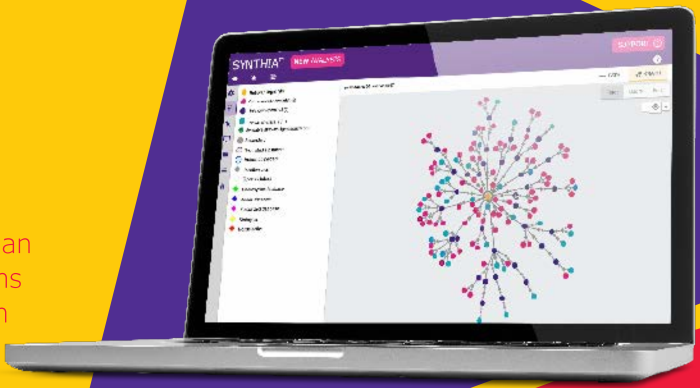
VOLUME 54, NO. 1 | **2021**
SPECIAL ISSUE: FOCUS ON ELECTROSYNTHESIS

MERCK

ALDRICHIMICA ACTA



Preparative Batch-Type Electrosynthesis: A Tutorial

Reductive Electrosynthesis: A New Dawn

Chemistry with Potential: Present Challenges and Emerging Trends in Organic Electrocatalysis

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The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

Interview[†] with

Dr. Matthias Heinzel

Welcome to Merck, Dr. Heinzel. Could you tell us and our readers very briefly about yourself?

It's my pleasure to introduce myself to our esteemed readers as I am getting to know this publication better. I've come to learn it's such a beacon for the global chemistry community, and I am excited to be engaging more with it.

I joined the company in April of this year as CEO of the Life Science business and a member of the Executive Board. Before taking on this exciting new opportunity, I served as an executive board member of DuPont and as President of DuPont's Nutrition & Biosciences business. Before joining DuPont, I held several international leadership roles in marketing, business strategy, and business development in the telecommunications industry. I started my career at McKinsey & Company in 1993.

I am originally from Germany, but I have been fortunate to work in several countries; e.g., the U.S., Denmark, and Australia; and I am always eager to get to know other cultures. When I am not working, I like to spend time with my wife and two daughters and to mountain-bike and play golf.

I know that you have been with the company for only a few weeks, but what do you find most fascinating about your job? What pleasantly surprised you the most?

The past weeks have already been a fantastic journey—from the very warm welcome by my new colleagues across the globe, to getting to know many of our teams and sites, and to diving right into important strategic business discussions. I am dedicating my first 100 days to listening and learning as I am immersing myself into our Life Science business. The variety of topics and the positive impact our work has in the scientific community are really fascinating. I am already invigorated by the opportunities this creates for our future.

I am currently travelling to some of our sites virtually, meeting teams from Europe, Asia, and North America. I don't want to say it surprised me that all colleagues I have met are very engaged—I knew that Merck was a highly regarded employer before I joined the company—but I still find the level of commitment and engagement impressive. Our roughly 10,000 frontline employees around the world have kept manufacturing and distribution moving throughout this pandemic, and our colleagues working from home have found new ways of virtually engaging with colleagues, customers, and the scientific community. I am proud to lead this business together with an incredible team through these unprecedented times and beyond, and I look forward to continuing to raise the bar for our performance, investments, and innovation. We have a unique opportunity to capitalize on this depth of knowledge and expertise, as well as the reputation for the highest quality tools and services, to make bold decisions that drive the future of the entire industry.

What do you think the company's potential for growth is, and where do you foresee this happening (in what research areas and which geographies)?

It is an amazing time to be in a leading science and technology company and, in particular, the Life Science business. All three business units within Life Science contribute to our growth. We are already active and lead in many key growth areas such as single-use monoclonal antibodies and actives and formulations. During the pandemic, we leveraged two decades' worth of experience in lipids and mRNA to accelerate the development of vaccines to fight COVID-19. Moreover, we are at the top of our game with gene-editing tools; lab water; our wide array of laboratory reagents; and the most comprehensive product range, innovative products, and enabling technologies for chemical research. Regionally, we expect to see further growth in APAC, for example in China, as a result of continued changes in the global value chain of the life science industry.

But we need to continue to push the boundaries in additional growth areas such as total chemistry solutions; including synthesis automation tools, connected lab devices, and sustainable chemistry. The growth in these areas is leading to increased demand for new and innovative products, services, and platforms. At Merck KGaA, Darmstadt, Germany, we are uniquely positioned to deliver just that.

Dr. Matthias Heinzel
Member of the Executive Board
CEO Life Science

[†] Dr. Matthias Heinzel was interviewed by Dr. Sharbil J. Firsan, Editor, *Aldrichimica Acta*.

The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

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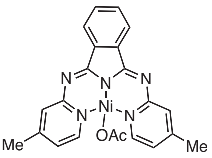
"PLEASE BOTHER US."

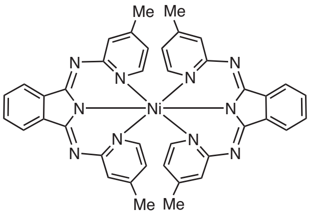
Dear Fellow Chemists,

Professor Christo S. Sevov of the Department of Chemistry and Biochemistry at The Ohio State University kindly suggested we offer (MeBPI)Ni-OAc (**919365**). This complex is employed as part of an electrocatalytic system and an overcharge protection strategy to effect the reductive cross-electrophile coupling (XEC) of a broad spectrum of aryl, heteroaryl, and vinyl bromides with primary and secondary alkyl bromides. The coupling protocol is general, scalable, and convenient to use. Additional attractive features of the system include inexpensive and readily accessible catalyst and shuttle ((MeBPI)$_2$Ni, **918105**), ambient reaction temperature, and isolated yields of the coupling products most often >75%. This method avoids the use of superstoichiometric quantities of additives, and the cross-coupling takes place even in the presence of a wide variety of functional groups and substituents on the C(sp^2) and C(sp^3) coupling partners.

(1) Truesdell, B. L.; Hamby, T. B.; Sevov, C. S. *J. Am. Chem. Soc.* **2020**, *142*, 5884. (2) Sevov, C. S.; Fisher, S. L.; Thompson, L. T.; Sanford, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 15378.



(MeBPI)Ni-OAc (**919365**)
catalyst



(MeBPI)$_2$Ni (**918105**)
shuttle

919365	(MeBPI)Ni-OAc	250 mg, 1 g
918105	(MeBPI)$_2$Ni	250 mg, 1 g

We welcome your product ideas. Email your suggestion to **techserv@sial.com**.

Daniel Boesch, VP
Head of Life Science Chemistry

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ABOUT OUR COVER

A primordial force of nature, lightning has both fascinated and terrified humans for millennia. It wasn't until the past few centuries that lightning started to be understood as a natural phenomenon and a breathtaking display of a force that we now know as electricity. Building on earlier simple observations and timid experimentations, a steady stream of pioneers of the past two centuries started studying electricity in earnest. The multitude of applications that have since been, and continue to be, developed for electricity have revolutionized and forever changed our way of life.

One such application is the wedding of chemistry and electricity (electrochemistry*) in particular electrochemical synthesis. In the past few decades, the realization that we cannot continue to rely on fossil fuels—not only because they are nonrenewable resources, but also because of their contribution to global warming—has rekindled interest in using electricity as an environmentally benign and sustainable reagent in electrochemical organic synthesis, which is the focus of this *Acta* issue.

Detail from ***Double Rainbow with Double Lightning Nebraska, USA.*** john finney photography/Getty Images.

We hope the information in this issue will prove insightful and valuable in your work and will serve as an impetus for you to try out the novel synthetic methods and techniques that are presented by some of the thought leaders in this rapidly evolving area of research.

* *For additional comments, visit* ***SigmaAldrich.com/Acta***

Preparative Batch-Type Electrosynthesis: A Tutorial


Mr. D. Pollok


Dr. B. Gleede


Mr. A. Stenglein


Prof. Dr. S. R. Waldvogel

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Keywords. electrochemistry; synthesis; electro-organic transformation; batch electrolysis; beaker-type cells; parameter; electrodes; anode; cathode; electrode fouling.

Abstract. Modern organic chemistry emphasizes sustainability in addition to high performance in synthetic processes. Electro-organic synthesis meets these two criteria well. Herein, beaker-type cells for batch-type electrolysis are highlighted along with a tutorial on starting an electrosynthesis with these cells and on how to treat the electrodes.

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1. Introduction

Presently, the rapid advances in organic synthesis methodologies have opened up a broad spectrum of novel reactivity and pathways in synthetic protocols. Milestone discoveries such as transition-metal catalysis have boosted scientific knowledge and research significantly.[1] In addition to atom, cost, and process efficiencies, sustainability has become a central focus of chemical synthesis design and execution. In this context, electro-organic synthesis has re-emerged as a promising option thanks in part to its inherent economic and ecological advantages compared to traditional processes.[2–6] The central idea of this approach is the use of common electric current as reagent for safely and tracelessly initiating or performing chemical reactions. This would satisfy the present trend toward avoiding the use of hazardous reagents and finite fossil fuel based resources as well as avoiding the generation of chemical waste by relying on inexpensive electricity generated preferably from renewable resources (**Figure 1**). In many cases, carbon-based materials are employed as the electrodes, which enhances the value of this approach since metal-free conditions are utilized.

Seminal developments as well as encouraging perspectives for future research in this area have been covered in several extensive review articles, including the synthesis of natural products and active pharmaceutical ingredients (APIs) by using electro-organic key transformations (**Figure 2**).[2–5,7] Moreover, because a growing number of chemists have started using electrochemical synthesis with varying levels of prior knowledge, guidelines were recently published explaining the important aspects to consider while setting up an electro-organic synthesis.[8] However, we discovered that a significant number of newcomers would appreciate a tutorial on how to set up an electrochemical apparatus in the laboratory. After briefly reviewing the various instrumentation available, we will offer below a tutorial on how to get started with electro-organic synthesis by focusing on the use of simple, batch-type electrolysis cells.

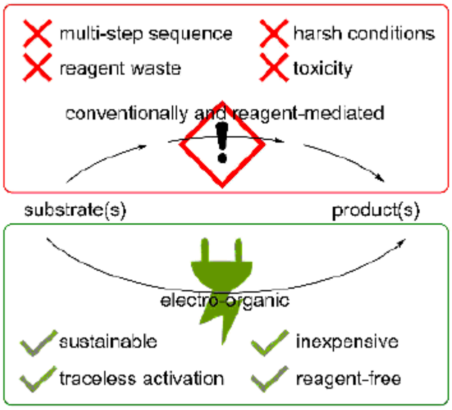


Figure 1. Comparison of the Features of Conventional, Reagent-Mediated Organic Synthesis with Those of Electro-Organic Synthesis.

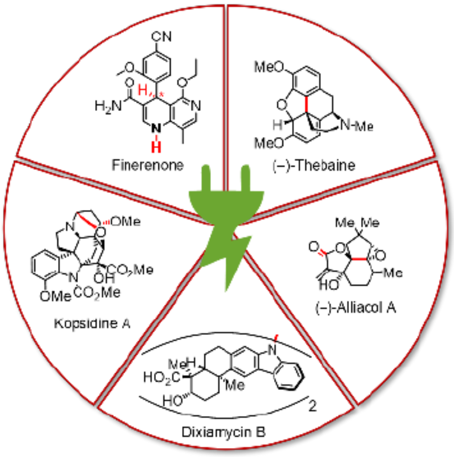


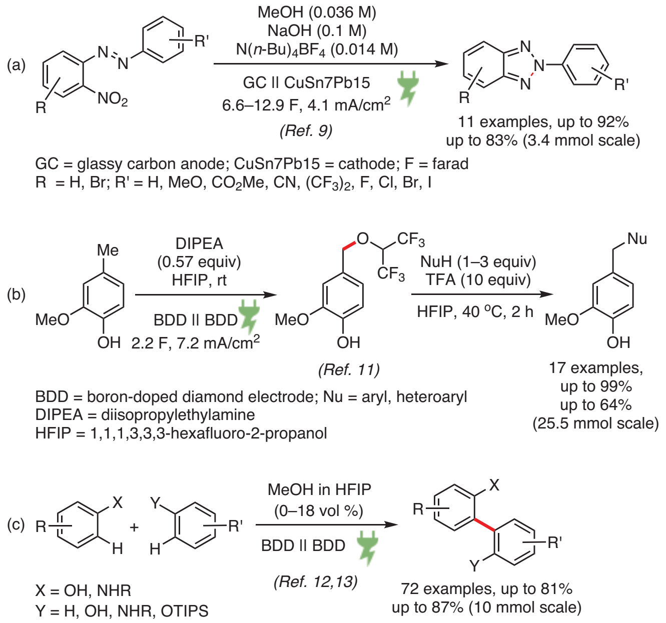
Figure 2. Selected Natural Products and APIs Successfully Accessed with Electro-Organic Key Transformations. The Newly Formed Bonds and Changes Induced by Electricity Are Highlighted in Red. *(Ref. 2–5,7)*

2. Highlights of Preparative Electro-Organic Synthesis

Herein, we focus on transformations that have not only been performed on a micromolar screening scale but also successfully transferred to a preparatively relevant millimolar scale. A selection of outstanding representative reactions which have been scaled up in beaker-type glass electrolysis cells is shown in **Scheme 1**.[9–13]

With a focus on the functionalization of arene moieties, robust cathodic processes were developed that selectively form N–N bonds of benzo[*d*]-1,2,3-triazoles by reduction of nitroarene precursors on leaded bronze electrodes (**Scheme 1**, Part (a)).[9] The triazole products were obtained in up to 92% yield on a screening scale and 83% yield on a 3.4 mmol scale. Conventional reagent-mediated syntheses of this class of compounds suffer from the use of transition metals and lack of regioselectivity. Moreover, carbon-based electrode materials have facilitated intermolecular electro-conversion of nitroarenes with aldehydes to the corresponding nitrones in up to 72% yield and similar yields in preparative-scale runs.[10]

A powerful method for anodic benzylic functionalization with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) has been demonstrated and the resulting intermediates were subsequently converted into diarylmethanes (Scheme 1, Part



Scheme 1. Examples of Preparative Small-Molecule, Electro-Organic Synthesis in Beaker-Type Glass Cells. *(Ref. 9–13)*

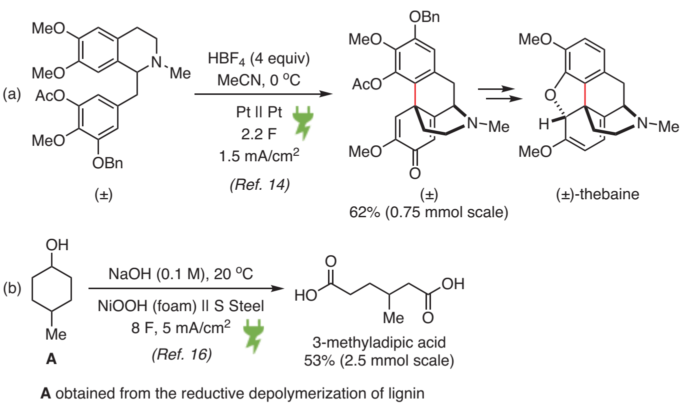
(b)).[11] The method enabled yields of the products in up to 99% on a screening scale and 64% on a preparative scale (e.g., 6.91 g of benzothiophene derivative). In contrast to known conventional syntheses, this protocol does not involve drastic reaction conditions or metal reagents.

