ACCOUNTS of chemical research

Article

Cite This: Acc. Chem. Res. 2020, 53, 72−83

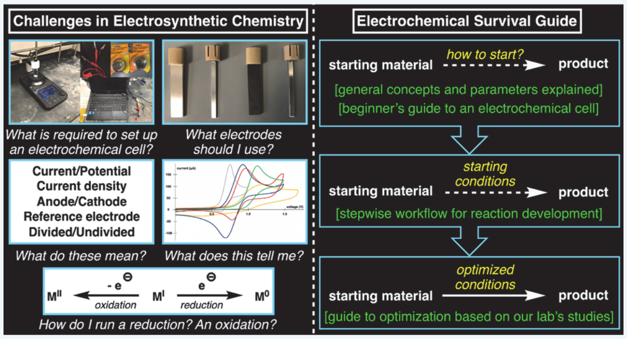
pubs.acs.org/accounts

A Survival Guide for the "Electro-curious"

Published as part of the Accounts of Chemical Research special issue "Electrifying Synthesis".

Cian Kingston, Maximilian D. Palkowitz, Yusuke Takahira, Julien C. Vantourout, Byron K. Peters, Yu Kawamata, and Phil S. Baran*

Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, California 93037, United States



CONSPECTUS: The appeal and promise of synthetic organic electrochemistry have been appreciated over the past century. In terms of redox chemistry, which is frequently encountered when forging new bonds, it is difficult to conceive of a more economical way to add or remove electrons than electrochemistry. Indeed, many of the largest industrial synthetic chemical processes are achieved in a practical way using electrons as a reagent. Why then, after so many years of the documented benefits of electrochemistry, is it not more widely embraced by mainstream practitioners? Erroneous perceptions that electrochemistry is a "black box" combined with a lack of intuitive and inexpensive standardized equipment likely contributed to this stagnation in interest within the synthetic organic community. This barrier to entry is magnified by the fact that many redox processes can already be accomplished using simple chemical reagents even if they are less atom-economic. Time has proven that sustainability and economics are not strong enough driving forces for the adoption of electrochemical techniques within the broader community. Indeed, like many synthetic organic chemists that have dabbled in this age-old technique, our first foray into this area was not by choice but rather through sheer necessity.

The unique reactivity benefits of this old redox-modulating technique must therefore be highlighted and leveraged in order to draw organic chemists into the field. Enabling new bonds to be forged with higher levels of chemo- and regioselectivity will likely accomplish this goal. In doing so, it is envisioned that widespread adoption of electrochemistry will go beyond supplanting unsustainable reagents in mundane redox reactions to the development of exciting reactivity paradigms that enable heretofore unimagined retrosynthetic pathways. Whereas the rigorous physical organic chemical principles of electroorganic synthesis have been reviewed elsewhere, it is often the case that such summaries leave out the pragmatic aspects of designing, optimizing, and scaling up preparative electrochemical reactions. Taken together, the task of setting up an electrochemical reaction, much less inventing a new one, can be vexing for even seasoned organic chemists. This Account therefore features a unique format that focuses on addressing this exact issue within the context of our own studies. The graphically rich presentation style pinpoints basic concepts, typical challenges, and key insights for those "electro-curious" chemists who seek to rapidly explore the power of electrochemistry in their research.

■ INTRODUCTION

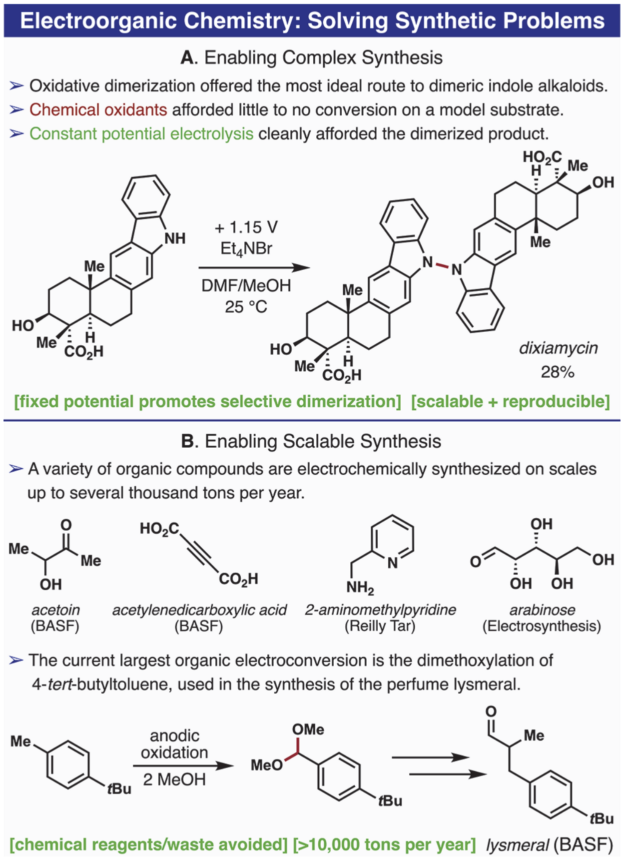
During the total synthesis of the bis-carbazole containing marine-derived natural product dixiamycin (Figure 1A), all attempts to dimerize the monomeric precursor were fruitless using chemical reagents.[1] After much trepidation, cyclic voltammetry (CV, see Figure 3 and discussion below) revealed that a specific potential could be "dialed-in" to achieve the desired dimerization; outside of that potential window either decomposition or no reaction was observed. This project was the inspiration for our involvement in the field of electrochemistry from both the vantage point of reaction and equipment design.[2−7] Although this synthesis was conducted on the milligram scale,[8] synthetic organic electrochemistry is traditionally performed on process scales ranging from kilograms to thousands of metric tons (Figure 1B).[9,10] For instance, lysmeral, one of the most widespread fragrant molecules, is produced at BASF through a double anodic oxidation of 4-*tert*-butyl toluene on >10,000 ton per year scale.[11] In stark contrast, the use of synthetic organic electrochemistry in the pharmaceutical and agrochemical industry is rare.

Beginning Synthetic Organic Electrochemistry: The Basics

The most frequent request we have received from "electro-curious" organic chemists is for a rapidly absorbable guide to understand the basics and begin setting up experiments.[12−14] This section seeks to serve that purpose, such that a chemist having no foreknowledge of the area could begin forays into electrochemistry with only this information as a launching point. Four basic features of an electrochemical reaction

Received: October 14, 2019
Published: December 11, 2019

DOI: 10.1021/acs.accounts.9b00539
Acc. Chem. Res. 2020, 53, 72−83



Electroorganic Chemistry: Solving Synthetic Problems

A. Enabling Complex Synthesis

- ➢ Oxidative dimerization offered the most ideal route to dimeric indole alkaloids.
- ➢ Chemical oxidants afforded little to no conversion on a model substrate.
- ➢ Constant potential electrolysis cleanly afforded the dimerized product.

B. Enabling Scalable Synthesis

- ➢ A variety of organic compounds are electrochemically synthesized on scales up to several thousand tons per year.

- ➢ The current largest organic electroconversion is the dimethoxylation of 4-*tert*-butyltoluene, used in the synthesis of the perfume lysmeral.

Figure 1. Electrochemistry enables (A) complex synthesis and (B) scalable synthesis.

differentiate it from a canonical organic reaction (Figure 2A). First, a typical electrochemical cell has a power source (i.e., battery, potentiostat) connected to three electrodes (the "anode", "cathode", and "reference"). (+)X/(−)Y is often used to denote the anodic (X) and cathodic (Y) materials. Second, the concept of potential (often described as voltage) explains the driving force behind the redox processes that take place. The power source pushes electrons into the cathode from the anode, resulting in a reductive environment at the cathode and an oxidative environment at the anode. Typically, the power source connected to the electrochemical cell controls potential between the "working electrode" and the reference electrode. "Working" refers to the electrode where the reaction of interest takes place, while the other electrode is called the "counter electrode". Note that either the anode or cathode could be denoted as the "working electrode". When the reference electrode is not used, the voltage difference between the anode and the cathode will be controlled by a power source. Third, the concept of current refers to the rate of electron movement, which facilitates redox processes and is inextricably linked to potential. Finally, the reactants or electrocatalysts (Figure 3) in solution undergo a heterogeneous interaction with either the anode (by donating electrons and getting oxidized) or the cathode (by accepting electrons and getting reduced). Both oxidative and reductive processes must occur. In essence, the reaction medium acts as a part of the circuit through which charged species pass.

