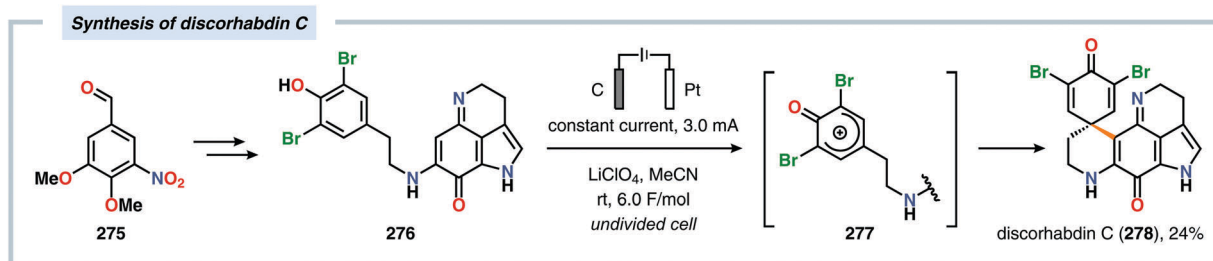
as well as heliannuol E (Scheme 88)^{671–673} and derivatives thereof.⁶⁷⁴

Catechols and related derivatives constitute another class of compounds that can undergo two-electron anodic oxidation to afford, for example, 1,2-benzoquinones.^{675–681} Considering their relatively low oxidation potentials, it is perhaps unsurprising that an assortment of nucleophiles are compatible with these processes without being subjected to oxidation. Here, amines,^{682–689} azide,^{690,691} enolates and other carbon nucleophiles,^{692–711} nitrate,⁷¹² sulfonates^{713–727} as well as thiols^{728–744} have been shown to engage in Michael additions with the anodically generated (imino)quinones. A variety of transformations for delivering annulated scaffolds have also been developed (Scheme 89). In the pursuit of this goal, a range of different benzofurans (291 and 293) have been accessed using 1,3-diketones,^{745–756} α -cyanoketones⁷⁵⁷ or chloranilic acid⁷⁵⁸ as

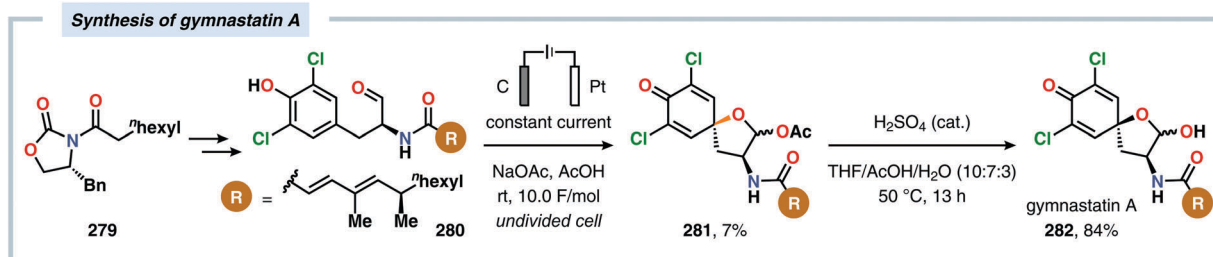




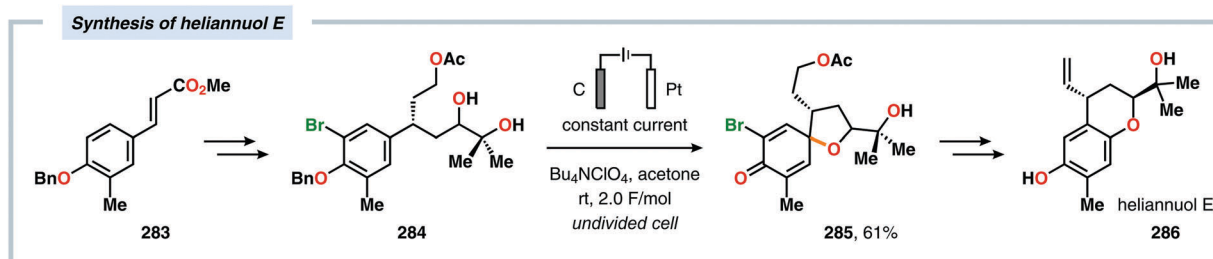
Scheme 85 Utilization of anodically generated phenoxonium ions in the synthesis of aeroplysinin.



Scheme 86 Synthesis of discorhabdin C using a phenoxonium ion-based strategy.



Scheme 87 Electrochemically-mediated spiro hemiacetal formation in the synthesis of gymnastatin A.

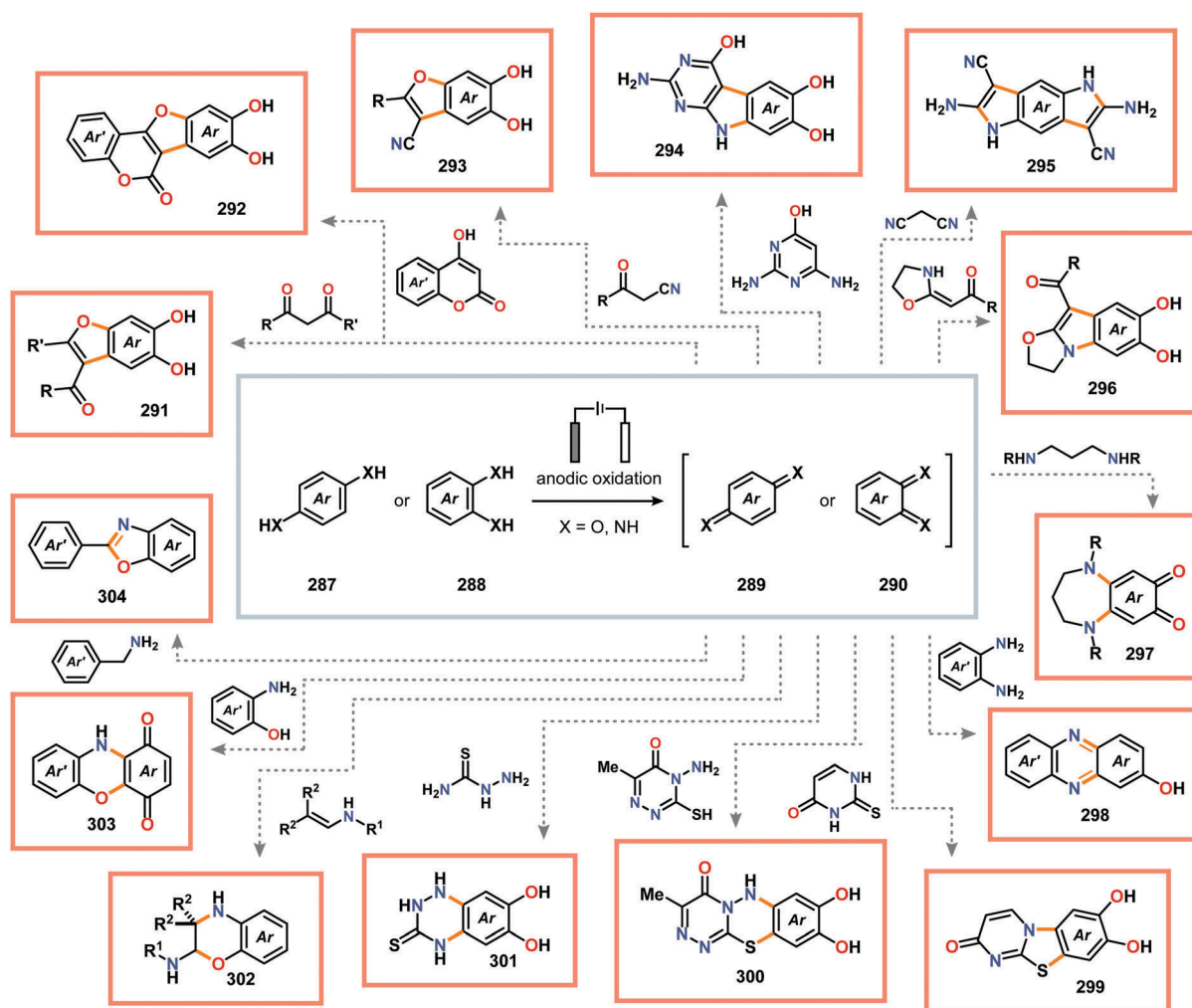


Scheme 88 Electrochemical production of a spirodienone in the synthesis of heliannuol E.

the nucleophile. Additional scaffolds that have been synthesized are benzo[*e*][1,2,4]triazino[3,4-*b*][1,3,4]thiadiazine (300),⁷⁵⁹ benzoxazine (302),^{760,761} benzoxazole (304),^{762,763} coumestan (292),^{764,765} dihydrobenzo[*e*][1,2,4]triazine-3(2*H*)-thione (301),⁷⁶⁶ indole (294–296),^{767–769} phenazine (298),^{770,771} phenoxazine (303)⁷⁷² tetrahydro-1*H*-benzo[*b*][1,4]diazepine (297)⁷⁷³ and thia-1,4*a*-diaz-fluorenone

(299)⁷⁷⁴ derivatives. Furthermore, the electrochemically generated benzoquinone derivatives can also engage in [4+2] cycloaddition in the presence of cyclopentadiene,^{775,776} produce trimerization products^{777–779} or engage in transfer hydrogenation catalysis.^{780–782} A dual electro- and organocatalysis strategy was outlined by Jørgensen and coworkers, which enabled the



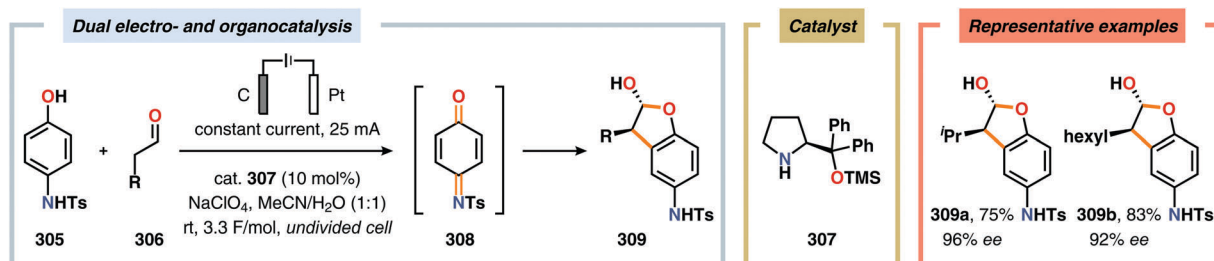


Scheme 89 Annulation of electrochemically generated benzoquinones and related derivatives.

enantioselective intermolecular α -arylation of aldehydes.^{783,784} Here, the combination of anodic oxidation and asymmetric enamine catalysis provided access to *meta*-alkylated anilines in good yields and excellent enantiomeric excess (Scheme 90).⁷⁸³

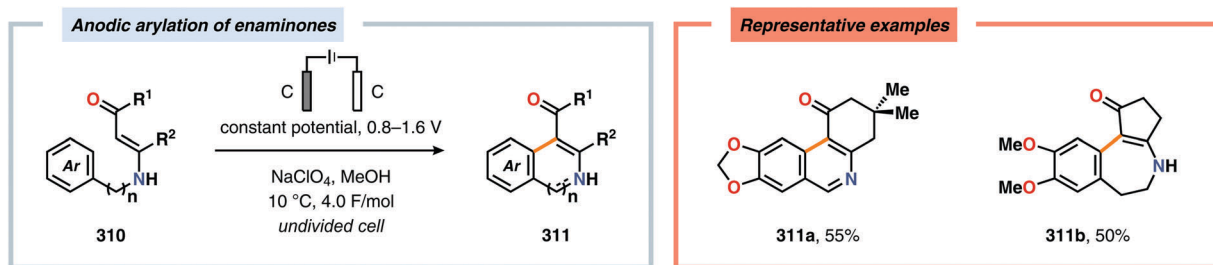
Several research groups have targeted the development of oxidative annulation protocols involving alkenes, and enol ethers or derivatives thereof. Based on earlier work that showed that enamines⁷⁸⁵ can be anodically dimerized to yield 3,4-diketopyrroles,^{786,787} Schäfer and Eilenberg reported that

N-benzyl- and β -phenethyl enamines undergo intramolecular arylation to produce isoquinolines and benzazepines upon anodic oxidation using an undivided cell (Scheme 91).⁷⁸⁸ Lei and coworkers explored a related strategy for synthesis of indoles **313**. The protocol relied on intramolecular dehydrogenative annulation of *N*-aryl enamines **312** and utilized iodide as a redox mediator.⁷⁸⁹ Mechanistic insight revealed that carrying out the annulation reaction in the absence of electricity but using *N*-iodosuccinimide (NIS) as an oxidant resulted in a high yield of

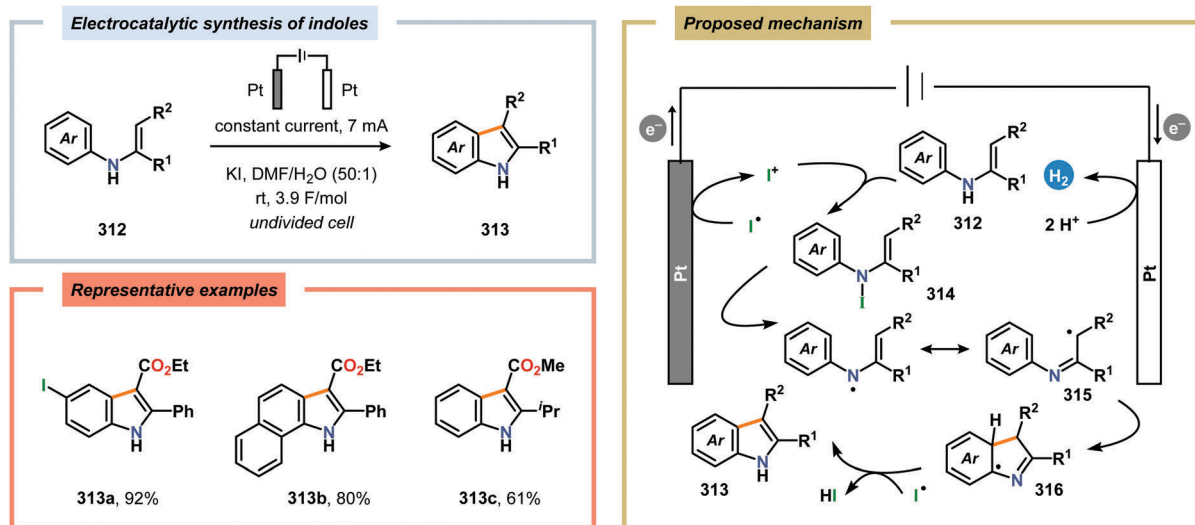


Scheme 90 α -Arylation of aldehydes through the merger of electrochemical oxidation and organocatalysis.





