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The Spectacular Resurgence of Electrochemical Redox Reactions in Organic Synthesis

Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling

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The Spectacular Resurgence of Electrochemical Redox Reactions in Organic Synthesis


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Dedicated to the memory of Prof. Dr. István E. Markó

Keywords. organic electrosynthesis; radicals; anodic oxidation; cathodic reduction; paired electrosynthesis.

Abstract. Electrochemistry has had a profound impact on green chemistry and in applications such as energy conversion and storage, electroplating, water treatment, and environmental monitoring, and it has also been embraced by various industries. It is therefore quite surprising that electrochemistry has seldom been used by synthetic organic chemists. This could be partly attributed to the misconception that the electron as a reagent cannot be tamed easily. In recent years, the application of electrochemistry to the synthesis of fine chemicals has had a resurgence, and many elegant solutions based on electrochemistry have been devised to address synthetic challenges with easy-to-use experimental setups.

Outline

1. Introduction

Chemistry is all about electrons. This general statement, though simple, is nonetheless true. In organic chemistry, many transformations are redox reactions, involving electrons being added to, or removed from, the molecule of interest. With this in mind, electrochemistry should be a natural choice for synthetic organic chemists. Indeed, what better reagent can there be for electron-transfer reactions than the electron itself? It is the cheapest possible reactant, its reducing power can easily be tuned by adjusting the potential at the electrode, and it does not generate any byproduct.

One of the best-known and useful organic electrosyntheses—the Kolbe reaction, in which a carboxylic acid is electrochemically decarboxylated and the resulting radical dimerizes—dates back to 1848.[1] Since then, many industrial processes that use organic electrochemistry have been developed, and huge tonnages of commodity organic chemicals are produced electrochemically.[2] In contrast and despite its success at the industrial scale, electrosynthesis has been more often than not one of the last options to use to perform a chemical transformation in the organic chemistry laboratory. Many reasons can be invoked to explain this reluctance, from lack of academic training, to wariness towards an almost magical reagent which cannot be weighed, to the reaction flask used. However, attitudes are rapidly evolving, and organic electrosynthesis is now back in the spotlight thanks to the "naturally green" electron, the easy interfacing with flow chemistry, and the direct scalability of electrochemical processes. This renewed interest is demonstrated by the number of recent review articles that have been published on the subject.[3-12] This review is not a comprehensive treatment of the topic, and is intended only to highlight recent, salient, and representative applications of electrochemical redox reactions in organic synthesis, with possible industrial development in mind.

2. Basic Principles

2.1. The Electrochemical Cell and Cathode and Anode Reactions

In the basic electrochemical cell, electron transfer takes place at the surface of the electrodes, and an electrolyte is required to ensure conduction of the current from one electrode to the other; in other words, to close the circuit. Typically, the electrolyte is the reaction solvent to which a salt has been added. However, when ionic liquids are used, they act both as solvent and electrolyte.[13] The cell can also be divided into separate anodic and cathodic compartments to avoid recombination of the products in the bulk. In that case, a membrane, diaphragm, or electrochemical junction is required. Finally, a reference electrode can be employed in addition to the anode and cathode, to better measure and control the potential.

2.2. Mediators and Electroauxiliaries

In the simplest cases, the desired reaction can be directly realized by electron transfer between the electrode and the substrate. This is referred to as direct electrolysis. In most cases, however, the desired transformation cannot be achieved in this way, notably because the oxidation or reduction potential required is too high in absolute value, giving rise to side reactions or electrode passivation, or is even beyond the accessible range due to degradative electrolysis of the solvent or electrolyte. Two strategies can then be envisioned to overcome these limitations. The first is to switch from direct electrolysis to indirect electrolysis using a mediator,[14,15] which is a substance that is activated electrochemically at the electrode, giving a transient species that then reacts with the substrate in solution. The potential required for the activation of the mediator should be lower than that of the substrate. In some cases, the reaction between the activated species and the substrate regenerates the mediator, which can then be used in catalytic amounts. The second strategy is to use a substrate containing a functional group that can enable the desired electron transfer to take place at a lower potential and in a more selective fashion. Such a functional group is called electroauxiliary.[16] Both approaches will be reported on in this article.

3. Anodic Oxidation

3.1. Alcohol Oxidation

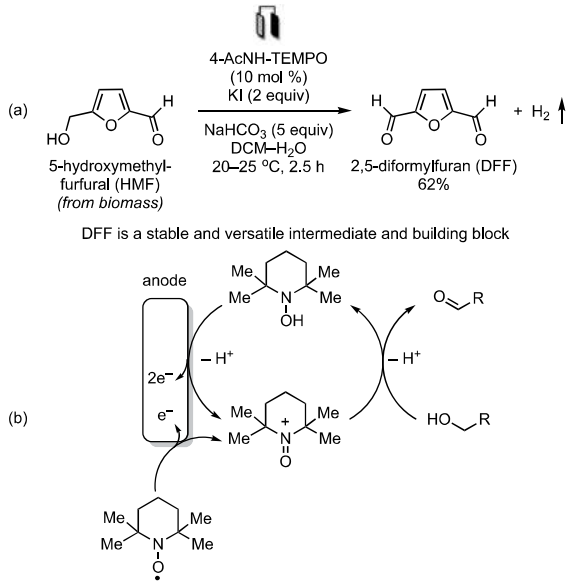
While a plethora of alcohol oxidation methods have been developed, the number of such reactions that are used on a large scale is quite small. This can be attributed to safety concerns over the fact that the three ingredients needed for combustion (oxidant, fuel, and energy) can be present in the reactor at the same time.[17] Proper design of reaction conditions and careful process safety studies can help mitigate the risks associated with large-scale oxidations. In practice, many API syntheses invoke such a transformation and the Anelli oxidation is often employed.[18] The advent of TEMPO-mediated electrochemical alcohol oxidation has spurred interest in many research groups, and has been met with considerable success, leading to the development of general electrochemical methods to oxidize alcohols with TEMPO-like radicals.[19] Previous electrochemical oxidation methods using in situ generated iodine have been replaced with more general variants.[20] The TEMPO-mediated alcohol oxidation has now become an enabling method, and is expected to be widely adopted in total synthesis and methodology development. This approach has found application in the context of innovative production of biosourced materials such as the formation of 2,5-diformylfuran (DFF) from the parent primary alcohol, 5-hydroxymethylfurfural (HMF) (**Scheme 1**, Part (a)).[21] Mechanistic studies were conducted using cyclic voltammetry to better understand the reactivity of various alcohols towards TEMPO and NHPI (Scheme 1, Part (b)),[22] and mechanistic studies of NHPI-mediated alcohol oxidation using rotating disc electrode voltammetry have also been published.[23]

When contemplating electrochemistry for synthesis, one should study the effect of a given electrode material on the reaction of interest, as well as the fact that electrodes can also be grafted with active chemical species. In some cases, this can result in increased TON for classical oxidations.[24] This intrinsically waste-free variant of the well-established TEMPO-mediated oxidation is conceptually appealing, but its wide

adoption is hampered by its inherent practical complexity. Moreover, electrochemical cells have been designed to intensify electrosynthesis processes, but the presentation of this technology is outside the scope of this review.[25] An interesting comparative approach was described during the synthesis of *N*-isobutyl-(2*E*,6*Z*)-dodecadienamides, which showed that not all reactions benefit from electrochemistry.[26] Although the comparison was primarily based on chemical yield, nevertheless it showed that electrochemical and classical tools can be complementary.

Badalyan and Stahl recently reported a cooperative electrocatalytic alcohol oxidation that employs tailor-designed, electron-proton-transfer mediators, and proceeds with faster rates and at lower overpotential than a similar process that uses only TEMPO.[27] The use of (2,2′-bipyridine)Cu(II) and TEMPO paves the way for the discovery and development of non-precious-metal electrocatalysts. The authors emphasized the potential applications of this approach in the field of energy conversion.