Before describing how the unique variables of an electrochemical cell are considered and deployed in actual electrosynthesis (Figure 3), it is useful to take a high-level look into each of its constituents (Figure 2B). The external power source can come in a variety of forms, and in the literature one often encounters constant current (galvanostatic condition) and constant potential (potentiostatic condition) experiments conducted with galvanostats or potentiostats, respectively. In the modern era, commercial power sources for electrosynthesis can perform both modes of electrolysis (Figure 3) and are colloquially referred to as potentiostats. Another major component of the electrochemical cell is the electrodes, which can vary in terms of their constitution, surface area, and reusability (e.g., a sacrificial anode[15] may be partially consumed during a reaction). As electron transfer takes place on the surface of the electrodes, the choice of material can have a significant impact on the outcome of a reaction. When a fixed potential is required a third "reference" electrode should be incorporated. The reference electrode is not essential for preparative constant potential experiments, but it is necessary in cases when an accurate and specific potential is required (including CV). Like any electrical circuit, increasing conductivity/reducing resistance is essential; in an electrochemical reaction, the solvent and electrolyte largely dictate these variables. The most commonly employed solvents are therefore polar aprotic with a capacity to dissolve electrolyte, substrate, and reactants. The presence of a charged species in solution is necessary to maintain the charge neutrality of the cell. Thus, electrolyte additives (charged species) are usually employed and can even play a key role in the reaction through modification of the electrode surface. Ammonium and alkali metal-based salts are among the most commonly employed electrolytes.[16] One of the key challenges for the field of synthetic organic electrochemistry was the nonstandardized nature of available equipment options, including the myriad of homemade electrochemical cells that permeate the literature (Figure 2C). This issue has been addressed by a number of researchers,[2,17−19] including a collaboration between our laboratory and IKA with the launch of ElectraSyn 2.0, an inexpensive device for synthetic electrochemistry designed to remove the time required to procure parts and engineer individual setups.[20,21] Since variabilities in electrode source and current density can lead to reproducibility problems, this standardized device is lowering the barrier to adoption of electrochemistry in both academic and industrial laboratories around the world. In certain reactions, it may be desirable for a species formed at one electrode not to react at another. In these cases, an alternative set up referred to as a "divided cell" can be employed, where the electrodes are located in two chambers separated by a permeable membrane or a frit (Figure 2D). Such setups are often more complicated (due to the separative membranes and inherently higher resistance), and thus for most applications, the use of an undivided cell is preferred. The implementation of electrochemical reactions relies on their ability to be scaled-up. In recent years, several groups have developed electrochemical flow setups that overcome the inherent challenges of mass transfer, rate, and stability of electrode materials to enable large scale transformations.[22,23]

A guide to conceptualizing and optimizing electrochemical reaction parameters is illustrated in Figure 3. The process commences with a consideration of electrode potential as the driving force and the redox regime of the transformation in question (Figure 3A). The electrode potential describes the strength of the oxidative/reductive conditions, analogous to

DOI: 10.1021/acs.accounts.9b00539
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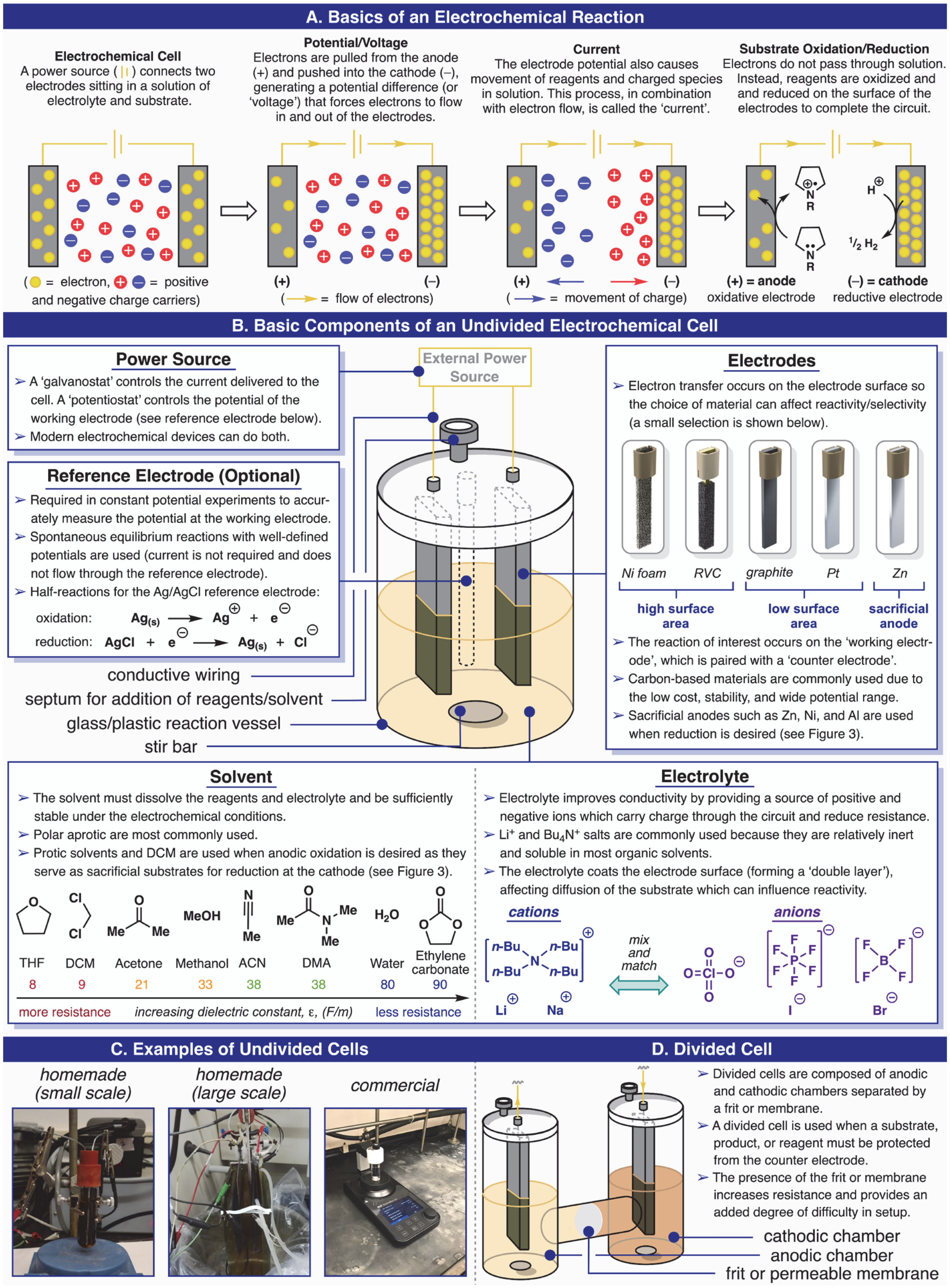


A. Basics of an Electrochemical Reaction

Electrochemical Cell
A power source ( ) connects two electrodes sitting in a solution of electrolyte and substrate.

Potential/Voltage
Electrons are pulled from the anode (+) and pushed into the cathode (−), generating a potential difference (or 'voltage') that forces electrons to flow in and out of the electrodes.

Current
The electrode potential also causes movement of reagents and charged species in solution. This process, in combination with electron flow, is called the 'current'.