Scheme 91 Anodic intramolecular arylation of enaminones.



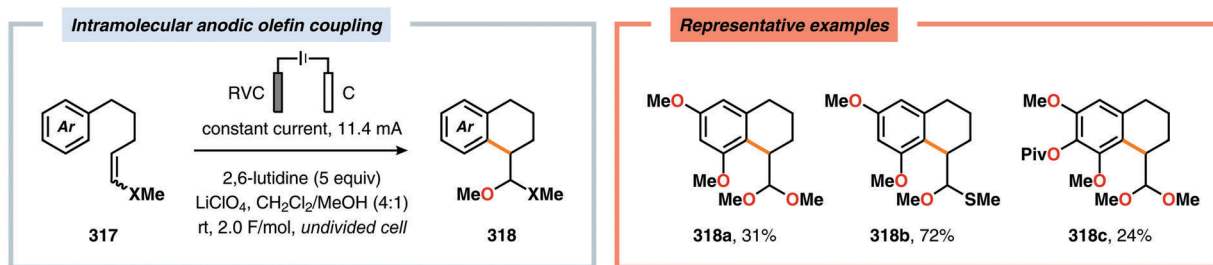
Scheme 92 Electrocatalytic synthesis of indoles using iodide as a redox mediator.

the desired indole. Furthermore, radical inhibition experiments with TEMPO did not produce any product. Based on these results and previous observations,⁷⁹⁰ a mechanism involving a hyperiodide intermediate (I^+) generated *via* anodic oxidation was proposed. The *in situ* produced I^+ subsequently reacts with the *N*-aryl enamine to furnish an *N*-iodo intermediate (314), which upon N–I bond homolysis provides radical intermediate 315. Finally, intramolecular radical addition, oxidation and deprotonation afford the target product (Scheme 92).^{789,791,792}

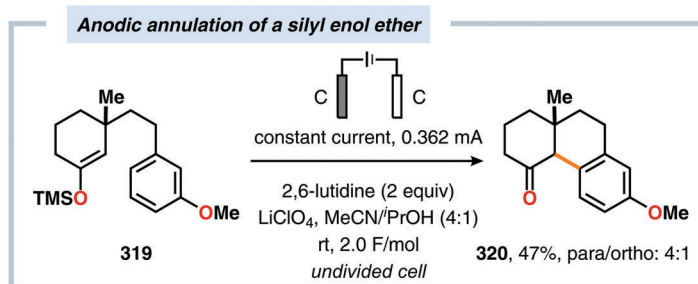
Pioneering studies by the Moeller group have demonstrated that alkenes, such as enol ethers, and electron-rich (hetero)arenes can be oxidatively coupled under electrochemical conditions. In these transformations, an alkene that is normally nucleophilic is initially oxidized at the anode to form a radical cation intermediate that is subsequently trapped by a second nucleophile to deliver anti-Markovnikov addition products (*vide infra*). Here, electron transfer confers umpolung reactivity of a functional group, thus enabling alternative retrosynthetic disconnections of complex structures through previously challenging bond disconnections.^{63,81} The Moeller^{793–795} and Wright⁷⁹⁶ groups have exploited the intramolecular anodic coupling of enol ethers or vinyl sulfides and electron-rich aromatic systems to deliver the fused, bicyclic or tricyclic ring skeletons in moderate to high yields (Schemes 93 and 94).

A related approach was also utilized by the Wright group for the synthesis of the hamigeran skeleton (Scheme 95).⁷⁹⁷ Heteroaromatic rings are also compatible coupling partners in these intramolecular anodic olefin coupling reactions. Here, different tethers can be employed to afford, for example, six- (Scheme 96)^{794,796,798,799} or seven-membered⁸⁰⁰ (Scheme 97) annulated furan systems, which can be readily transformed into various carbo- and oxacyclic motifs.^{801–807} These electrochemical annulations are presumed to involve initial oxidation of the silyl enol ether moiety rather than the furyl group.⁸⁰⁰ Additional heterocycles that have been utilized consist of imidazoles,⁸¹ pyrroles⁷⁹⁴ as well as thiophenes.^{808–810} The applicability of the anodic olefin coupling reaction between silyl enol ethers and furans has also been exploited in syntheses of natural products. Moeller and coworkers employed the methodology as the key step in their synthesis of alliacol A^{65,66} (Scheme 98) while an anodic coupling strategy enabled the construction of the central seven-membered ring in Trauner's synthesis of guana-castepene E (Scheme 99).^{67,68} Furthermore, the arteannuin ring skeleton has been assembled through the use of a pair of anodic coupling reactions (Scheme 100). Here, both coupling reactions exploited the furan moiety as the coupling partner in which the first cyclization made use of a chiral *N,O*-ketene acetal initiating group to provide the desired bicyclic product in high yield and the second

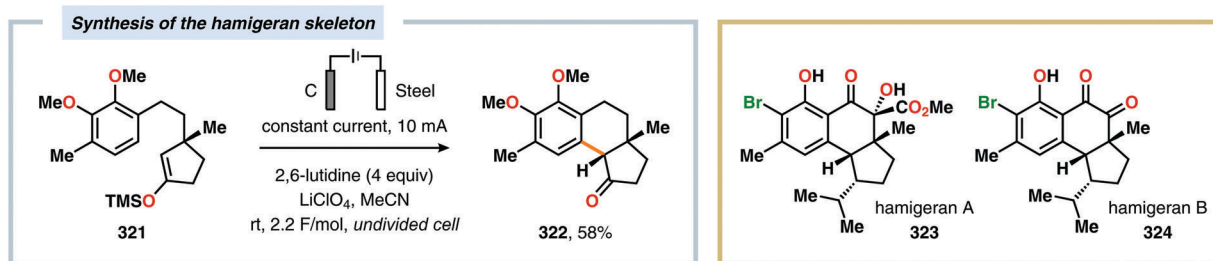




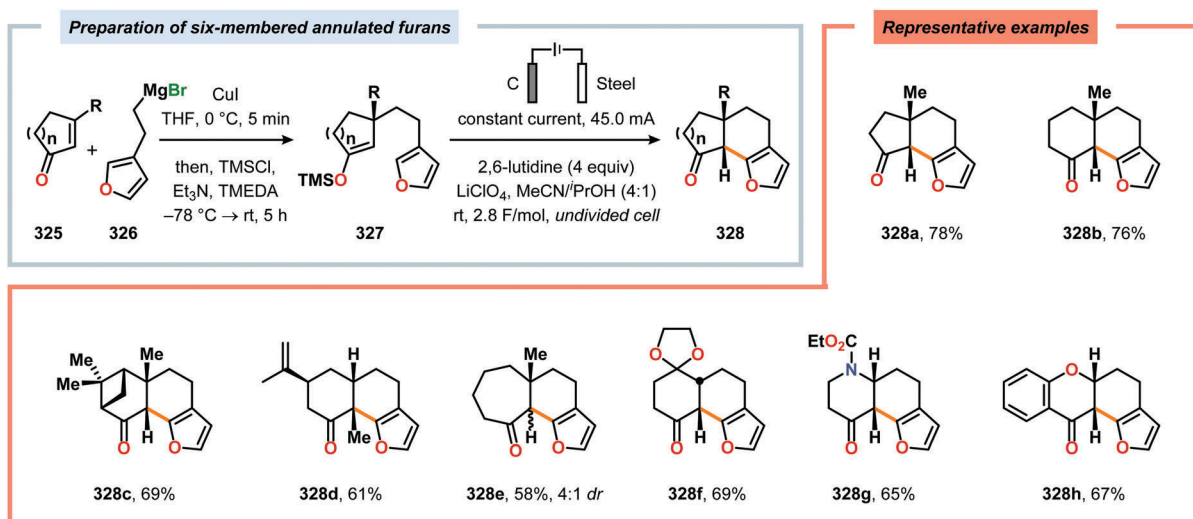
Scheme 93 Intramolecular anodic olefin coupling.



Scheme 94 Anodic annulation of a silyl enol ether and an electron-rich arene.

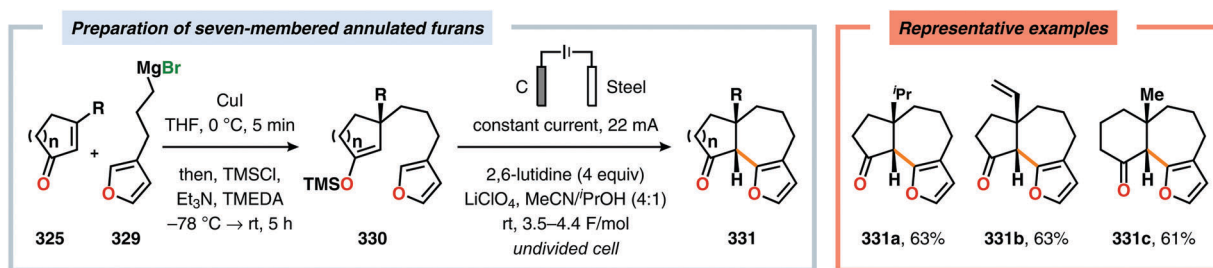


Scheme 95 Synthesis of the hamigeran skeleton through anodic coupling with an electron-rich arene.

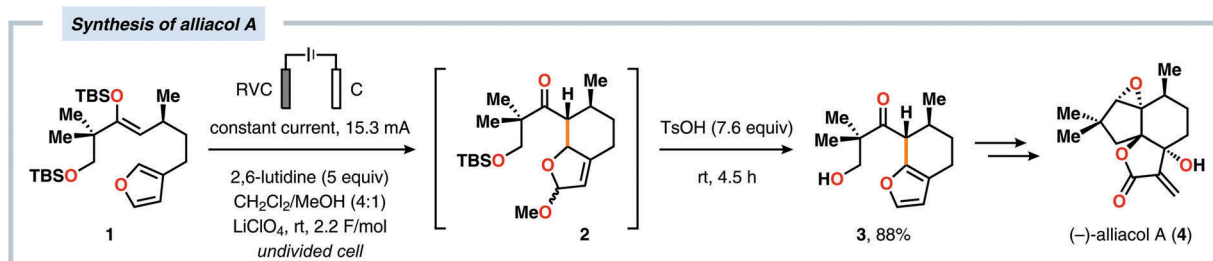


Scheme 96 Electrochemical coupling of silyl enol ethers and furans for synthesis of six-membered annulated furans. Yields are reported for two steps based on the starting enone as the limiting agent.

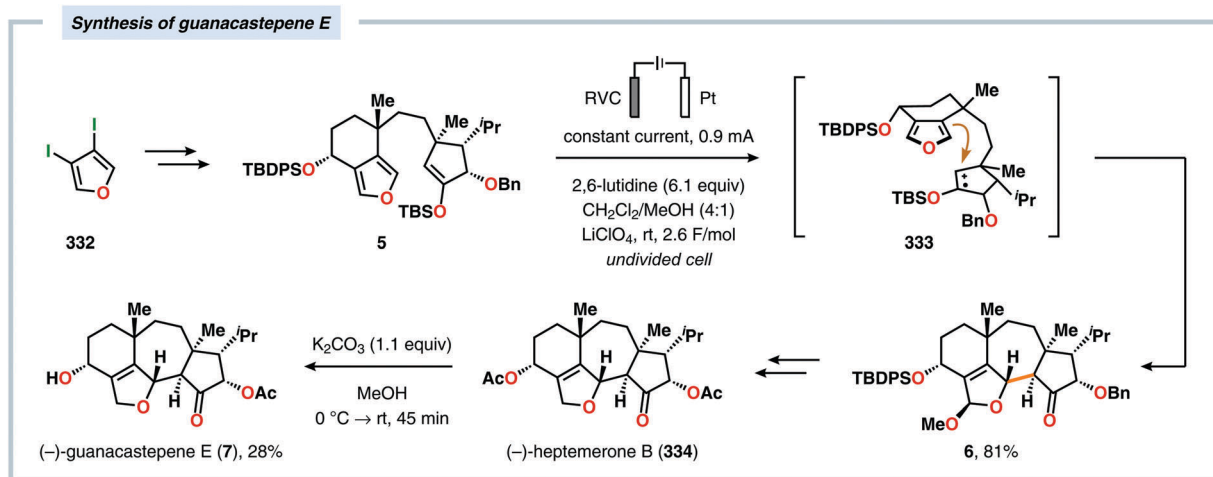




Scheme 97 Anodic coupling for synthesis of seven-membered annulated furans. Yields are reported for two steps based on the starting enone as the limiting agent.



Scheme 98 Application of the anodic olefin coupling in the synthesis of (-)-alliocol A.



Scheme 99 Utilization of the anodic olefin coupling in the synthesis of (-)-guanacastepene E.

anodic coupling afforded the tricyclic core while generating the required quaternary stereocenter.⁸¹¹

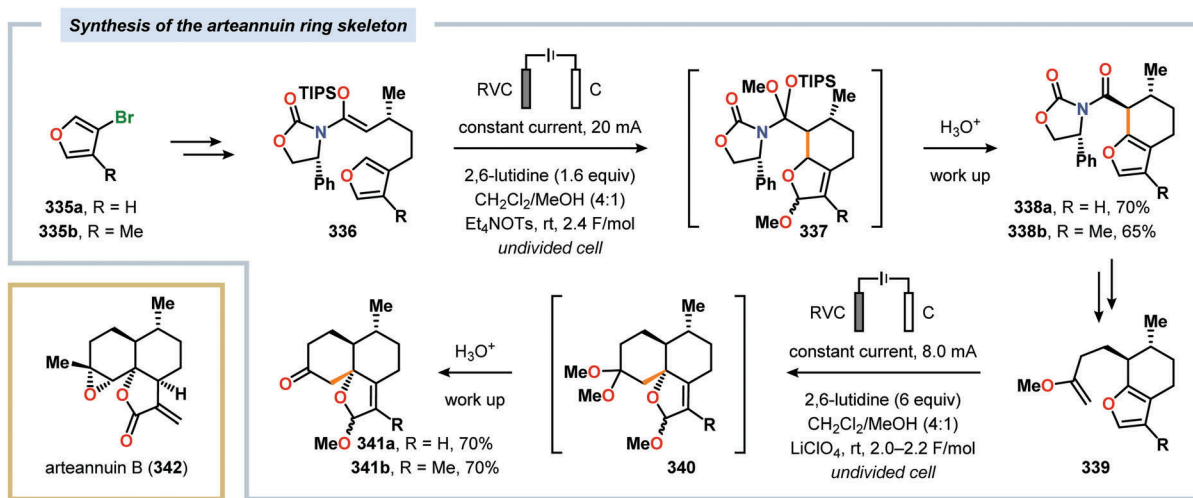
Enol ether radical cations are also prone to undergo intermolecular [2+2] and [4+2] cycloaddition with another alkene or diene. Upon intermolecular C–C bond formation, the inclusion of an electron-rich arene ring in either the enol ether or alkene moiety facilitates intramolecular electron transfer from the aryl ring to form the final cycloadduct.^{812–822} The arene radical cation subsequently generates a second equivalent of the enol ether radical cation through intermolecular electron transfer.⁸²³ A characteristic feature of these “redox-tag”⁸²⁴ mediated cycloaddition reactions is

that only small amounts of electricity are needed to initiate the radical chain process.⁸²⁵

3. Electrochemical approaches to carbon–nitrogen (C–N) bond formation

Nitrogen-containing compounds constitute essential motifs and are present in natural products, pharmaceutical agents, agrochemicals and material science. Chemists have actively





Scheme 100 Sequential anodic couplings for synthesis of the arteannuin ring skeleton.

targeted the development of facile and selective C–N bond formation platforms. However, despite the recent advances in C–N cross-coupling reactions, these approaches normally require elevated temperatures, prefunctionalized starting materials, such as aryl halides or pseudohalides, stoichiometric oxidants or the use of expensive catalysts. In this context, methods for direct C–H amination have emerged as efficient, step- and atom-economical alternatives, and have expanded the repertoire of reaction manifolds.^{826,827} In the following sections, the development of electrochemical methodologies for construction of C–N bonds and nitrogen-containing motifs is examined.