Moreover, a valuable synthetic strategy has been established to access C–C homo- and cross-coupling products of phenols or anilides with other arenes on boron-doped diamond (BDD) electrodes (Scheme 1, Part (c)).[12,13] These reactions are essential for the synthesis of precursors for various relevant ligands. The precursors were obtained in high yields up to 87% on a 10 mmol scale at high current density. The latter aspect is crucial to achieve time-efficient synthetic processes and for shortening conventional reaction pathways.

Small-molecule synthesis is nicely demonstrated by the examples in Scheme 1. However, electro-organic conversion can also facilitate key reactions in the synthesis of natural products and active pharmaceutical ingredients, as successfully demonstrated with the preparative synthesis of thebaine (**Scheme 2**, Part (a))[14] and oxycodone.[15] These morphines were synthesized with an electro-organic transformation as a key step (up to 62% yield, 0.75 mmol scale) and in continuous flow electrolysis.

Besides its application in synthesis protocols, a highly valued aspect of the electro-organic transformation is its application in the generation of fine chemicals from renewable resources. In this regard, recent developments highlighted the sustainable generation of lignin-derived dicarboxylic acids at NiOOH electrodes in yields of up to 60% (Scheme 2, Part (b)).[16]

It is thus clear that a wide variety of reactions can be enabled by both cathodic and anodic transformations. These reactions have been performed on a screening scale as well as on a preparatively relevant scale. Beaker-type glass cells have often been employed for the latter, which will be the focus of the rest of this review article.



Scheme 2. Examples of (a) Preparative Electro-Organic Synthesis of API's and (b) Sustainable Electrosynthesis from Renewable Sources in Beaker-Type Glass Cells. *(Ref. 14–16)*

3. Instrumentation for Electrosynthesis

Compared to conventional, reagent-mediated organic synthesis, an elaborate setup is required to perform a controlled electrolysis. However, once the equipment and apparatus are assembled, the electrolytic step is simple to conduct. A universal setup consists of a power source that facilitates the controlled application of electrical current as reagent either in constant current (CCE) or constant potential (CPE) electrolysis. A CCE enables rapid transformations with simple scale-up protocols owing to the two-electrode arrangement of a working electrode (WE) and a counter electrode (CE). Here, a very simple and inexpensive DC power source can be applied. In contrast, CPE maintains the applied potential by adjusting the current. Therefore, a third (reference) electrode (RE) is required. This enhances the opportunities for dialing-in desired reactions but faces operational drawbacks such as a prolonged synthesis and a sophisticated setup. However, CPE is not required in most electro-organic conversions, since the most easily electrochemically converted substrate will undergo the redox reaction. For convenience, some power sources have coulomb counters included, which allows the termination of the CCE electrolysis automatically after the desired amount of charge (as equivalent of reagent) has been applied. The central part of an electrosynthesis setup is the electrolysis cell containing electrodes immersed in an electrolyte. The electrolyte consists of the substrate, a solvent, and usually additional supporting electrolyte(s) to facilitate sufficient electrical conductivity. Successfully applied supporting electrolytes are either salts, acids, or bases.[17] In most cases, the electrolyte is stirred during electrolysis with a magnetic stirrer and a reflux condenser or inert gas inlets are optionally employed, depending on the reaction conditions and the nature of the reactants and intermediates.

The growing importance of electro-organic synthesis has led to the design, use, and refinement of several different kinds of apparatus over the past few decades. Therefore, a distinction needs to be made between batch-type electrolysis, which is performed in a vessel, and a continuous flow process whereby a constant stream of reactants is passed through an electrical field with electricity flowing to effect the desired transformation. While this tutorial will highlight the differences between various setups for batch-type electrolysis, the interested reader can find in-depth information on flow electrolysis elsewhere.[18]

3.1. Screening Reaction Scale

Most exploratory scientific research is carried out on a small scale utilizing small amounts of reactants and solvents in order to save on economic and ecological resources. Thus, small vessels are commonly used when developing the optimal reaction conditions in conventional synthesis as well as in electro-organic synthesis. Thus, initial electrolysis trials in a laboratory are often performed with readily available simple equipment such as customary 6 V batteries as an inexpensive DC power source,[19] three-necked round-bottom flasks, (**Figure 3**, Part (A))[20] and test tubes (Figure 3, Part (B))[21]. In these straightforward setups, the electrodes are often mounted with rubber stoppers, with the most obvious difference between the setups being the arrangement of the electrodes. In a three-necked round-bottom flask, the tilt of the electrodes results in a heterogeneous electric field that leads to local potential hot spots which result in the enhancement of side reactions. To help new users of the technique, several research groups have developed systems that are now commercially available. For example, a versatile and robust setup that allows up to eight electrolyses at a time to take place in divided or undivided electrolysis cells has been developed by our group using Teflon® cells to withstand the harsh reaction media such as the use of hydrofluoric acid (Figure 3, Part (C), and **Figure 4**).[22,23] In an all-in-one approach, the ElectraSyn® 2.0 was co-developed by IKA® and Professor Phil Baran's group (Figure 3, Part (D)).[24] This equipment can easily be upgraded with several extensions to fit the specific needs of an electro-scientist.

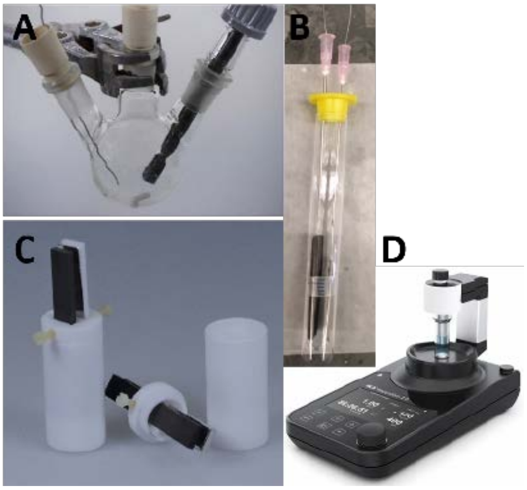


Figure 3. Simple, Screening-Scale Setups for Electro-Organic Synthesis. (A) Home-Built Setup Based on a Three-Necked Round-Bottom Flask *(Reproduced with Permission from Reference 20. © 2017 American Chemical Society)*. (B) Home-Built Test-Tube-Based Setup with Electrodes Mounted on Wires *(Reproduced with Permission from Reference 21. © 2017 American Chemical Society)*. (C) Commercially Available Teflon® cells with 1 cm × 7 cm Electrodes *(Reproduced with Permission from Reference 20. © 2017 American Chemical Society). (D) ElectraSyn® 2.0 (Reproduced with Permission from Reference 24. © 2020 IKA-Werke GmbH & CO. KG).*

Figure 4. Typical Multicell Setup for Galvanostatic Electro-Organic Transformations (Available as IKA® Screening System for Electrosynthesis).

More and more screening of electro-organic transformations is being performed on a micromolar scale using for example the IKA® e-Hive extension for the ElectraSyn® 2.0.[25] Although this allows for fast screening of reaction parameters with minimal amounts of chemicals, the setup is not designed for electro-synthesis in the proper sense as it does not provide precise results and materials by isolation. In contrast, the multicell screening setup shown in Figure 4 has been successfully used since 2010 as a standard for optimizing processes that provides sufficient yields for isolation.[22] The key here is to get accurate data that provides the basis for a subsequent straightforward mathematical treatment such as regression analysis.

3.2. Batch-Type Scale-up

To successfully incorporate electrochemical transformations in organic synthesis protocols, the micromolar scale employed in the screening-scale setups is not ideal if sufficient product is required for further reaction steps. Moreover, scaled-up reactions are advantageous as they provide more reliable yields for making a subsequent business case for a given synthetic route. Not unlike for conventional, reagent-based reactions, a considerable challenge is also encountered in the scale-up of electro-organic transformations. Here, two central points need to be emphasized—the type of electrolysis required and reproducibility of the results. In terms of the technical relevance of a given electrolytic process, not only high yields and cost-efficiency are important, but also the practicality of the process. In this regard, the simple two-electrode arrangement of a galvanostatic electrolysis has proven advantageous. As mentioned earlier, several types of home-built electrolysis apparatus have been assembled from readily available laboratory equipment such as round-bottom flasks with wide joints,[26] simple bottles with screw caps (**Figure 5**, Part (A)),[27] or beakers (Figure 5, Part (B)).[21] However, many home-built setups often suffer from reproducibility issues and from leaks that jeopardize workplace safety. The aforementioned ElectraSyn® 2.0 features different vessels for electrolysis with volumes of up to 20 mL, while other types of electrochemical cell with volumes of up to 50 mL are now also available commercially.[28]

3.3. Robust Beaker-Type Glass Cells

The need for simple and inexpensive preparative-scale electrolysis cells prompted our group to develop and demonstrate easy-to-operate batch-type electrolysis cells for reaction volumes of 50 to 200 mL (**Figure 6**). The ease of handling as well as the ability to cool or heat the electrolyte using a temperature-control jacket add to the attractiveness of the system. Moreover, the varied reaction volumes that it can accommodate enables the scale-up of the electrosynthesis step to produce sufficient amounts of desired intermediates that can be elaborated further. This setup has been widely adopted and employed in electro-organic syntheses of a broad range of molecule types including natural products and APIs.[13–15,29]

As many home-built setups are only assembled to perform a specific electrolysis, awareness of workplace safety is usually lacking. The beaker system featured in Figure 6 addresses several important aspects of workplace safety with (i) a firm stand, (ii) an open reaction system, (iii) a stopper to fix the electrodes in place to prevent their movement during electrolysis and changing local electrical fields as well as electric short circuits, and (iv) electric contacts of the power source not being exposed to the electrolyte which enhances the longevity of the apparatus. Moreover, the materials employed in fabricating the vessel (glass) and the plug (Teflon®) are common and resistant laboratory materials that exhibit high robustness toward a broad range of transformations and chemicals. The perfectly fitting electrodes for the respective cell size enable a highly active electrode surface in the electrolyte and thus short reaction times in a homogeneous electric field. This is ensured by preassembled stainless-steel electrode holders in the Teflon® plug that are sealed by several widely chemically inert ethylene-propylene-diene-monomer-rubber (EPDM). The jacket for temperature control which operates on a separate circuit ensures that no cooling or heating liquid accidentally interferes with the electrolysis. A cryostat, thermostat, or simply water can easily be connected using conventional GL 14 threads and tubing. An NS14 ground-glass joint allows for introducing inert gas or fitting the beaker with a reflux condenser. The latter is recommended if elevated temperatures, close to the boiling point of the solvent, are employed and the electrolyte level needs to be maintained during electrolysis over a long period of time to ensure a constant current density. In addition, the modular system facilitates a specific-use assembly, and permits different power sources to be employed for generating higher or lower currents. Furthermore, a common magnetic stirrer can be utilized to homogenize the electrolyte during electrolysis due to the variable placement of the electrode independently from the electric equipment which the stirrer is connected to.

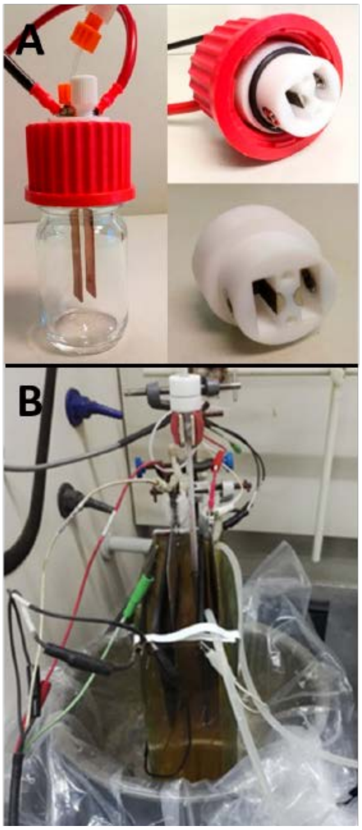


Figure 5. Scaled Batch-Type Setups for Electro-Organic Synthesis. (A) Bottle Reactor with Teflon® Inlet in the Cap for Mounting the Electrodes on the Stainless-Steel Contacts *(Reproduced with Permission from Reference 27. © 2020 American Chemical Society).* (B) Improvised Open-to-Air Batch-Type Setup for Large Scale-up to 50 g *(Reproduced with Permission from Reference 21. © 2017 American Chemical Society).*

4. Operational Guide

Because of the simplicity of the system featured in Figure 6, one can quickly learn how to use it, lowering the threshold for its adoption in the synthetic organic laboratory. To demonstrate this, an illustrated tutorial is offered in the following paragraphs that highlights the steps involved, from preparing the electrolysis experiment to the cleaning of all the materials which have been exposed to chemicals, in particular the electrodes since they have a major impact on subsequent experiments.