Substrate Oxidation/Reduction
Electrons do not pass through solution. Instead, reagents are oxidized and and reduced on the surface of the electrodes to complete the circuit.

B. Basic Components of an Undivided Electrochemical Cell

Power Source
- A 'galvanostat' controls the current delivered to the cell. A 'potentiostat' controls the potential of the working electrode (see reference electrode below).
- Modern electrochemical devices can do both.

Reference Electrode (Optional)
- Required in constant potential experiments to accurately measure the potential at the working electrode.
- Spontaneous equilibrium reactions with well-defined potentials are used (current is not required and does not flow through the reference electrode).
- Half-reactions for the Ag/AgCl reference electrode:

oxidation: $Ag_{(s)} \longrightarrow Ag^{\oplus} + e^{\ominus}$

reduction: $AgCl + e^{\ominus} \longrightarrow Ag_{(s)} + Cl^{\ominus}$

Electrodes
- Electron transfer occurs on the electrode surface so the choice of material can affect reactivity/selectivity (a small selection is shown below).

- The reaction of interest occurs on the 'working electrode', which is paired with a 'counter electrode'.
- Carbon-based materials are commonly used due to the low cost, stability, and wide potential range.
- Sacrificial anodes such as Zn, Ni, and Al are used when reduction is desired (see Figure 3).

Solvent
- The solvent must dissolve the reagents and electrolyte and be sufficiently stable under the electrochemical conditions.
- Polar aprotic are most commonly used.
- Protic solvents and DCM are used when anodic oxidation is desired as they serve as sacrificial substrates for reduction at the cathode (see Figure 3).

Electrolyte
- Electrolyte improves conductivity by providing a source of positive and negative ions which carry charge through the circuit and reduce resistance.
- Li^{+} and Bu_4N^{+} salts are commonly used because they are relatively inert and soluble in most organic solvents.
- The electrolyte coats the electrode surface (forming a 'double layer'), affecting diffusion of the substrate which can influence reactivity.

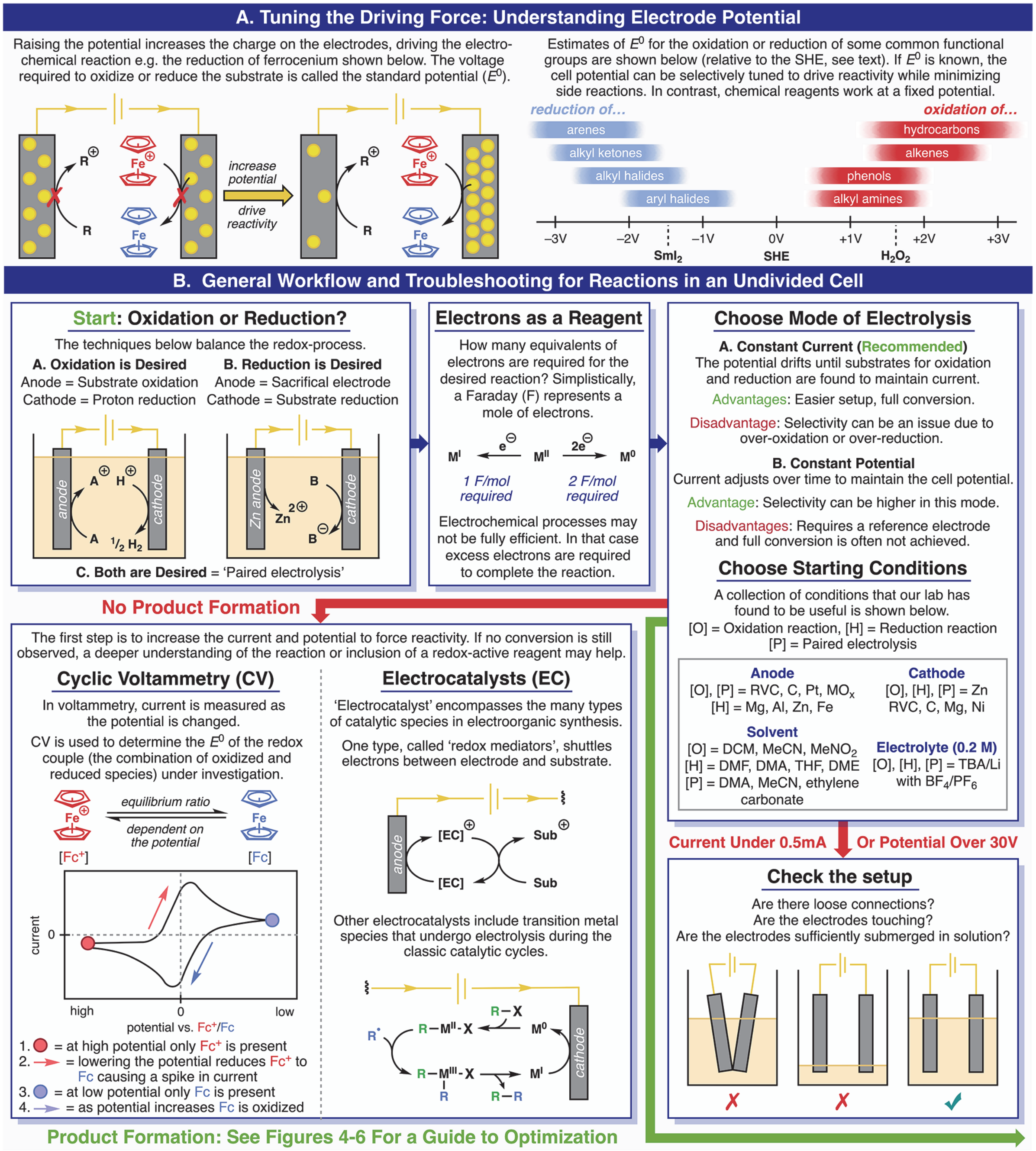
C. Examples of Undivided Cells

D. Divided Cell
- Divided cells are composed of anodic and cathodic chambers separated by a frit or membrane.
- A divided cell is used when a substrate, product, or reagent must be protected from the counter electrode.
- The presence of the frit or membrane increases resistance and provides an added degree of difficulty in setup.

Figure 2. (A) Basic features of an electrochemical reaction. (B) An overview of the undivided electrochemical cell. (C) Various undivided cells. (D) The divided cell.

the strength of oxidant or reductant one would commonly employ in a purely chemical transformation. In this regard, knowing the typical electrode potentials required for redox reactions involving standard functional groups (e.g., oxidation of amines, reduction of ketones) is a good way to match chemical intuition to electrochemical reactivity. The reduction of protons to form hydrogen gas at a platinum electrode, known as the standard hydrogen electrode (SHE), is used as reference point set to 0 V.

A simple flow-chart can be used to aid in the choice of variables at the outset of a synthetic organic electrochemical exploration (Figure 3B). For practical considerations, this guide is focused on the use of an undivided electrochemical cell. First, both oxidation and reduction reactions occur at the



A. Tuning the Driving Force: Understanding Electrode Potential

Raising the potential increases the charge on the electrodes, driving the electrochemical reaction e.g. the reduction of ferrocenium shown below. The voltage required to oxidize or reduce the substrate is called the standard potential (E^0).

Estimates of E^0 for the oxidation or reduction of some common functional groups are shown below (relative to the SHE, see text). If E^0 is known, the cell potential can be selectively tuned to drive reactivity while minimizing side reactions. In contrast, chemical reagents work at a fixed potential.

B. General Workflow and Troubleshooting for Reactions in an Undivided Cell

Start: Oxidation or Reduction?

The techniques below balance the redox-process.

A. Oxidation is Desired
Anode = Substrate oxidation
Cathode = Proton reduction

B. Reduction is Desired
Anode = Sacrifical electrode
Cathode = Substrate reduction

C. Both are Desired = 'Paired electrolysis'

Electrons as a Reagent

How many equivalents of electrons are required for the desired reaction? Simplistically, a Faraday (F) represents a mole of electrons.