As the usefulness of electrooxidation becomes more and more obvious, contemporary trends, proof-of-concept studies, and modern applications are being published. A recent report by Berlinguette's group details the tandem reduction of CO_2 into CO along with the TEMPO-mediated oxidation of alcohols into the corresponding ketones at the anode.[28] In some instances, electrochemical oxidation can mimic the enzymatic oxidation that occurs when molecules are metabolized by the liver. This feature was employed to replicate hepatic oxidation conditions in continuous-flow electrosynthesis, and the technology can help understand the fate of potential drug candidates prior to in vitro or in vivo testing.[29]



Scheme 1. (a) The 4-AcNH-TEMPO-Mediated Electrochemical Oxidation of Alcohols and (b) Proposed Mechanism for the TEMPO-Mediated Variant. *(Ref. 21,22)*

3.2. C–Y Bond Formation

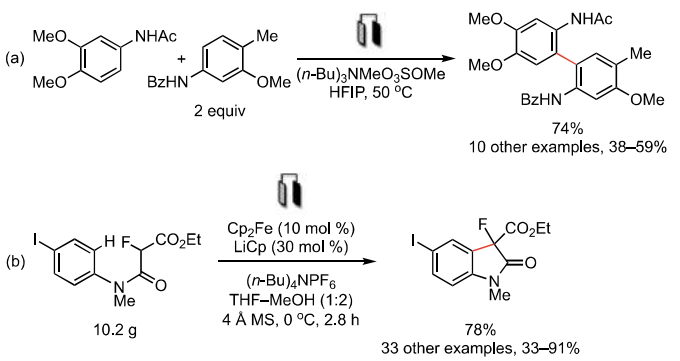
One of the great strengths of electrochemistry lies, not only in the possibility of turning existing C–O bonds into C=O bonds, but also in the possibility of creating C–C, C–N, C–O, and C–S bonds from C–H bonds, thus broadening the scope of this technology.

At present, the prevalence of (hetero)aromatic compounds in the pharmaceutical industry's inventory of drugs is undisputable. Therefore, a plethora of methods for assembling such scaffolds have been developed, whereby industrial chemists routinely use the Suzuki, Heck, Negishi, or Kumada coupling. Despite the fact that these couplings are robust in terms of selectivity and efficiency, they often need a heavy metal catalyst and ligands that need to be carefully removed. Consequently, the associated processes end up being expensive. Electrochemistry can help pave the way to cleaner and more efficient variants.

3.2.1. C–C Bond

The C–C cross-coupling reaction is an essential tool for organic chemists. In this regard, a high-yield, selective, and metal- and reagent-free anodic cross-coupling of electron-rich aromatics (aniline derivatives) has been developed by Waldvogel and co-workers (**Scheme 2**, Part (a)).[30] This electrochemical transformation does not require a leaving group to direct the nucleophilic attack from the anilide starting materials, and avoids the formation of homocoupling dimers, which is a typical side reaction. Similarly, anodic cross-coupling reactions of phenols have been reported by Waldvogel's and other research teams.[31–35]

Another type of interesting C–C cross-coupling is the intramolecular oxidative cyclization of substituted anilides to thermally unstable C-3-fluorinated oxindoles, which typically requires a stoichiometric amount of external oxidant such as a Cu(II) salt, hypervalent iodine reagent, NBS, or O_2. In contrast, the electrochemically induced variant does not require any of these reagents, and is therefore inherently safer and more efficient (Scheme 2, Part (b)).[36] Similarly, indoles can be accessed easily and in good-to-excellent yields



Scheme 2. Electrochemical C–C Inter- and Intramolecular Cross-Couplings. *(Ref. 30,36)*

from the corresponding enamines through an electrocatalytic, intramolecular, and dehydrogenative annulation that is oxidant- and transition-metal-free.[37] Interestingly, the anodic oxidation of unactivated cyclooctene leads to the formation of the [2 + 2] cycloaddition syn dimer in 70–80% yield.[38]

Markó and co-workers disclosed an efficient, safe, and environmentally benign conversion of ω-unsaturated aliphatic acids into carbocycles, tetrahydrofurans, and tetrahydropyrans in good yields and straightforward manner. The synthesis relies on a Kolbe decarboxylation followed by a radical cyclization and radical capture.[39] The radical capture is made possible by the decarboxylation of a second, short-chain carboxylic acid (co-acid) that can trap and terminate the radical pathway. Different co-acids can be used, but acetic acid was shown to be the most efficient. The only ingredients needed for this transformation are 2 electrons and 1 molar equivalent of the co-acid, giving rise to the desired products along with carbon dioxide.

Core structures of many biologically active natural products consist of polycyclic systems containing six-membered rings. The intramolecular anodic coupling of alkenes involving radical cations from enol ethers has been effectively used as a key step for the construction of a six-membered ring that is part of the ring skeleton of arteannuins, a class of natural products with potential antimalarial and antitumor activities (**Scheme 3**).[40] Of interest also is the direct functionalization of a C(sp^2)–H bond in azaaromatics, which has been successfully carried out under mild electrochemical oxidative conditions to produce unsymmetrical (hetero)biaryls in 63–99% yields.[41] This step- and atom-economical S_NH reaction offers the clear advantage of not requiring the use of metal catalysts, stoichiometric quantities of chemical oxidants, or haloaromatics as reactants.

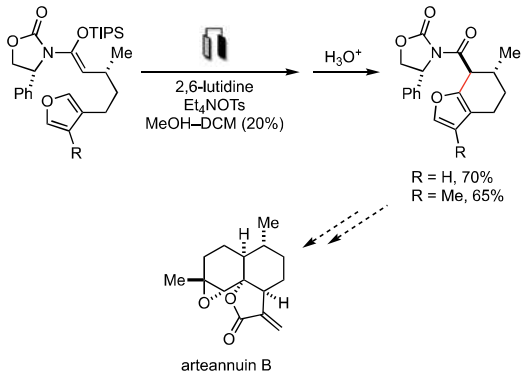
Yoshida and co-workers have recently developed a stabilized-cation-pool method for the metal-free and oxidant-free cross-coupling of benzylic and aromatic C–H bonds.[42] 4-Methoxytoluene was initially used as the substrate for screening of the stabilizing groups, which led to identifying diphenylsulfilimine (Ph_2S=NTs) as the best precursor of a stabilized benzyl cation. This approach was successfully applied to a streamlined, formal total synthesis of TP27, a protein tyrosine phosphatase (PTPase) inhibitor (**Scheme 4**).[42]

A straightforward method for late-stage functionalization of pharmacophores has very recently been proposed by Zeng's group.[43] This catalytic electrochemical method is a variant of the traditional Minisci reaction, and involves the selective monoacylation of electron-deficient azaaromatics (mostly pyrazines) at the 2 position with α-keto acids in the presence of NH_4I as a redox catalyst. The reaction exhibits high functional-group tolerance and a wide substrate scope, generating the monoacylated products in 18–65% yields. In contrast, under the traditional Minisci conditions, the first acylation often activates the arene towards further acylation. In the electrochemical transformation, the carboxylate anion—generated by protonation of the heteroarene with the α-keto acid—is oxidized in the presence of a catalytic amount of ammonium iodide to the corresponding carboxylate hypoiodite [$RC(O)CO_2I$]. The latter undergoes decarboxylation to generate the acyl radical [RC(O)•], which adds to the 2 position of the protonated heteroarene in a regioselective manner. The ensuing radical cation is further oxidized and deprotonated to give the monoacylated heteroarene. Hexafluoroisopropanol was found to be a key additive, and the reaction tolerates alkyl and aryl α-keto acids.

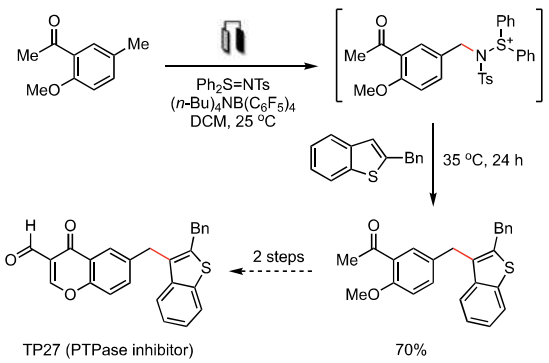
3.2.2. C–N Bond

An efficient, practical, and gram-scale electrochemical method for the α-amination of ketones using simple conditions has been reported by Liang et al.[44] The protocol involves a metal- and additive-free cross-dehydrogenative coupling of ketones with secondary amines, and provides the desired products in up to 75% yields. The reaction exhibits a broad substrate scope, but requires the use of aromatic ketones to ensure high yields.

