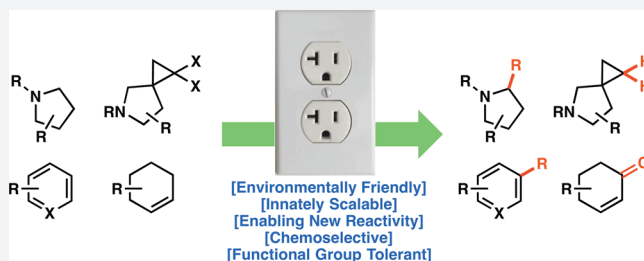


Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method

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ABSTRACT: While preparative electrolysis of organic molecules has been an active area of research over the past century, modern synthetic chemists have generally been reluctant to adopt this technology. In fact, electrochemical methods possess many benefits over traditional reagent-based transformations, such as high functional group tolerance, mild conditions, and innate scalability and sustainability. In this Outlook we highlight illustrative examples of electrochemical reactions in the context of the synthesis of complex molecules, showcasing the intrinsic benefits of electrochemical reactions versus traditional reagent-based approaches. Our hope is that this field will soon see widespread adoption in the synthetic community.



INTRODUCTION

The field of synthetic organic chemistry is under constant and extreme selection pressure. It is challenged not only to create ever-increasingly complex molecules but also to do so in a timely, atom-economic, and sustainable fashion.^{1–3} Due in part to these external stimuli, classic technologies such as photochemistry⁴ and electrochemistry^{5–9} have reemerged, providing tools that enable chemists to do more with less. As early as the late 19th century, preparative electrolysis began to be used as an industrial process to prepare bulk chemicals on ton-scale. Classic examples include the chloralkali process,¹⁰ wherein aqueous sodium chloride is electrolyzed to give chlorine gas and sodium hydroxide, and the Hall–Héroult process,¹¹ which provides elemental aluminum by electrolysis of Al₂O₃. These profoundly enabling uses of electrochemistry persist to this day, producing millions of metric tons of these valuable chemicals. Yet, examples of electrochemistry for use in organic synthesis and the fine chemicals industry remain scarce. This is perplexing given the fact that this technique generally features relatively mild conditions, good functional group tolerance, and high chemoselectivity. Furthermore, the ease with which many electrochemical reactions can be scaled up, as well as the intrinsic “greenness” of the reactions (because electric current is used in place of stoichiometric oxidants or reductants), make this chemistry attractive in a process chemistry setting. It is, in fact, an innately practical technique.

Those advantages notwithstanding, practicing organic chemists have generally been reluctant to adopt this technology into their own laboratories. In our experience, electrochemistry is widely feared by practicing organic chemists due to the perceived complex reaction setup (potentiostat, divided/undivided cell, electrode composition, experiment type, etc.), the seemingly endless number of reaction variables (electrolyte, electrode composition, cell type, etc.), and the common misconception that only aqueous solvents may be employed

and that product separation is difficult. The barrier to adoption becomes higher when one discovers that a “standard” instrument for preparative electrolysis does not exist, and many of the recent elegant literature examples utilize home-built rather than commercially available equipment. This daunting situation certainly discouraged us from exploring electrochemical transformations—indeed it was the difficulty in accessing the dimeric natural product dixiamycin B (**1**, Figure 1) that brought us to embrace the technology.¹²

The most simple retrosynthetic analysis of **1** triggered an N–N bond-forming reaction to couple two xiamycin monomers (**2**). Despite extensive screening, no reagent-based oxidant was capable of forging the necessary N–N bond. It was only after these exhaustive evaluations that we began to consider the possibility of utilizing an electrochemical oxidation for this key dehydrodimerization step. A literature search revealed studies from Ambrose and co-workers on the reactivity of carbazolium radical cations.¹³ By substantially modifying the reaction conditions, we found that treating carbazole **2** under a constant potential of 1.15 V vs Ag/AgCl using graphite rod electrodes in a tetraalkylammonium electrolytic solution of 19:1 DMF/MeOH led to formation of dixiamycin B (**1**) in 28%. The ability to “dial-in” the oxidative strength of the reaction and accomplish what no chemical reagent could was, to us, a convincing demonstration of the power of electrochemistry in organic synthesis, particularly in complex settings that require exquisite chemoselectivity.