The first step is mounting the electrodes onto the appropriate stainless-steel holder and tightening the screws to

Figure 6. Beaker-Type Glass Cells for Batch-Type Electrosynthesis (25 mL) with Temperature-Control Jacket. Front: Electrode Holder with Mounted Electrode and a 1 Euro Coin for Size Comparison (Diameter 23.25 mm / 0.915 inch).

fix the electrodes in position and maintain sufficient electric conductivity (**Figure 7**, Part (A)). One should make sure that the plate is centered with respect to the stainless-steel holder! Afterwards, the two electrode–holder assemblies are inserted into the Teflon® plug from the holder side all the way up to the end, making sure that the electrodes are parallel to each other to ensure a homogeneous electric field (Figure 7, Part (B)).

In the second step, the reactants, solvents, electrolytes, and additives are added directly into the glass cell equipped with a magnetic stir bar or stir cross (**Figure 8**, Part (A)). Subsequently, the Teflon® plug (with the electrodes in it) is inserted into the glass cell with one or two optional Teflon® sleeves to ensure easier handling in terms of material expansion when different temperatures are applied. When the plug is in place, the electrodes are pushed down until there is only a small clearance between them and the stirr bar (Figure 8, Part (B)). In this step, great care should be taken to avoid immersing any part of the stainless-steel holders into the electrolyte as they may not be chemically resistant to the chemicals in the reaction mixture, and may interfere as conductive material during the electrolysis by generating another electric field and offering another active surface for electron transfer. Once everything is in place and the electrodes are aligned parallel to each other, the plug is removed briefly from the cell and the immersion depth is measured with a conventional ruler to determine the required current with the given current density. This should be done carefully since the current density often has a major influence on the transformations being the equivalent of the speed with which a reagent is added to a reaction mixture. The immersion depth can often be easily seen as liquid residues on the electrodes directly after removing them from the electrolyte.

The plug is put back in place, the cell is positioned on a magnetic stirrer, and the required connections are made including connection to a cryostat or thermostat if needed (Figure 8, Part (A)). If elevated temperatures close to the boiling point of the solvent are used, a conventional reflux condenser can be mounted onto the NS14 joint. Afterwards, it is highly recommended that the electrolyte be stirred for 20–30 min to allow it to reach the desired temperature. Moreover, if an air- or moisture-sensitive reaction is performed or temperatures below 0 °C are necessary, the use of an inert gas inlet is highly recommended.

The last steps before starting the electrolysis include: (i) connecting the power source to the electrodes by using cables with crocodile clips (**Figure 9**, Part (A)), and (ii) setting the coulomb counter and electric current to the desired values. The electrolysis is then run until the coulomb counter terminates the flow of electric current or the scientist does that manually after the calculated time [t (s) = Q (C) / I (A)] has elapsed. During application of the amount of charge, it is recommended not to touch any of the non-isolated electricity-conducting parts, especially at high currents, to avoid the risk of an electric shock (Figure 9, Part (B)). *Caution: Prior to any manipulation of the electrolytic cell, the electricity should be shut off at the source!*

After the electrolysis is terminated, the attachments are removed in the reverse order of their assembly. The electrolyte can easily be transferred to another vessel by decanting the solution out of the NS14 joint at the side of the cell. Cleaning of the electrolysis cell can be performed similarly to the way a

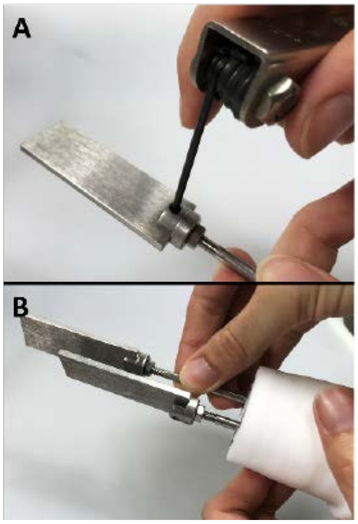


Figure 7. Setting Up for a Preparative Electro-Organic Synthesis with Beaker-Type Cells: (A) Mounting the Electrodes onto the Stainless-Steel Holder and (B) Inserting Them into the Teflon® Plug.

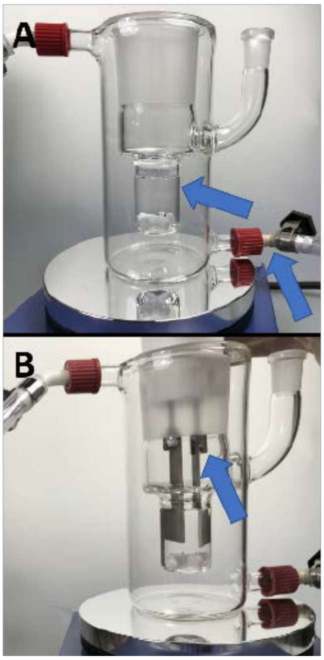


Figure 8. Setting Up a Preparative Electro-Organic Synthesis in a Beaker-Type Cell: (A) Connecting the Tempering Jacket to the Respective Cryostat or Thermostat and Adding the Electrolyte (Reactants, Solvent, Supporting Electrolytes). (B) Immersing Electrodes into the Reaction Mixture.

round-bottom flask is cleaned. However, when the electrodes are tackled, more care has to be exercised as explained in some detail in the next section (**Figure 10**).

5. How to Treat Your Electrodes

Reproducibility of experiments is an important consideration in electro-organic transformations. A major influence on the outcome of an electro-organic synthesis is the handling and treatment of the electrodes. The electron transfer and, thus, the desired reaction occurs heterogeneously at the surface of the respective electrode. In the best case, multiple use of the same electrodes supports the sustainability aspects of electrosynthesis when no corrosion or damage to the electrode is observed. However, in the course of running an electro-organic reaction, undesired side reactions can occur. These might modify or deactivate the electrodes, or residues can adsorb onto their surfaces rendering them unusable. The properties of electrode materials and their potential fields of application have been very recently surveyed by Heard and Lennox.[30]

5.1. Electrode Fouling

As electrolysis generates highly reactive radical species by single-electron transfer (SET) at the electrode–electrolyte interface, various different subsequent processes can take place. Electrode fouling can occur from undesired side reactions of the solvent, substrates, products, or intermediates. Thus, over-oxidation can lead to oligomer and polymer formation if the oxidation potential of the product is lower than that of the starting material(s). Such macromolecules, especially if cross-linked, would not be soluble in the electrolyte and would deposit onto the electrode surfaces.[31] This leads to passivation of the electrode surface, which can have a significant adverse impact on the performance of the transformation.[32]

5.2. Noble Metals

5.2.1. Platinum

One of the most commonly utilized electrode materials is platinum. This noble metal has outstanding properties with respect to overpotentials and (electro)chemical stability. Consequently, platinum has emerged as a versatile electrode material commonly used as platinum sheets or platinum wires in quasi-divided approaches. The platinum electrode is often used as thin sheet due to the high cost of the material. To hold the platinum foil properly in the stainless-steel electrode holder and suppress movement during electrolysis and a changing electric field, the use of Teflon® supports is highly recommended (**Figure 11**).

The following treatment is valid for every morphology of platinum, with the only stipulation being that a wire should be mounted carefully in an electrode holder to avoid shifting position during electrolysis. Platinum is prepared for an electrolysis experiment by mechanical flattening and thermal removal of organic and carbonaceous contaminants by flame treatment. After each electrolysis, the platinum electrodes should be rinsed with solvents to remove any adsorbed organic materials. To enhance this process, ultrasonication in organic solvents or water is an additional possibility for impurities that are slightly soluble in the rinsing solvents. It is also worth noting that metals ranging from lithium to transition metals can migrate into the platinum and deteriorate the outstanding features. Therefore, also rinsing with diluted nitric acid removes them efficiently

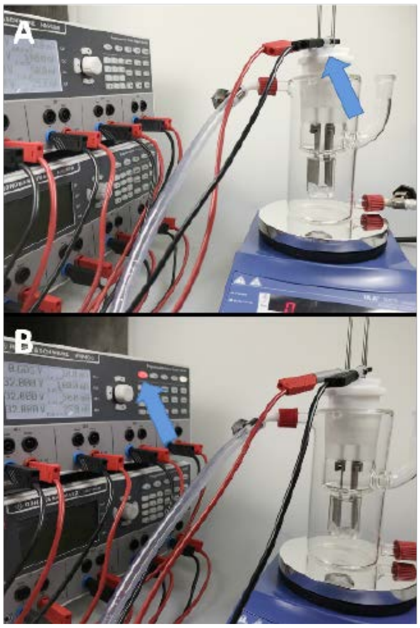


Figure 9. Setting-up a Preparative Electro-Organic Synthesis in a Beaker-Type Cell: (A) Connecting the Power Source and (B) Starting the Electrolysis.

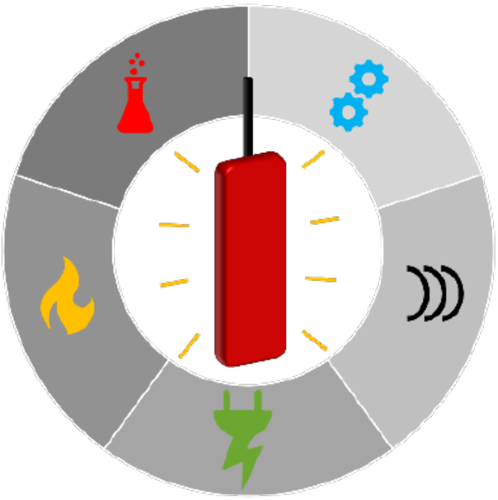


Figure 10. Approaches for Cleaning the Electrodes Mechanical Treatment, Ultrasonication, Electrochemical Purification, Flame Treatment, and Chemical Rinsing.

prior to flame treatment. Importantly, using platinum anodes with chlorides and hydrochloric acid should be avoided, since these strongly promote corrosion of the platinum.[33]

5.2.2. Gold, Palladium, and Silver

As with any other electrode material, the surface of a gold, palladium, or silver electrode should be cleaned prior to and after an electrolysis using the proper solvents. However, unlike with platinum, no flame treatment of the electrode is recommended due to the relatively low melting point of these metals. Thus, only rinsing and mechanical treatment can be used to flatten the often-applied foil electrode. Wrinkles of the metal anode often represent electrochemical hot spots which promote side reactions.

5.3. Other Metals and Their Alloys

In comparison to the noble metals mentioned in the previous two sections, other (transition) metals and their alloys often require a different handling, in particular if different morphologies or geometries are used.

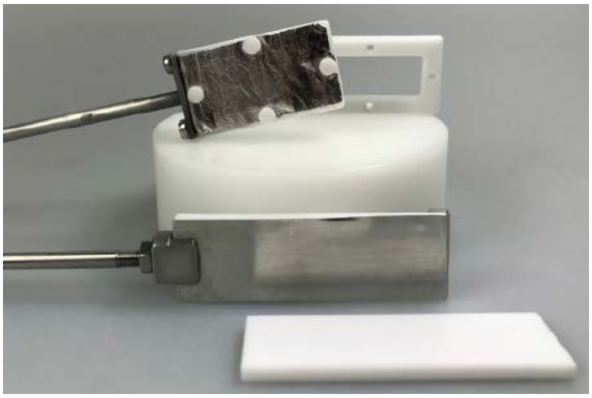


Figure 11. Electrode Holders for Thin-Layered Metals Like Platinum. Front: Conventional Stainless-Steel Electrode Holder and Solid Teflon® Support. The Platinum Foil Is Fixed by Wrapping It around the Bottom Part of the Teflon® Support. Back: Platinum Foil Mounted on the Teflon® Frame and Attached to a Stainless-Steel Electrode Holder.

Figure 12. Standard Stainless-Steel Electrode Holder for Solid Electrode Materials. Front: View of the Flattened Side of the Electrode Holder. Back: Rear Side of the Electrode Holder with Screw and Mounted Electrode.

5.3.1. Nickel and Molybdenum

The pre- and post-electrolysis treatment of nickel and molybdenum plate electrodes are done analogously to the treatment of almost every other electrode material by mounting in the stainless-steel electrode holder prior to electrolysis and rinsing with proper solvents following reaction (**Figure 12**). In addition to that, mechanical treatment of these electrodes using fine sandpaper (e.g., grain size 1200) is recommended as this removes non-soluble contaminants and ensures a homogeneous and clean surface.

The use of nickel electrodes is highly valued because of the low overpotential for hydrogen evolution. However, if different morphologies such as nickel foams are required, the mechanical treatment of the electrode is limited. Mounting these foam electrodes can be performed by using modified stainless-steel electrode holders to suppress movement of the foam during electrolysis (**Figure 13**). An interesting special aspect of nickel electrodes is their optional application as activated electrodes, possible in every modification. In this case, pretreatment of the electrodes is often required, but can also occur in situ during the desired electro-organic synthesis as seen in the aryl–aryl coupling with active molybdenum and nickel anodes in HFIP or in the presence of nickel fluoride salts (NiF_x).[34] The pretreatment of nickel electrodes simply by electrolysis of an activation electrolyte often significantly enhances the yields of transformations. Examples are the treatment of lignin with NiOOH electrodes that have been electrochemically activated in soda or caustic soda.[35]

5.3.2. Iron and Stainless Steel

Iron and several grades of steel are some of the inexpensive electrode materials, widely available, and, thus, often used as cathodes. Their outstanding stability in alkaline media and ease of handling makes them attractive for process development.