An earlier contribution from Yoshida's group described the chemoselective and metal-free C–N coupling of adequately protected imidazoles and electron-rich aromatic or benzylic compounds.[45] The authors reported that unprotected imidazole



Scheme 3. Intramolecular Anodic Coupling of Alkenes Involving Radical Cations from Enol Ethers. *(Ref. 40)*

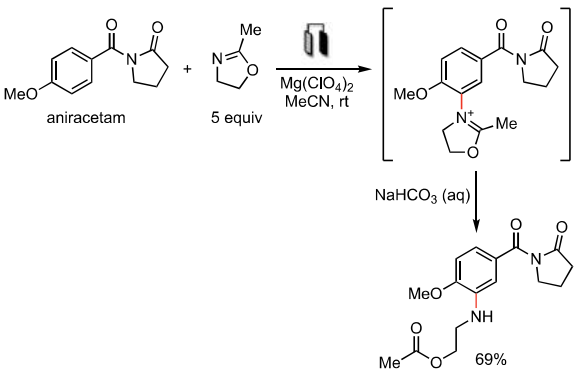


Scheme 4. Benzylic C–H/Aromatic C–H Cross-Coupling via the Stabilized-Cation-Pool Method. *(Ref. 42)*

was not a suitable coupling partner, because the initial imidazolium product easily undergoes overoxidation, and that mesylate and tosylate protection prevented the overoxidation. The final N-substituted imidazole product is obtained after non-oxidative deprotection. A robustness screen according to the protocol described by Collins and Glorius[46] was also performed by Yoshida's group and showed the coupling conditions to be compatible with a wide variety of frequently encountered functional groups.

A conceptually similar strategy was employed by the same group to design an electrochemically mediated coupling of functionalized alkylamines with aromatic compounds.[47] For similar reasons, the reaction could not be run using unprotected alkylamines, so this was circumvented through transformation of the nucleophiles into transient heterocycles. The latter are electrochemically coupled to aromatic compounds, and the alkylamine is obtained upon treatment with aqueous $NaHCO_3$. This work demonstrates, once again, the complementarity of chemical and electrochemical approaches. The scope of this chemoselective and metal- and chemical-oxidant-free route to *N*-alkylaniline derivatives bearing either oxygen or nitrogen in the alkyl group is quite broad, and offers synthetic platforms for further elaboration. The value of this methodology was demonstrated in the selective functionalization of aniracetam, a modulator of AMPA receptors (**Scheme 5**).[47]

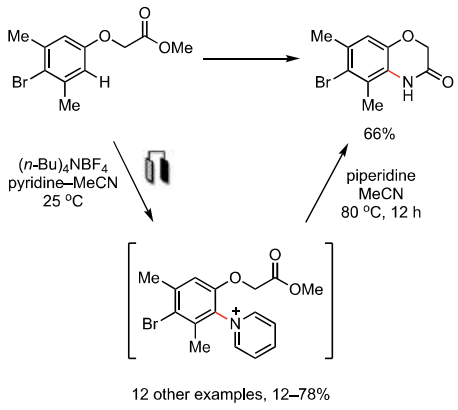
Very recently, Waldvogel and co-workers developed a very efficient, sustainable, and direct anodic C–H amination of phenoxy acetates, leading to 1,4-benzoxazin-3-one scaffolds, which are important structural features in biologically active molecules and natural products such as DIBOA and DIMBOA.[48] The reaction sequence includes anodic oxidation of the aromatic substrate via pyridine-enabled amination. The resulting pyridinium intermediate (Zincke-type salt) is then treated with a secondary amine such as piperidine to release the desired primary aniline, which immediately undergoes ring-closing condensation with the ester functional group to access the valuable scaffolds (**Scheme 6**).[49]



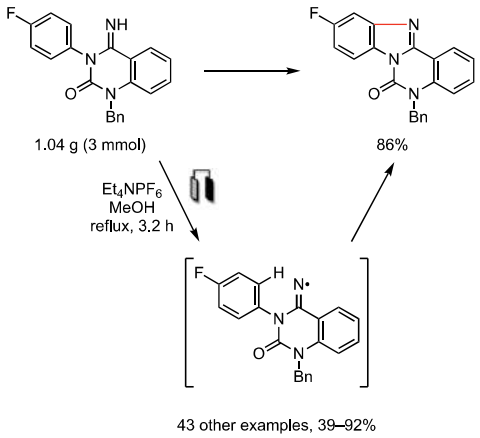
Scheme 5. The Heterocyclization-Enabled Electrooxidative Coupling of Functional Primary Alkylamines with Aromatics as Applied to the Functionalization of Aniracetam. *(Ref. 47)*

Amidinyl radical formation through anodic N–H cleavage has been employed by Xu's group as a sustainable, atom-economical, scalable, and metal- and reagent-free method for C–H bond functionalization in (hetero)aromatics (**Scheme 7**).[50] This approach generates polycyclic benzimidazoles and pyridoimidazoles highly chemoselectively. The sequence proceeds through anodic oxidation of the N–H bond of the amidine group in the substrate to give rise to an amidinyl radical that reacts in a selective intramolecular fashion to produce the desired polycyclic benzimidazole or pyridoimidazole in very good yield. Similar high-yielding reactions were developed to produce heterocyclic benzoxazoles and benzothiazoles,[51] anilines,[52] cyclic carbamates,[53,54] and (aza)indoles.[55]

Xu and co-workers have recently developed an amidyl radical cyclization cascade of urea-tethered diynes for the efficient electrochemical synthesis of polycyclic *N*-heteroaromatics by using ferrocene as catalyst (**Scheme 8**).[55,56] A distinct advantage of this method is the circumvention of the use of stoichiometric amounts of toxic metal hydrides such as $(n\text{-Bu})_3SnH$.



Scheme 6. Efficient, Sustainable, and Direct Anodic C–H Amination Leading to 1,4-Benzoxazin-3-Ones. *(Ref. 48,49)*



Scheme 7. C–H Bond Functionalization in (Hetero)aromatics through Anodic N–H Cleavage and Amidinyl Radical Formation. *(Ref. 50)*

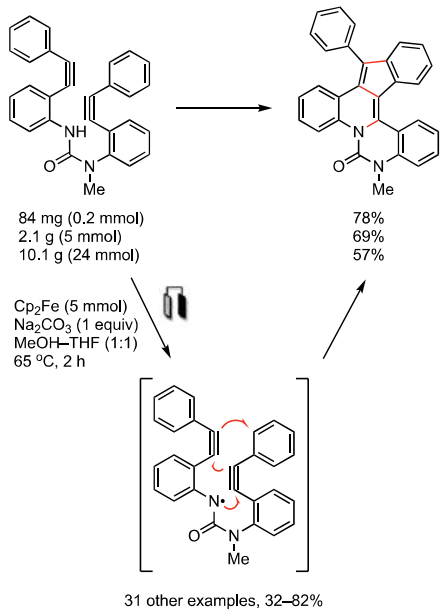
In 2017, Lin's group reported an approach to synthesize vicinal diamines through a Mn(II)-catalyzed electrochemical diazidation of alkenes.[57] Following voltammetric and spectrophotometric studies, the authors proposed a mechanism in which a radical adduct ($RHC^{\bullet}-CH_2N_3$) is generated after transfer of an azidyl group from the active metal azidyl [Mn(III)–N_3] to the less substituted end of the alkene. A second C–N bond is then formed selectively using another Mn-assisted azidyl transfer to the more-substituted carbon of the alkene to form the desired diazide product ($RHCN_3-CH_2N_3$). This method offers the benefits of being environmentally friendly and operationally simple. It also takes place under mild conditions, is compatible with a large number of substrate types and functional groups, and generates 1,2-diazide products (62–98% yields) that can be easily reduced to the corresponding vicinal diamines.

3.2.3. C–O Bond

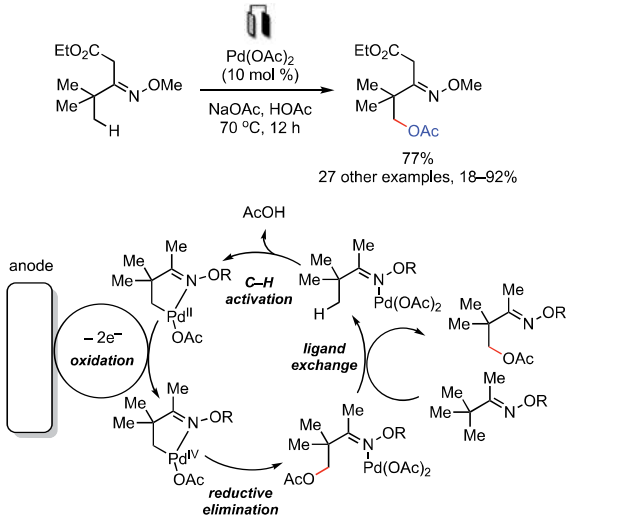
A very recent paper reported the first example of a Pd(II)-catalyzed electrochemical activation and oxygenation with oxyanions of C(sp^3)–H bonds contained in oxime derivatives.[58] This method, which is environmentally benign and avoids the use of strong chemical oxidants, exhibited broad substrate and oxygenated nucleophile scopes (**Scheme 9**). The proposed mechanism involves coordination of $Pd(OAc)_2$ to the nitrogen atom of the oxime followed by activation of a proximal C–H. The resulting palladacycle is oxidized at the anode to a Pd(IV) complex, which undergoes reductive elimination to yield, after ligand exchange, the oxygenated product and the catalyst. The authors rigorously compared the results of the electrochemical synthesis with those obtained following the aerobic C(sp^3)–H oxygenation method developed by Sanford and which employs $NaNO_3$ as catalyst.[59]