It is the goal of this Outlook to allay the aforementioned fears by presenting a forward-looking perspective of electrochemical transformations specifically in complex settings. Although our entry into this area was guided by necessity, we hope that electrochemistry will soon become a routinely

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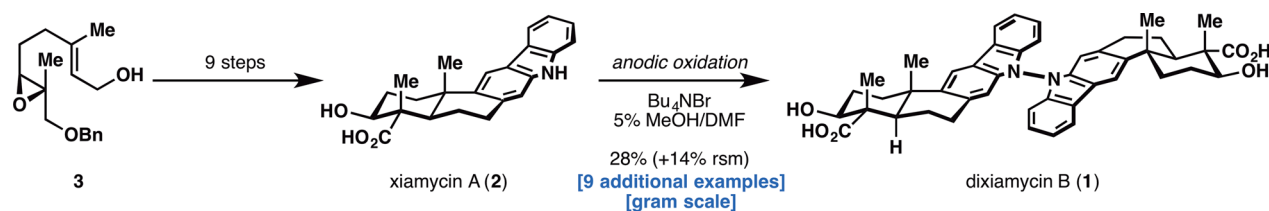


Figure 1. Synthesis of dixiamycin B by Baran and co-workers.

employed technique in modern organic chemistry laboratories in order to simplify and enable synthetic pathways.

ELECTROCHEMISTRY VIGNETTES IN SYNTHESIS

Though reports of electrochemical transformations in the synthesis of complex molecules are scarce, there are nonetheless several applications illustrative of its complexity-generating power. An early example is the application of a Kolbe decarboxylative dimerization in Corey's 1958 synthesis (Figure 2) of pentacyclosqualene (6), α -onoceradiene (not shown), and

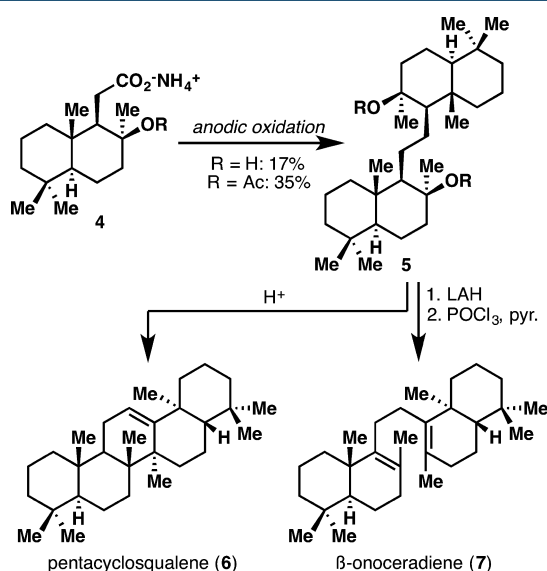


Figure 2. Synthesis of pentacyclosqualene and β -onoceradiene by Corey and co-workers using Kolbe electrolysis.

β -onoceradiene (7).¹⁴ Subjecting the ammonium carboxylate salt 4, which was prepared in three steps from sclareolide, to electrolysis at high current density in refluxing methanol resulted in decarboxylation followed by radical dimerization to yield 5 in 17% (R = H) or 34% (R = Ac) yield. Subsequent treatment of the diol with perchloric acid resulted in cyclization to pentacyclosqualene (6), while elimination using POCl_3 in pyridine led to β -onoceradiene (7). It is particularly noteworthy that, even today, the invention of reagents to accomplish this type of Csp^3 – Csp^3 coupling is still the subject of ongoing research in many groups.¹⁵

As early as the late 19th century, preparative electrolysis began to be used as an industrial process to prepare bulk chemicals on ton-scale.