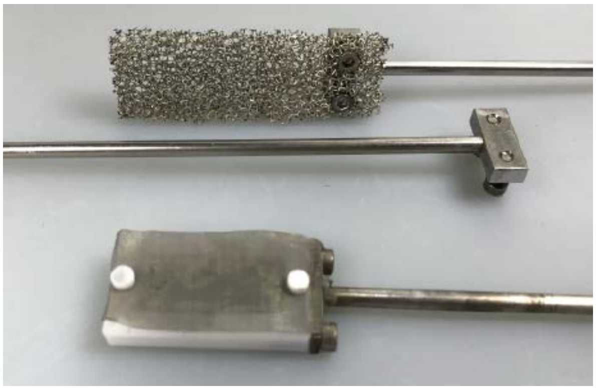


Figure 13. Modified Electrode Holders for Porous Electrode Materials such as Nickel Foam. Front: Stainless-Steel Electrode Holder with Teflon® Frame for Mounting Meshes. Center: Back Side of the Stainless-Steel Electrode Holder for Mounting Foams. Back: Electrode Holder for Foams with Mounted Electrode.

5.3.3. Copper

Copper electrodes can be handled analogously to the previously mentioned metal cathodes. Copper has valuable properties such as high stability in acidic media, but it has to be handled carefully as dissolution of copper ions is possible after completed electrolysis if the electrodes are still immersed in the electrolyte. An example of this is the formation of copper sulfate in electrolytes containing sulfuric acid which are widely used due to their ready availability and affordability.

5.3.4. Aluminum, Magnesium, Tin, and Zinc

Aluminum, magnesium, tin, and zinc are commonly employed as sacrificial electrodes, and mounting and treating them are done similarly to the way other non-noble transition metals are mounted and treated. However, being sacrificial electrodes limits their recyclability due to dissolution of their metal salts during the electrolysis.

5.3.5. Lead, Leaded Bronzes, and Lead(IV) Oxide

Lead has been recognized for a long time as a valuable cathode material with high overpotential for the hydrogen evolution reaction. Its high stability in sulfuric acid led to various applications in the early days of electro-organic conversions. However, handling lead as electrode material can be unpleasant because of its inherent toxicity and mechanical softness which leads to easy mechanical deformation. Moreover, a passivation layer can form on the lead electrode while being exposed to oxygen and the layer has to be mechanically removed prior to electrolysis. This results in high amounts of toxic lead dust, which has led to a search for alternatives. In addition, when the concentration of sulfuric acid is too low, cathodic corrosion can occur due to the formation of organometallic species; however, the use of specific cations such as tetraalkylammonium and alkyldiammonium salts can suppress the corrosion efficiently.[36]

In terms of next-generation electrode materials, leaded bronze has been demonstrated as a safe alternative to lead.[37] In many cases, the reactivity is very similar to lead, even though only low double-digit percentages of lead are present in the copper matrix. The microphase separation of the material leads to outstanding surface properties and, thus, possibilities for electro-organic transformations. The handling is far better than that of lead as it is a harder material and can be handled analogously to other metal-based electrodes.

Lead(IV) oxide is often used since its large oxygen-evolution overpotential results in a large potential range for transformations. Handling this electrode material is simple and does not require special precautions as long as the concentration of the sulfuric acid is high enough.

5.3.6. Mercury

Mercury was a common cathode material in the early days of electro-organic synthesis. In contrast to most other electrode materials, mercury is liquid at room temperature which is why it is used either as a dropping electrode or as a pool electrode.[38] In the latter use, mercury can be handled below the electrolyte as the magnetic stirring bar can be placed on the mercury electrode and can thus provide a fresh mercury electrode surface. However, the inherent toxicity of mercury limits its present applications, which is why this material is not covered in detail in this article.

5.3.7. Other Metal-Based Electrodes

The metals covered in the preceding sections are the most commonly employed electrode materials up to date. However, niche materials used as electrodes—e.g., vanadium, tungsten, niobium, tantalum, chromium, and cobalt—can often be handled analogously. It should be mentioned that some materials such as tungsten are not as easily mechanically cut, and thus extra care has to be taken if electrodes are prepared from larger metal pieces.

5.4. Carbonaceous Materials

Since an important requirement for a material to be usable as an electrode is sufficient electric conductivity, it is obvious why metals have traditionally been employed. Nevertheless, there are commonly utilized carbonaceous materials that have immense advantages over metals. Besides very simple handling, the most valuable aspect is the absence of metals which is highly appreciated in the synthesis of natural products and APIs.[39] This has led to the development of a variety of carbon forms ranging from simple isostatic graphite to boron-doped diamond (BDD) as next-generation electrode materials with outstanding properties for electrochemical synthesis.[40]

5.4.1. Graphite

The carbon modification most commonly used as electrode material is graphite which has favorable conductivity along the carbon sheets. Materials such as SIGRAFINE®, a commercial brand name for isostatic graphite in its most isotropic form, are very affordable and are thus being employed in a huge variety of different reactions as anode as well as cathode materials. The electrodes can be mounted in the usual stainless-steel electrode holders analogously to the metal-based plate electrodes, and can be cleaned by rinsing with suitable solvents or polished mechanically even though the latter cleaning process will remove layers of the graphite. Moreover, ultrasonication has to be used carefully as it might remove layers of the material as well. It is worth noting that graphite as layered material has the intrinsic properties of intercalating extraneous molecules; this property necessitates elaborate cleaning procedures to obtain contamination-free graphite electrodes. In addition, most graphite contains metals as ashes and is, therefore, not completely metal-free.

5.4.2. Graphite Cloth or Felt

SIGRACELL®, a carbon cloth or carbon felt, is a material similar to graphite with attractive properties such as flexibility and easy machinability. SIGRACELL® is particularly useful in reactions where isostatic graphite reaches its limits; for example, hydrofluoric acid leads to decomposition of isostatic graphite, whereas graphite foil gives satisfactory yields.[41] Mounting these electrodes onto the holders is analogous to mounting foam electrodes (see Figure 13). An alternative is to mount the material on a holder for thin foils to suppress movement during electrolysis. The material has to be handled carefully in terms of solvent uptake by the capillary effect during electrolysis. Therefore, immediate removal of the electrode from the electrolyte after electrolysis is highly recommended. Cleaning the electrode can be done by rinsing with solvents, as foam electrodes can be harshly polished mechanically in the pores. Moreover, since these electrode materials are among the least expensive ones, they can also be discarded after use.

5.4.3. Glassy Carbon and RVC

Another popular electrode material is reticulated vitreous carbon (RVC), a foamy form of glassy carbon, marketed as Duocel®. RVC is a very brittle material and difficult to clean as it has to be handled with great care. In contrast, solid glassy carbon is commercially available as compact, durable, and very stable material sold under the tradename SIGRADUR®. However, glassy carbon can only be harshly cut due to the fact that its mechanical strength increases when pressure is applied; thus, only laser cutting is a feasible method for preparing the corresponding electrode. Mounting and cleaning these electrodes can be done analogously to the way electrodes from other materials are treated (see Figures 12 and 13). While rinsing with solvents is suggested, the use of mechanical polishing is not recommended since it would cause rupture of the material surface.

5.4.4. Boron-Doped Diamond (BDD)

A novel electrode material is based on the diamond form of carbon. Doping diamond with boron leads to possible electric conductivity in the sp^3-hybridized form which is partially sp^2-hybridized due to the doping. This material has exhibited outstanding properties in multiple different electrosyntheses due to its wide potential range that can be attributed to the high overpotentials for hydrogen and oxygen evolution reactions. This permits the researcher to go far beyond the potential regimes associated with other electrode materials,[40,42] such as preparing high-performance oxidizers in ex-cell approaches.[43]

However, a special treatment of the electrodes is required to ensure long-term stability. BDD electrodes, like the commercially available DIACHEM®, are manufactured by coating a niobium, tantalum, silicon, graphite, or ceramics support with a thin layer of BDD.[40,42,44] The thin layer is mechanically fragile since the support material might be soft, and this requires careful handling to avoid scratching the layer surface or breaking its corner as this would expose the support to the electrolyte. Since the support material is often not (electro-) chemically inert its exposure to the electrolyte would cause destruction of the electrode by reaction and/or dissolution of the support. Thus, the recommended handling includes the avoidance of scratches by using special Teflon® electrode holders with a stainless-steel spring leaf connecting the stainless-steel part of the holder with the BDD plate to ensure conductivity (**Figure 14**). In smaller electrolysis cells such as the screening setups (see Figure 3), aluminum foil is wrapped around the top of the BDD electrode to enable contact between the crocodile clamp and the electrode while reducing the possibility of rupture. Careful handling during cleaning of these electrodes is also called for. Besides the customary procedure of rinsing the surface with solvents, mechanical treatment should not be firmly applied to coated electrodes or mechanically sensitive materials. However, anodic electrolytic cleaning with high current densities, e.g. 100 mA/cm^2 in diluted aqueous sulfuric acid (20% v/v), is highly recommended to remove residues and ensure sufficient reproducibility. During this cleaning procedure, one should refrain from using pole changers which promote corrosion of the electrode surface due to the fast generation of hydroxyl groups or protons at the surface. Moreover, when using BDD electrodes, electrode fouling can be limited if water is used in the electrolysis and higher cell potentials are applied. This so called “self-cleaning” is often attributed to the generation of hydroxyl radicals which suppress undesirable polymerization side reactions.[4,5,42,44,45]

5.5. Specially Functionalized Materials

Besides these common metal- and carbon-based electrodes, sophisticated modifications of electrode materials have been done, which allow surface structuring of the electrode as well as imprinting of information for selective transformations. An example of this new technology was recently reported by Kuhn, Wattanakit, and co-workers who developed and applied chiral imprinted nickel mesoporous surfaces to the stereospecific electroreduction of acetophenone to phenylethanol in up to 80% ee’s.[46] A less popular but auspicious electrode is made up

Figure 14. Electrode Holders for Mechanically Sensitive Electrode Materials. From Front to Back: Teflon® Electrode Holder with Stainless-Steel Spring Leaf for Facilitating Electrical Conductivity. The Leaf Is Fixed to the Electrode Holder with a Teflon® Screw. Side View of the Electrode Holder with a BDD Electrode Attached. Second Version of Teflon® Electrode Holder with Stainless-Steel Spring Leaf. Backside View of the Electrode Holder with Stainless-Steel Screws to Hold the Mounted BDD Electrode in Place.

of a mixed metal oxide (e.g., Ru–Ir–TiO_2) or dimensionally stable anode (DSA), which has high conductivity as well as inherent properties of corrosion resistance.[47] The most common use of these electrodes is to easily generate O_2 by decomposing water at moderate potentials.

Gas-diffusion electrodes (GDEs) are commonly applied in fuel cells to convert chemical energy into electrical energy by reacting hydrogen with oxygen to form water. However, recent developments in electro-organic synthesis have demonstrated their possible applications using gaseous substrates in liquid electrolytes with solid electrodes.[48]

6. Troubleshooting

One frequently encountered problem is the electrolysis reaching the voltage limit of the galvanostat used. This occurs in most cases because of insufficient electric conductivity in the electrolyte, when other obvious problem sources (e.g., unconnected cables) have been ruled out. For example, the contacts of the electrode holders should be checked for cleanliness and sufficient contact area. To overcome this challenge, the addition of more supporting electrolyte or an entirely different combination of solvent and supporting electrolyte is recommended.

The planned electrolysis is not possible due to a short circuit in the system. Often, this problem occurs when the electrodes are not fixed properly and are touching each other. This can either happen because of the turbulence generated by stirring the electrolyte and/or a foil electrode not sticking to its respective support. Another possible source of the short circuit could be the growth of a conductive layer on the electrodes if the distance between them is only slight.

Moreover, the application of high currents is accompanied by high Ohmic resistance which causes temperatures to rise. Thus, the application of higher currents will require modifying the experimental setup by using for example lager crocodile clamps.

7. Conclusion

In summary, the protocol of setting up an electrolysis is as simple as setting up a conventional, reagent-mediated chemical transformation in a round-bottom flask, and does not require much time or prior knowledge. Thus, it fits the requirements of advanced users of electrosynthesis as well as those of newcomers in this field. The compiled information about batch-type setups for electrosynthesis shows the wide variety of approaches that are possible, from home-built setups up to commercially available systems. The treatment of electrodes prior to or following electrosynthesis should be done carefully, as this is one of the keys to success in electro-organic synthesis.

8. Acknowledgment

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Reductive Electrosynthesis: A New Dawn


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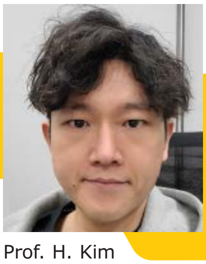
Prof. H. Kim


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Abstract. The renewed interest in synthetic organic electrochemistry has led in recent years to a surge in literature reports on new electrochemical reaction methods and synthetic strategies. While oxidative electrochemistry has been extensively studied in organic synthesis, reductive electrosynthesis in comparison remains substantially underexplored. Recent developments in this area have introduced innovative strategies to enable new transformations and control reaction selectivity. Here, we highlight examples of recent advances in direct reductive electrolysis, indirect reductive electrolysis, and reductive electrophotocatalysis.