Electrochemical processes may not be fully efficient. In that case excess electrons are required to complete the reaction.

Choose Mode of Electrolysis

A. Constant Current (Recommended)
The potential drifts until substrates for oxidation and reduction are found to maintain current.
Advantages: Easier setup, full conversion.
Disadvantage: Selectivity can be an issue due to over-oxidation or over-reduction.

B. Constant Potential
Current adjusts over time to maintain the cell potential.
Advantage: Selectivity can be higher in this mode.
Disadvantages: Requires a reference electrode and full conversion is often not achieved.

Choose Starting Conditions

A collection of conditions that our lab has found to be useful is shown below.
[O] = Oxidation reaction, [H] = Reduction reaction
[P] = Paired electrolysis

Anode
[O], [P] = RVC, C, Pt, MO_x
[H] = Mg, Al, Zn, Fe

Cathode
[O], [H], [P] = Zn
RVC, C, Mg, Ni

Solvent
[O] = DCM, MeCN, $MeNO_2$
[H] = DMF, DMA, THF, DME
[P] = DMA, MeCN, ethylene carbonate

Electrolyte (0.2 M)
[O], [H], [P] = TBA/Li with BF_4/PF_6

No Product Formation

The first step is to increase the current and potential to force reactivity. If no conversion is still observed, a deeper understanding of the reaction or inclusion of a redox-active reagent may help.

Cyclic Voltammetry (CV)

In voltammetry, current is measured as the potential is changed.

CV is used to determine the E^0 of the redox couple (the combination of oxidized and reduced species) under investigation.

1. ● = at high potential only Fc^+ is present
2. → = lowering the potential reduces Fc^+ to Fc causing a spike in current
3. ● = at low potential only Fc is present
4. → = as potential increases Fc is oxidized

Electrocatalysts (EC)

'Electrocatalyst' encompasses the many types of catalytic species in electroorganic synthesis.

One type, called 'redox mediators', shuttles electrons between electrode and substrate.

Other electrocatalysts include transition metal species that undergo electrolysis during the classic catalytic cycles.

Current Under 0.5mA Or Potential Over 30V

Check the setup

Are there loose connections?
Are the electrodes touching?
Are the electrodes sufficiently submerged in solution?

Product Formation: See Figures 4-6 For a Guide to Optimization

Figure 3. (A) Understanding potential as a driving force. (B) A guide to developing an electrochemical reaction using an undivided cell.

anode and cathode, respectively, and thus both elementary processes need to be considered to balance the electrochemical equation. If an oxidative (anodic) reaction is desired, then a proton donor is often employed to satiate the reductive (cathodic) process (thereby liberating H_2). On the other hand, cathodic processes often use what is known as sacrificial metal anodes that are themselves oxidized (liberating the corresponding metal cation) instead of any substrate in solution. Paired electrolysis refers to cases where both oxidation and reduction are desired. In a standard chemical reaction, reagent stoichiometry is one of the first variables to consider. Similarly, in an electrochemical reaction one should consider how many equivalents of electrons are desired. The Faraday (F) is the unit by which electrons are measured (one Faraday is simplistically equal to a mole of electrons), and depending on the type of reaction, the practitioner may need catalytic quantities (for example, the initiation of a radical chain process), equimolar quantities, or excess (when the efficiency with which electrons are used in the electrochemical reaction, commonly known as "Faradaic" or "current" efficiency, is low). In practice, for reactions where one or more electrons per substrate are required, the reaction can simply be monitored for conversion after each equivalent of electrons is added. Faradaic efficiency is a general metric of success for electrochemical experiments, especially for the comparison of two sets of electrochemical conditions. However, as practicing

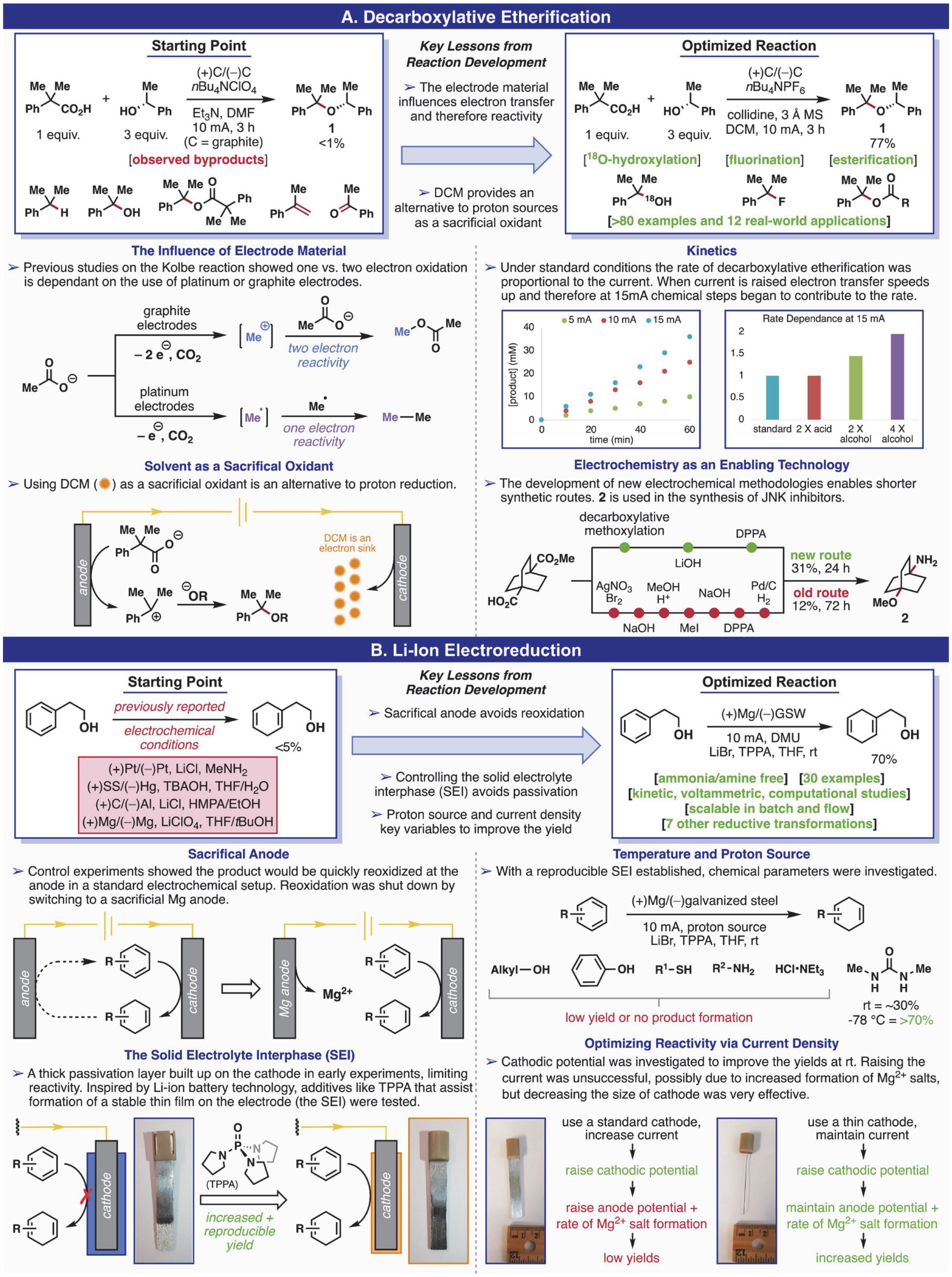


Figure 4. Case studies in canonical oxidative and reductive electrochemistry: (A) decarboxylative etherification and (B) Li-ion electroreduction.

organic chemists, the most relevant comparison is normally between the electrochemical approach and the corresponding chemical reagent. Thus, the yield of the reaction is the primary metric of success (unless the Faradaic efficiency is vanishingly small). During the course of the investigations described below (Figures 4–6) differences in Faradaic efficiencies between substrates were found to be relatively small and therefore inconsequential to the success of the transformation. Determining the quantity of electrons added to a system can either be done through elementary calculation or dialed-in on the potentiostat itself.

$$\text{time (s)} = nF/I$$

where n = theoretical moles of electrons required, F = Faraday constant = 96,485 coulombs/mol, and I = current applied in amperes.