Some of the most substantial advancements in electrochemical oxidative coupling reactions of the past 20 years have been developed by the Moeller^{16–33} and Wright^{34–39} groups. In this way, anodic oxidation has been shown to enable the coupling of two nucleophilic functional groups, thereby leading to new broadly useful umpolung disconnections. An elegant example of this is Moeller's synthesis of alliacol A (8, Figure 3),^{28,33} whereby the enoxysilane and furan nucleophiles present

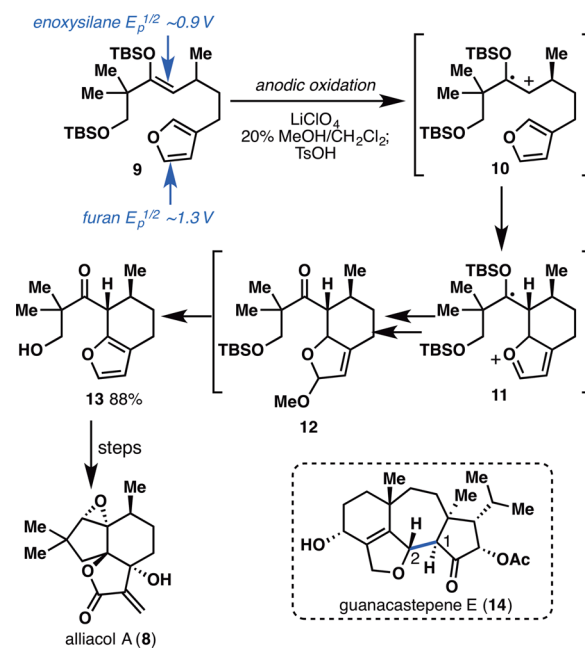


Figure 3. Moeller's synthesis of alliacol A via an intermolecular anodic coupling.

in 9 can be coupled together under electrochemical conditions. This reaction proceeds via selective oxidation of the enoxysilane to give radical cation intermediate 10, which undergoes cyclization by attack of the furan to provide the radical oxonium ion 11. Subsequent single electron oxidation at the anode, trapping of the resulting carbocation with methanol, and elimination with TsOH provides furan 13 in 88% yield. At first glance, it may not be clear what the origins of this remarkable selectivity would be. Since oxidation of the functional group with the lowest oxidation potential takes place first, the enoxysilane ($E_p^{1/2} \sim 0.9 \text{ V}$ vs Ag/AgCl) is predictably and selectively oxidized in the presence of a furan ($E_p^{1/2} \sim 1.3 \text{ V}$ vs Ag/AgCl). The oxidation potentials of the individual functional groups in a molecule can be easily approximated by analyzing a cyclic voltammogram of a simple model substrate that contains only the functional group in question. As evidenced by the conversion of 9 to 13, a unique advantage of electrochemistry is the selectivity and tunability of the reaction based on the redox potentials of the functional groups present in the molecule. It is

therefore trivial to sequence anodic coupling reactions (and many other electrochemical transformations) since, unlike reagent-based oxidants, the selectivity of the oxidation can be known at the outset and precise control of the potential can be essentially “dialed-in”. In addition, these reactions are tolerant to a wide array of functional groups, as long as the oxidation potential of the group is higher than that of the group that is to be oxidized. The power of this particular transformation has been recognized on numerous occasions, arguably most impressively in Trauner’s synthesis of guanacastepene E (14),⁴⁰ where stereoselective formation of the C1–C2 bond is accomplished using a similar anodic oxidative coupling.

Extensive studies in the synthesis of complex terpenes by us and others led to the realization that no practical, sustainable method for allylic C–H oxidation existed.

The scalable synthesis of DZ-2384 (15) by Harran and co-workers further enumerates the remarkable functional group compatibility of many electrochemical reaction conditions (Figure 4).⁴¹ DZ-2384, a diazomide-inspired preclinical candidate for oncology, was recently prepared using an intramolecular electrochemical oxidative coupling of 16 between the phenol and indole motifs to give macrocycle 17. Previously, this transformation was accomplished on similar substrates using oxidants such as $\text{PhI}(\text{OAc})_2$;⁴² unfortunately, this reagent-based system also led to considerable byproduct formation, such that this reaction became the most problematic bottleneck in material throughput, hampering access to desperately needed material for downstream studies. The electrochemical conditions for accomplishing this transformation were a marked improvement in terms of selectivity, as well as lower cost and environmental footprint, enabling the reaction to be easily carried out on 60 g of indole substrate 16. It is clear from the successful execution of this transformation that electrochemical reactions can solve not only problems with respect to reactivity but practical challenges in the context of scale-up and process chemistry.