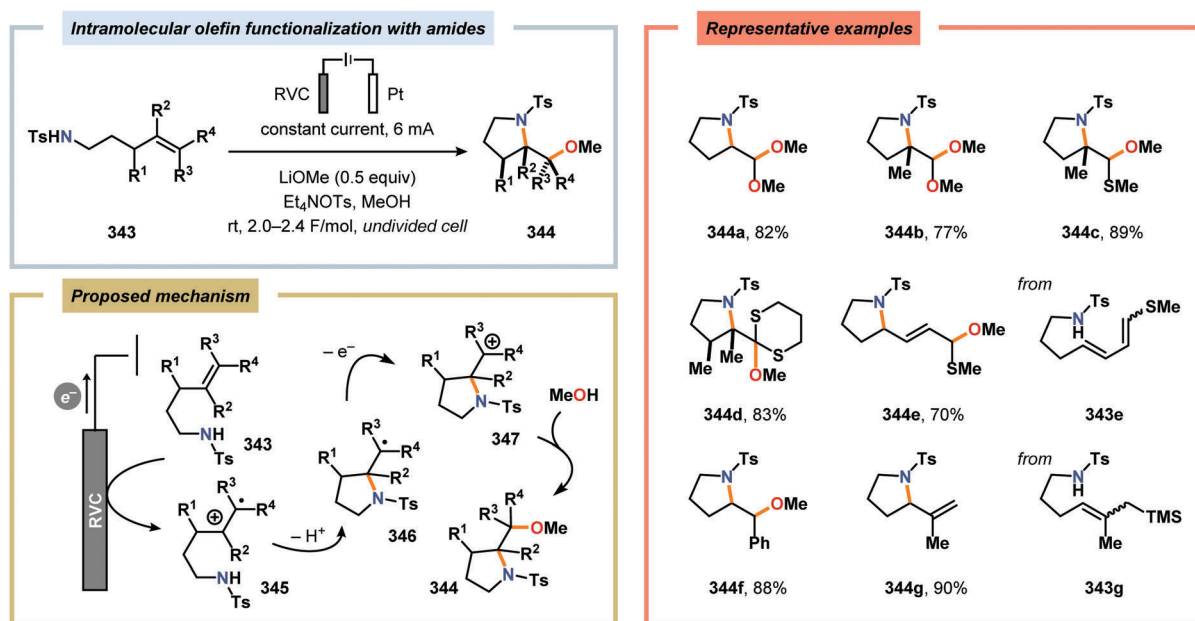
3.1. Amination of alkenes and alkynes

Considerable efforts have been devoted to the development of methods that facilitate the addition of, for example, N–H (hydroamination) and arene C–H bonds (hydroarylation) across alkenes and alkynes. Here, atom-economical and regioselective platforms for direct functionalization of double or triple bonds allow access to a range of functionalized products, thereby offering considerable opportunities for strategic chemical synthesis.^{828–848}

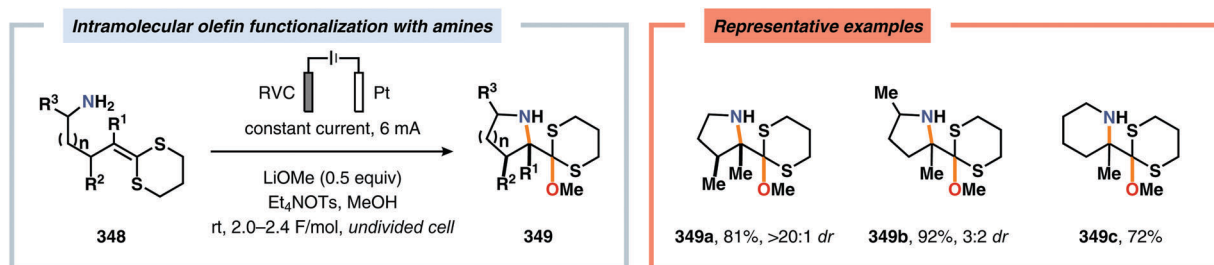
In addition to the intramolecular anodic olefin coupling reactions discussed in the previous section, other carbon-^{849–862} as well as oxygen-based^{863–875} nucleophiles have also been utilized in radical cation-initiated cyclization protocols for constructing C–C and C–O bonds, respectively. Furthermore, Moeller and coworkers have designed systems for direct functionalization of alkenes using nitrogen functionalities as trapping groups. It was demonstrated that the nature of the substituents on the generated radical cation intermediate had a profound influence on its ability to react with various trapping groups.⁸⁷⁶ Thus, more polarized radical cations tend to favor C–C bond forming reactions, while less polarized radical cations are beneficial when using heteroatomic trapping groups. Employing more basic reaction conditions also had a dramatic influence on the cyclization reactions. Here, the use of a strong base, such as LiOMe, was considered to increase the nucleophilicity of the nitrogen trapping group by facilitating formation of the sulfonamide anion (Scheme 101). Although five-membered ring

systems were accessible in a relatively straightforward fashion, coupling reactions leading to six-membered rings presented problems due to competing elimination of a proton from the carbon-center next to the radical cation intermediate.^{877,878} Ensuing mechanistic studies aimed at examining the relative reactivity of olefin-based radical cations toward various intramolecular nucleophiles. To address this, an electron-rich olefin tethered to two different nucleophiles/trapping groups, an alcohol and a sulfonamide, was exploited. Trapping of the formed radical cation with the alcohol moiety was shown to be facile and reversible, affording the kinetically favored product. In contrast, sulfonamide cyclization was demonstrated to furnish the thermodynamically favored product and can be enhanced with nonpolar reaction conditions, elevated temperatures, and low current. In these reactions, the normally nucleophilic olefin functionality is initially oxidized to a radical cation intermediate. This intermediate is subsequently trapped by the sulfonamide anion to form the desired C–N bond. However, a mechanistic portrayal involving initial anodic oxidation of the sulfonamide anion to produce a nitrogen-centered radical that is subsequently reduced through intramolecular electron transfer from the olefin unit to afford an olefinic radical cation cannot be ruled out for certain substrates.^{879–881} The Moeller group has also employed photovoltaic cells in which sunlight is harnessed as the power source for driving anodic olefin cyclization reactions.⁸⁸² Following on from these reports, the Moeller group disclosed a potentially more practical approach that took advantage of unprotected amines as the trapping group (Scheme 102). Although the method employed a dithioetene acetal group as the electron-rich olefin, the oxidation potential of the secondary amine moiety in the product is lower than that of either functional group in the starting material, suggesting that overoxidation of the product should be of concern. However, this reasoning does not take into consideration that rapid cyclization reactions can lower the oxidation potential of the substrate. Hence, in the developed protocol the intramolecular cyclization is so rapid that it causes a 460 mV drop in the oxidation potential of substrate **348**.





Scheme 101 Intramolecular anodic olefin coupling reactions with sulfonamides.



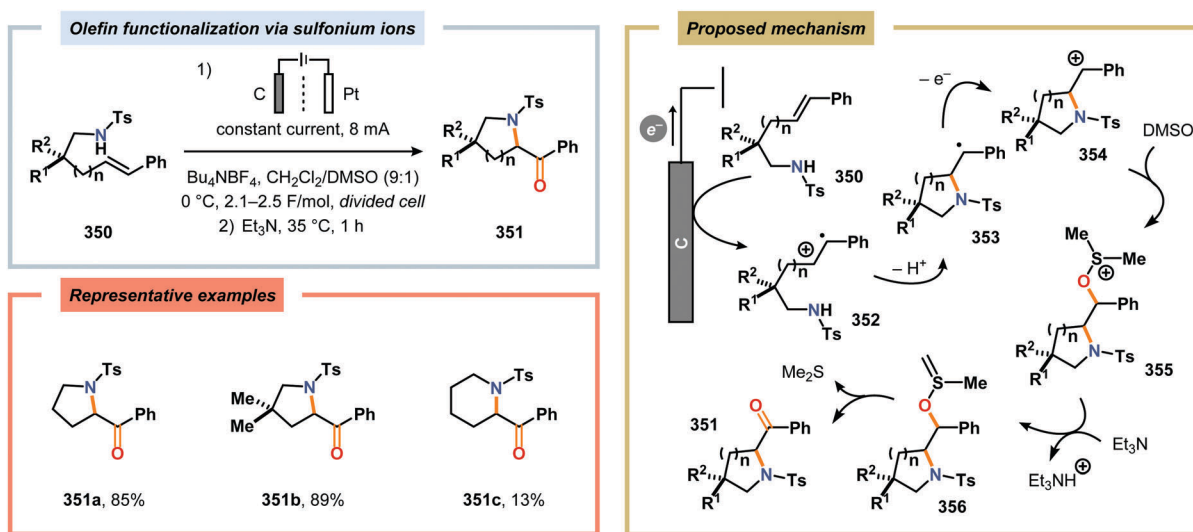
Scheme 102 Anodic coupling of amines and dithioetene acetals.

This effect is so dramatic that the substrate potential is now significantly lower than that of the product, highlighting that a simple analysis of oxidation potentials for isolated functional groups can be deceiving when attempting to predict the success of an oxidative cyclization reaction.⁸⁸³ Yoshida and coworkers have demonstrated that anodic cyclization and chemical oxidation manifolds can be successfully integrated in a one-pot, sequential manner (Scheme 103). Here, anodic oxidation of the olefinic bond is followed by intramolecular cyclization by the tethered nucleophilic moiety to ultimately afford a carbocation **354** upon a subsequent one-electron oxidation. In the presence of DMSO as an external nucleophile, efficient trapping of intermediate **354** occurs to provide the corresponding alkoxy-sulfonium ion **355**. This intermediate is sufficiently stable at low temperatures and subsequent treatment with Et_3N gives a sulfur ylide (**356**) that can undergo an intramolecular proton transfer event, resulting in elimination of dimethylsulfide and the exocyclic ketone **351**.^{467,884}

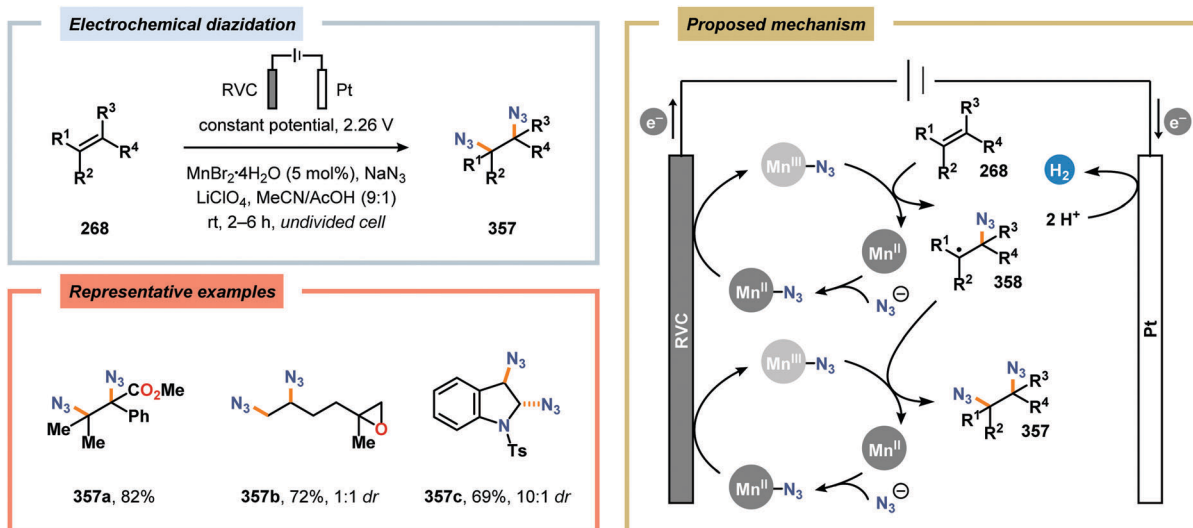
Recently, the Lin laboratory presented an electrochemical protocol for the diazidation of alkenes. The reported operationally

simple and environmentally friendly method converted alkenes and NaN_3 to 1,2-diazides (Scheme 104). The merger of electrochemical oxidation and an earth-abundant manganese catalyst enabled the transformation to proceed under mild reaction conditions. The system exhibited a broad substrate scope and high functional group compatibility. For example, substituents typically susceptible to nucleophilic displacement by N_3^- , such as epoxides, esters, alkyl halides, were tolerated by the metal-catalyzed electrochemical diazidation strategy. Furthermore, the authors showed that several 1,2-diazides, including those that contain reductively labile groups, could be chemoselectively converted to the corresponding 1,2-diamines. This can be performed consecutively and circumvents elaborate isolation of any intermediates, providing a general and operationally simple alternative for synthesis of vicinal diamine. Finally, mechanistic insight through radical clock experiments confirmed the intermediacy of radical adduct **358**.⁸⁸⁵⁻⁸⁸⁸ Based on this platform, the Lin group subsequently reported a manganese-catalyzed electrochemical protocol for dichlorination⁸⁸⁹ as well as chlorotrifluoromethylation⁸⁹⁰ of alkenes.⁸⁹¹





Scheme 103 Integrated electrooxidative cyclization followed by chemical oxidation of alkenes via alkoxy-sulfonium ions.



Scheme 104 Metal-catalyzed electrochemical diazidation of alkenes.