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2. Direct Reductive Electrolysis
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    2.3. Electroreductive Olefin Functionalizations
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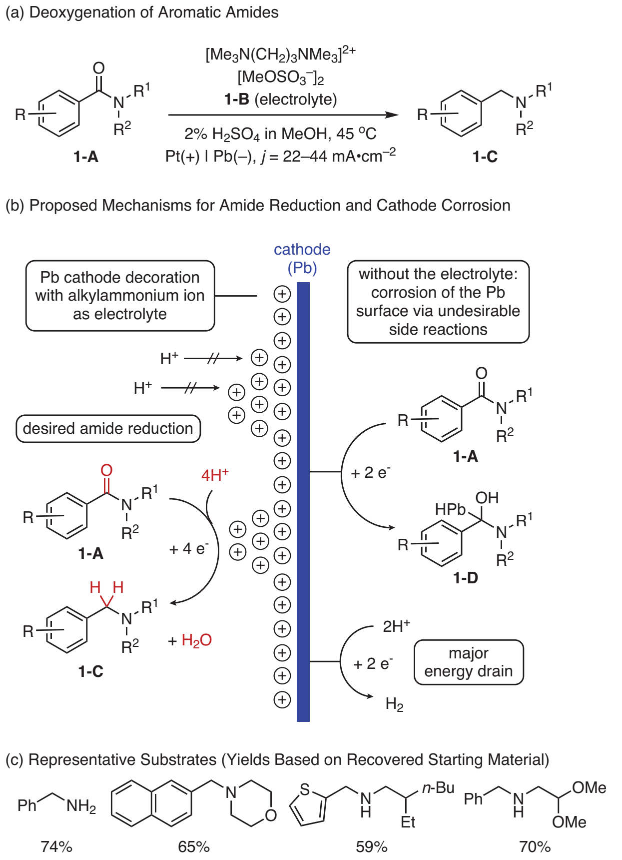
1. Introduction

The rapidly expanding field of organic electrochemistry promises to provide enabling new tools for chemical synthesis and sustainable alternatives to classical redox reactions.[1–4] In electrosynthetic transformations, stoichiometric quantities of often hazardous and expensive chemical oxidants and reductants are replaced by an electric current, thereby minimizing the generation of wasteful byproducts.[5] Moreover, the applied electric potential or current density can be easily adjusted to control the reaction rate and suppress undesired redox events, providing a unique opportunity to control the reaction outcome. Furthermore, these electrochemical approaches can provide higher energy efficiencies as compared to thermal and photochemical processes.[6–7] Finally, a number of features unique to electrochemical reactions such as the theoretically infinite redox range and the temporal and spatial controls of current/potential input offer new opportunities to address difficult synthetic challenges.

Despite extensive studies on oxidative electrochemistry,[8] reductive electrochemistry has yet to find widespread application in modern organic synthesis. Compared with anodic oxidation, cathodic reduction chemistry presents several intrinsic challenges. For example, competing proton and O_2 reduction can occur at relatively low overpotentials on most electrodes, thereby requiring many such reactions to be carried out under moisture- and air-free conditions. In addition, finding a suitable oxidation reaction on the counter electrode can be challenging. Compared to the most commonly employed counter reaction for anodic oxidation, hydrogen evolution, the counter reaction for cathodic reduction (e.g., oxidation of a sacrificial anode or an amine) could introduce undesired side products that interfere with the desired transformation. Finally, under deeply reducing potentials, electrode passivation can also take place. Therefore, careful reaction design is often necessary to achieve high levels of reactivity and selectivity at reasonable electrode potentials.

Despite these challenges, significant progress has been made in recent years in the area of electroreductive chemistry. These advances have been propelled by the introduction of new reaction strategies, the development of redox mediators, and the understanding of reaction mechanisms enabled by advanced electroanalytical tools.[9–12] In addition, the strategic application of research tools and approaches reported in the literature of battery, fuel cell, and electroplating studies has led to creative solutions to such vexing problems as electrode fouling and catalyst degradation.



Scheme 1. Waldvogel's Reduction of Amides to Amines on a Lead Cathode Surface. *(Ref. 19)*

Herein, we highlight recent developments in electroreductive synthesis by using a number of representative examples and with an emphasis on the application of novel reaction strategies as well as mechanistic hypotheses that underpin reaction development. In some of the examples, the replacement of heterogeneous or air-sensitive reductants allows the desired reductive transformation to be carried out in a practical and scalable manner. In other examples, electrochemistry enabled new chemical reactivities that are otherwise difficult to achieve or previously unknown. These advances in methodology fall in three categories: direct reductive electrolysis, indirect reductive electrolysis, and the nascent area of reductive electrophotocatalysis. This article is not meant to be a comprehensive review on the topic of electroreductive synthesis; readers are referred to related recent reviews[12–16] for specific topics of interest.

2. Direct Reductive Electrolysis

The direct reductive electrolysis under highly biased electrode potentials provides a simple means to activate strong chemical bonds in redox-inert organic substrates. For example, simple and abundant substrates such as ketones, olefins, arenes, and organohalides have been engaged in novel organic reactions by employing direct reductive electrolysis.[17] In such reaction systems, substrate molecules undergo electron transfer with the cathode surface, leading to the accumulation of highly reactive radical and radical anion intermediates in the electric double layer. Some of these high-energy species can engage in further functionalization reactions either within the double layer or in the bulk solution depending on their lifetime and diffusion rate. However, these reactive intermediates can also decompose unproductively, causing electrode deactivation and substrate decomposition. Recently, several creative strategies have been employed to prevent electrode passivation and maintain high reaction efficiencies. The next subsections describe several recent examples that show how direct electrolysis can be utilized to improve existing transformations or enable new reactivities.

2.1. Reduction of Amides

Due to their very negative reduction potentials, previous methods for the electroreduction of carboxamides required either substrate activation by concentrated sulfuric acid or trapping of the radical anion intermediate with an oxophilic metal ion or a silylating agent.[18,19] In 2014, Edinger and Waldvogel reported an improved method that utilizes a dilute sulfuric acid solution as the activating agent under mild conditions (Scheme 1).[19] The method converts aromatic amides to the corresponding amines in moderate-to-good yields in the absence of a metal catalyst or a stoichiometric potent reductant.

Importantly, the authors reported that the use of tetraalkylammonium salts as the electrolyte enhances the selectivity for the desired reduction over side reactions. In the absence of an alkylammonium electrolyte, a reduced yield of the amine product was observed along with corrosion of the lead cathode and competing hydrogen evolution. Employing *N,N,N,N′,N′,N′*-hexamethyl-1,3-propanediammonium methylsulfate (**1-B**) as the electrolyte afforded the desired reactivity in 2% sulfuric acid in MeOH. The authors proposed that the chosen electrolyte is optimal in achieving a compact cationic coating of the lead cathode, avoiding unproductive side reactions on its surface and electrode fouling.

The reaction scope predominantly involves aromatic substrates with pendant acyclic or cyclic amine groups, generating various benzyl amines in up to 62% isolated yield and with 15–52% Faradaic efficiency. It was noted that aliphatic amides were not viable substrates as they were unreactive even at a high sulfuric acid concentration (30% in MeOH) and high current densities (up to 110 mA/cm^2).

2.2. Birch-Type Reduction

In 2019, Neurock, Minteer, Baran, and co-workers reported an electrochemical method for Birch-type reduction under mild conditions (**Scheme 2**).[20] This protocol does not require the generation of solvated electrons from ammonia and alkali metals, which are utilized in the classic Birch reduction.[21–23] Prior to this work, Cheng and co-workers achieved the electrochemical hydrogenation of alkenes, alkynes, and aryl ketones without reducing the aromatic rings and using gaseous ammonia as a hydrogen source.[24]

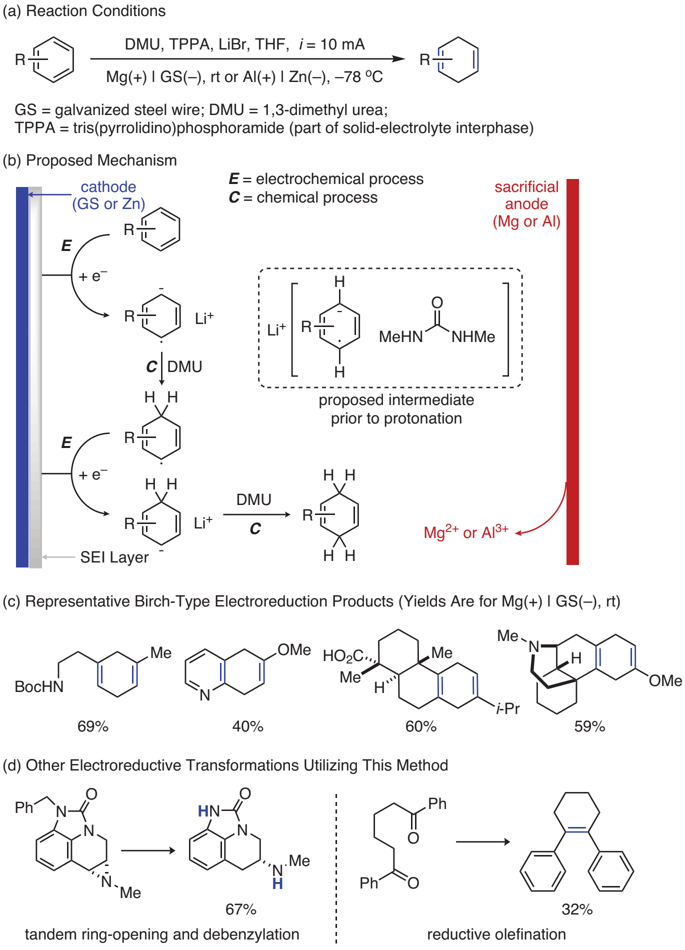
The introduction of a solid electrolyte interphase (SEI) is one of the key features in this protocol. The SEI is a passivation layer that plays a crucial role in Li-ion battery technology as a solid electrolyte that can facilitate the ion transport in a redox reaction.[25,26] The SEI, formed by an intricate interplay between additives, solvent, and electrolyte, also prevents undesired passivation at the electrode.[27–29] This results in a more active and stable electrode interface even under extreme potentials, as supported by X-ray photoelectron spectroscopy measurements. The optimal conditions of this electroreduction protocol involved the use of a magnesium anode, galvanized steel wire cathode, LiBr as electrolyte, the weakly acidic dimethyl urea (DMU) as the proton source, and tris(pyrrolidino)phosphoramide (TPPA) as an additive. Additives such as hexamethylphosphoramide (HMPA) are known for dissolving the passivating Li_2O layer on the electrode and reducing the effects of overcharging in Li-ion batteries.[30] For this purpose, TPPA, a safer alternative to HMPA, was found to be the optimal additive.

The proposed mechanism for this direct Birch-type electroreduction is depicted in Scheme 2, Part (b). Mechanistic studies revealed that the reaction likely proceeds through an electrochemical-chemical-electrochemical-chemical (*ECEC*)-type process. Square wave voltammetry (SWV) experiments indicated that two distinguishable electrochemical reduction steps occur at similar potentials under the standard electrolysis conditions, but that these electron-transfer events are separated by a chemical protonation step.

Under the optimal reaction conditions, a variety of functional groups such as carbamates and carboxylic acids were tolerated. The reaction was also applied to the reduction of N-heteroarenes and natural product derivatives (Scheme 2, Part (c)). The methodology was successfully extended to reactions other than dearomatization, such as the deprotection of benzyl amines and ethers, epoxide and aziridine ring openings, deoxygenation of ketones, the McMurry coupling, and reductive cyclizations (Scheme 2, Part (d)). The method was scalable to the 100-g scale in both batch and flow reactors.

2.3. Electroreductive Olefin Functionalizations

While a number of electrooxidative olefin functionalization reactions have been reported in the past,[31-35] the development of electroreductive protocols for the difunctionalization of olefins remains an underexplored research area. A general and effective approach for achieving such a transformation involves a radical–polar crossover mechanism initiated by the electroreduction of a radical precursor. The incipient radical intermediate reacts with the olefin substrate, and a subsequent



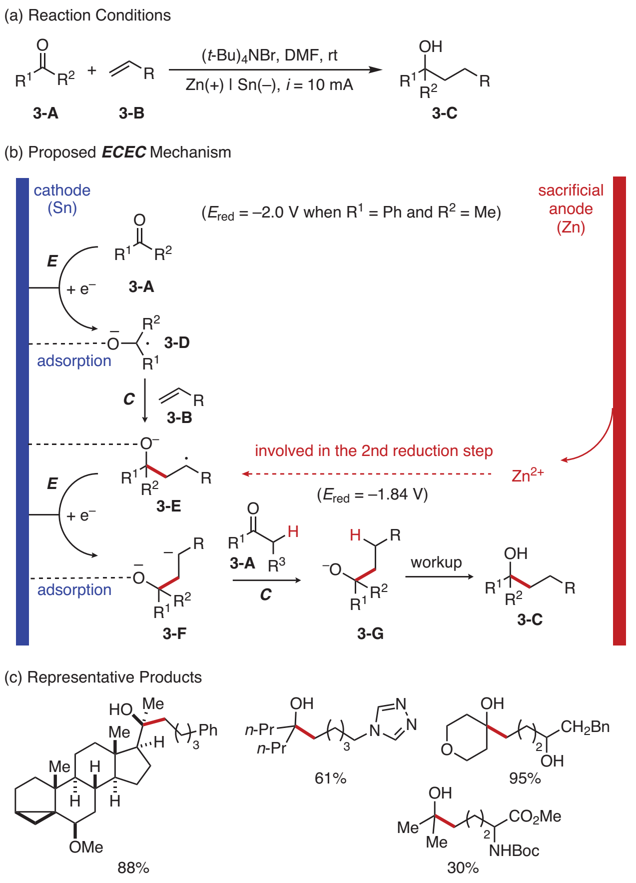
Scheme 2. Birch-Type and Other Organic Electroreductions. *(Ref. 20)*

reduction of the resulting radical species generates a carbanion. This anionic nucleophile is then subjected to reaction with various electrophiles in a 2-electron pathway, thus completing the difunctionalization.

2.3.1. Reductive Coupling of Carbonyls and Olefins

Recently, Minteer, Baran, and co-workers reported the synthesis of tertiary alcohols by the electroreductive coupling of unactivated ketones and olefins (**Scheme 3**).[36] The main advantages of the reaction include mild conditions, absence of the need to exclude air and moisture, elimination of stoichiometric strongly reducing agents, and broad functional group compatibility. The authors noted that this protocol can potentially replace canonical methods for generating the same type of product (e.g., Grignard addition to ketones), thereby improving the synthesis of biologically active compounds.