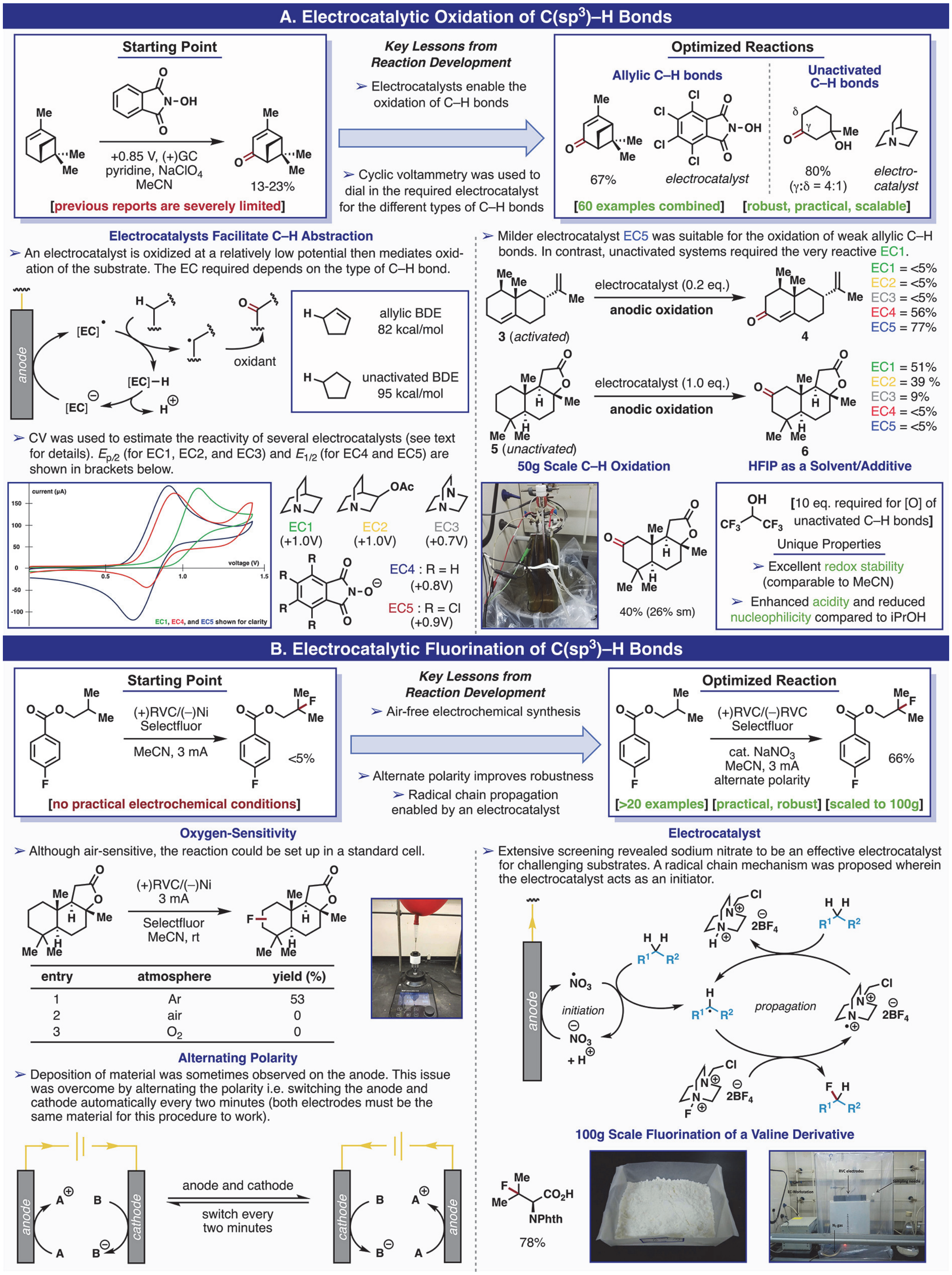
Next, with a specific redox strategy in place (oxidative, reductive, or paired), the mode of electrolysis can be selected. The most convenient electrolysis mode to begin with uses constant current, which benefits from a simpler setup and higher conversions as the potential gradually increases until all redox-active species are consumed. The trade-off here is one of selectivity as undesired redox-processes can be encountered at higher conversion. When a lack of selectivity leading to low isolated yield is an issue, switching to constant potential mode makes sense. However, for accuracy this will require a reference electrode (Figure 2B) and full conversion is often not achieved due to the decreasing concentration of redox-active species, which lowers the current over time. The choice of electrodes, solvent, and electrolyte can often be a cause for consternation among newcomers to the area. A useful set of go-to choices are therefore listed to aid in selection based on the type of redox reaction. If abnormally large potential or low current is observed in first trials be sure that the setup is free of technical blunders such as loose connections or electrodes that are either in contact or insufficiently submerged in solution. The next round of troubleshooting would involve simply increasing the current and potential until a redox event occurs. If these tips do not work then turning to CV will aid in understanding the underlying redox events.[24−26] CV essentially diagnoses the feasibility of the redox event; for example, one may find that the desired transformation takes place outside of the potential range accommodated by the solvent (called the "solvent potential window"). In such a case, it can be worth considering the addition of an electrocatalyst that can be oxidized or reduced within the solvent window and subsequently interacts with the substrate. Generally, an electrocatalyst can either act as a simple shuttle for electrons, traversing from the heterogeneous electrode surface to homogeneous contact with the substrate (also known as a redox mediator),[27−31] or be incorporated into catalytic cycles wherein access to reduced or oxidized states of transition metals can enable bond formation.[32−39]

After initiating the reaction and observing product, how does one go about optimizing an electrochemical reaction? The following case studies (Figures 4−6) provide contextualized insight from our group's experience over the past few years spanning the spectrum of oxidative, reductive, and paired processes.

Canonical Oxidative and Reductive Electrochemistry

Hindered Ether Synthesis through Oxidatively Electrogenerated Carbocations. The Kolbe electrolysis, the earliest synthetic organic electrochemical transformation first performed by Faraday,[40] accomplishes the decarboxylative formation of radical species.[41−43] In certain cases, those radicals, formed at the surface of the anode, can be further oxidized to carbocations in what is often referred to as an "interrupted" Kolbe reaction. The Hofer−Moest (H-M) reaction, a variant of this reactivity known for over a century, has been used to make ethers by capture of those carbocations with an alcohol solvent.[44] Unlike the Kolbe, the H-M reaction remained underutilized due to the requirement of solvent quantity of an alcohol and demonstrably limited scope. This powerful transformation would potentially find mainstream use if the scope were extended to ether linkages not attainable by the venerable Williamson ether synthesis, specifically hindered and complex systems. Such structures are widespread in the literature and still require laborious routes for preparation.