Baran's group, in collaboration with researchers from Bristol–Myers Squibb published a breakthrough paper in 2016 detailing the development of an electrochemical allylic oxidation method.[60] While this transformation was already known in the literature, Baran's team set out to better understand the underlying properties of the system and introduced several innovative modifications such as the use of (i) a reticulated vitreous carbon electrode, (ii) *tert*-butylhydroperoxide (*t*-BuOOH) instead of molecular oxygen as a co-oxidant, and tetrachloro-*N*-hydroxyphthalimide (Cl_4NHPI, a cheap and readily available flame retardant) as the mediator. Their optimized procedure, with its easy setup, is far more efficient and environmentally acceptable than the standard, metal-based stoichiometric allylic oxidations. The proposed mechanism involves the electrochemical oxidation of the anion of the mediator (likely formed through an acid–base reaction with a nitrogen base such as pyridine). The resulting oxygen-centered radical abstracts a hydrogen atom from the allylic position to form a carbon-centered allylic radical. Subsequent reaction with *t*-BuOOH, followed by a second oxidation and cleavage of the resulting allylic peroxide affords the α,β-unsaturated ketone product. The reaction conditions were easily scalable, and several oxidations were performed on a 100 gram scale with no special setup. This paper, along with other applications of electrochemistry, was the focus of a recent short review from the same group.[61]

In keeping with previous reports, the Baran laboratory, along with Asymchem Life Science and Pfizer's Global R&D, recently reported a quinuclidine-mediated electrochemical oxidation of unreactive methylene and methine motifs.[62,63] These moieties



Scheme 8. Amidyl Radical Cyclization Cascade of Urea-Tethered Diynes for the Efficient Electrochemical Synthesis of Polycyclic N-Heteroaromatics. *(Ref. 56)*



Scheme 9. Environmentally Benign Pd(II)-Catalyzed Electrochemical Activation and Oxygenation of C(sp^3)–H Bonds in Oxime Derivatives. *(Ref. 58)*

often exhibit a high oxidation potential, making their mediator-free electrochemical functionalization elusive. Initial screening revealed that tertiary amines were superior mediators to the more frequently encountered TEMPO or hydroxyphthalimide derivatives. The reaction conditions were optimized and scaled up (50 g scale) for sclareolide (**Scheme 10**),[62] an exceedingly useful platform for further chemical modification such as the synthesis of (+)-2-oxo-yahazunone. HFIP is a key additive, while oxygen likely serves as the terminal oxidant. This newly developed methodology compares well with the more classical approaches such as the Gif-type chemistry developed by Barton or the methyl(trifluoromethyl)dioxirane (TFDO) based oxidation. The proposed mechanism involves oxidation of quinuclidine into a highly reactive radical cation that is capable of abstracting the more accessible hydrogen from the substrate. The ensuing carbon-based radical is quenched with oxygen to yield the corresponding ketone (from secondary C–H's) or tertiary alcohol (from methine C–H's) after peroxide decomposition.

3.2.4. C–S Bond

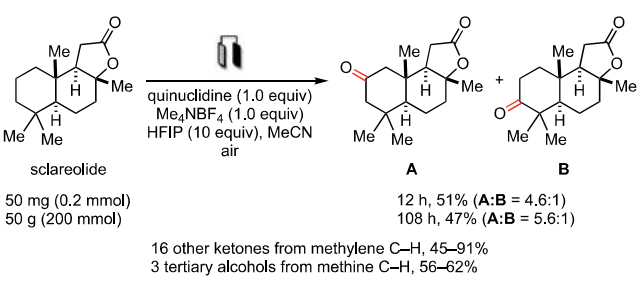
Fewer C–S bond-forming reactions are known as compared to reactions that generate C–C and C–N bonds. This could be due to the fact that sulfur-containing molecules can be good metal scavengers. Electrochemical synthesis could pave the way to developing C–S cross-coupling reactions mainly because heavy-metal catalysts, such as palladium, are not needed for reaction. In this regard, synthesis of (*E*)-vinyl sulfones has been developed via an electron-mediated, oxidative N–S bond cleavage of aromatic sulfonylhydrazides (Ar^1SNHNH_2). This robust method works well for a broad range of halogenated and heterocyclic substrates. Mechanistically, the oxidative cleavage of Ar^1SNHNH_2 at the anode releases N_2 and a sulfonyl radical ($Ar^1SO_2^{\bullet}$). The latter reacts with an α,β-unsaturated carboxylate [(*E*)-$Ar^2CH{=}CHCO_2^-$] to generate an α-sulfonyl carboxylate [$Ar^2CH^{\bullet}{-}CH(Ar^1SO_2)CO_2^-$] that can easily undergo decarboxylation to selectively access the (*E*)-unsaturated sulfone [(*E*)-$Ar^2CH{=}CH(Ar^1SO_2)$] in good yield.[64,65]

Another type of C–S cross-coupling has been achieved in generally good yields (24–99%) by Lei's group by reacting *N*-methylindoles with thiophenols in an electrochemical cell. A broad range of aryl and heteroaryl thiols, as well as electron-rich arenes, served as good substrates for this electrocatalytic and environmentally benign reaction (**Scheme 11**, Part (a)).[66] The electron-mediated and oxidant-free cross-coupling is carried out under simple reaction conditions, and can be run on a gram scale. After extensive mechanistic studies, the authors found that formation of an aryl radical cation by anodic oxidation of the indole or electron-rich arene was the key step in the transformation. Coupling of this radical cation with the aryl sulfide radical (ArS•), followed by rearomatization, leads to the observed cross-coupling product.

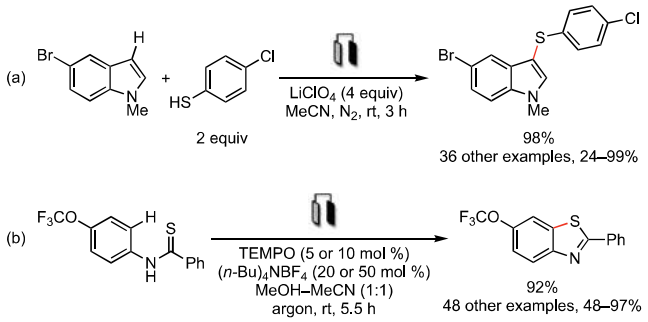
An intramolecular variant, leading to a broad range of benzothiazoles and thiazolopyridines from *N*-(hetero)-arylthioamides, was recently reported by Qian et al. (Scheme 11, Part (b))[67] Electron-rich and electron-poor (hetero)aromatics were suitable substrates, and a catalytic amount (5 mol %) of TEMPO was necessary to produce the active thioamidyl radical species, which undergoes radical cyclization and subsequent rearomatization to produce the desired products. This methodology proved useful in a formal total synthesis of CL075, a toll-like receptor 8 (TLR8) agonist. *N*-Arylthioureas can be generated in situ directly from the reaction of isothiocyanates with secondary amines such as morpholine or dialkylamine under electrolytic conditions [$(n\text{-}Bu)_4NBF_4$ (6 equiv), MeCN–H_2O (9:1), 70 °C, 4 h]. The *N*-arylthioureas thus formed undergo, in a similar fashion, intramolecular dehydrogenative C–S cross-coupling to yield 2-aminobenzothiazoles in up to 99% yield. As with the other C–S cross-coupling variants, this transformation is also external-oxidant-free, metal-free, and be carried out on a gram scale.[68]

3.2.5. C–Cl Bond

An elegant electrochemical Mn(II)-catalyzed dichlorination of alkenes with $MgCl_2$ as a nucleophilic chlorine source has been reported by Lin and co-workers. One important advantage of this sustainable, operationally simple, chemoselective, and scalable protocol is its compatibility with oxidatively labile groups on the alkene such as amines, alcohols, sulfides, and aldehydes (**eq 1**).[69]



Scheme 10. Efficient and Scalable Electrochemical Functionalization of Unactivated C(sp^3)–H Bonds. *(Ref. 62)*



Scheme 11. The Electrochemical C–S Cross-Coupling Reaction. *(Ref. 66–68)*

3.3. N–Y Bond Formation

3.3.1. N–N Bond

A novel, electrochemical N–N coupling induced by anodic oxidation has been developed as a favorable and sustainable alternative to conventional methods for the synthesis of pyrazolidin-3,5-diones, which are important motifs in medicinal and veterinary drugs (**eq 2**).[70] This approach relies on the oxidative N–N cyclization of malonic dianilides through the intermediacy of an amidyl radical. It avoids the use of toxic *N,N'*-diarylhydrazines as starting materials, tolerates a broad substitution pattern, is applicable to unsymmetrical substrates, and forms the desired pyrazolidin-3,5-diones in moderate-to-good yields.