As depicted in Scheme 3, Part (b), the ketyl radical species **3–D**, generated by the initial electrochemical reduction of ketone **3–A**, adds to the olefin which then undergoes electrochemical reduction to form di-anion **3–F**. SWV analysis showed that the electrochemical reduction of **3–E** leading to **3–F** was facilitated by the presence of Zn^{2+} as a thermodynamic sink. Thus, zinc proved to be a superior anode material to other electrode materials. The *ECEC* mechanism is completed by protonation of dianion **3–F** to yield tertiary alcohol **3–C**.

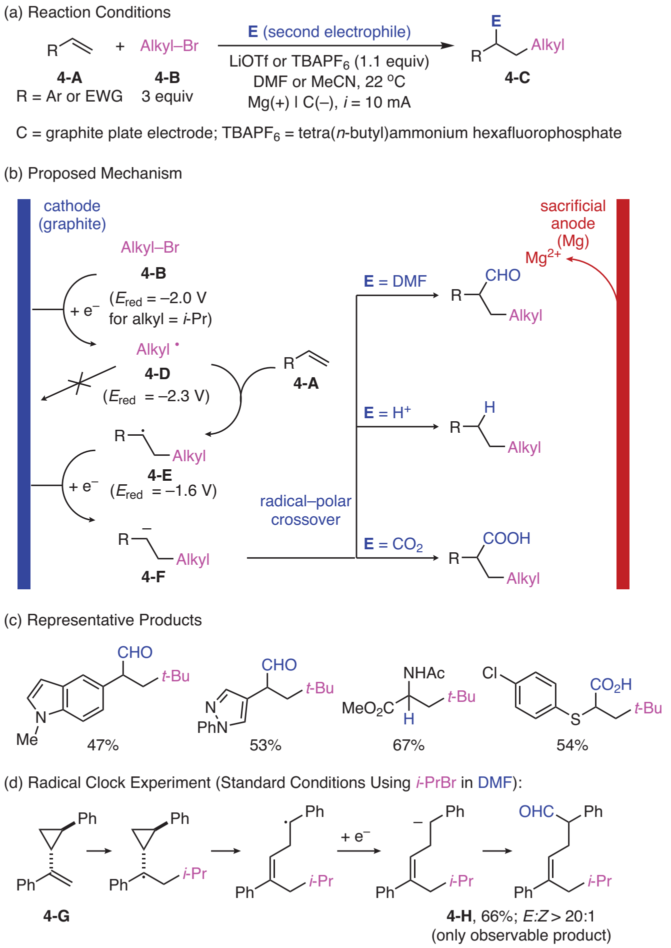


Scheme 3. Electroreductive Ketone–Olefin Coupling for the Mild Synthesis of Tertiary Alcohols. *(Ref. 36)*

In this protocol, a suite of ketones and olefins were compatible, although lower efficiencies were observed with polysubstituted olefins as a result of steric repulsion in the ketyl radical addition step. The reaction was successfully performed on a 100-g scale using a flow system, affording a yield similar to that obtained in the small-scale batch run.

2.3.2. Olefin Functionalization via Reduction of C–Br and Si–Cl Bonds

In 2020, Zhang and Lin further expanded the scope of reductive electrosynthesis to the carbofunctionalization of olefins (**Scheme 4**).[37] The transformation proceeds through the aforementioned radical–polar crossover mechanism in which alkyl-radical and carbanion intermediates are generated via cathodic reduction of common alkyl bromides and olefins. By judiciously choosing the coupling partners based on their



Scheme 4. Lin's Electroreductive Difunctionalization of Olefins with Two Distinct Electrophiles via a Radical–Polar Crossover Mechanism. *(Ref. 37)*

redox potential and polarity, the authors devised a series of reaction methods for the intermolecular carboformylation, *anti*-Markovnikov hydroalkylation, and carbocarboxylation of olefins. These reactions functionalize olefins with two distinct *electrophiles* under simple transition-metal-free conditions, and exhibit a broad substrate scope and high functional-group tolerance.

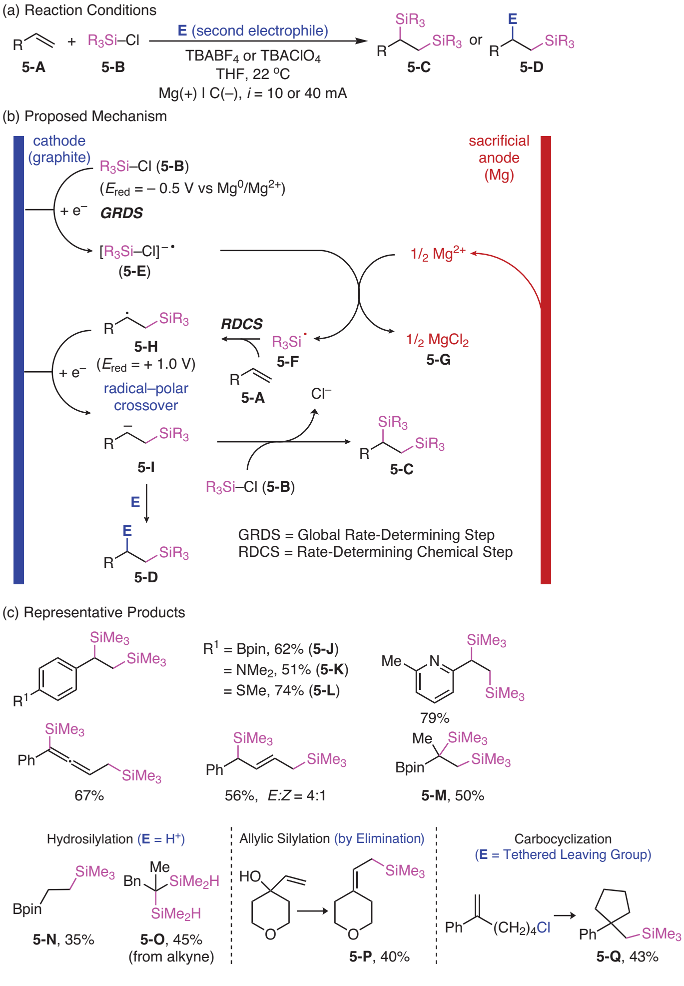
The authors suggested an *ECEC*-type mechanism, wherein a radical–polar crossover is initiated by alkyl halide electrochemical reduction (Scheme 4, Part (b)). This hypothesis is consistent with the reduction potentials of the reactants and intermediates involved in the mechanism. Specifically, the reduction of the alkyl bromide, **4–B**, to the alkyl radical, **4–D**, is followed by addition of the latter to a radical acceptor olefin, **4–A**, and the incipient electrophilic *C*-centered radical, **4–E**, undergoes electrochemical reduction to carbanion **4-F**. The initial alkyl halide reduction event is rate-determining, whereas the subsequent olefin addition and second reduction of radical **4–E** are facile—meeting the criteria for an *ECEC*-type mechanism. Trapping of **4–F** by a second electrophile, **E**—such as DMF, MeCN (H^+ source), or CO_2—yields the difunctionalized product. Electrophiles **E** are more difficult to reduce than the alkyl halide substrate, thus ensuring high cross-selectivity for olefin functionalization. A radical-probe experiment was conducted to further support the proposed mechanism. Using a cyclopropane-derived substrate **4–G**, the ring-opened carboformylation product **4–H** was observed exclusively in DMF (Scheme 4, Part (d)).

This mechanistic paradigm was recently extended by Lin and co-workers to the radical silylation of olefins (**Scheme 5**).[38] In this work, the generation of silyl radicals was achieved by the electroreductive activation of the Si–Cl bond in readily available chlorosilanes. The new reactivity provides a different strategy for the construction of valuable $C_{(sp3)}$–Si bonds that are relevant in synthetic, medicinal, and materials chemistry. Traditionally, this chemistry had been largely inaccessible due to the challenging reduction of chlorosilanes which contain strong Si–Cl bonds.[39]

This electroreductive strategy was first demonstrated in an olefin disilylation reaction to construct vicinal disilanes (Scheme 5). Various functionalities that are potentially sensitive to chemical redox agents; such as boronate (**5–J**), tertiary amine (**5–K**), and thioether (**5–L**); were compatible with the reaction conditions. Several electron-deficient and electron-rich heterocycles were also tolerated, while simple aliphatic olefins suffered from lower reactivity and chemoselectivity, likely due to the lack of anion-stabilizing substituents. Interestingly, other types of π-systems such as allenes, internal alkynes, conjugated dienes, and enynes afforded a range of allyl and vinyl silane products, which could be derivatized further by using cross-coupling and allylation reactions. Moreover, vinyl boronates were suitable substrates, providing products with *gem*-(B,Si) substitution (**5–M**), which is a versatile functional group in organic synthesis.

In this reaction, a magnesium sacrificial anode was important for achieving high reactivity. Through a series of control experiments, the authors excluded reaction pathways involving electrogeneration of Mg^0. Instead, CV data suggested that the anodically formed Mg^{2+} facilitates the reduction of R_3SiCl likely by binding to the chloride leaving group (Scheme 5, Part (b)). Additional CV and kinetic data showed that the overall reaction is analogous to the previously reported olefin carbofunctionalization, wherein an *ECEC*-type mechanism allows for the installation of the vicinal C–Si bonds via a radical–polar crossover pathway. In some reactions, when competing Mg^{2+} reduction led to passivation of the cathode surface, a temporary reversal of the electrode polarity was employed to dissolve the passivation layer and restore reactivity.

The scope of the radical silylation protocol was also expanded to include olefin hydrosilylation, an industrially important transformation that relies traditionally on noble-metal catalysts in combination with hydrosilanes.[40] By changing the solvent from THF to the weakly acidic MeCN, the carbanion intermediate **5–I** can be intercepted through protonation (Scheme 5, Part (c), bottom left). Thus, a collection of

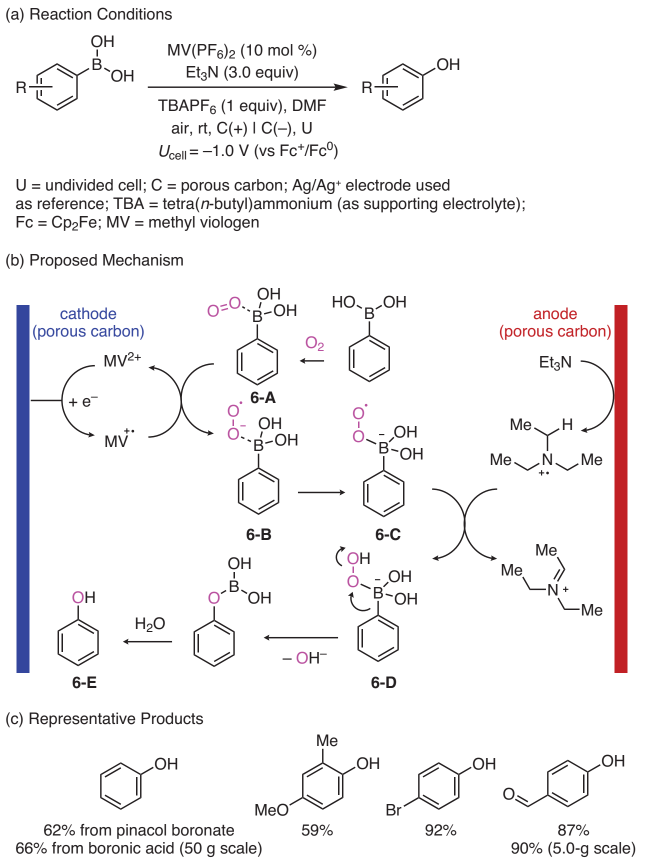


Scheme 5. Electroreductive Radical Silylation of Unsaturated Carbon–Carbon Bonds. *(Ref. 38)*

hydrosilylated products (e.g., **5-N** and **5-O**) were synthesized from olefin and alkyne substrates. Moreover, when a suitable leaving group is positioned within the olefinic substrate, allylic silylation (via elimination; **5–P**) and carbosilylation (via nucleophilic substitution; **5–Q**) were achieved.

3. Indirect Reductive Electrolysis

Indirect reductive electrolysis is performed by employing a redox mediator that acts as an electron shuttle to deliver electrons from the electrode surface to the substrate of interest.[1,41–43] When the redox mediators are used in sub-stoichiometric amounts, they are referred to as homogeneous electrocatalysts. Redox mediators can decrease the overpotential required for substrate reduction, thus allowing the desired reactions to occur under milder conditions and with improved chemoselectivity. In many cases, the introduction of a mediator can also circumvent common issues associated with direct reductive electrolysis such as electrode fouling. While organic redox mediators have found applications in electroreductive chemistry, nickel complexes have been studied in cross-electrophile coupling reactions. This section presents and discusses—with a special focus on reaction design and mechanistic hypotheses—selected recent examples of indirect reductive electrosynthesis that utilizes organic or metal-based redox mediators.



Scheme 6. Methyl Viologen (MV^{2+}) Catalyzed Mild Aerobic Oxidation of Boronic Acids to Phenols. *(Ref. 47)*

3.1. Methyl Viologen (MV^{2+})

Methyl viologen (MV^{2+}) is an inexpensive and potentially scalable electrocatalyst that can undergo a fast and reversible single-electron reduction.[44] These qualities have made MV^{2+} an attractive redox mediator for organic synthesis. The reduced MV$^{•+}$ species is highly air-sensitive and undergoes oxidation by O$_2$ to yield superoxide (O$_2^{•–}$).[45] The propensity for MV^{2+} to photolytically generate superoxide in plant photosystems[46] inspired Liu's group to investigate its reactivity in the aerobic hydroxylation of arylboronic acids (**Scheme 6**).[47] The reaction takes place under mild conditions with a relatively broad scope of arylboronic acid substrates and even a pinacol boronate. Electron-deficient arenes provided the desired phenolic products in higher yield than electron-rich ones, and it is believed that over-oxidation of arenes is a major competing reaction. The scalability of this method was demonstrated on both a 5-g and a 50-g scale.