Figure 4A outlines how the challenge of extending the scope of the H-M reaction was addressed. Optimization commenced with ether **1** as the target, and under precedented H-M conditions (except using 3.0 equiv of alcohol donor), only trace product was observed accompanied by multiple by-products.[45] Graphite electrodes were initially selected as they have been typically employed in the H-M reaction. Indeed, selectivity for radical versus carbocation formation via electrochemical oxidative decarboxylation is known to be dependent on the anode material. In general, platinum and nonporous carbon favor single electron oxidation (radical) products, whereas graphite promotes the removal of a second electron to generate a carbocation. The discrepancy in reactivity between these two materials may be due to the difference in current density at the anode surface, which results in differing concentrations of radical species.[42] The reactivity difference between platinum and graphite has also been attributed to increased attraction of the radical species to the graphite electrode due to its greater paramagnetic nature, thereby promoting oxidation of the second electron.[46] Solvent quantities of alcohol are required in classic H-M reactions for three main reasons: (i) the alcohol acts as a proton source to facilitate cathodic H_2 evolution, (ii) the alkoxides formed from H_2 liberation act as electrolyte, and (iii) high concentrations of the alcohol nucleophile were presumably required to trap the carbocation and form the ether product. Consequently, reducing the amount of alcohol to synthetically useful levels (1−3 equiv) poses several challenges, especially since competing alcohol oxidation is also observed. In addition, certain substrates suffer from inefficient nucleophilic attack to the carbocation, resulting in side reactions such as elimination and hydration. These issues were addressed by combining chemical intuition with electrochemical mechanistic analysis. First, the selection of base was crucial as under the highly oxidizing conditions Et_3N and related bases were rapidly consumed. Pyridine analogs such as collidine, which are difficult to oxidize and more sterically encumbered, provided the first hit, increasing the yield from <1% to reliably observable quantities (5−10%). Among the numerous solvents screened, DCM, a solvent rarely employed in electrosynthesis due to its low dielectric constant (Figure 2B), emerged as an unusually effective choice. CV revealed that DCM could be easily reduced under the reaction conditions, serving the role of an efficient sacrificial oxidant (a silver salt was also occasionally employed). It also suppressed undesired elimination of the carbocation intermediate, presumably due to enhanced alcohol nucleophilicity. Competing hydration was relatively easy to solve by the addition of molecular sieves. Finally, kinetic analysis was employed to further understand the reaction, revealing that under standard conditions the current dictates the rate of the reaction (the behavior is typical of reactions involving heterogeneous electron transfer). However, when the current was raised sufficiently high (15 mA), a positive order was observed for concentration of alcohol indicating nucleophilic addition to be the chemical rate-determining step. These findings were found to be particularly useful to simplify access to a myriad of known hindered ethers, as illustrated by the dramatically shortened synthesis of ether **2**. The electrogenerated carbocations could



Key Lessons from Reaction Development

- Electrocatalysts enable the oxidation of C–H bonds
- Cyclic voltammetry was used to dial in the required electrocatalyst for the different types of C–H bonds

Electrocatalysts Facilitate C–H Abstraction

- An electrocatalyst is oxidized at a relatively low potential then mediates oxidation of the substrate. The EC required depends on the type of C–H bond.
- Milder electrocatalyst EC5 was suitable for the oxidation of weak allylic C–H bonds. In contrast, unactivated systems required the very reactive EC1.
- CV was used to estimate the reactivity of several electrocatalysts (see text for details). $E_{p/2}$ (for EC1, EC2, and EC3) and $E_{1/2}$ (for EC4 and EC5) are shown in brackets below.

Unique Properties

- Excellent redox stability (comparable to MeCN)
- Enhanced acidity and reduced nucleophilicity compared to iPrOH

Key Lessons from Reaction Development

- Air-free electrochemical synthesis
- Alternate polarity improves robustness
- Radical chain propagation enabled by an electrocatalyst

Oxygen-Sensitivity

- Although air-sensitive, the reaction could be set up in a standard cell.

entry	atmosphere	yield (%)
1	Ar	53
2	air	0
3	O_2	0

Electrocatalyst

- Extensive screening revealed sodium nitrate to be an effective electrocatalyst for challenging substrates. A radical chain mechanism was proposed wherein the electrocatalyst acts as an initiator.

Alternating Polarity

- Deposition of material was sometimes observed on the anode. This issue was overcome by alternating the polarity i.e. switching the anode and cathode automatically every two minutes (both electrodes must be the same material for this procedure to work).

Figure 5. Case studies in electrocatalysis: (A) oxidation and (B) fluorination of C(sp^3)−H bonds.

also be intercepted with other nucleophiles such as water, fluoride, nitriles, or benzoic acids.

Deeply Reducing Electrochemistry: Birch-type Reductions Made Simple. Despite the many reports and variants of electrochemical Birch reductions spanning nearly a century, few appealed to safety and scalability, and none to sustainability.[47−51] More problematic was the low reproducibility of this literature in standardized, commercially available electrochemical devices and the near absence of demonstrable chemoselectivity. Motivated by the incredible utility of the

DOI: 10.1021/acs.accounts.9b00539
Acc. Chem. Res. 2020, 53, 72−83

Birch reduction, the development of a robust, general, and sustainable electrochemical version was pursued (Figure 4B).[52] Li-based electrolytes and THF as solvent were chosen for initial screening due to their reductive stability. As is good practice in any electrochemical venture, product stability is very important and should be determined even using very generic conditions, which can be ascertained using the principles outlined above (Figures 2 and 3). Thus, the authentic 1,4-diene product was tested and found to easily rearomatize with nonsacrificial anodes. Hence, with a few experiments, Al and Mg were identified as suitable sacrificial anodes along with a Zn-based cathode (chosen based on literature precedent). Under these conditions, however, almost no Birch product was observed for a variety of arenes tested. Instead, the buildup of a thick layer of solids around the cathode was observed, which was accompanied by high cell resistance. This is known as a solid electrolyte interphase (SEI) layer, a common feature in Li-ion battery technology.[53] Fortunately, there was a large volume of literature on additives that have been used to chemically engineer the properties of this layer, including the thickness.[54,55] Upon screening, tris(pyrrolidino)phosphoramide (TPPA) was found to be exceptionally good at tempering the thickness of the SEI and promoting product formation.[56] However, yields were still low, plagued by over-reduced material and isomer formation. At this juncture, chemical intuition rather than any electrochemical knowledge led us to study the effect of the proton source. The outcome of this investigation was that ureas rather than alcohols and other common proton sources provided high selectivity for product formation. Although selectivity was high, the reactions would stall after approximately 30% product formation when run at room temperature. A parameter that had not yet been investigated rigorously was cathodic material. After screening Cu, glassy carbon (GC), and Fe and obtaining similar results, it was apparent that the reaction was insensitive to the cathodic material. However, running the reaction at −78 °C furnished yields in excess of 70%. A higher cell potential was observed at the lower temperature due to increased resistance, which implied that a higher cathodic potential positively influenced product formation. In order to mimic this high cathodic potential at room temperature, the current of the reaction was raised but low yields were still observed. Another way to raise cathodic potential would be to decrease the surface area of the cathode. Current density increases when the current is focused onto a smaller electrode surface, and if there is not a sufficient supply of reactants to absorb the electrons the cathodic potential will also increase. Putting this logic to the test, it was found that cell potential did increase when a thin galvanized steel wire was used for the cathode at room temperature, but more rewarding was the tremendous increase in the yield of the reaction to the point of being competitive to the chemical Birch! We are not entirely certain why merely increasing the current of the reaction did not improve the yields. However, a plausible explanation is that raising the current simultaneously increases the flow of Mg-ions into solution from the sacrificial anode, which were shown to be deleterious through additional experiments.