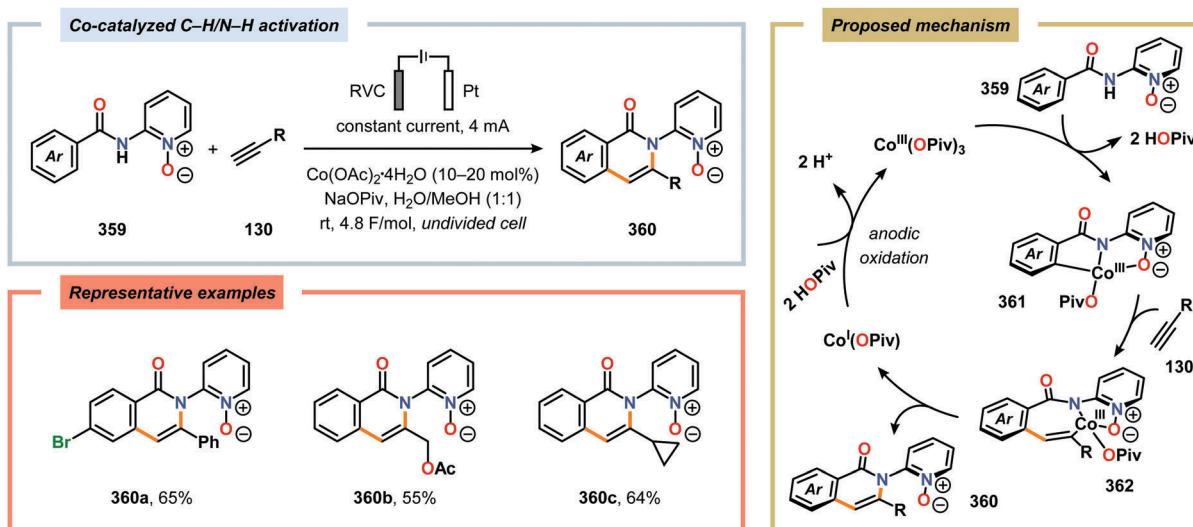
Alkyne annulations are typically limited to high reaction temperatures and/or the use of stoichiometric amounts of toxic metals as sacrificial oxidants. Recently, the Ackermann⁸⁹² and Lei⁸⁹³ groups independently reported methods for cobalt-catalyzed electrochemical C–H/N–H annulation of alkynes, such as ethyne, as well as ethylene (Schemes 105 and 106). The cobalt-catalyzed electrochemical strategies allowed for efficient C–H functionalization of *ortho*-, *meta*- and *para*-substituted amides, and aryl halides while obviating undesired coupling reactions. Subsequently, the two groups independently disclosed methods for electrochemical cobalt-catalyzed C–H amination of arenes with alkylamines.^{894,895} Furthermore, a ruthenium-catalyzed electrochemical dehydrogenative annulation reaction of aniline derivatives and alkynes for the synthesis of indoles was recently described.⁸⁹⁶ Here, the electric current was proposed to promote reoxidation

of the active ruthenium-based catalyst and facilitate H_2 evolution.

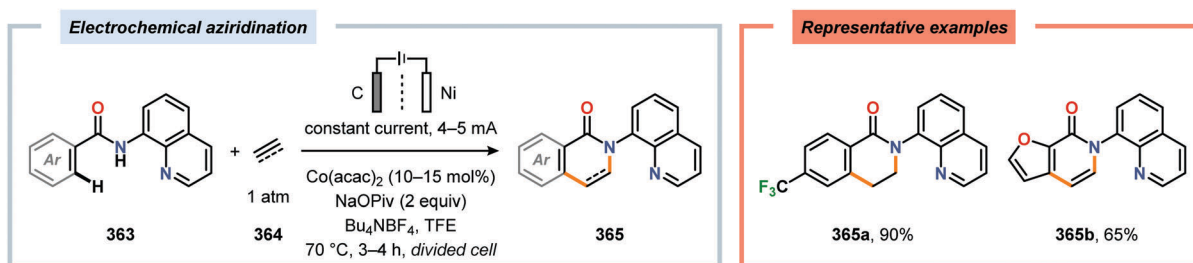
3.2. Electrochemical generation of nitrogen-centered radicals

The term nitrogen-centered radical refers to species where the generated radical is localized on a nitrogen atom. In contrast to carbon-centered radicals, nitrogen-centered radicals have historically been relatively underutilized from a synthetic viewpoint. This was mainly due to a lack of mild and reliable methods for generating nitrogen-centered radicals, which constrained their applicability in academic and industrial settings.^{897–900} However, strategies based on nitrogen-centered radicals have recently been shown to expedite C–N bond construction and have therefore received considerable attention from the scientific community. Nitrogen-centered radicals have, for example, been demonstrated to add to alkenes, alkynes, dienes





Scheme 105 Cobalt-catalyzed electrochemical C-H/N-H annulation of alkynes.



Scheme 106 Cobalt-catalyzed electrochemical C-H/N-H annulation of ethylene or ethyne.

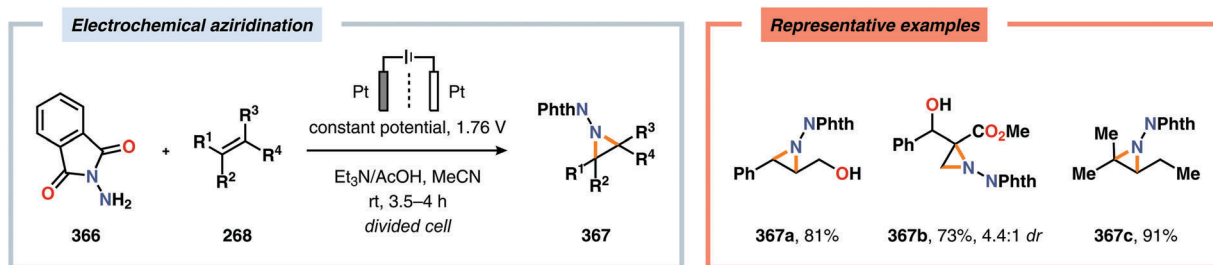
and engage in C-H functionalization, making them versatile intermediates in contemporary organic synthesis.^{13m,901-908}

Early work from the Yudin group demonstrated that electrochemical aziridination of olefins could be achieved in the presence of *N*-aminophthalimide (366), a reaction that typically is hampered by the use of stoichiometric amounts of toxic Pb^{IV} oxidants. In this reaction, nitrene-transfer from *N*-aminophthalimide to olefins occurs under mild conditions on platinum electrodes (Scheme 107). Using the developed approach, both electron-rich and electron-poor olefins were effectively converted to aziridines in good to excellent yields. Although some olefins displayed similar oxidation potentials as the nitrene-transfer reagent, the crucial factor that accounts for the high levels of chemoselectivity in the transformations is the overpotential. It was noted that the nature of the electrode material was found to be critical for the reaction to proceed. For example, replacing the platinum electrodes with carbon-based ones resulted in termination of the nitrene-transfer reactions. Thus, under particular conditions various substrates possess different overpotentials depending on, for example, the electrode material. This highlights that reactive species can be selectively generated by maximizing the difference in overpotentials between the substrate and the reagent, thereby avoiding detrimental background reactions.⁹⁰⁹⁻⁹¹¹ Likewise, under similar reaction

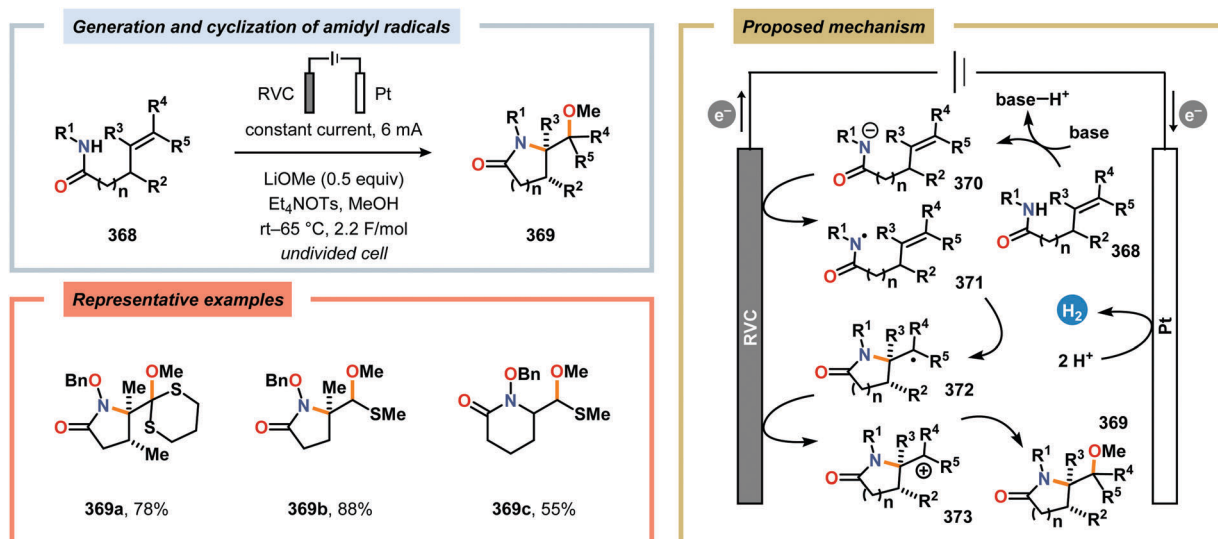
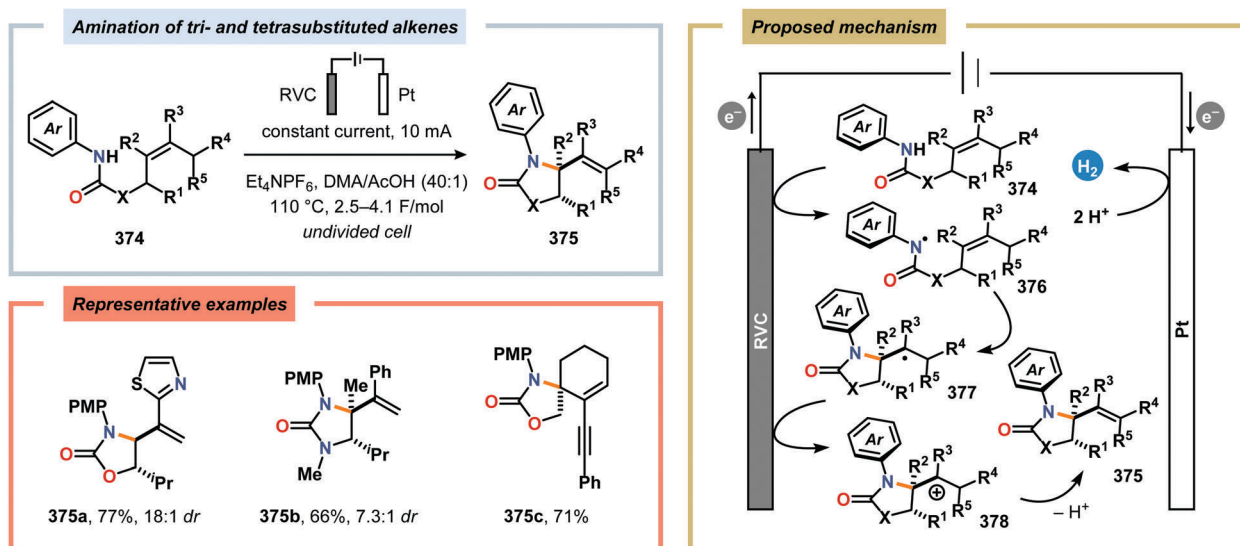
conditions a variety of sulfoxides could be chemoselectively converted into the corresponding sulfoximines.⁹¹²

The Moeller group developed a protocol for synthesis of γ - and δ -lactams using *O*-benzyl hydroxamates or *N*-phenyl amides.⁹¹³ Here, the anodically generated nitrogen-centered amidyl radicals 371 underwent cyclization reactions with electron-rich olefins to form carbon-centered radicals 372 that are subsequently oxidized to furnish carbocations 373. These carbocations can then be trapped with nucleophiles, such as MeOH, to provide the target lactams 369 (Scheme 108). In general, ketene dithioacetal motifs were found to be the most effective coupling partners for the developed cyclization strategy. While the *O*-benzyl hydroxamate derivatives efficiently underwent 6-*exo*-trig radical cyclization to produce the six-membered ring products, the related *N*-phenyl amides produced a complex mixture of products. Furthermore, attempts to induce 7-*exo*-trig radical cyclizations were unsuccessful and instead resulted in dimerization to afford the corresponding hydrazide. Thus, the success of these amidyl radical cyclization reactions is influenced by the energetics of the cyclization relative to the competing pathways, such as radical-radical dimerization and hydrogen atom abstraction. Further advances in this field were made by Xu and coworkers and enabled the intramolecular oxidative amination of tri- and tetrasubstituted alkenes (Scheme 109).⁹¹⁴



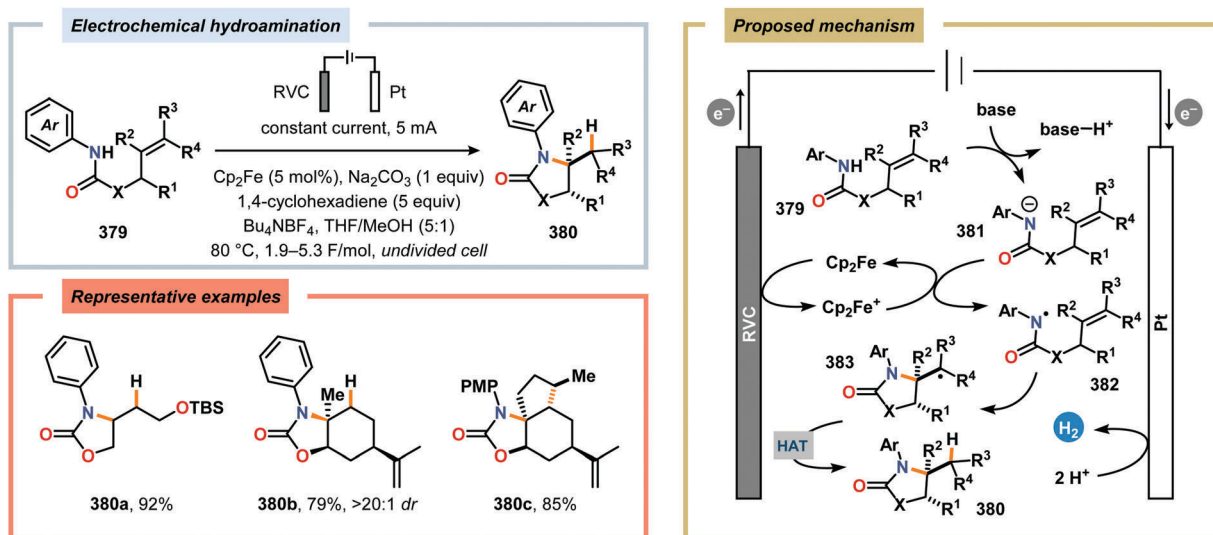


Scheme 107 Electrochemical aziridination of olefins.

Scheme 108 Electrochemical generation of amidyl radicals for synthesis of γ - and δ -lactams.