A striking testament to the utility of electrochemistry in an industrial process setting stems from a recent collaboration between the Waldvogel group and Novartis involving the electrochemical reduction of a geminal dihalide (Figure 5).^{43,44} In this case, reduction of dibromocyclopropane 18 to cyclopropane 19, an important intermediate for HCV NSSA inhibitors, was accomplished in a separated cell using a leaded bronze cathode and $[\text{Et}_3\text{NMe}]\text{O}_3\text{SOMe}$ as supporting electrolyte. This method ameliorated several problems that plagued

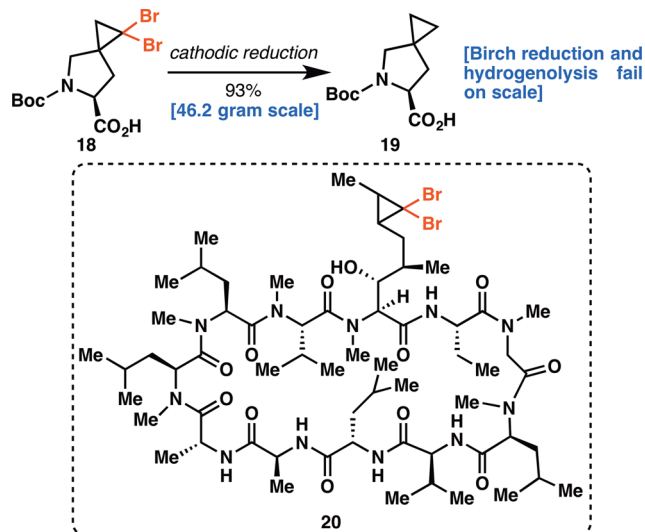


Figure 5. Synthesis of NSSA inhibitor intermediate and reduction of cyclosporin A analogue by Waldvogel and co-workers.

alternative routes to 19 including ring-opened products and racemization. Equally important from a process chemistry perspective, the electrochemical method also proved to be significantly more cost-efficient and resulted in considerably less waste generation, making this a “green” process. Highlighting the functional group tolerance of this transformation in a complex setting, the reaction conditions were also applied to the reduction of cyclosporin A analogue 20 to give the reduced product in 98% yield.

Extensive studies in the synthesis of complex terpenes by us and others led to the realization that no practical, sustainable method for allylic C–H oxidation existed. This fact, combined with the knowledge that an ongoing project at Bristol-Myers Squibb (BMS) required such an oxidation, inspired a collaborative exploration into the use of electrochemistry as a potential solution (Figure 6).⁴⁵ While this type of transformation can be readily accomplished through a variety of reagent-based systems (e.g., chromium, palladium, rhodium, ruthenium, etc.), most of these systems are unsuitable in an industrial process setting due to toxicity or cost associated with these reagents. Conditions developed in our laboratory employ an *N*-hydroxyphthalimide catalyst that undergoes anodic oxidation to a highly reactive oxygen-centered radical and engages a substrate through selective allylic C–H atom abstraction. Using this protocol, more than a dozen natural product scaffolds were selectively oxidized, as exemplified by the 100 g scale oxidation of dehydroepiandrosterone derivative 21 to the corresponding enone 22 (performed by Asymchem Life Sciences literally in a bucket). To verify the improved

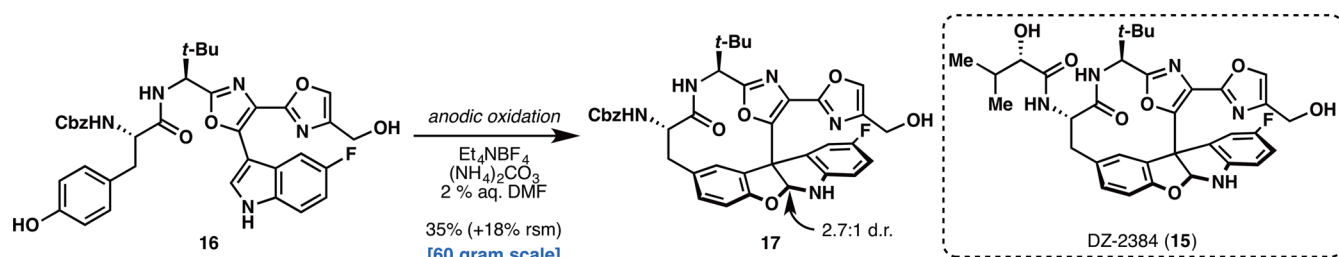


Figure 4. Synthesis of diazomide-inspired drug development candidate DZ-2384 by Harran and co-workers.