Electrocatalysis

Oxidative Electrocatalysis: C(sp^3)−H Oxidation. While direct anodic oxidations of C−H bonds are known and can be extremely useful, such as the venerable Shono oxidation,[57,58] they are usually limited to weaker C−H bonds (α-heteroatom) or to simple substrates where chemoselectivity is not a concern (e.g., the synthesis of lysmeral, Figure 1B). As the process chemistry group at BMS encountered difficulty in economically scaling up an allylic C−H oxidation, a collaboration was initiated to determine if electrochemistry could offer a solution (Figure 5A). Since direct anodic oxidation was not an option, the team turned to an electrocatalytic approach. Electrochemical allylic C−H oxidation was originally reported by Masui and co-workers employing *N*-hydroxyphthalimide (NHPI) as an electrocatalyst, in which a reactive *N*-oxyl radical generated upon anodic oxidation cleaves the allylic C−H bond through hydrogen-atom transfer (HAT), resulting in the formation of an enone after capture with air.[59] This valuable precedent served as the starting point for our investigations.[60] Although numerous modifications were made to the conditions (electrolyte, electrode, and solvent) and terminal oxidant (*t*BuOOH) employed, the exploration of new electrocatalysts was found to be the most impactful factor. After extensive investigation, it was found that the tetrachloroderivative of NHPI (TCNHPI) effected a dramatic improvement in yield. The determination of a half-wave potential (commonly denoted as $E_{1/2}$ for a reversible redox event) or a half-peak potential (commonly denoted as $E_{p/2}$ for an irreversible event) via CV is a useful technique to assess the thermodynamics of an electron-transfer event.[61] TCNHPI displayed an increased $E_{1/2}$ over NHPI, and therefore its enhanced performance in the C−H oxidation was attributed to the more electron deficient nature of the *N*-oxyl radical. Encouraged by the success of electrochemical allylic oxidation, attention turned to the more challenging functionalization of unactivated C−H bonds.[62] Using CV to guide the optimization process, $E_{1/2}$ or $E_{p/2}$ was determined for a variety of structures that can produce reactive *O*- or *N*-centered radicals, and quinuclidine was identified as a promising candidate ($E_{p/2}$= +1.0 V vs Ag/AgCl reference electrode, higher than $E_{1/2}$ of +0.9 V for TCNHPI). It should be noted that although $E_{1/2}/E_{p/2}$ was used to guide optimization in this case it does not necessarily correlate with reactivity. Quinuclidine was found to be completely ineffective for methylene C−H oxidation under the allylic oxidation conditions, which used a Li-based electrolyte. Extensive screening of the reaction conditions revealed the critical (and unrecognized at the time) role that an electrolyte can have in such a reaction as simply switching to an ammonium-based electrolyte turned on reactivity that was absent in the presence of Li^+ (the CV studies would not reveal this). This can perhaps be attributed to coordination of Li^+ to quinuclidine, which may alter its redox behavior or reactivity. A second key finding for us was that the addition of a mild acid such as HFIP was crucial for efficient oxidation, as this buffers the basicity of quinuclidine as well as providing electron-accepting protons at the cathode. The dichotomous reactivity of NHPI- and quinuclidine-based electrocatalysts is apparent in complex settings where each serves a uniquely enabling role (see **3** to **4** and **5** to **6**). Finally, both oxidation systems have been tested on a range of substrates and shown to be easily scalable.

Radical-Chain Electrocatalysis: C(sp^3)−H Fluorination. The C−H oxidations outlined in the previous section attracted industrial (Eisai Co. and Enamine Ltd.) interest in a fluorinative variant (Figure 5B). Although both photochemical and purely chemical approaches to C−H fluorination were precedented, an electrochemical congener was expected to be beneficial in terms of scalability and practicality.[63] First forays

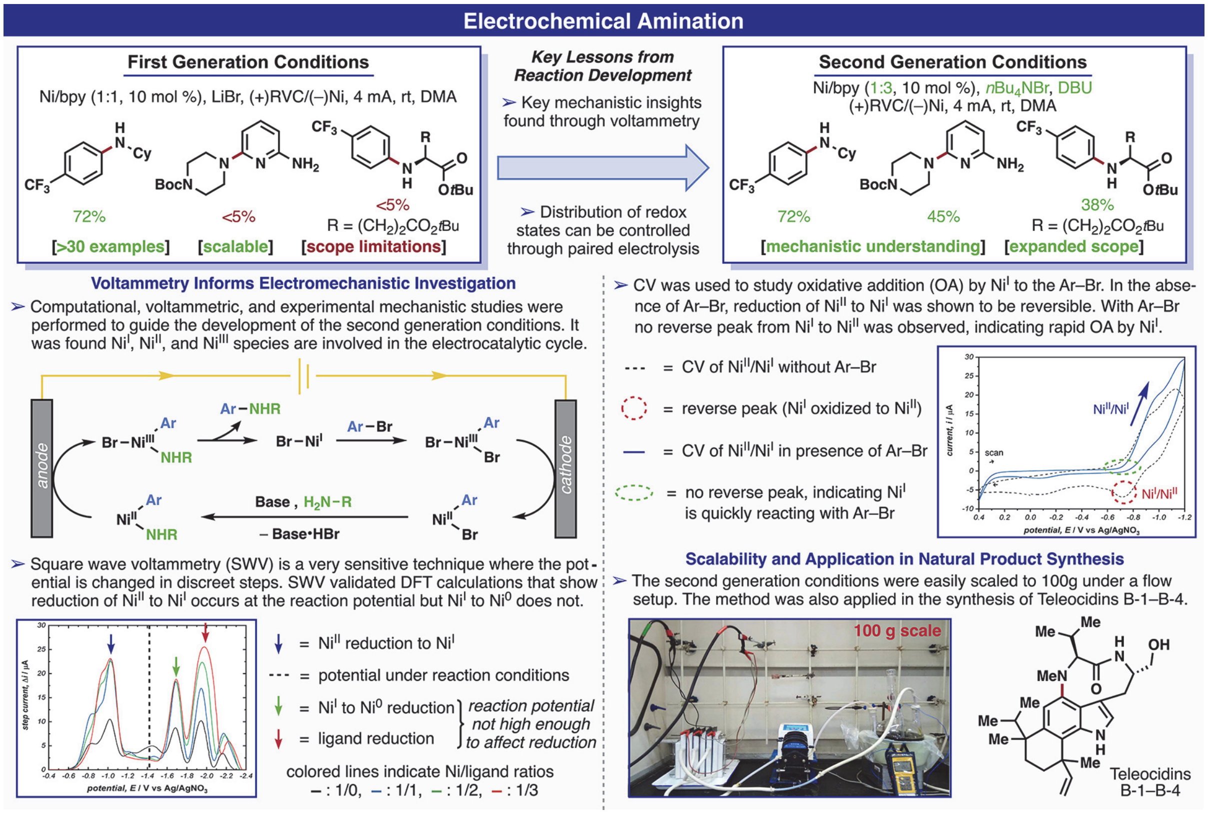


Figure 6. An example of paired electrolysis: electrochemical amination.

using quinuclidine as an electrocatalyst in the presence of Selectfluor resulted in product formation.[64] Puzzlingly, however, the control study leaving out the quinuclidine and even the electrolyte led to the same result. It was reasoned that Selectfluor was functioning as the reagent, electrolyte, and HAT-catalyst. In addition, it was presumed Selectfluor acted as a sacrificial oxidant to satisfy the cathodic process. Despite this promising initial finding, the reaction exhibited poor reproducibility. We suspected that this reaction was occurring through a radical chain process due to the observation of >100% current efficiency in the fluorination of sclareolide. In other words, when only 0.25 equiv of electrons were applied, the yield was 52%. The irreproducible nature of the reaction was presumably due to oxygen contamination, decomposition of substrate (unidentifiable deposition on the anode), and substrate-dependent, inefficient radical chain propagation. The first issue could be addressed by simply running the reaction under an inert atmosphere. The second problem was rectified using a function known as alternating polarity, wherein the potentiostat switches the identity of the cathode and anode with a specific frequency. Alternating the current every 2 min (automatically done by the potentiostat) suppressed the anode deposition that led to higher voltages and irreproducibility, thereby improving the robustness of this protocol. Finally, to diminish the variable results obtained with different substrates, an electrocatalyst was sought to aid in the radical initiation step. In accord with this hypothesis, the addition of a nitrate source, an electrocatalyst previously used as a HAT-catalyst for alcohol oxidation,[65,66] dramatically enhanced reactivity for challenging substrates. Indeed, a CV study revealed that oxidation of nitrate anion likely occurred before any direct anodic C(sp^3)−H abstraction, supporting the mechanistic picture outlined in Figure 5B. This simple and scalable fluorination protocol covered a wide range of substrates including amino acid derivatives and actual intermediates used in medicinal chemistry, and the ease of scale up was evidenced by the 100 g scale fluorination of a valine derivative without erosion of enantiopurity.