3.3.2. N–S Bond

Zeng, Little, and co-workers have reported an efficient method for the synthesis of sulfonamides through the oxidative amination of sodium sulfinates (**eq 3**).[71] Ammonium iodide is employed both as a substoichiometric redox catalyst and a supporting electrolyte, thus eliminating the need for additional conducting salt and simplifying reaction workup and product isolation. Moreover, the anode serves as co-oxidant, obviating the need for a terminal chemical oxidant.

3.4. Shono Oxidation

Since the first reports by Shono,[14,72] this type of oxidation has been extensively studied and thoroughly reviewed.[73–75] Alkyl amides [$R^1CONCH_2R^2R^3$] or carbamates [$R^1OCONCH_2R^2R^3$] can easily undergo anodic oxidation to the corresponding N-centered radical cations [$R^1CON^+{}^\bullet CH_2R^2R^3$], which then lead to the *N*-acyliminium intermediate [$R^1CON^+(=CHR^2)R^3$]. This iminium ion is instantaneously trapped by a nucleophile (classically by alcohols used as solvents) to yield a hemiaminal [$R^1CON(CH(OMe)R^2)R^3$]. Under the action of a Lewis acid, this hemiaminal can revert back to the iminium ion and then be trapped by another nucleophile. A variety of nucleophiles such as heteroaromatic primary amines[76] and chiral enamines[77] have been employed in this transformation to build C–N and C–C bonds, respectively.

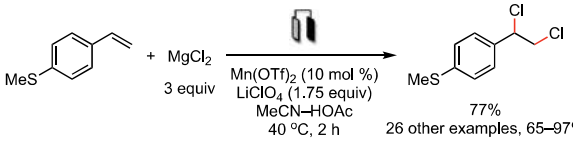
To broaden the scope of this anodic oxidation, the concept of the cation pool method was developed by Yoshida.[78–80] Taking advantage of the cation pool method and flow chemistry, Ley and co-workers accomplished a rapid (two-step) synthesis of nazlinine, a biologically active indole alkaloid, as well as a small library of its unnatural relatives (**Scheme 12**).[81]

Silicon-, sulfur-, and tin-based electroauxiliaries can facilitate electron transfer by lowering the oxidation potential of the substrate resulting in better control of the regioselectivity of the Shono oxidation. For example, introduction of a phenylthio group in the α position of methyl 1-pyrrolidinecarboxylate lowers the oxidation potential from 1.9 V to 1.2 V (vs Ag/AgCl), enabling the oxidative C–S bond cleavage in the presence of electron-rich olefins such as allyltrimethylsilane.[82] Several applications of the cation pool and the Shono reaction strategies are described in this reference.

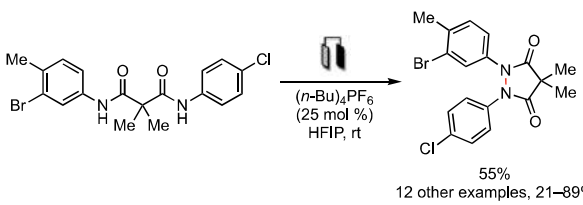
3.5. Miscellaneous Reactions

3.5.1. [3 + 2] Annulation

A scalable, green, and efficient electrochemical oxidative [3 + 2] annulation between C-2 or C-3 substituted *N*-acetylindoles and phenols was reported from Lei's laboratory. This external-oxidant-free and metal-free reaction produces benzofuroindolines (important structural motifs in bioactive natural products such as phalarine, diazonamides, and azonazines) in good-to-excellent yields (up to 99%) under atmospheric conditions. Depending on the position of the substituent in the *N*-acetylindole starting material, the reaction leads to either benzofuro[3,2-*b*]indolines (C-3 substitution) or benzofuro[2,3-*b*]indolines (C-2 substitution) (**Scheme 13**).[83]

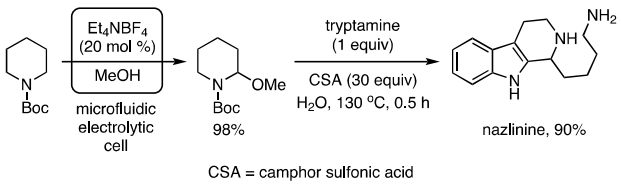


eq 1 *(Ref. 69)*



eq 2 *(Ref. 70)*

eq 3 *(Ref. 71)*



Scheme 12. Flow Electrochemistry as an Enabling Methodology for the Synthesis of a Small Library of Indole Alkaloids. *(Ref. 81)*

3.5.2. Fluorination

The electrochemical fluorination of C–H bonds with HF or fluoride, the Simons process, is of paramount importance in the preparation of perfluorinated compounds.[84] Although it is very much substrate-dependent and not well-suited for the introduction of a single fluorine atom due to competitive polyfluorination, this method remains an essential fluorination protocol when compared to more conventional ones.[85] Fuchigami's group has studied extensively the partial electrochemical fluorination of organic compounds, and these studies have shown that sulfides are privileged reaction partners.[86]

3.5.3. Other Reactions

Fuchigami's group has also studied the electrochemical properties of sulfur-containing organoboranes and organotrifluoroborates. The reduction of electrochemical potential between a boronic acid (or ester) and its ate-complex can be used to introduce various nucleophiles including fluorides.[87] In Pd-catalyzed C–H functionalizations, replacing strong chemical oxidants with electrochemical oxidation has enormous potential in streamlining chemical syntheses of complex molecules and, at the same time, provides an opportunity to develop efficient processes. This has been recently reviewed by Mei's group at the Shanghai Institute of Organic Chemistry.[88]

4. Cathodic Reduction

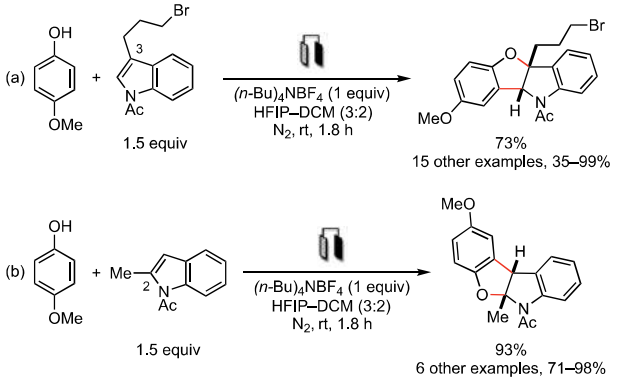
4.1. C–Y Bond Formation

4.1.1. C–C Bond

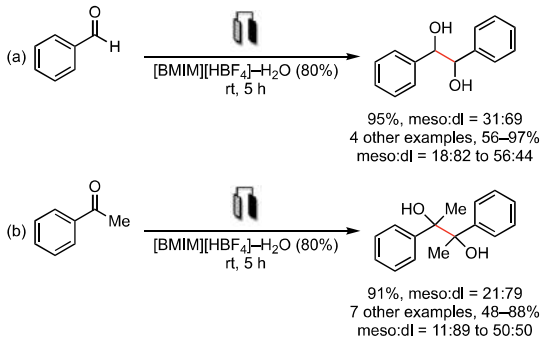
The reductive electrochemical pinacol coupling of ketones and aldehydes has been successfully carried out in an 80% mixture of a room-temperature ionic liquid (RTIL) and water {[BMIM][BF_4]–H_2O}. This scalable process obviates the need for a catalyst–cocatalyst system, avoids the generation of metallic and salt byproducts, and simplifies the product separation and purification steps. Moreover, the electrolyte was recycled and reused up to five times without loss of activity. The 1,2-diol products were obtained in high yields and moderate diastereoselectivities (**Scheme 14**).[89] A more recent example of an electroreductive C–H functionalization is the direct arylation of pyrroles with various aromatic halides.[90] This novel C–C bond-forming reaction employs a sacrificial zinc anode and 10 mol % of perylene-3,4,9,10-tetracarboxylic acid diimides (PDIs) as electron-transfer mediators. It readily takes place at room temperature in [EMIM][NTf_2]–DMSO in the absence of metal catalysts or bases, and provides the cross-coupling products (ortho-arylated pyrroles) in moderate-to-good isolated yields.