Kinetic studies using cyclic voltammetry revealed a mechanism distinct from a previously reported one for the aerobic photocatalytic oxidation of arylboronic acids using Ru(bpy)$_3$Cl$_2$.[48] In lieu of direct activation of O$_2$, Liu and co-workers proposed a trimolecular transition state in the key reduction step (**6-A** → **6-B**) that consists of one MV$^{•+}$, one O$_2$, and one molecule of the substrate. Specifically, an initial Lewis acid/base adduct (**6-A**) is formed between an O$_2$ lone pair and the empty p-orbital of boron. The activated O$_2$ is then reduced by the electrochemically generated MV$^{•+}$ to form the superoxo-arylboronic acid radical anion **6-B**. Hydrogen-atom abstraction from anodically oxidized TEA by **6-C** gives rise to an arylperoxyborate anion (**6-D**) that decomposes via a 1,2-aryl shift from boron to oxygen, which expels hydroxide and affords the phenolic product (**6-E**) upon hydrolysis. However, given the weak Lewis basicity of O$_2$, an alternative mechanism cannot be ruled out in which a slow and endergonic reduction of O$_2$ by MV$^{•+}$ is followed by a rapid and irreversible reaction of the resultant superoxide with the boronic acid substrate.

3.2. Perylene Diimides (PDIs)

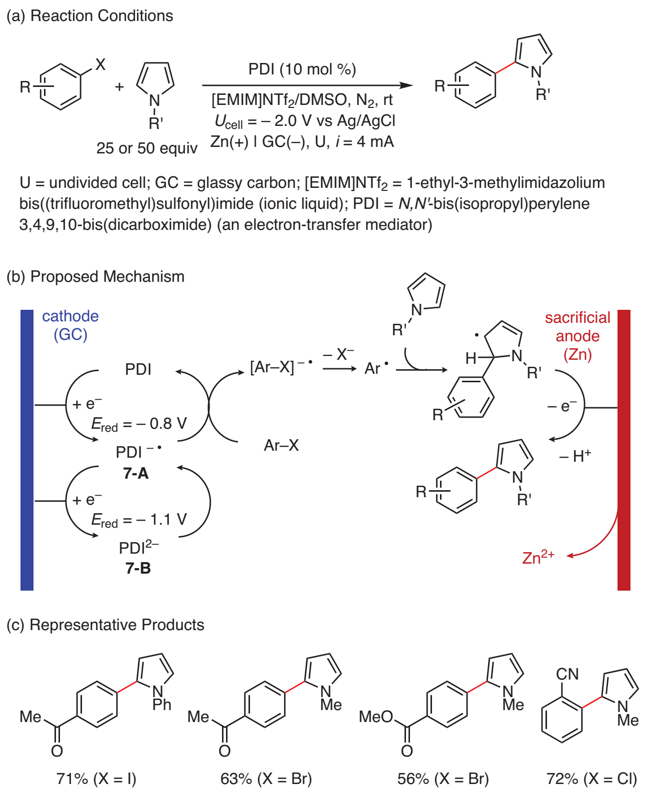
Zhu and co-workers have reported the indirect electroreductive coupling of aryl halides and pyrroles using perylene diimides (PDIs) as redox mediators (**Scheme 7**).[49] Such catalysts have previously been utilized as organic redox mediators in photocatalysis.[50] In Zhu's work, cyclic voltammetry showed that PDIs can undergo consecutive reductions to form the corresponding radical anions **7–A** at –0.8 V vs Ag/AgCl and dianions **7–B** at –1.1 V, depending on the applied potential. In an imidazolium-based ionic liquid electrolyte solution, various electron-deficient aryl halides can be coupled with free or N-substituted pyrroles to form biaryl products. In contrast, other five-membered-ring heterocycles including furans, thiophenes, and indoles were unreactive.

The proposed mechanism involves the reduction of PDI at a glassy carbon cathode to generate the radical anion and dianion species (Scheme 7, Part (b)). Under constant current electrolysis, PDI radical anion **7–A** is preferentially generated from neutral PDI and then delivers an electron to the aryl halide substrate to form the aryl halide radical anion. This species undergoes mesolytic cleavage of the C–X bond to yield an aryl radical (Ar•), which reacts with the pyrrole partner to yield the $C_{(sp2)}$–$C_{(sp2)}$ coupling product. Although both the PDI radical anion (**7-A**) and dianion (**7-B**) are observed under electrolysis conditions, the authors proposed that **7–A** is likely the more active catalyst species, because a higher reaction yield was observed when the reaction was conducted at a lower electrode potential.

3.3. Ni-Catalyzed Cross-Electrophile Couplings

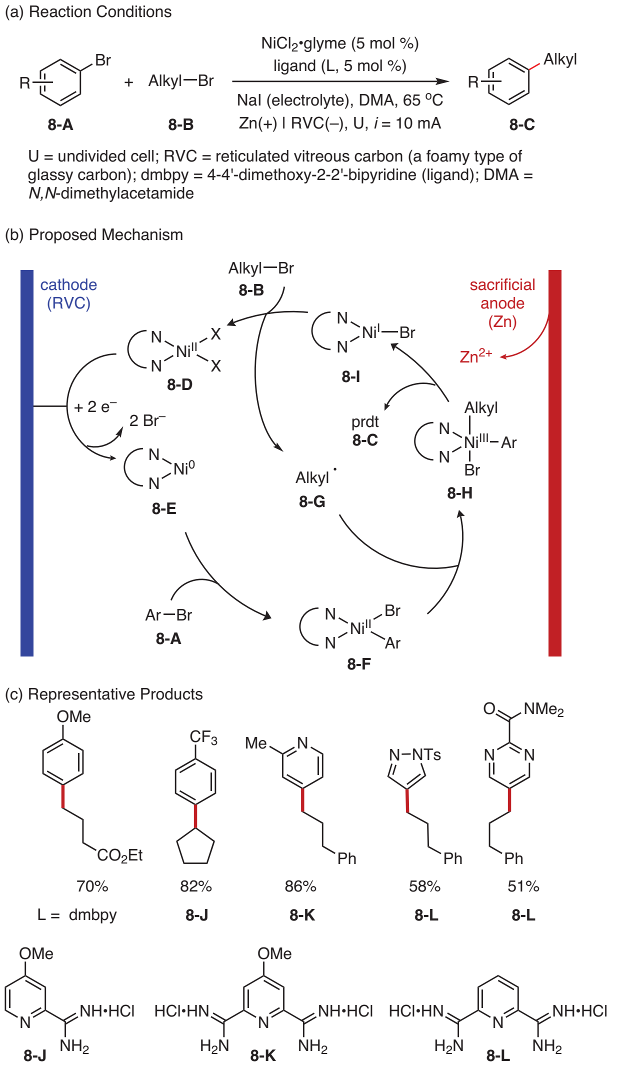
The nickel-catalyzed, cross-electrophile coupling (XEC) reaction has emerged as a powerful method for constructing C–C bonds by joining two electrophiles in the presence of a terminal reductant.[51] XEC reactions avoid the stoichiometric use of highly basic organometallic reagents employed in traditional cross-coupling protocols. A typical, nonelectrochemical XEC reaction requires a super-stoichiometric quantity of a metal powder, often Mn^0 or Zn^0, as a heterogeneous terminal reductant to turn over the Ni catalyst. This requirement can often limit its scalability and reproducibility largely due to the variable quality of commercially available metal reductants, inconsistent stirring rates, and the generation of wasteful side products. In recent years, electrochemical turnover of Ni catalysts has been explored as an alternative strategy to eliminate the need for chemical reductants in XEC reactions.

In 2017, Hansen's group reported an electrochemical method for Ni-catalyzed $C_{(sp2)}$–$C_{(sp3)}$ XEC reactions (**Scheme 8**).[52] It was hypothesized that such reactions start with the reduction of Ni^{II} to Ni^0 (**8-D → 8-E**) followed by oxidative insertion of the latter into the aryl bromide substrate (Scheme 8, Part (b)) to produce the Ni^{II} intermediate **8-F**. Addition of an alkyl radical (**8–G**) to **8–F** generates Ni^{III} intermediate **8–H**, which undergoes reductive elimination to form cross-coupling product **8–C** and Ni^I species **8–I**. **8–I** then reacts with alkyl bromide substrate **8–B** to produce alkyl radical **8–G** and regenerate Ni^{II} (**8-D**).



U = undivided cell; GC = glassy carbon; [EMIM]NTf_2 = 1-ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide (ionic liquid); PDI = *N,N'*-bis(isopropyl)perylene 3,4,9,10-bis(dicarboximide) (an electron-transfer mediator)

Scheme 7. Perylene Diamide (PDI) Catalyzed Reductive Heteroarylation of Aryl Halides. *(Ref. 49)*



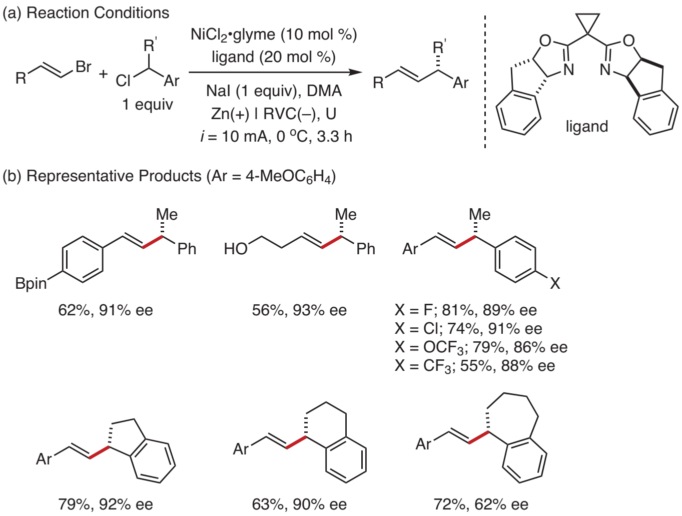
U = undivided cell; RVC = reticulated vitreous carbon (a foamy type of glassy carbon); dmbpy = 4-4'-dimethoxy-2-2'-bipyridine (ligand); DMA = *N,N*-dimethylacetamide

Scheme 8. Hansen's Nickel-Catalyzed Electroreductive $C_{(sp2)}$–$C_{(sp3)}$ Cross-Electrophile Coupling (XEC). *(Ref. 52)*

The authors also postulated that a balancing act between temperature, which alters the rate of chemical steps in the catalytic cycle, and current, which controls the rate of electroreductive generation of Ni^0, was important to achieve a high current efficiency and selectivity. In this system, a current of 77 mA per mmol of catalyst was found to be optimal, leading to the hypothesis that it permits the matching of the rate of Ni reduction to the rate of regeneration of the Ni^{II} species.

In 2019, DeLano and Reisman reported an enantioselective, Ni-catalyzed electroreductive cross-coupling of alkenyl and benzyl halides (**Scheme 9**).[53] This method avoids the use of stoichiometric reductants[54–57] such as Mn^0 and TDAE [tetrakis(*N*,*N*-dimethylamino)ethylene] and affords products bearing allylic and benzylic stereogenic centers with high enantioselectivity. Notably, the method does not require an excess of either of the coupling partners. The optimal conditions consist of $NiCl_2{\cdot}dme$ with an indanyl-fused bis(oxazoline) ligand as the catalyst in a DMA solution of NaI as the electrolyte with the electroreductive coupling carried out in an undivided cell with an RVC cathode and a sacrificial Zn anode. The amount of current applied was shown to influence both reaction efficiency and enantioselectivity; doubling and halving the current intensity resulted in lower product yields and enantiomeric excesses. A broad range of organohalides were suitable substrates in this XEC reaction (Scheme 9, Part (b)). Functional groups such as aryl pinacol boronic ester, free primary alcohol, and aryl halides (F, Cl) were compatible with the reaction conditions.

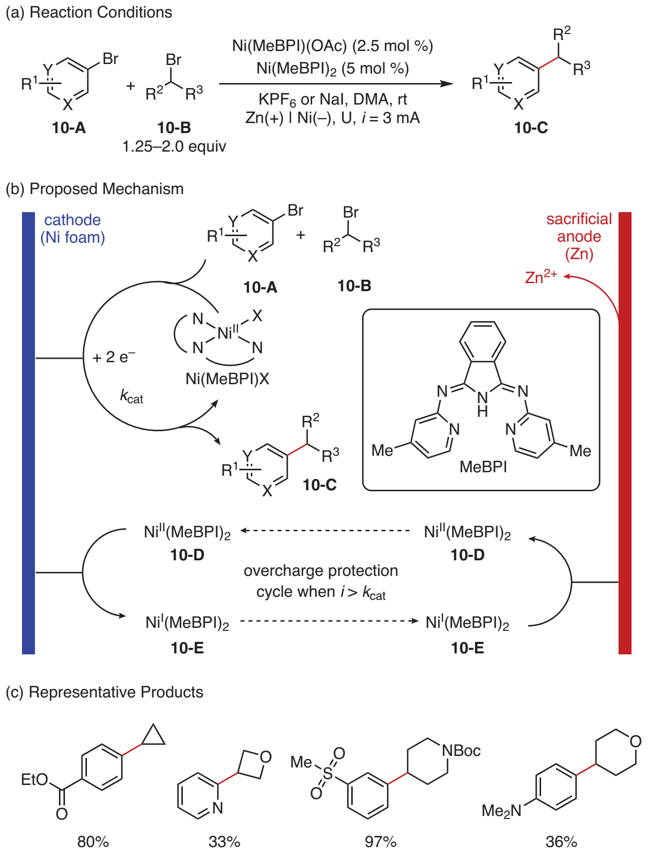
Recently, Sevov and co-workers reported an improved catalytic system for the $C_{(sp2)}–C_{(sp3)}$ XEC reactions (**Scheme 10**).[58] In this work, a catalytically inactive redox shuttle **10–D** was introduced into the electrochemical system, which helps to protect the active Ni catalyst from overreduction. This strategy was key to solving the challenge of catalyst degradation in cross-coupling reactions.