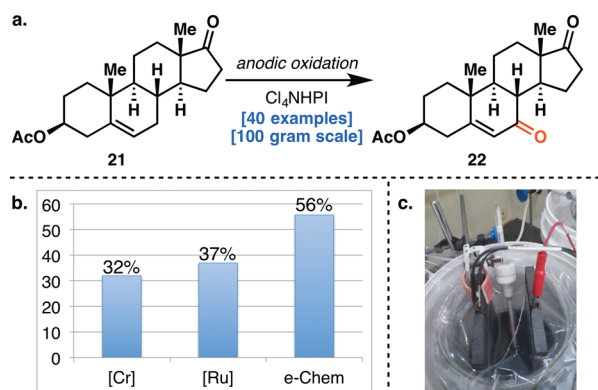


Figure 6. (a) Electrochemical allylic oxidation by Baran and co-workers. (b) Process greenness score (PGS) for Cr, Ru, and electrochemistry. (c) 100 g scale allylic oxidation conducted in a bucket. Panels b and c reprinted with permission from ref 45. Copyright 2016 Nature Publishing Group.

environmental footprint and efficiency of this reaction, the conditions for the conversion of 21 to 22 were compared against commonly employed Cr-promoted and Ru-catalyzed methods in the literature, the latter of which was developed by Schering process chemists. Using the Process Greenness Score (PGS), a metric used at BMS to evaluate greenness of a process, the electrochemical method was found to be a nearly 50% improvement over the previously mentioned methods.

Selective arene C–H functionalization has seen considerable interest throughout the synthetic community over the past several years,^{46–54} in large part due to demands in the context of drug discovery. In particular, the ability to functionalize arenes in a selective and predictable fashion in the presence of multiple other functional groups has immediate applications toward the diversification of late stage drug intermediates. A noteworthy example of addressing this challenge has been recently reported by Yoshida and co-workers to accomplish arene C–H amination in a stunning series of reports (Figure 7).^{55–57} Electrolysis of electron-rich arenes in the presence of

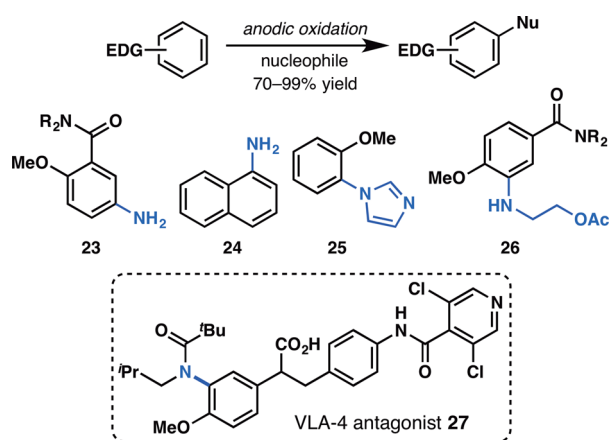


Figure 7. Electrochemical arene amination by Yoshida.

electron-deficient nitrogen heterocycles (e.g., pyridine, *N*-methanesulfonylimidazole, etc.) leads to selective oxidation of the arene to an electrophilic radical cation and trapping by the heterocycle to forge a new C–N bond. Further treatment of the crude reaction mixture under mild conditions provides one of several nitrogen-functionalized arenes, including anilines (e.g.,

23 and 24), heterocycles (25), and secondary *N*-aryl amines (26). The ability to rapidly, selectively, and predictably conduct this C–H amination reaction led to an improved synthesis of a key intermediate in the synthesis of VLA-4 antagonist 27, dramatically reducing the overall step count and increasing the overall yield.