One of the classical C–C bond forming reactions is the Michael addition. Shono and co-workers noted as early as 1980 that electroreduction of α,β-unsaturated esters or α,β-unsaturated nitriles in the presence of aldehydes or ketones and TMSCl leads directly to γ-lactones or γ-hydroxynitriles in 51–86% yields (**Scheme 15**).[91] A similar approach reported by Kise's group employed aromatic ketones with 1,3-dimethyluracils or coumarins as the activated olefins.[92,93]

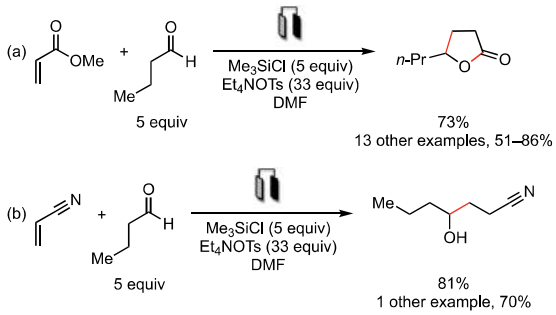
Only recently has the transition-metal catalyzed C(sp^3)–C(sp^3) coupling been explored in the context of electrochemistry. In 2017, Lai and Huang reported the palladium-catalyzed Barbier–Negishi-type allylation of alkyl or benzyl halides in air and in aqueous medium by using a Zn cathode. This novel, ligand-free cross-coupling takes place through the intermediacy of an in situ



Scheme 13. Regioselective, Intermolecular, Electrooxidative [3 + 2] Annulation Leading to Benzofuro[2,3-*b*]indolines and Benzofuro[3,2-*b*]indolines. *(Ref. 83)*



Scheme 14. Electroreductive Pinacol Coupling of Aldehydes and Ketones. *(Ref. 89)*



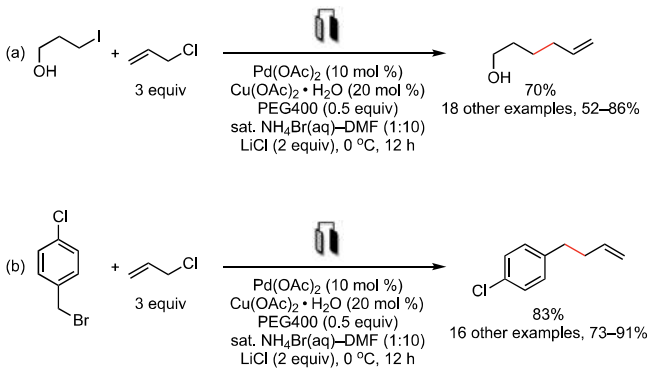
Scheme 15. Electroreductive Coupling of Activated Olefins with Carbonyl Compounds Leading to γ-Lactones or γ-Hydroxynitriles. *(Ref. 91)*

generated alkylzinc reagent, and it complements the traditional reaction employing air-sensitive organometallic reagents and requiring protection–deprotection of acidic hydrogens in the substrates (**Scheme 16**).[94]

The same year, Hansen and co-workers from Pfizer's R&D reported the nickel-catalyzed C(sp^2)–C(sp^3) cross-coupling of electrophilic aryl bromides with electrophilic alkyl bromides using a sacrificial Zn anode and a reticulated vitreous carbon (RVC) cathode. This protocol gave the cross-coupling products in 51% to 86% yields, offered access to a broader substrate scope, and resulted in selectivities that are comparable to, or higher than, those achieved with activated metal powder reductants such as zinc powder.[95]

4.1.2. C–B Bond

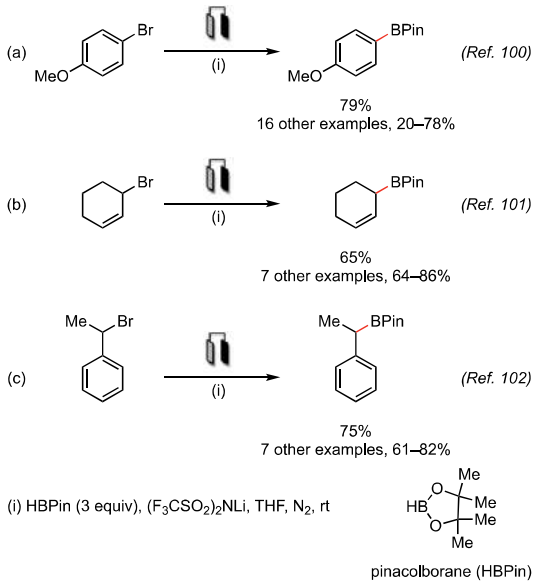
While organoboron compounds such as boronic esters and acids are versatile reactants, as evidenced by their extensive use in industry,[96,97] their industrial-scale preparation remains a challenge. Indeed, classical approaches to arylboron compounds require low temperatures (for the metalation step) or expensive catalysts and reagents (in the case of the Miyaura borylation reaction). To overcome these drawbacks, Duñach and co-workers[98] reported an electrochemical alternative for synthesizing aryl-, heteroaryl-,[99,100] allyl-,[101] and benzylboronic[102] acids and esters (**Scheme 17**). The reactions were performed at room temperature in a single-compartment cell using a consumable magnesium or aluminum anode. Pinacolborane (or trialkylborate) was the electrophilic boron source of choice. The scope ranges from aromatics bearing electron-withdrawing or electron-donating groups to polyhalogenated aryl derivatives.[103] The role of the electrochemical cell is to cause a polarity inversion (umpolung) of the electrophile Ar–X into nucleophile Ar^- and the generation of Mg^{2+} from the sacrificial anode. This combination produces a formal Grignard reagent "ArMgX", which reacts with the electrophilic boron (HBPin) to form an ate-complex and generate the targeted boronic acids after hydrolysis.



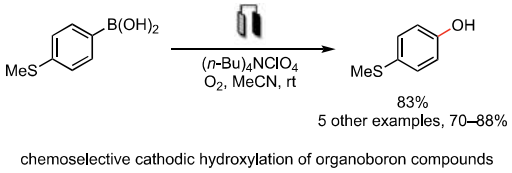
Scheme 16. Palladium-Catalyzed Electrochemical Allylic Alkylation in Air and in Aqueous Medium. *(Ref. 94)*

4.1.3. C–O Bond

The transformation of a C–B bond into a C–O bond can also be achieved by electrochemical means. Indeed, cathodic hydroxylation of organoboron compounds under an O_2 atmosphere leads to the corresponding phenols with high chemoselectivity (**eq 4**).[104] The method could be used in the presence of easily oxidizable functional groups such as a thioether group, and is superior to classical methods that employ H_2O_2 under basic conditions, since, in the latter case, unselective oxidation of both the thioether and the C–B bond takes place. Mechanistically, oxygen undergoes a one-electron reduction at the cathode to generate the superoxide radical anion (O_2•$^-$), which reacts rapidly with the neutral boron atom to form a peroxy radical [ArB(OH)O–O•]. Reduction of the peroxy radical at the cathode or by O_2•$^-$ leads to a three-membered ring intermediate in which the aryl group migrates from boron to oxygen to produce the phenol precursor ArOB(OH)O^-. Hydrolysis of this last species under acidic conditions generates the desired phenol.