Scheme 109 Oxidative amination of tri- and tetrasubstituted alkenes.

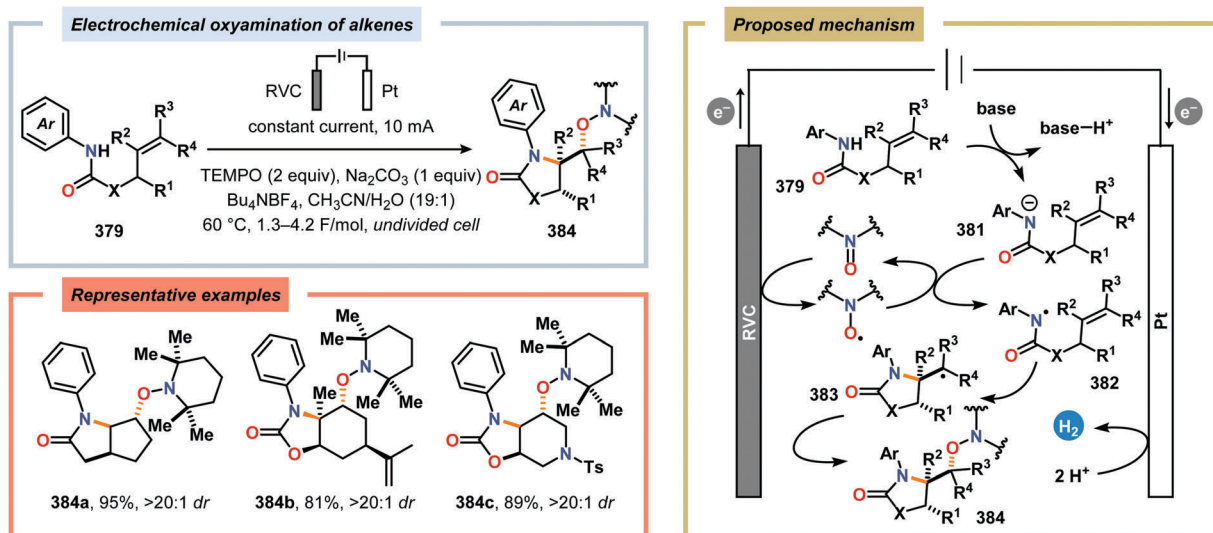


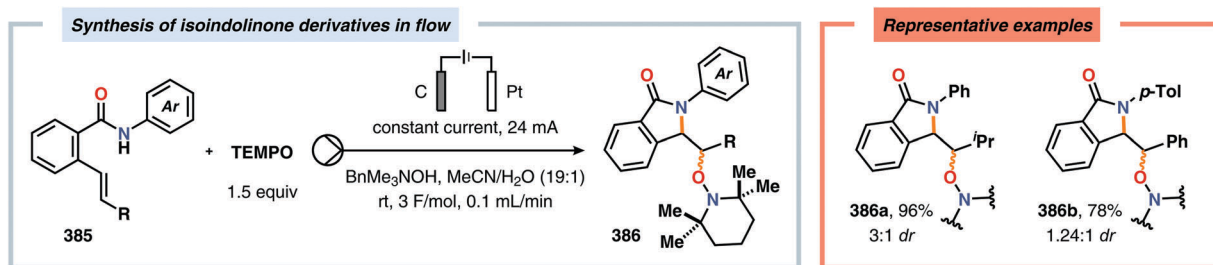
Scheme 110 Electrochemical hydroamination of alkenes *via* ferrocene-mediated generation of amidyl radicals.

A wide range of amide, carbamate and urea derivatives carrying various trisubstituted or sterically demanding tetrasubstituted alkenyl moieties were all viable substrates. The protocol was compatible with a variety of (hetero)aryl-, alkyl- and alkynyl-substituted olefins and a range of functional groups were tolerated, including alcohols, alkynes, aryl bromides, esters, pyridines, silyl ethers, thiazoles and thiophenes. Upon radical cyclization, proton elimination occurred regioselectively at the distal carbon center, providing the cyclized products 375 in good to high diastereoselectivity. Alternatively, the generated carbon-centered radical can also engage in hydrogen atom abstraction to provide hydroamination products⁹¹⁵ *via* ferrocene-mediated generation of amidyl radicals (Scheme 110) or be trapped with *N*-oxyl radicals, such as TEMPO, to give oxyamination products (Scheme 111).⁹¹⁶ The latter reaction has also been conducted using an electrochemical

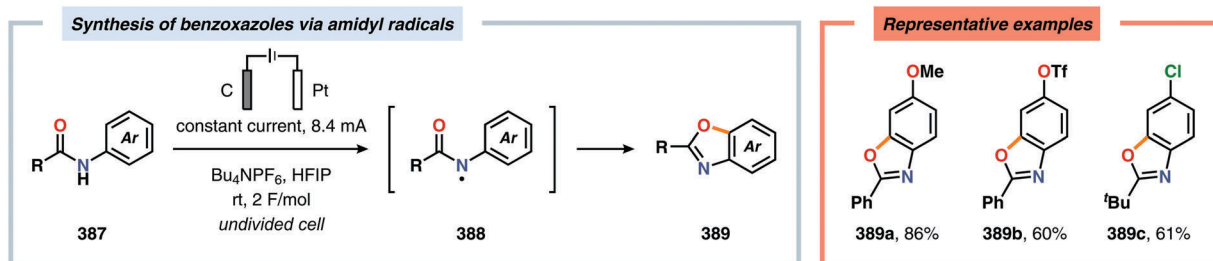
flow microreactor (Scheme 112), making the process less costly and enabling easier purification.⁹¹⁷ Here, TEMPO has a dual function, being the mediator as well as the oxygen source.

The Waldvogel and Moeller groups have exploited the electrochemical generation of amidyl radicals from anilides, enabling the direct synthesis of benzoxazoles (Scheme 113).⁹¹⁸ Although methanol has been commonly applied in electrochemical transformations involving amidyl radicals, this proved to be incompatible, leading to degradation of anilides 387. This observation suggested that the intramolecular cyclization process was slow. Of the screened solvents, only HFIP was found to efficiently stabilize the electrochemically generated radical intermediates, affording the desired benzoxazoles 389 in good to high yields. The authors also demonstrated that the aromatic moiety connected to the produced amidyl radicals was of substantial radical nature as the

Scheme 111 Electrochemical oxyamination of alkenes *via* TEMPO-mediated generation of amidyl radicals.



Scheme 112 Synthesis of isoindolinones using an electrochemical flow microreactor.

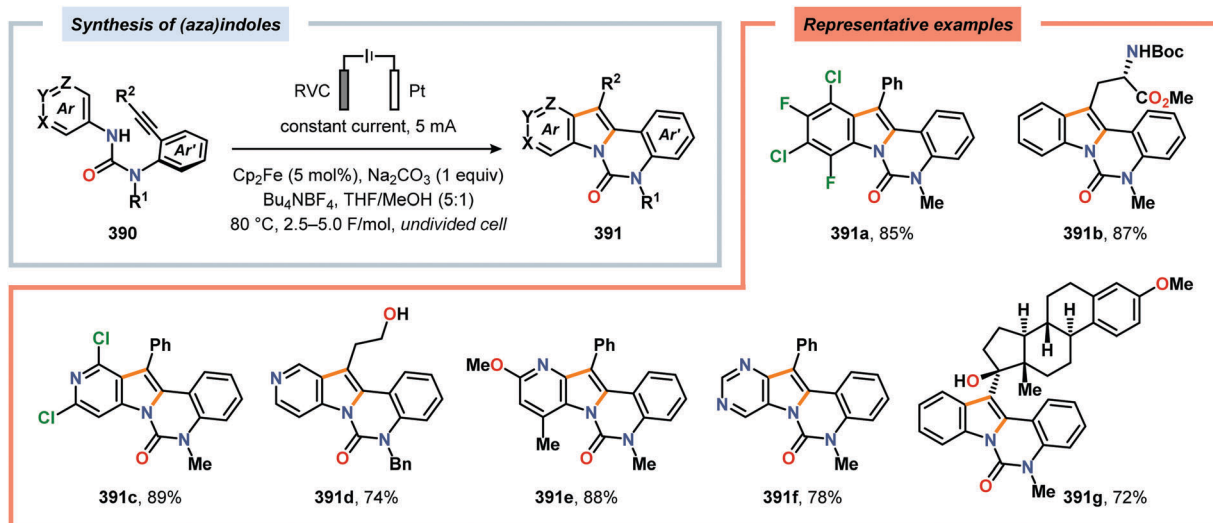


Scheme 113 Electrochemical synthesis of benzoxazoles from anilides.

para-position of the *N*-substituted arene ring had to be substituted in order to prevent coupling reactions at this position.

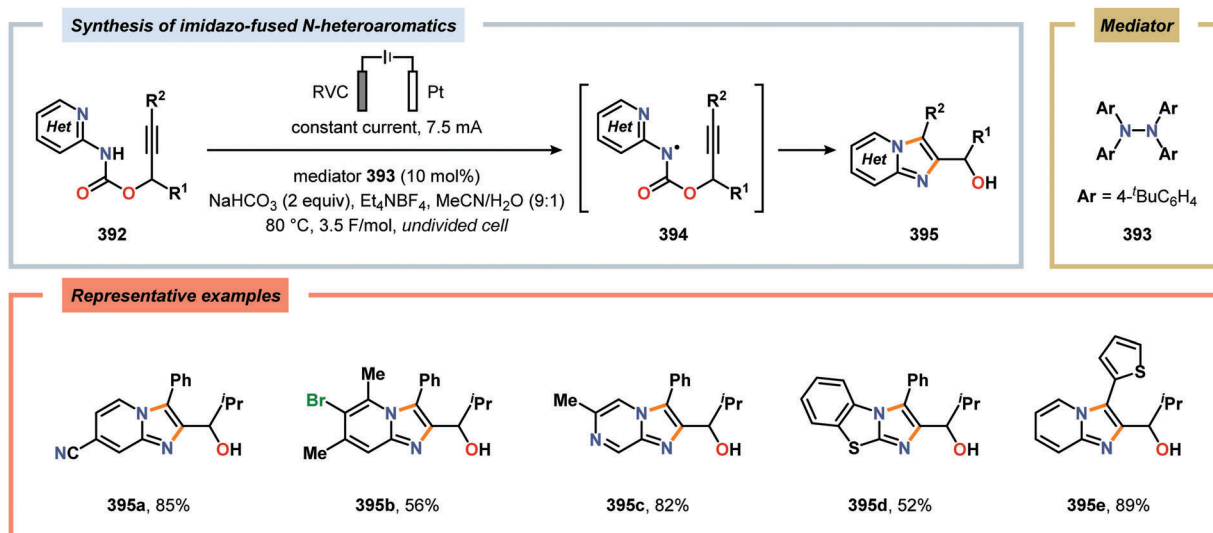
The Xu group has recently made significant contributions through the design of distinct reaction manifolds that capitalize on nitrogen-centered radicals. Various mediator-based radical cyclization manifolds using (hetero)arylamines containing tethered alkynes have been developed. In this context, functionalized (aza)indoles **391** were accessed through an oxidative alkyne annulation reaction (Scheme 114).^{919,920} The broad functional group tolerance of the electrochemical protocol was illustrated by the preparation of (aza)indoles housing assorted substituents, such as acetals, alcohols, aldehydes, *N*-aryl carbamates, dipeptides, halides,

ketones, (*ortho*)esters and sulfonamides. The reaction is believed to be initiated with the anodic oxidation of $[\text{Cp}_2\text{Fe}]$ to $[\text{Cp}_2\text{Fe}]^+$. Subsequent SET between $[\text{Cp}_2\text{Fe}]^+$ and the deprotonated urea derivative results in regeneration of $[\text{Cp}_2\text{Fe}]$ and furnishes a nitrogen-centered radical. This radical is suggested to engage in 6-*exo*-dig cyclization, which is followed by a second cyclization with the aryl moiety. Finally, rearomatization of the generated arene radical through oxidation and loss of a proton provides (aza)indoles **391**. A related mediator-based radical cyclization cascade approach was applied to the preparation of imidazo-fused *N*-heteroaromatic compounds (**395**), including imidazo[1,2-*a*]pyridines, imidazo[1,2-*b*]pyridazines and



Scheme 114 Synthesis of (aza)indoles using ferrocene as mediator.





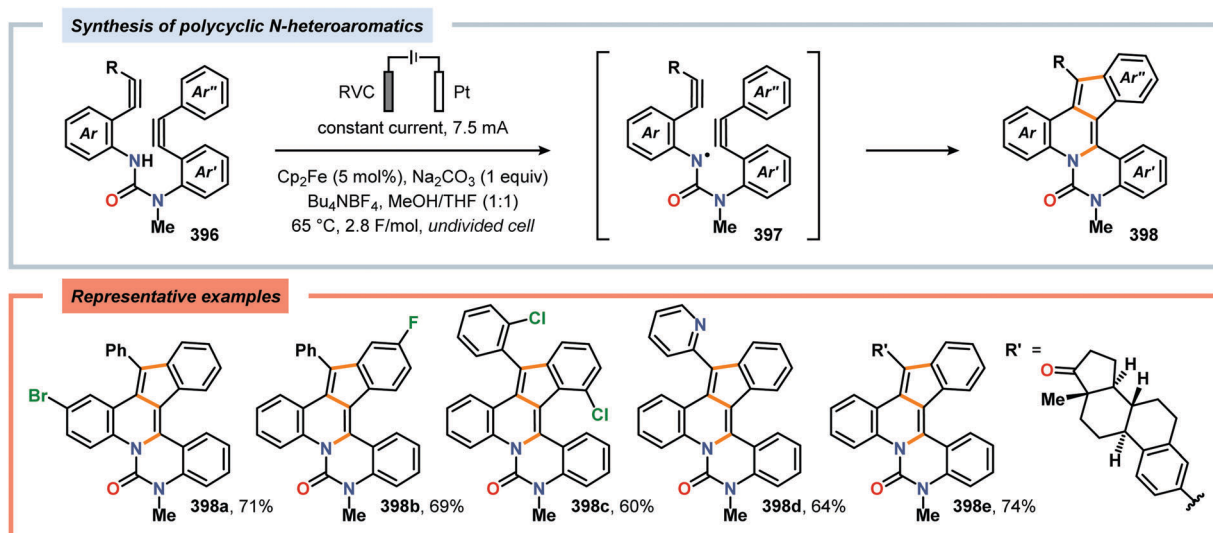
Scheme 115 Synthesis of imidazo-fused N-heteroaromatic compounds through a radical cyclization cascade.