Radical-based C–H functionalization methods using sulfinate-reagents have emerged as a useful means to modify both simple and complex heterocycles in a medically relevant way.^{58–63} Although this technique utilizes TBHP, a cheap industrial oxidant, the superstoichiometric quantities required can be a deterrent for large-scale applications. In addition, certain types of heterocycles gave consistently lower yields of functionalized product. In collaboration with the Blackmond group, anodic oxidation of sulfinate salts enabled an increase in the yield of the process and eliminated the use of a chemical oxidant altogether (Figure 8).⁶⁴ Furthermore, anodic oxidation

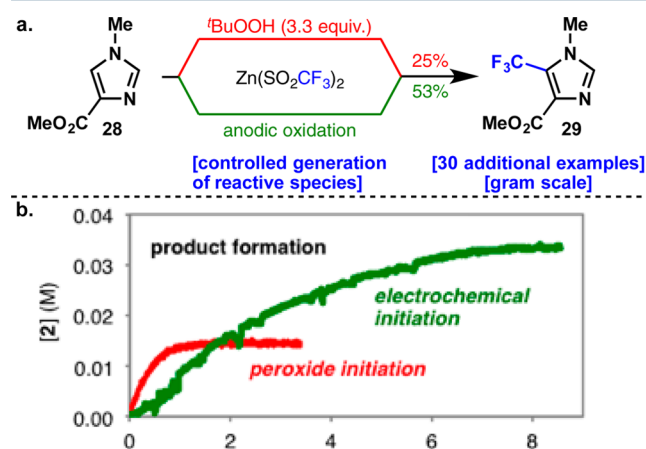


Figure 8. (a) Electrochemical fluoroalkylation of heterocycles by Baran and Blackmond and co-workers. (b) Formation of 29 using *t*-BuOOH and electrochemical protocols. Reprinted with permission from ref 64. Copyright 2014 WILEY-VCH Verlag GmbH & Co. KGaA.

allowed for precise control over the rate of radical formation, slowing the decomposition of the sulfinate salt and dramatically improving the overall reaction.

Finally, we believe that for electrochemistry to really take off in all areas of synthetic organic chemistry, more standardized and simplified instrumentation needs to be developed specifically for this community.

It is evident from the above examples that anodic oxidations and cathodic reductions are enabling tools for the construction of natural products and small molecule medicines. Nonetheless, concerns about the practical aspects of the reaction setup still act as a barrier to entry for many practicing bench chemists. The assumption that specialized equipment is required to try electrochemical experiments could not, in fact, be further from reality. Recently, Aubé and Moeller have demonstrated a remarkably practical setup to promote the C–H oxidation of

complex polycyclic lactams such as **30** utilizing a repurposed cell phone charger as the power supply, and #7 mechanical pencil lead as electrodes (Figure 9).⁶⁵ The methoxy amide

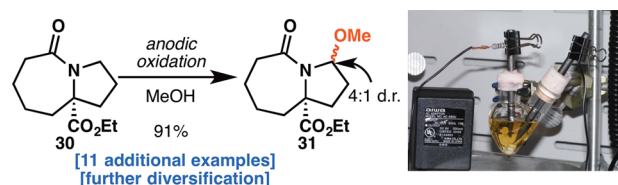


Figure 9. Synthesis of functionalized polycyclic lactams by Aubé and co-workers using a repurposed mobile phone charger. Reprinted with permission from ref 65. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA.

products such as **31** can be further diversified to a variety of useful functionalized products. This elegant, readily accessible experimental setup should serve to lower the barrier to entry for chemists contemplating using organoelectrochemistry, since no specialized equipment (potentiostat or unusual electrodes) is needed. In a similar vein, Moeller previously demonstrated that many electrochemical transformations, including that shown in Figure 3, can be carried out using a 6 V lantern battery, easily obtained from any neighborhood hardware store, as an even simpler power supply.³³ Obviously, these simple configurations are not without limitations, because potential and current are not as easily controlled; however, because these setups are so accessible, we hope this information will encourage the average synthetic chemist to incorporate electrochemical transformations into their synthetic toolkit.

SUMMARY AND FUTURE DIRECTIONS

This outlook is not meant to be an exhaustive review of this ever-expanding field but rather a brief introduction to the area that will inspire others to try electrochemical reactions or use

the platform to invent new transformations. For those interested in learning more, several extensive reviews and monographs have been published in this area.³ In addition, Figure 10 showcases a number of exciting contributions that are representative of the vibrant and creative directions that are being explored using electrochemistry.