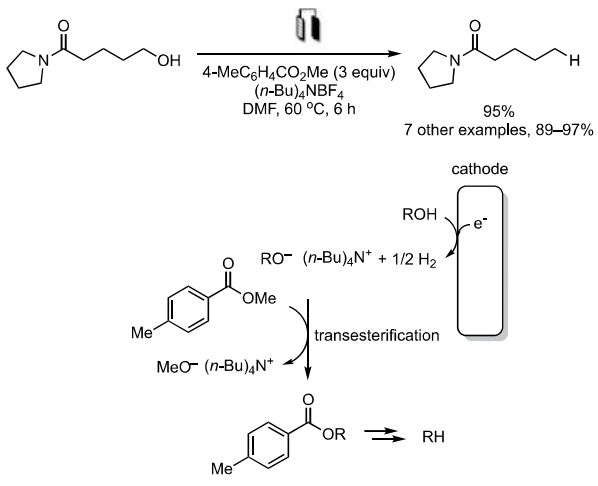
Scheme 17. Electrochemical Synthesis of Aryl-, Allyl-, and Benzyl-boronic Esters.



eq 4 *(Ref. 104)*

4.2. Markó-Lam Reduction

Replacement of a hydroxyl group with hydrogen is an exceedingly useful transformation in organic synthesis. In addition to the Barton–McCombie reaction and to more recent alternatives,[105] Lam and Markó reported a novel and elegant electrochemical method for the deoxygenation of the alcohol moiety in toluate esters.[106] The protocol tolerates the presence of a broad range of functional groups, and eliminates the need for metals, toxic co-solvents, and unstable xanthates all of which are employed in traditional alcohol deoxygenations. This efficient and economical method provided the corresponding deoxygenated products in good yields in the case of secondary and tertiary toluates and moderate yields in the case of primary ones. In the proposed mechanism, the reaction is initiated by reduction of the ester starting material to the corresponding radical anion [$ArCO^{\bullet-}$–OR], which decomposes to give a benzoate anion ($ArCO_2^-$) and an alkyl radical ($R^\bullet$). The alkyl radical is then rapidly captured to give the corresponding alkanes.[107] The authors also reported that addition of a protic source to the reaction mixture quenches the radical anion [$ArCO^{\bullet-}$–OR] and generates a hemiketal [ArCHOH–OR] that leads to alcohols $ArCH_2OH$ and ROH. These observations demonstrated that toluate esters can be useful protecting groups for alcohols and that their electrochemical deprotection is highly chemoselective and efficient.[108] Furthermore, the authors described a new, scalable, and one-pot process for the direct conversion of primary alcohols into the corresponding alkanes without prior esterification by using an excess of methyl toluate. The significant advantage of this protocol is that it leads to uniformly high yields, tolerates a wide variety of functional and protecting groups, and is a greener and less expensive alternative to classical deoxygenation methods (**Scheme 18**).[109] The same authors have also reported that diphenylphosphinates can be used as alternatives to toluate esters in this electrochemical transformation.[110]



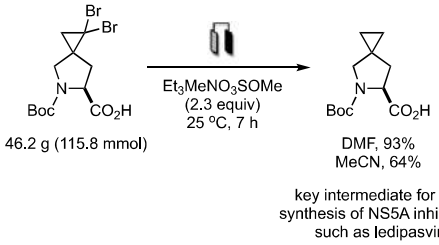
Scheme 18. Lam and Markó's New, Scalable, and One-Pot Process for the Direct Conversion of Primary Alcohols into the Corresponding Alkanes without Prior Esterification. *(Ref. 109)*

4.3. Dehalogenation

In 2015, Waldvogel's group, in collaboration with a team from Novartis, described a cathodic debromination of 1,1-dibromocyclopropane under batch and flow conditions.[111,112] This type of reaction provides efficient access to the cyclopropane ring of a key intermediate for the synthesis of the NS5A inhibitor ledipasvir (used in the treatment of hepatitis C infection). The authors highlighted the crucial role of the solvent used in the electrolyte in the formation of monodebrominated or didebrominated compound. Indeed, switching from MeCN to DMF and decreasing the proton concentration afforded the didebrominated cyclopropane in 93% yield (**eq 5**). Compared to classical, purely chemical methods, the electrochemical dehalogenation is sustainable and exhibits higher selectivity and better yields. The application of this method on a gram scale both in batch-type electrochemical cell and in a continuous-flow gap cell clearly demonstrates the promising potential of organic electrochemistry in the synthesis of key pharmaceutical intermediates.

4.4. Cyclopropane Synthesis

The cyclopropane moiety is an essential building block in medicinal chemistry,[113,114] and, consequently, efforts have been undertaken to explore further the electrosynthesis of cyclopropanes. Although, there are few examples of anodic cyclopropane synthesis, there are many examples of cathodic cyclopropane formation.[115] Several of the reports on the direct electrochemical synthesis of cyclopropanes can be classified into four types of reaction (**Scheme 19**): (i) Cyclization of 1,3-dihalogens or 1,3-dimethanesulfonates,[116] (ii) [2 + 1] cycloaddition with electrogenerated carbene (electrochemical version of the Simmons–Smith reaction),[117] (iii) Michael addition of halogenobenzylphosphonate anion to an alkene followed by ring closure,[118] and (iv) the electrochemical version of the Perkin reaction.[119] The cyclopropane can also be formed indirectly by electrogeneration of the conjugate base of a C–H acid at the cathode and electrogeneration of I_2 from a catalytic amount of KI at the anode. Reaction of the base with I_2 leads to an α-iodoketone intermediate, which undergoes deprotonation and intramolecular S_N2 reaction to yield the cyclopropanated compound under very mild conditions.[120]



eq 5 *(Ref. 112)*

4.5. Electrogenerated Bases

4.5.1. β-Lactam Synthesis

As mentioned previously, it is possible to generate a base by electrolysis of compounds containing an acidic proton. Such an electrogenerated base can engage in a number of reactions. In 2005, Feroci's group disclosed a high-yield, electrochemical synthesis of β-lactams from bromoamides through C–N bond formation.[121] A year later, the same laboratory extended this approach to substrates bearing an acidic proton such as amido esters to access β-lactams by C–C bond formation instead of C–N bond formation (**Scheme 20**). Of the solvents tested, MeCN proved to be the solvent of choice for the generation of a solvent-derived strong base that is capable of deprotonating the C–H bond of the substrate and thus initiating the first step of the overall process.[122]

4.5.2. C–N Bond Formation

Building on the results with the electrochemically generated acetonitrile anion discussed in Section 4.5.1, Feroci and co-workers developed a similar protocol for the alkylation of *N*-Boc-protected 4-aminopyridines. A mixture of the substrate, electrolyte, and acetonitrile was electrolyzed and then treated with various alkyl and benzyl halides (**Scheme 21**). Again, the acetonitrile anion was sufficiently strong to abstract the N–H proton of the 4-aminopyridine. Some of the resulting N-alkylated 4-aminopyridines exhibited antifungal and antiprotozoal activity.[123]

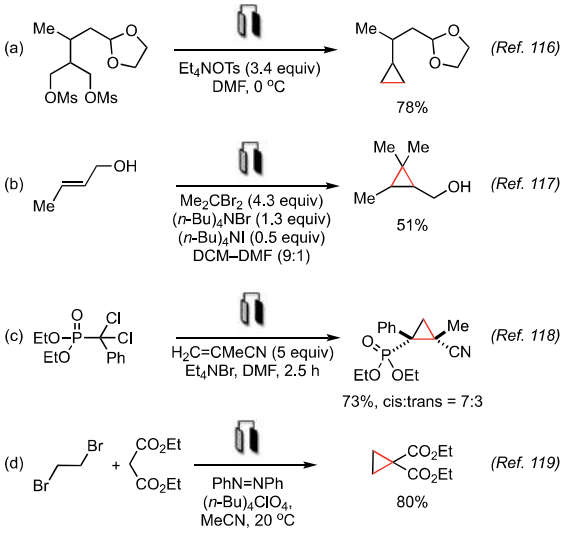
4.5.3. C–C Bond Formation

Arcadi's group has reported another application of the electrochemically generated cyanomethide ion. In this versatile and mild protocol, alkynes containing proximate malonyl functional groups undergo intramolecular cyclization to afford functionalized butenolides, quinolones, and 3-pyrrolin-2-ones in good-to-excellent yields, obviating the need for transition-metal catalysts and bases.[124]

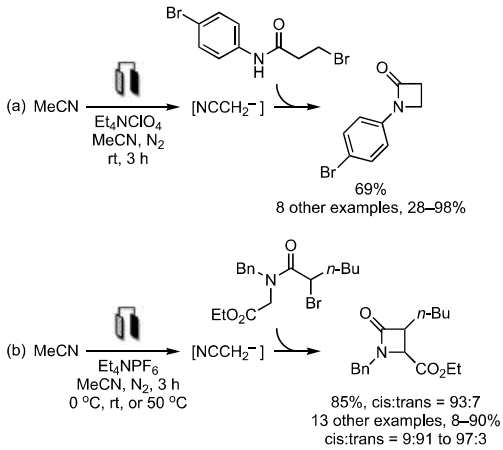
It is worth mentioning in this context that, when the product of an electrochemical C–C bond-forming reaction bears another acidic proton, it could engage in further bond-forming reactions, which would open the door to electrochemically induced tandem and sequential reactions. For instance, Massa, Palombi, and co-workers have shown that addition of malonate or malonitrile anions to cyanobenzaldehydes leads to isoindolinones,[125] which could be functionalized further by Michael reaction with acrylates (**Scheme 22**). By now, it is quite apparent that MeCN is a versatile precursor of strong base under electrolysis conditions. Nevertheless, EtOH, MeOH, and NHCs derived from ionic liquids can also serve as valuable precursors of bases, as has been demonstrated by various research groups.[120,126–128]

5. Paired Electrosynthesis

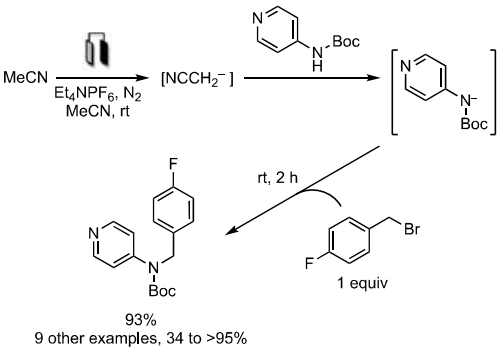
In many electrochemical syntheses, the expected product is generated at one electrode, while the reaction at the other



Scheme 19. Examples of Cathodic Cyclopropane Synthesis.