Electrocatalytic Amination Using Nickel. In 2017, we reported an electrochemically driven Ni-catalyzed aryl amination that displayed a broad substrate scope for the coupling of aryl halides and triflates with amines, alcohols, and amides (Figure 6).[67] The reaction uses commercially available RVC and Ni-foam electrodes in concert with an abundant and inexpensive Ni catalyst at room temperature. At the time, with no real understanding of the mechanism, we envisioned that these electrochemical conditions favored the coexistence of multiple different Ni-oxidation states during the course of the reaction to enable C−N bond formation. Indeed, electrochemistry is highly suitable when both oxidation and reduction of the electrocatalyst is required (often referred to as paired electrolysis) because these redox events can take place separately at the anode and the cathode, respectively. However, the scope of the first-generation conditions was limited to electron-poor aryl halide coupling partners, and attempts with heteroaryl halides did not afford satisfactory yields. In addition, the choice of amine was restricted to primary and secondary alkyl substrates. All attempts to further optimize the reaction conditions were hampered due to a lack of mechanistic understanding. Thus, a comprehensive investigation of the catalytic cycle was initiated in order to overcome the scope limitations.[68] Various electrochemical and analytical techniques were employed to delineate the elementary steps of the catalytic cycle. CV provided crucial insights for deciphering the complex redox behavior of the Ni catalyst. For example, both Ni(0) and Ni(I) could be generated by cathodic reduction of a Ni(II) precursor; it was suggested from square-wave voltammetry (SWV, a more sensitive version of CV) and the observed experimental cathodic potential that Ni(I) is likely the main species at this step. Furthermore, oxidative addition by Ni(I) to the aryl bromide could also be observed using CV, which indicated that this step is fast and not likely to be rate-determining. In addition, UV−vis spectroscopy revealed that Ni(II) precatalyst exists as a mixture of multiple species in solution. These studies revealed that the Ni/ligand ratio of the first generation conditions predominantly afforded unligated Ni(II) with a lower catalytic activity thus prompting an increase of the ligand loading. Finally, DFT calculations proved that addition of external base improves the thermodynamics of the rate-determining step (amine coordination/bromide displacement). Collectively, this mechanistic inquiry led to the development of second-generation conditions which offer a much broader scope including amino acids, heteroaryl halides, nucleoside analogs, DNA, natural products, and oligopeptides. Scale-up was readily accomplished using a flow system, and the new conditions were subsequently applied in the total synthesis of teleocidins B1−B4.[69]

■ CONCLUSION

The unique reactivity benefits of electroorganic chemistry have been unlocked for the synthetic community through the development and standardization of electrochemical instrumentation. However, the perception that electrochemistry is a “black box” must be dispelled before widespread adoption of this venerable technique can occur. The aim of this Account is to shed light on both the governing principles of electrochemistry and the practical aspects of designing and optimizing electroorganic synthetic methodologies. By “pulling back the curtain” on the development of canonical and electrocatalytic oxidative, reductive, and paired methods within our own laboratory, we hope this Account will serve as a useful guide for the “electro-curious”.

■ AUTHOR INFORMATION

Corresponding Author

*Email: pbaran@scripps.edu.

ORCID

Cian Kingston: 0000-0002-2907-4260
Julien C. Vantourout: 0000-0002-0602-069X
Phil S. Baran: 0000-0001-9193-9053

Funding

The authors thank the George E. Hewitt Foundation for a Postdoctoral Fellowship (Y.K.), Swedish Research Council (Vetenskapsrådet, VR 2017-00362) for a Postdoctoral Fellowship (B.K.P.), AGC Inc. for financial support for Y.T., and Bristol-Myers Squibb, Eisai, Asymchem, and Pfizer for financial support of the described research. Aspects of this work were also funded by the NSF (CCI Phase 1 grant 1740656), NIH (GM-118176), and The Scripps Research Institute.

Notes

The authors declare no competing financial interest.

Biographies

Cian Kingston received his B.Sc. in Medicinal Chemistry from University College Dublin in 2013. He completed his Ph.D. under the supervision of Professor Pat Guiry at the same institution in 2017 and subsequently began postdoctoral research with Professor Phil S. Baran at Scripps Research. His current research involves the study of radical and electrochemical cross coupling reactions.

Maximilian D. Palkowitz received his undergraduate education from Boston College in 2018 conducting research under Professor James Morken. Currently, he is a graduate student in Professor Baran’s research group investigating electrochemical cross coupling methodologies.

Yusuke Takahira completed his Ph.D. at Tohoku University in 2009. Since then he has been working at AGC Inc. (former Asahi Glass Co., Ltd.) as a research scientist. Concurrently, he is working in the laboratory of Professor Phil S. Baran at Scripps Research as a Professional Scientific Collaborator.

Julien C. Vantourout received his Masters in Organic Chemistry from the University of Lyon I in 2014. He completed his Ph.D. in 2018 from the collaborative program between the University of Strathclyde and GlaxoSmithKline, U.K. Thereafter, he started a postdoctoral appointment at Scripps Research with Prof. Phil Baran and is currently Staff Scientist of the Baran lab.

Byron K. Peters completed his undergraduate and Masters studies under the supervision of Prof. Thavandren Govender at the University of KwaZulu Natal in 2010. Afterwards, he moved to Uppsala and then Stockholm University to complete his Ph.D. in 2015 under the supervision of Prof. Pher Andersson. Thereafter, he returned to the University of KwaZulu Natal as a postdoctoral researcher with Prof. Tricia Naicker. He is currently pursuing the development of electrochemical methods as a postdoctoral fellow in the Baran lab.

Yu Kawamata completed his undergraduate education, Master’s degree, and Ph.D. under the supervision of Professor Keiji Maruoka at Kyoto University. During his Ph.D., he undertook an internship at Scripps Research working on natural product synthesis with Professor Phil S. Baran. Upon completion of his doctoral studies, he returned to the Baran laboratory and is currently staff scientist overseeing organic electrochemistry.

Phil S. Baran completed his undergraduate education at New York University in 1997. After earning his Ph.D. at The Scripps Research Institute (TSRI) in 2001, he pursued postdoctoral studies at Harvard University until 2003, at which point he returned to TSRI to begin his independent career. He was promoted to the rank of professor in 2008 and is currently the Darlene Shiley Professor of Chemistry. The mission of his laboratory is to educate students at the intersection of fundamental organic chemistry and translational science.

■ ACKNOWLEDGMENTS

We are especially grateful to the co-workers that made much of this work possible (names listed in references) and our many industrial collaborators from Bristol-Myers Squibb, Eisai, Pfizer, Asymchem, Syngenta, Merck, Minakem, International Flavors and Fragrances (IFF), Vividion, Enamine, and LEO Pharma for financial support and intellectual contributions.

■ ABBREVIATIONS

BDE, bond dissociation energy; bpy, 2,2′-bipyridyl; CV, cyclic voltammetry; Cy, cyclohexyl; DFT, density functional theory; DMU, *N*,*N*′-dimethylurea; EC, electrocatalyst; F, Faraday; Fc, ferrocene; GC, glassy carbon; GSW, galvanized steel wire; H-M, Hofer−Moest; HAT, hydrogen-atom transfer; HFIP, hexafluoro-2-propanol; HMPA, hexamethylphosphoramide; JNK, c-Jun N-terminal kinase; MO_x, metal oxide; NHPI, *N*-

hydroxyphthalimide; RAE, redox-active ester; OA, oxidative addition; RVC, reticulated vitreous carbon; SEI, solid electrolyte interphase; SHE, standard hydrogen electrode; SS, stainless steel; Sub, substrate; SWV, square wave voltammetry; TBA, tetra-*n*-butylammonium; TCNHPI, *N*-hydroxytetrachlorophthalimide; TPPA, tris(pyrrolidino)phosphoramide

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