The examples outlined herein represent only a tip of the iceberg in terms of the types of major problems that electrochemistry can solve. As sustainability becomes a prime directive for organic synthesis, one could argue that there should be no reason to use superstoichiometric reagents to accomplish simple redox manipulations of functional groups (e.g., alcohol to ketone or ester to alcohol) when the same transformations can be efficiently achieved using electrochemistry. The unique tunability and chemoselectivity of electrochemistry holds great potential for reaction invention in areas such as C–H functionalization, catalysis, and total synthesis. Finally, we believe that for electrochemistry to really take off in all areas of synthetic organic chemistry, more standardized and simplified instrumentation needs to be developed specifically for this community. Although it is great that certain reactions can be run using crude, homemade equipment such as a lantern battery or a cell phone charger, this can lead to reproducibility concerns (battery type, electrode material, etc.). Furthermore, the lack of “out of the box”, standardized equipment for preparative electrolysis certainly discourages widespread adoption of this technique.

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Notes

The authors declare no competing financial interest.

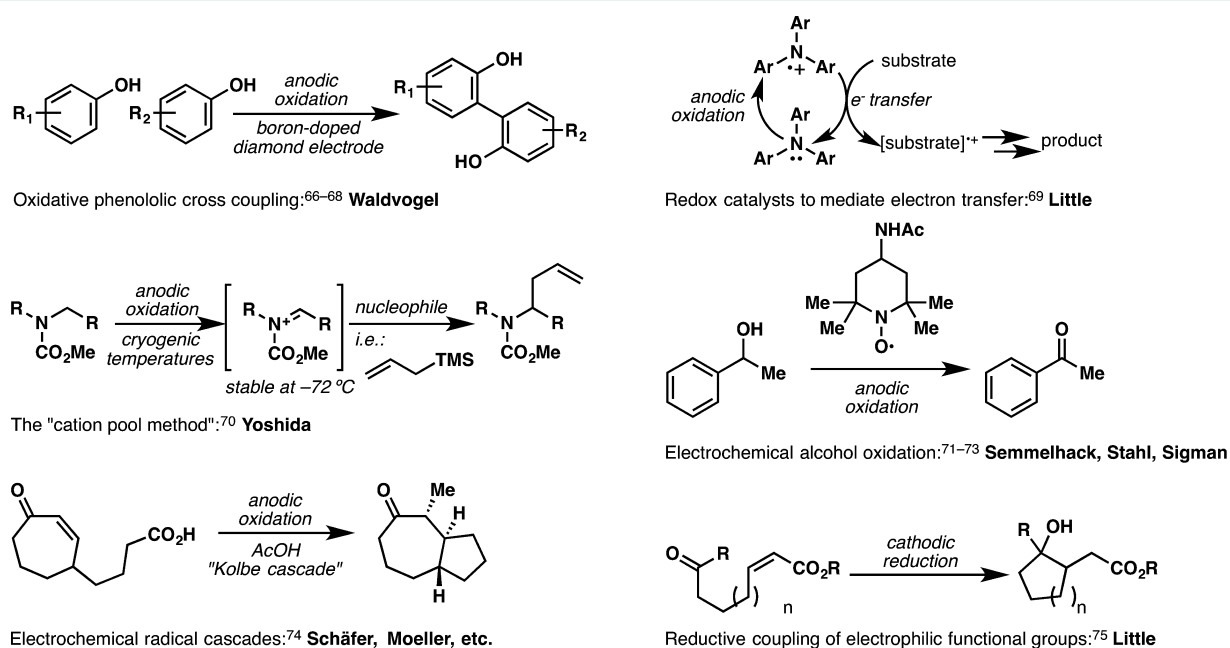


Figure 10. Suggested topics for further reading. Reprinted with permission from refs 66–75. Copyright 2002, 2010, and 2014 WILEY-VCH Verlag GmbH & Co. KGaA. Copyright 1983, 2012, and 2015 American Chemical Society. Copyright 2014 Royal Society of Chemistry. Copyright 1988 Elsevier B.V. Copyright 1996 Springer.

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