imidazo[1,2-*a*]pyrazines (Scheme 115).^{921,922} However, here tetraarylhydrazine **393** was found to be the optimal redox catalyst. Nitrogen-centered radicals have also been harnessed for synthesis of nitrogen-doped polycyclic aromatic hydrocarbons (Scheme 116).^{923–925} In the presence of ferrocene, the urea-tethered diynes **396** underwent efficient radical cyclization to afford a variety of electron-rich polycyclic aromatic hydrocarbons (**398**). The use of a mild redox catalyst to facilitate the cascade cyclization instead of carrying out direct electrolysis was crucial to avoid overoxidation of the products as the diynes **396** are oxidized at a higher potential than that of products **398**. Strategies relying on direct electrolysis for generation of nitrogen-centered radicals have also been achieved. Based on this concept, amidinyl and iminyl radicals have been exploited for preparing polycyclic imidazole derivatives^{926,927} (Scheme 117) and assorted pyridine-fused aromatic motifs⁹²⁸ (Scheme 118), respectively. In addition to

using nitrogen-centered radicals in C–N bond coupling manifolds, nitrogen–nitrogen (N–N) bond formation has also been accomplished. These intermediates have, for example, been explored for N–N dimerization⁹²⁹ in the synthesis of dixiamycin B,^{930,931} phthalazin-1,4-diones⁹³² and pyrazolidin-3,5-diones.^{933,934}

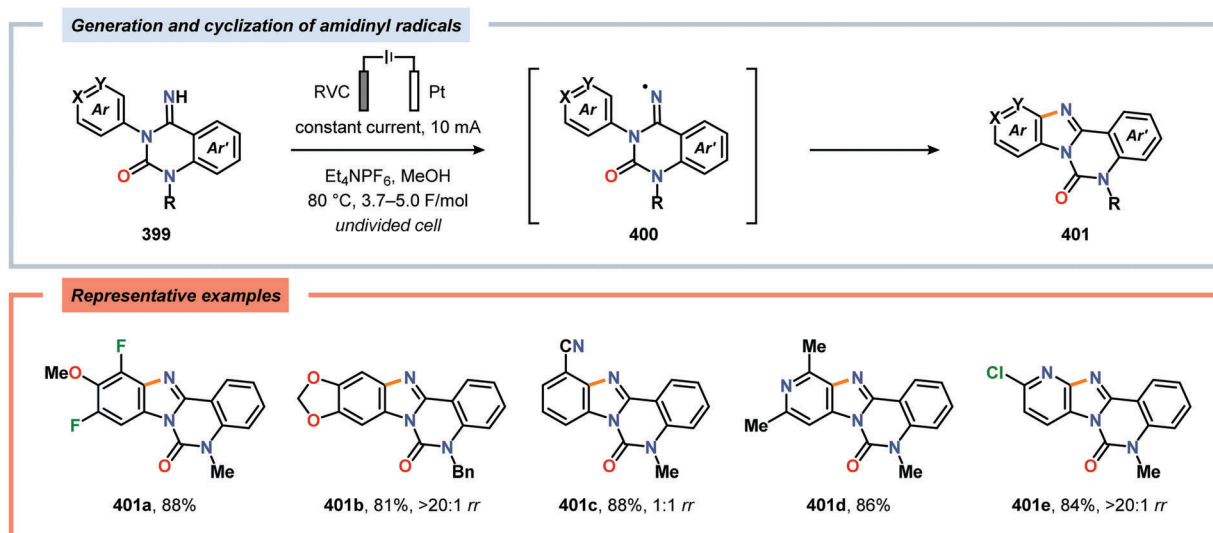
3.3. Pyridine and related nitrogen-containing heterocycles as nitrogen sources

Seminal work by Lund during the 1950s highlighted that aromatic hydrocarbons could be oxidized at a Pt electrode in acetonitrile solutions containing pyridine and NaClO₄ to afford the corresponding pyridinium perchlorate species.⁹³⁵ Although related electrochemical amination reactions were studied by other research groups,^{936–943} it took more than five decades until Yoshida and coworkers disclosed an efficient and practical method for C–H amination of aromatic compounds based on electrochemical

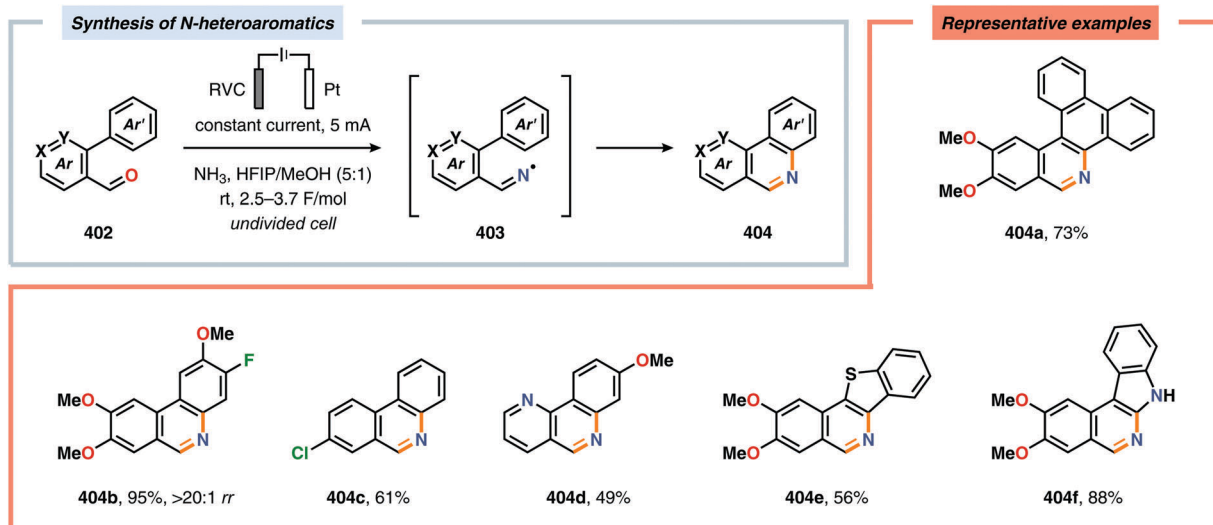


Scheme 116 Electrochemical synthesis of nitrogen-doped polycyclic aromatic hydrocarbons through radical cyclization of diynes.





Scheme 117 Electrochemical generation of amidinyl radicals for synthesis of tetracyclic benzimidazoles and pyridoimidazoles.



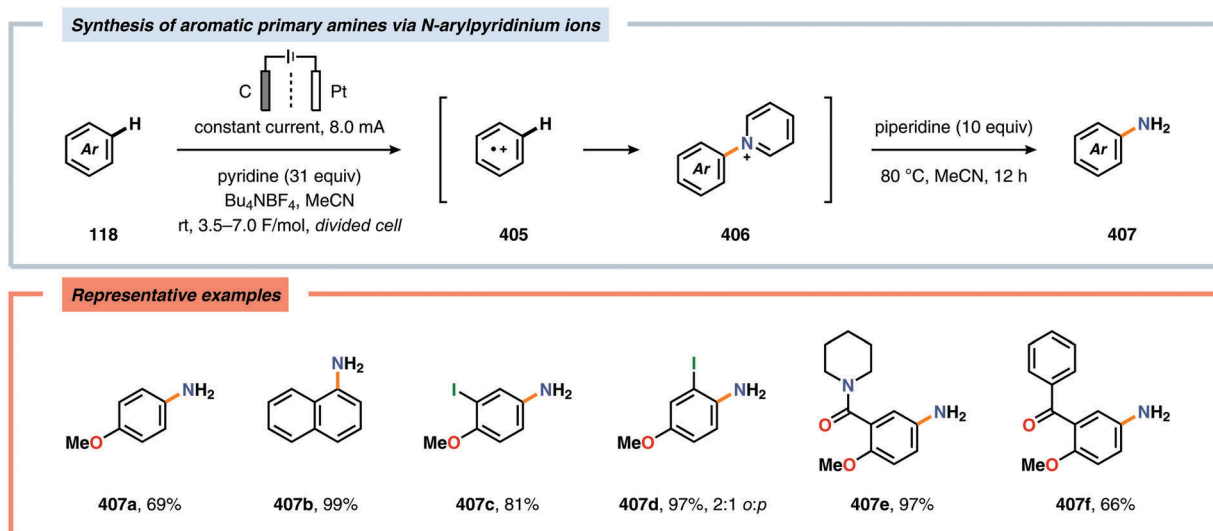
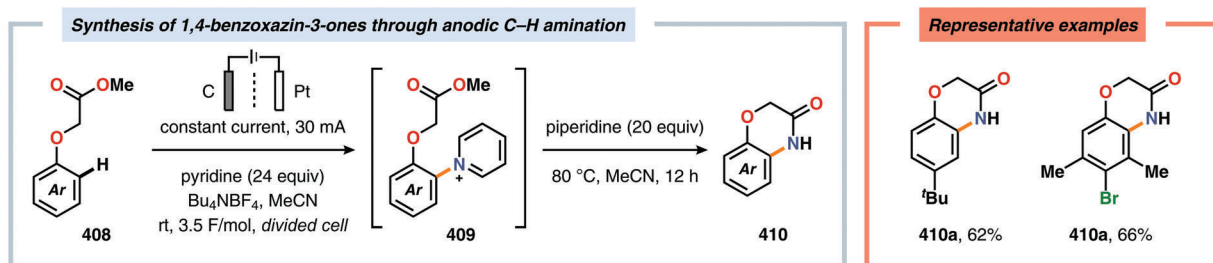
Scheme 118 Synthesis of pyridine-fused polycyclic aromatic motifs via iminyl radicals.

oxidation of aromatic compounds in the presence of pyridine (Scheme 119).^{56,944,945} Conducting the electrochemical oxidation in an H-type divided cell at ambient temperature furnished *N*-arylpyridinium ions (**406**), so called Zincke intermediates,^{946–948} which upon treatment with an alkylamine resulted in primary amines **407**.⁵⁶ Here, the high oxidation potential of pyridine enables selective oxidation of the aromatic compound in the presence of pyridine. Furthermore, the high nucleophilicity of pyridine allows for efficient trapping of the generated arene radical cation and the introduction of multiple amino groups is avoided due to the strong electron-withdrawing effect of the pyridinium moiety in **406**, thereby suppressing overoxidation. However, one drawback was that only electron-rich and activated substrates, such as anisole derivatives, were viable substrates. Subsequently, the Waldvogel group demonstrated that the use of

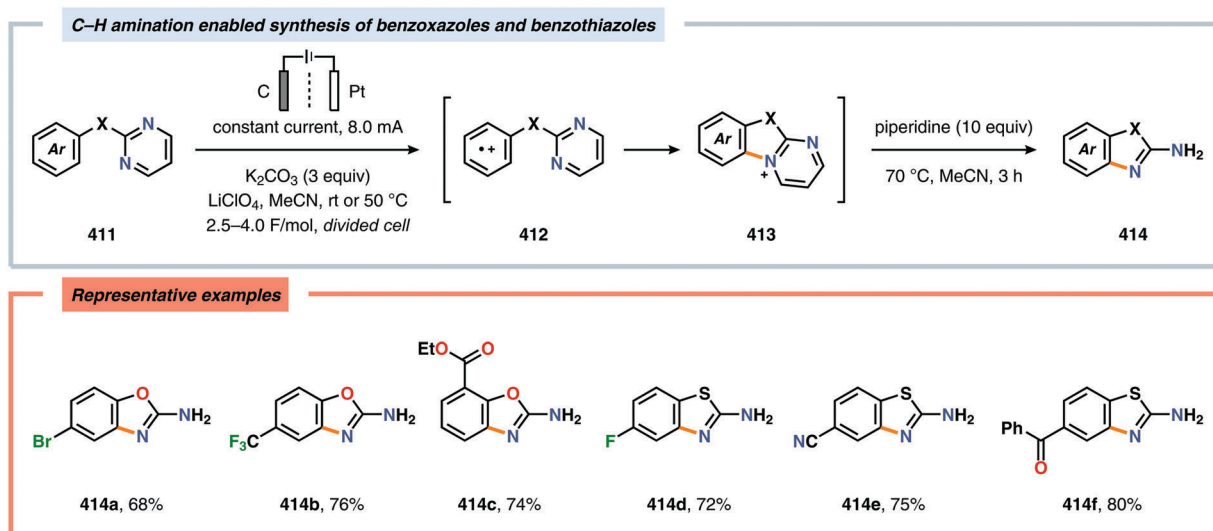
BDD anodes allowed for amination of less activated substrates⁹⁴⁹ as well as diamination.⁹⁵⁰ Furthermore, a protocol for the anodic C–H amination of phenoxy acetates was shown to provide efficient access to 1,4-benzoxazin-3-ones (Scheme 120).⁹⁵¹ Alternatively, rendering the C–H amination intramolecular through the use of arenes containing a tethered 2-pyrimidyl moiety provided access to 2-aminobenzoxazoles and 2-aminobenzothiazoles (Scheme 121).^{952,953}

Work on expanding the scope of the nitrogen nucleophiles revealed that *N*-protected imidazole derivatives were suitable trapping agents. The choice of an appropriate protecting group was crucial to the success of the developed C–H amination method. After an initial examination of various protecting groups, the use of *N*-methylsulfonyl (Ms) protected imidazole afforded the C–N coupled product in the highest yield. The developed protocol



Scheme 119 Electrochemical synthesis of aromatic primary amines via *N*-arylpiperidinium ions.

Scheme 120 Synthesis of 1,4-benzoxazin-3-ones via anodic C–H amination.

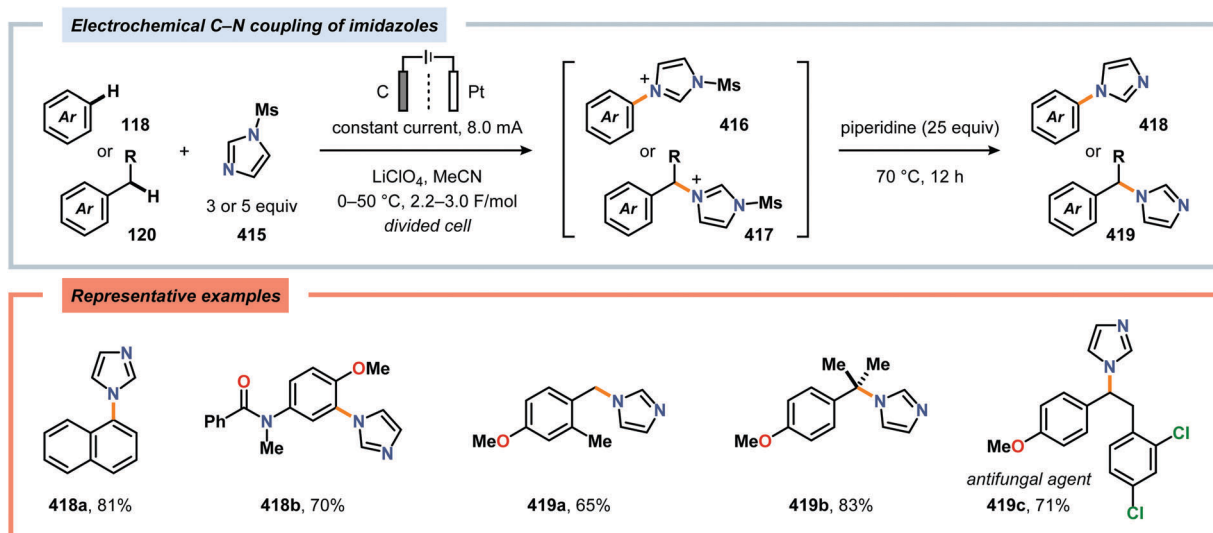


Scheme 121 Preparation of 2-aminobenzoxazoles and 2-aminobenzothiazoles via electrochemical intramolecular C–H amination.