Scheme 20. Synthesis of β-Lactams by C–N or C–C Bond Formation through a Process Initiated by an Electrogenerated Strong Base [$NCCH_2^-$]. *(Ref. 121,122)*



Scheme 21. Application of the Electrogenerated Strong Base Protocol to the Alkylation of *N*-Boc-protected 4-Aminopyridines. *(Ref. 123)*

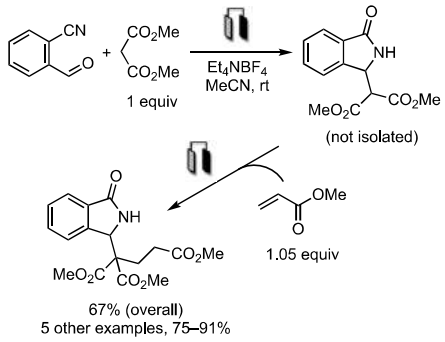
electrode ensures electroneutrality. Paired electrosynthesis takes advantage of the two simultaneous reactions to generate a product. It can be classified into four types of reaction mode: (i) parallel, (ii) convergent, (iii) linear, and (iv) divergent.[129] In terms of sustainability, the pairing of electrode processes is the best way to reduce energy consumption.

In 2016, Kubiak, Moeller, and co-workers reported an elegant parallel paired electrosynthesis in a divided cell that could serve as a model for the sustainable production of fine chemicals in a closed system that does not use sacrificial redox reagents (**Scheme 23**).[130] Production of a "privileged" benzimidazole building block took place in the anode compartment by oxidative condensation of syringaldehyde (derived from the lignin in sawdust) with 1,2-diaminobenzene mediated by ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$]. The paired half-reaction in the cathode compartment consisted of the reduction of CO_2 to CO (which is a valuable starting material) facilitated by Re(bipytBu)$(CO)_3$Cl.

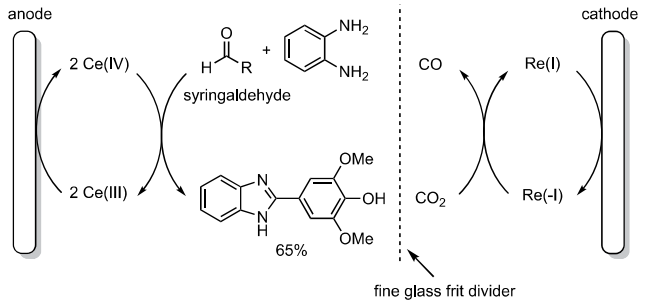
Senboku's group has described the carboxylation of benzylic halides by using a convergent paired electrosynthesis (**Scheme 24**).[131] It is the first report of this type of reaction that does not employ a sacrificial electrode. Reduction of the C(sp^3)–Br bond at the cathode generates a benzylic anion which is trapped by CO_2 to form the corresponding carboxylate anion. At the anode, DMF is oxidized in the presence of (i-Pr)$_2$NEt to an N-acyliminium ion, which reacts with the carboxylate anion to form the final product.

In 2015, Hartmer and Waldvogel reported a linear, paired electrosynthesis for the dehydration of aldoximes into the corresponding nitriles under mild conditions without the need for halogens. Anode oxidation of the aldoxime leads to a nitrile oxide intermediate, which then deoxygenates at the cathode to produce the nitrile final product.[132] It is noteworthy that the efficiency of this step is highly dependent on the nature of the electrode employed.

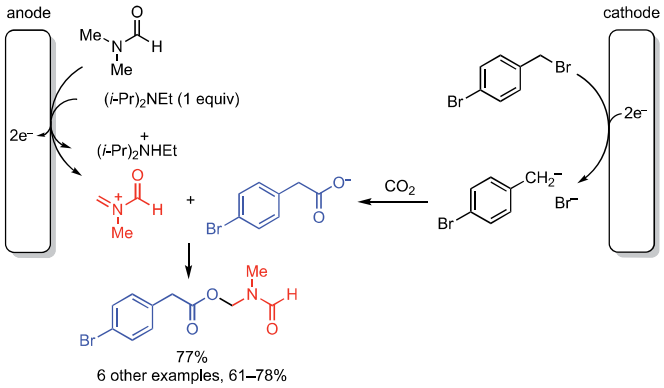
An example of "double" linear paired electrolysis was reported by Baran's group and collaborators from Pfizer's Global R&D and Asymchem Labs.[133] The authors described a nickel(II)-catalyzed, base-free electrochemical amination of aryl halides with alkyl amines. This reaction takes advantage of the ability of nickel to react with less reactive electrophiles and the fact that different oxidation states of the nickel can be accessed by electrochemical means. In particular, high-valent nickel is prone



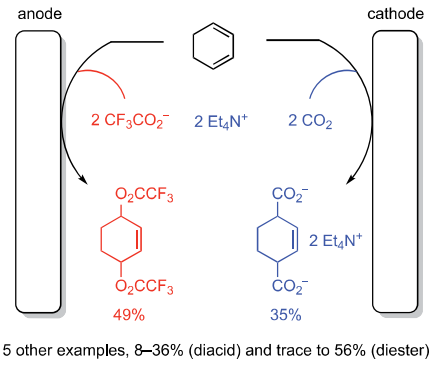
Scheme 22. Electrochemically Initiated, One-Pot Sequential Reactions Leading to Functionalized Isoindolinones. *(Ref. 125)*



Scheme 23. Parallel, Paired Electrosynthesis Produces a "Privileged" Benzimidazole Derivative at the Anode and Reduces CO_2 to the More Valuable CO at the Cathode. *(Ref. 130)*



Scheme 24. Three-Component-Coupling Products of Benzyl Halides, CO_2, and DMF via a Convergent Paired Electrosynthesis. *(Ref. 131)*



Scheme 25. Divergent, Paired Electrosynthesis of α,β-Unsaturated Diacids and Protected Allylic Diols. *(Ref. 134)*

to reductive elimination. The reaction scope included a large number of aryl donors (Ar–X; X = Cl, Br, I, OTf) and amines (primary and secondary).

A novel and divergent paired electrosynthesis of α,β-unsaturated di(trifluoroacetate esters) (as diol precursors) and dicarboxylate salts has been reported by De Vos and co-workers (**Scheme 25**).[134] The synthesis starts with conjugated dienes, which react with CO_2 at the cathode to generate the dicarboxylate salt. Simultaneously, the dienes react at the anode with tetraethylammonium trifluoroacetate to form the trifluoroacetate-protected allylic 1,4-diols. Good-to-excellent yields are obtained, and the use of an inert and stable non-sacrificial graphite anode makes this process a promising one for implementation in continuous-flow systems. However, a high substrate dependence—both with respect to alkyl substitution and molecular configuration—was found, which makes it difficult to extend this approach to other conjugated dienes.

6. Conclusion and Outlook

The field of electrochemistry is experiencing such a spectacular revival that it is on the verge of being used by non-specialists, whether in academia or in industry. Electrochemistry is developing new variations of old reactions and, more importantly, is creating new reactivity pathways. Perhaps more exciting is the fact that much remains to be discovered in this field. In the twentieth century, the complexity of reaction setups and lack of universal tools and methodologies slowed down considerably the development of electrochemistry as an enabling technique. Such tools and methodologies are currently being developed by some of the best scientists around the globe, and it is our hope that others will invest in these efforts to ultimately invent better chemistry. As Maslow put it, "I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail.":[135] electrochemistry has the potential of becoming a key asset of the chemist tool box. It is our sincere hope that the examples showcased in this review do provide the reader with a glimpse of the practical applications of this vibrant field of research.

7. Acknowledgment

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8. References

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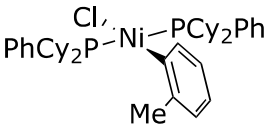

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