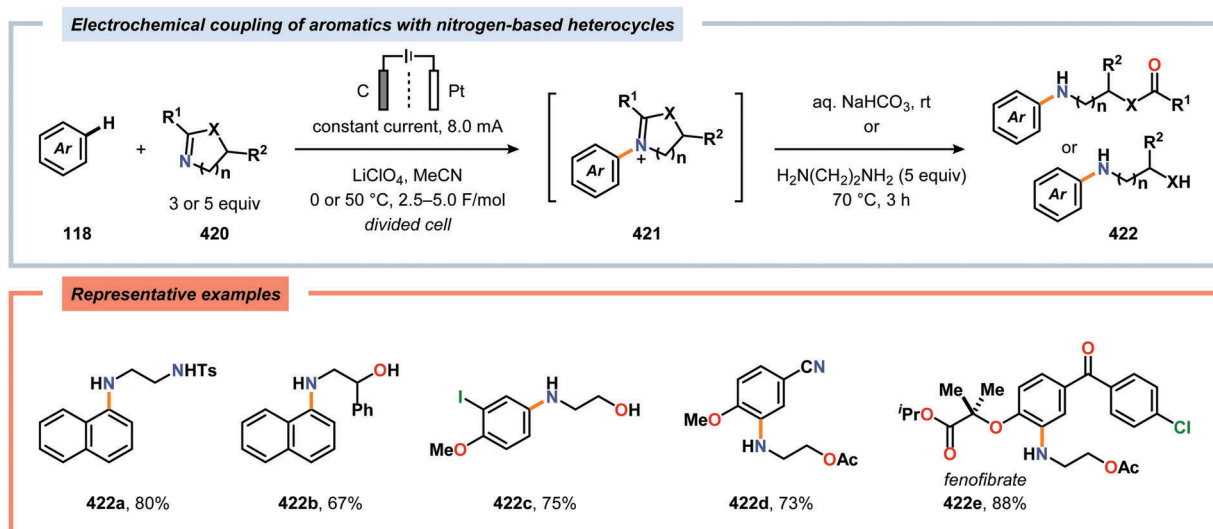
was applicable not only to aromatic but also to benzylic C–H amination. Here, the initial *N*-aryl or *N*-benzylimidazolium cations can be subjected to non-oxidative removal of the protecting group,

resulting in cleavage of the sulfonyl protecting group to produce the corresponding *N*-aryl or *N*-benzylimidazoles (Scheme 122). Similar to *N*-arylpiperidinium ions **406**, the intermediate imidazolium ions





Scheme 122 Direct C–N coupling of imidazoles with aromatic and benzylic compounds.

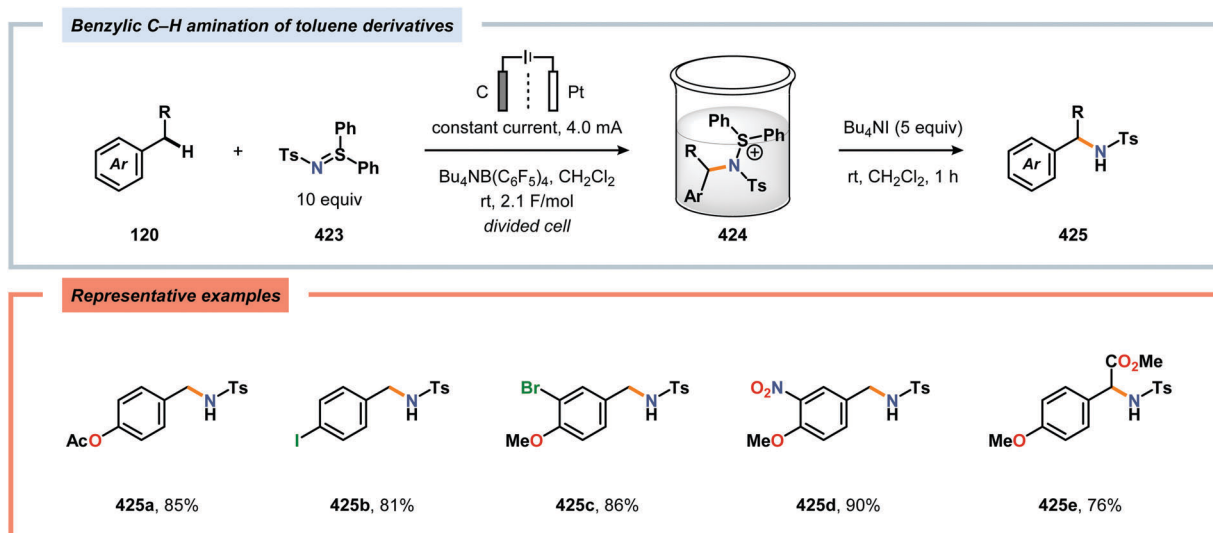
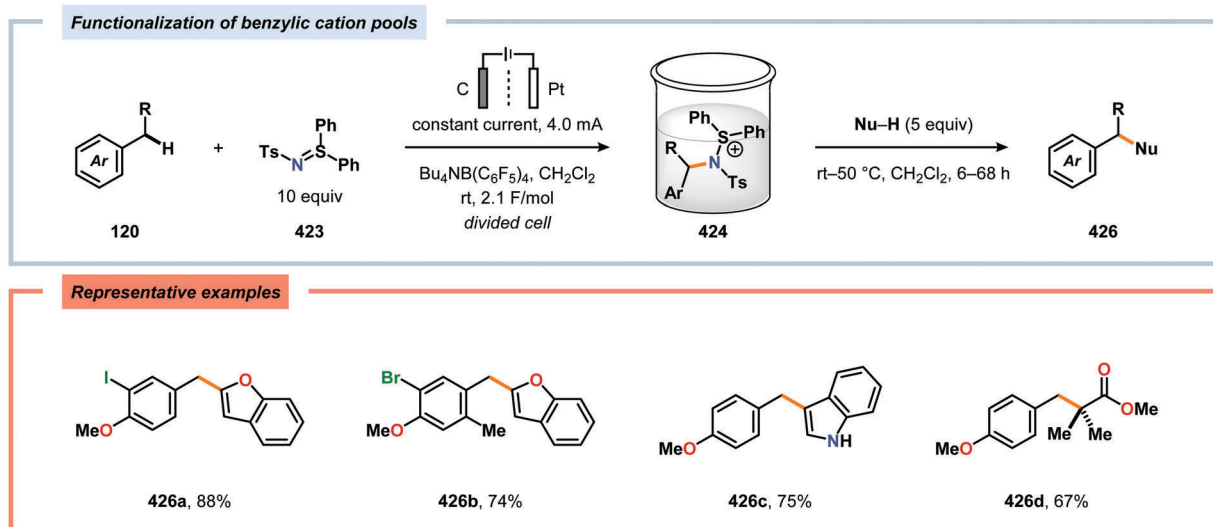


Scheme 123 C–N bond coupling of aromatic compounds and nitrogen-containing heterocycles.

416 and **417** are electrochemically inactive, thus preventing over-oxidation and allow these intermediates to be converted to the corresponding imidazole products **418** and **419**.^{954–956} Subsequently, the Yoshida group reported a mechanistically similar reaction for the coupling of aromatics and masked primary alkyl amines bearing additional oxygen or nitrogen functionalities (Scheme 123). The masked primary amines **420** were prepared by treatment of the amines with nitriles or derivatives thereof to afford the target five- or six-membered heterocycle. Under electrochemical conditions, these heterocycles undergo coupling with arene radical cations to give cationic intermediates **421**, which can be chemically converted to the desired cross-coupling products **422** under non-oxidative conditions.⁹⁵⁷ The same group also developed an electrochemical approach for C–H amination

of toluene derivatives employing *N*-tosyldiphenylsulfilimine **423** as the amination reagent (Scheme 124). This enabled the preparation of *N*-tosylbenzylaminosulfonium ions **424**, which upon treatment with an iodide source, such as Bu₄NI, under non-electrolytic conditions results in N–S bond cleavage to yield the corresponding *N*-tosylbenzylamines **425**.⁹⁵⁸ Alternatively, the generated benzylaminosulfonium ions **424** can react with added aromatic nucleophiles to give the corresponding cross-coupling products **426** (Scheme 125).⁹⁵⁹ In these transformations, the high oxidation potential of *N*-tosyldiphenylsulfilimine **423** allows a wide range of toluene derivatives to be oxidized and functionalized. Finally, Lei and coworkers have developed an electrochemical strategy for amination of C(sp³)–H bonds. Here, C(sp³)–H bonds adjacent to heteroatoms, such as nitrogen, oxygen and sulfur, could



Scheme 124 C–H amination *via* electrochemically generated benzylaminosulfonium ions.Scheme 125 Benzylic cross-coupling *via* electrochemically generated benzylaminosulfonium ions.

be functionalized with various amines to give the corresponding C–N coupled products **429** in moderate to good yields (Scheme 126).^{960,961}

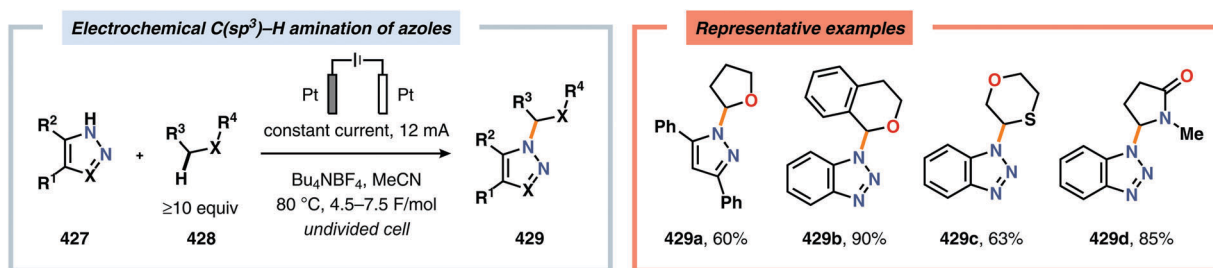
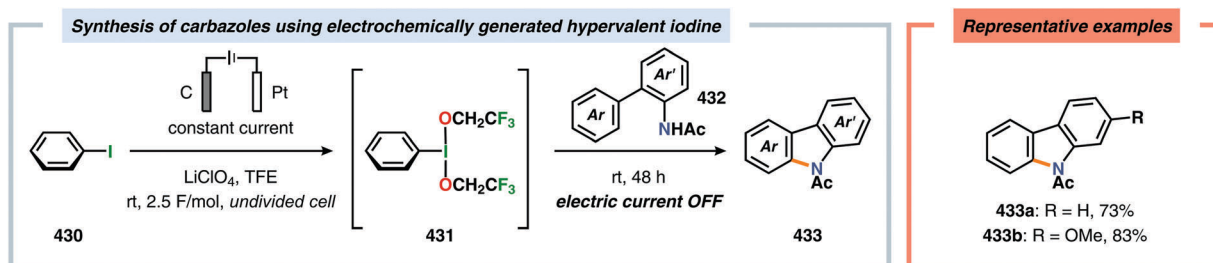
3.4. Halide-mediated approaches to C–N bond coupling

Hypervalent iodine compounds have been extensively employed in organic synthesis as selective metal-free oxidants and environmentally friendly reagents. Synthetic applications of these versatile reagents include, for example, aminations, C–C bond-forming reaction manifolds, halogenations, oxidations, rearrangements, and various dual catalytic activation modes.^{962–969} In this context, hypervalent iodine species electrochemically generated from the corresponding iodoarenes have been applied for the synthesis of various heterocyclic frameworks, such as carbazoles⁹⁷⁰ (Scheme 127), pyrroloindoles,⁹⁷¹ quinolinone derivatives⁹⁷² (Scheme 128) and spirocycles (Scheme 129).^{973,974} The utility of

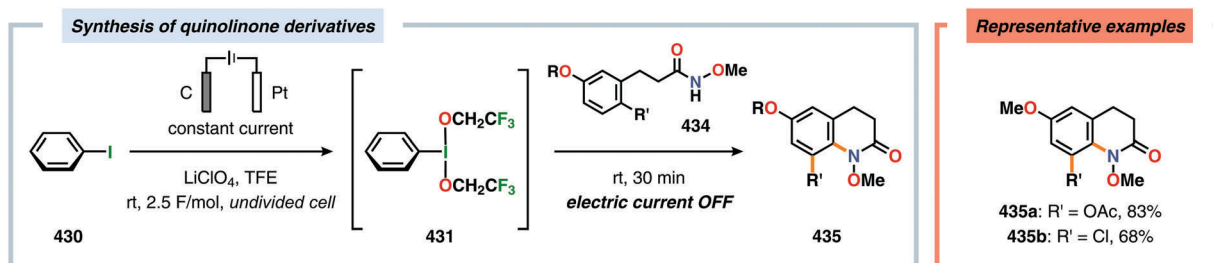
electrochemically generated hypervalent iodine reagents has also been demonstrated in the synthesis of glycozoline⁹⁷⁰ and tetrahydropyrroloiminoquinone alkaloids.^{975,976} The supporting electrolyte has also been merged with the iodine mediator through tethering of the redox-active iodophenyl moiety to an alkylammonium moiety. The ionically tagged iodophenyl motif was applied to several oxidative C–N bond coupling scenarios and allowed for straightforward recovery and reuse of the ionic mediator.^{977,978} A related approach was also employed for the synthesis of benzoxazoles.⁹⁷⁹ Additionally, various oxidative amination strategies for preparing 2-substituted benzoxazoles using iodide as a redox mediator have also been reported.^{980–982}

An electrochemical protocol for α -amination of ketones was recently reported using iodide as a redox catalyst (Scheme 130).⁹⁸³ Here, NH_4I was found to be the optimal redox catalyst for facilitating

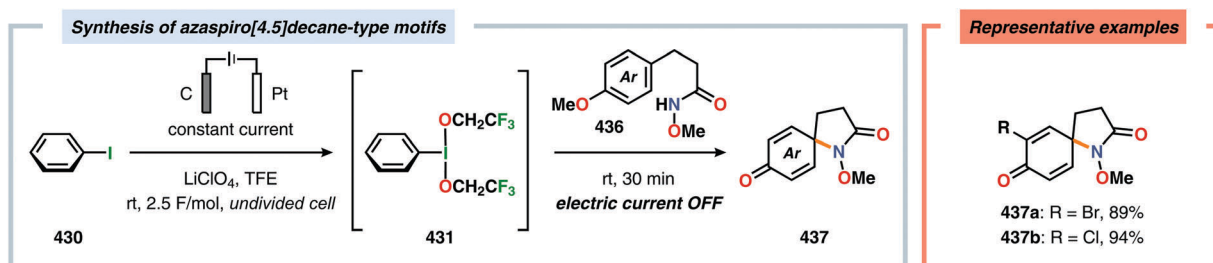


Scheme 126 Electrochemical C(sp³)-H amination of azoles with heterocycles.

Scheme 127 Synthesis of carbazoles using an electrochemically generated hypervalent iodine oxidant.



Scheme 128 Preparation of quinolinone derivatives through oxidative cyclization and concomitant rearrangement of the functional group.



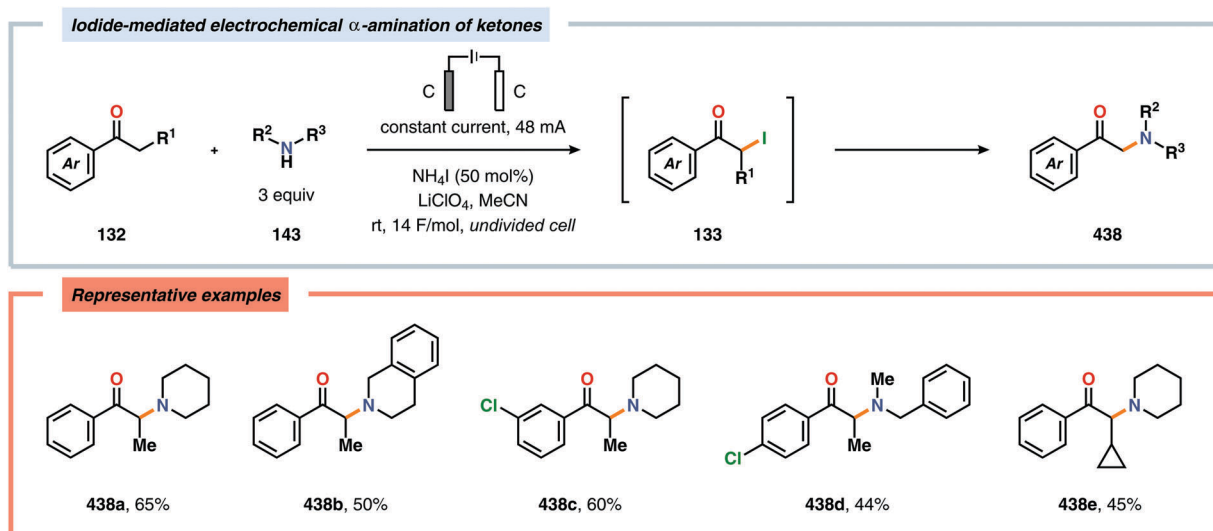
Scheme 129 Hypervalent iodine-mediated synthesis of azaspiro[4.5]decane-type motifs.

the coupling of ketones and secondary amines at ambient temperature. The reactions were conveniently carried out in a simple undivided beaker-type cell and were believed to proceed *via* initial α -iodination of the ketones (**132**) with the anodically generated I₂, followed by nucleophilic substitution of the amines (**143**), thus avoiding isolation of the key α -iodo ketone intermediate **133**. It was noted that the addition of radical scavengers, such as TEMPO,

terminated the α -amination process and did not yield any product. Related halide-mediated procedures for cleavage of β -O-4 lignin model compounds,^{984–986} thiocyanation⁹⁸⁷ as well as synthesis of 3-amino-2-thiocyanato- α,β -unsaturated carbonyl derivatives⁹⁸⁸ and β -keto sulfones⁹⁸⁹ have also been developed.⁹⁹⁰

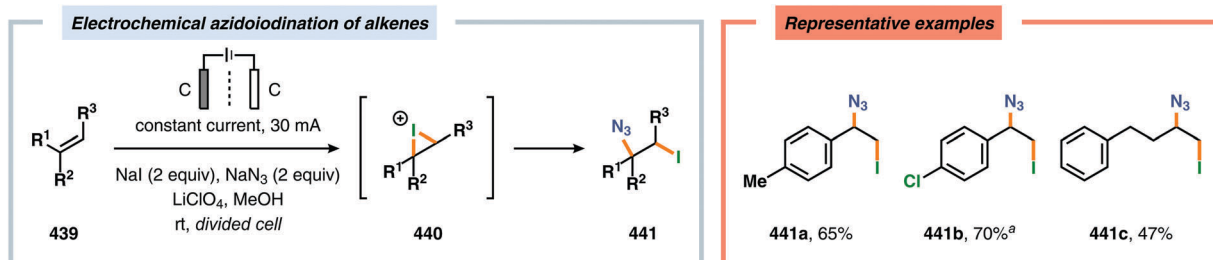
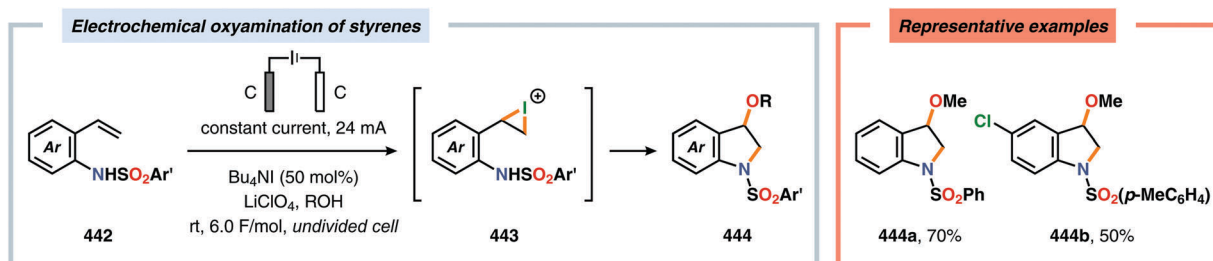
Halide-mediated protocols for C–N bond coupling with alkenes have also been targeted. Zeng, Little and coworkers



Scheme 130 Electrochemical α -amination of ketones using NH_4I as redox catalyst.

demonstrated an efficient approach for aziridination of alkenes Bu_4NI as a redox catalyst and *N*-aminophthalimide (**366**) as the source of electrophilic nitrogen (*cf.* Scheme 107). The process was carried out at a constant current in an undivided cell and was proposed to follow a radical mechanism where hydrogen atom abstraction from *N*-aminophthalimide by I^\bullet generates a nitrogen-centered radical that is subsequently trapped by the alkene.⁹⁹¹ Based on earlier precedent,⁹⁹² the Zeng group presented an indirect electrochemical method for synthesis of vicinal iodoazides (Scheme 131). In the developed protocol, IN_3 is electrochemically generated *in situ*, thus avoiding the use of

external oxidants or corrosive I_2 . Furthermore, the reaction proceeds *via* a cyclic iodonium intermediate to afford regioselective azidoiodination products in a Markovnikov-type fashion.⁹⁹³ Finally, an electrochemical strategy for oxyamination of styrenes for accessing indoline derivatives was recently achieved (Scheme 132).⁹⁹⁴ The electrochemical reactions were conducted under constant current conditions in a simple undivided cell using Bu_4NI as a redox catalyst. This paired electrolysis process avoids the use of external bases and oxidants, representing an appealing and environmentally benign route for synthesis of these heterocyclic compounds. Mechanistic insight suggested that the reaction

Scheme 131 Electrochemical regioselective azidoiodination of alkenes *via in situ* generation of IN_3 . ^a Carried out in $\text{MeOH}/\text{H}_2\text{O}$ (5 : 1).

Scheme 132 Electrochemical oxyamination of styrenes for synthesis of indolines.



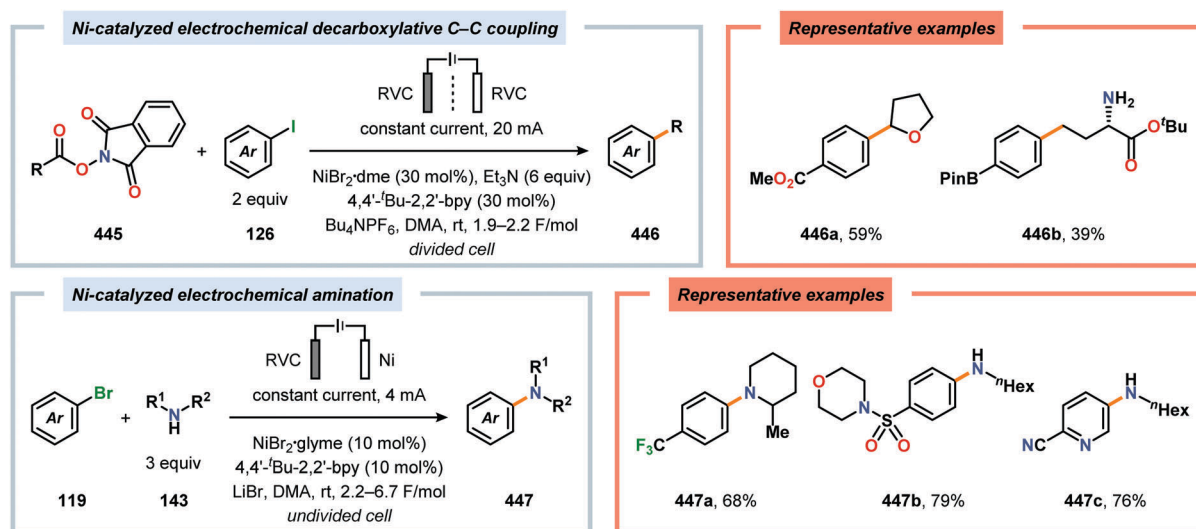
commences with the anodic oxidation of iodide to generate I_2 , which subsequently reacts with alkene **442** to afford the corresponding iodonium intermediate **443**. Finally, intramolecular cyclization with the pendant sulfonamide followed by nucleophilic substitution by alkoxide yields the indoline product **444**. The examples discussed here highlight that halide ions are versatile mediators capable of promoting a collection of different transformations.

4. Conclusions and outlook

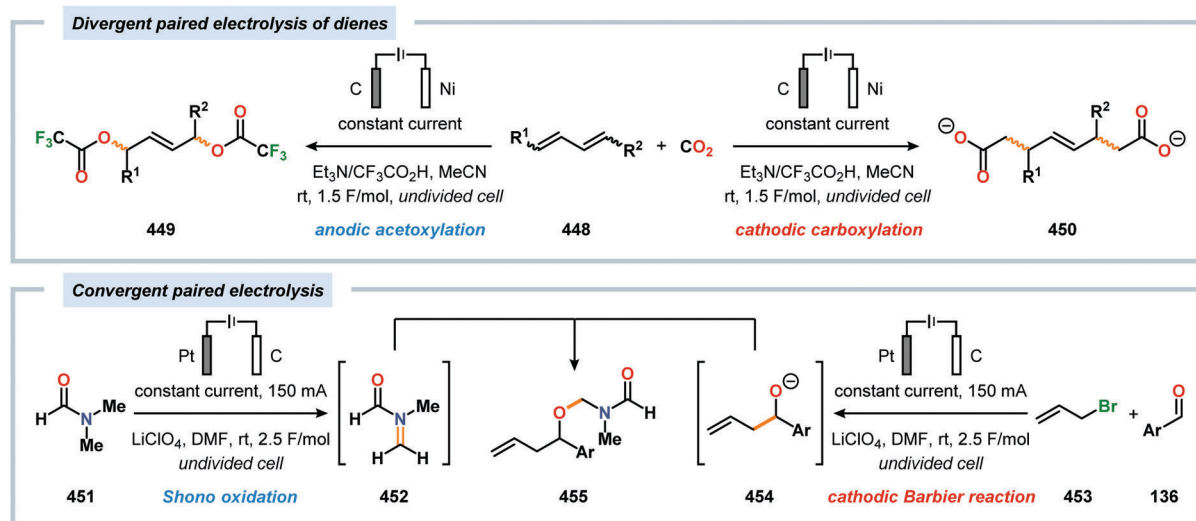
During the last few decades, the imperative to develop and adopt more sustainable and atom economical methodologies for synthetic purposes has not been overlooked by the scientific community. In this regard, electrochemistry serves as an

appealing platform since only electrons serve as reagents,⁹⁹⁵ thereby minimizing production of reagent waste while allowing the reactions to be carried out at milder conditions.^{996,997}

Organic electrochemistry can be classified into two categories, direct and indirect electrolysis. Here, the initial electron transfer between the electrode and a substrate to produce a radical intermediate does not generally pose a problem. Instead, it is crucial to control the reactive intermediates that are subsequently generated throughout the process. Although related activated species can be accessed using traditional organic reagents, there is a dramatic difference in the nature of these species.⁹⁹⁸ While the activated species are uniformly distributed throughout the solution in conventional organic reactions, these species are only produced at the surface of the electrode in electrochemical reactions. This difference in distribution of the reactive species will thus affect the chemical behavior as well as reactivity and selectivity.



Scheme 133 Ni-catalyzed electrochemical coupling platforms.



Scheme 134 Divergent and convergent paired electrolysis.



For an unexperienced electrochemist it might seem that there are a wide range of experimental variables that need to be optimized, such as cell type, electrode composition and electrolyte.⁹⁹⁹ However, this should be seen as an opportunity for accessing unique selectivity and expediting unconventional reaction pathways for challenging bond construction, thus enabling novel and strategic bond disconnections in synthetic endeavors. Since organic chemists are rather unfamiliar with the concept of using electric current to facilitate chemical reactions, the purpose of the present review is to highlight the potential of applying organic electrochemistry to organic synthesis. Here, an overview of the development of electro-synthetic reaction manifolds for C–H bond functionalization and C–N bond formation is provided. The electrochemical strategies and methods discussed in this review clearly showcase the diversity of transformations that can be facilitated through organic electrosynthesis. Furthermore, the refinement and expansion of reaction engineering methods and wider commercial availability of electrochemical reactors provide a multifaceted and powerful toolbox for efficient generation of reactive intermediates from an ensemble of organic substrates. These include, among others, the development of dual catalytic platforms (Scheme 133),^{1000–1007} paired electrolysis^{1008–1012} (Scheme 134) and electrochemical flow cells,^{1013–1019} which have contributed to advancing the field of electrosynthesis. Based on these unique features and the current renaissance in synthetic electrochemistry, it is anticipated that this field will soon be considered as a reliable and versatile platform by the broader scientific community for nontraditional bond construction in organic chemistry.

Conflicts of interest

There are no conflicts of interest to declare.

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