Scheme 9. Enantioselective Electroreductive Coupling of Alkenyl and Benzyl Halides Catalyzed by Nickel. *(Ref. 53)*

In a constant current electrolysis, when the rate of the electrochemical step exceeds that of the chemical steps, overreduction of the catalyst can take place, leading to catalyst degradation and side reactions. The addition of a redox shuttle can circumvent this problem by absorbing excessive electrons from the cathode and transporting them to the anode when the rate of reduction is greater than the rate of coupling. Such degenerate electron transfer between electrodes acts to short-circuit the electrochemical cell and protect the coupling catalyst from further reduction.

The homoleptic Ni complex with bis(pyridylamino)isoindoline (BPI) ligands (**10–D**) was the most suitable redox shuttle, owing to its mild reduction potential compared to the cross-coupling reaction potential (–1.8 V vs –1.9 V, measured vs Fc/Fc^+). It was also found that the concentration of **10–D** should be kept low to prevent excessive short-circuiting that inhibits the desired reaction. The notable differences in yield between reactions with added redox shuttles (generally >80%) and those without (generally <20%) highlight the remarkable impact of this overcharge protection strategy in Ni-catalyzed XECs.



Scheme 10. Sevov's Overcharge Protection Strategy for Nickel-Catalyzed Electroreductive Cross-Electrophile Coupling (XEC) Reactions. *(Ref. 58)*

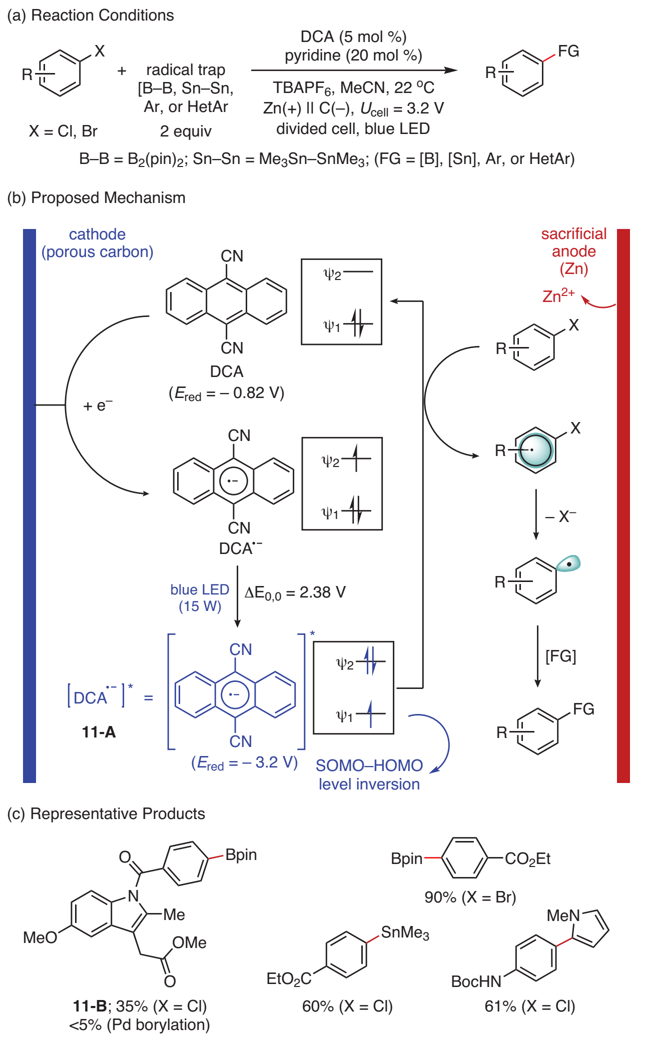
4. Reductive Electrophotocatalysis

Electrophotocatalysis is an emerging strategy for achieving extremely oxidizing or reducing potentials by using a single catalytic species that is sequentially activated via electrolysis and photoexcitation.[14,15] The potency of the electrophotocatalyst results from the combination of its redox potential and the energy of the absorbed photon.[59] This strategy has recently been employed to promote reductive organic transformations of highly inert starting materials.

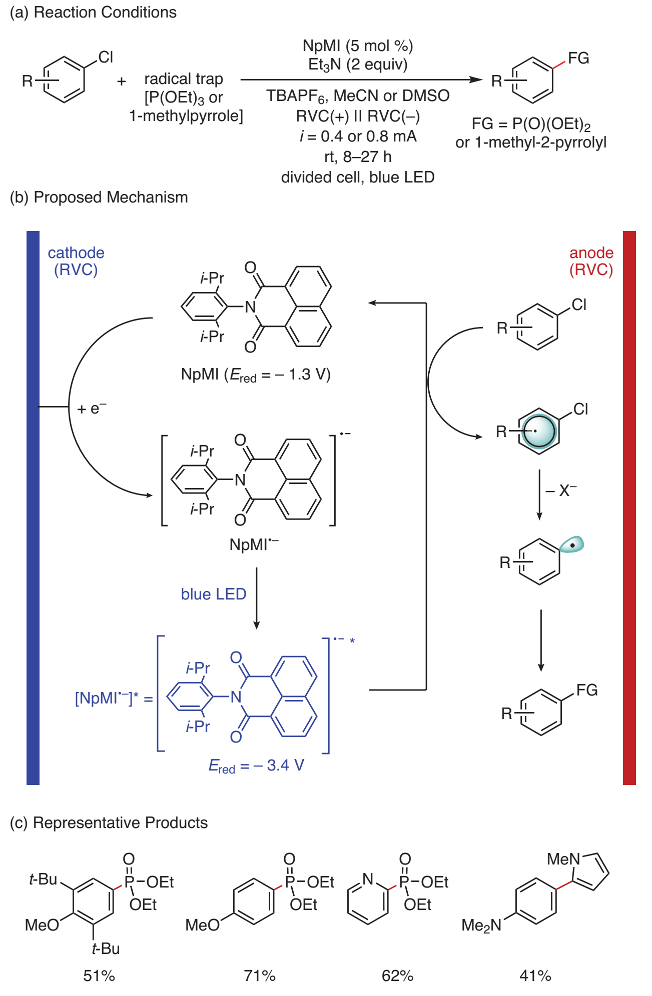
In 2020, Lin's and Lambert's groups reported in a joint paper a reductive electrophotocatalytic system that utilizes 9,10-dicyanoanthracene (DCA) as an electrophotocatalyst (**Scheme 11**).[60] The LUMO (Ψ_2) of DCA is first populated with an electron from cathodic reduction to become the SOMO of $DCA^{\bullet-}$. Upon photoexcitation of $DCA^{\bullet-}$, an electron transition from the HOMO (Ψ_1) to SOMO (Ψ_2) gives rise to an unusual SOMO–HOMO level inverted electronic structure. The exceptionally potent reducing power of this electrophotocatalyst (–3.2 V vs SCE) is attributed to the energy obtained from electron repopulation of these high-lying frontier orbitals.

Under the optimal reaction conditions, the excited-state $DCA^{\bullet-}$ (**11-A**), generated via tandem electrophotochemistry, enabled the activation of aryl halides with very high reduction potentials (E_{red} = –1.9 to –2.9 V, Scheme 11, Part (b)). The resulting aryl radicals engaged with radical traps in various transformations to furnish arylboronate, arylstannane, and biaryl compounds. Notably, the method can tolerate aryl halide substrates with Lewis basic coordinating groups such as peptide **11-B**, which was not compatible with canonical Pd-catalyzed Miyaura borylation conditions likely due to catalyst deactivation.

Concurrently, Wickens and co-workers reported a similar transformation that employs a naphthalene-based monoimide (NpMI) as electrophotocatalyst (**Scheme 12**).[61] In this method, phosphorylation and biaryl coupling of aryl chlorides (Scheme 12, Part (c)) were achieved with reduction potentials of up



Scheme 11. Reductive Electrophotocatalysis That Utilizes 9,10-Dicyanoanthracene (DCA) as an Electrophotocatalyst. *(Ref. 60)*



Scheme 12. Wickens's Reductive Electrophotocatalysis Using a Naphthalene-Based Monoimide (NpMI) as an Electrophotocatalyst. *(Ref. 61)*

to –3.3 V vs SCE. The high chemoselectivity observed was attributed to the strongly reducing catalytic species produced in small concentrations at low applied electrochemical potentials. Electrophotocatalysis, therefore, promises to grant access to challenging organic reactivities that require extreme reduction potentials.

5. Conclusion

Recent advances in synthetic organic electrochemistry have resulted in the development of a plethora of methods for reductive electrosynthesis. Direct reductive electrolysis allows for the activation of inert organic molecules at highly reducing potentials. Alternatively, indirect electrolysis facilitates reactions under mild conditions with precise control of selectivity. Very recently, electrophotocatalysis has emerged as a new approach for reductive electrosynthesis by utilizing photoexcitable redox mediators. Under these different mechanistic manifolds, a large number of useful organic transformations have been achieved, including cross-coupling, dearomatization, amide reduction, and olefin functionalization. We anticipate that new developments in electroreductive methods will continue to enrich the growing field of electroorganic synthesis and provide practical solutions to synthetic challenges.

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Chemistry with Potential: Present Challenges and Emerging Trends in Organic Electrocatalysis

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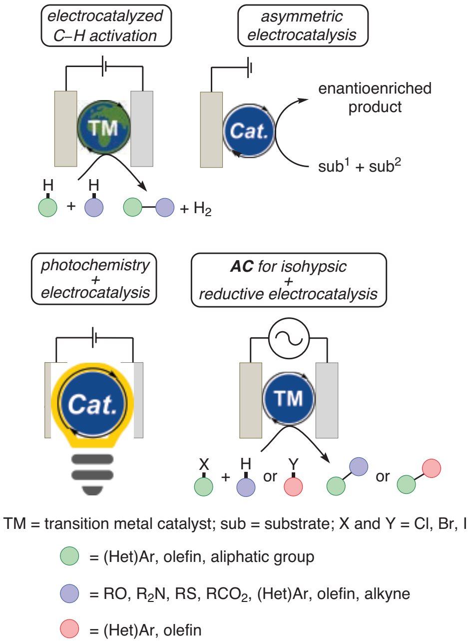
Keywords. 3d metals; C–H activation; asymmetric electrocatalysis; electrophotocatalysis; mechanism; sacrificial anode.

Abstract. In this short article, we present our perspective on present challenges and emerging trends in electro-organic synthesis with the aim of familiarizing and encouraging synthetic chemists to explore this field of research that holds significant promise for advancing the art and science of organic synthesis.

In molecular synthesis, scientists commonly use molecules as energy carriers to ensure effective chemical oxidation or reduction reactions. However, the stoichiometric carrier molecule is typically consumed and often gives rise to toxic and/or expensive chemical waste products. Consequently, chemists have sought ways to utilize electricity directly to input energy into reaction systems. Following the early contributions by Kolbe from Göttingen on the electrolysis of carboxylic acids,[1] organic electrosynthesis underwent a roller-coaster ride during the last century, and a majority of the synthetic community neglected the opportunities offered by electrochemical transformations. Stimulated by the recent significant increase in global awareness of the importance of sustainable chemical synthesis and by the continued demand for innovative synthetic strategies, electrochemical synthesis has experienced a resurgence within the last few years.[2,3] In addition to the inherently green nature of electrosynthesis,[4] a major advantage is full control of the oxidation and reduction potentials available for a chemical reaction, providing practitioners in academic and industrial settings with a convenient and knowledge-based platform for controlling reagent-free redox operations.[5] Presently, emerging research areas that are challenging but offer the most promise include electrocatalyzed C–H activations, asymmetric electrophotocatalysis, and the use of alternating current for isohypsic and reductive electrosynthesis (**Scheme 1**). Exceptionally mild reaction conditions and high



Scheme 1. Emerging Areas in Electro-organic Synthesis: Electrocatalyzed C–H Activation, Ideally with Earth-Abundant Metal Catalysts *(Ref. 9,10)*. Asymmetric Electrocatalysis *(Ref. 11,12)*. Symbiotic Exploitation of Photochemistry and Electrocatalysis *(Ref. 20–23)*. Avoiding the Use of Sacrificial Electrodes, e.g. via Alternating Current (AC), for Isohypsic and Reductive Electrocatalysis *(Ref. 17)*.

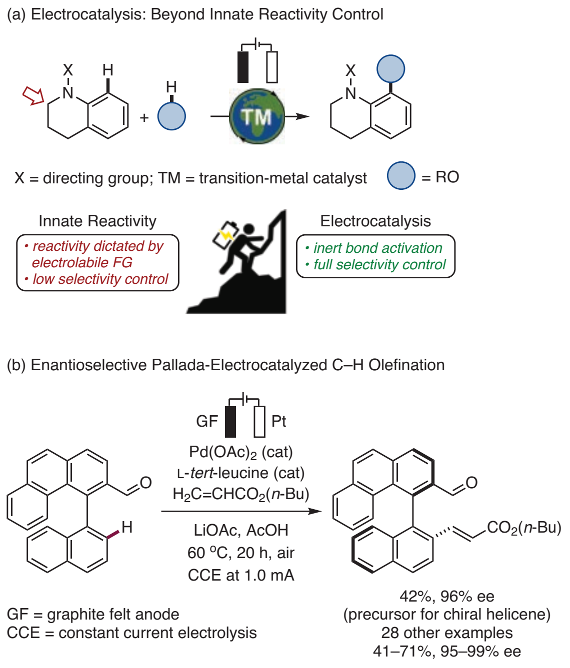
levels of selectivity control in electrocatalytic synthesis hold the greatest potential for future advances in challenging molecular transformations.

Unfortunately, the charge-transfer selectivity is ultimately dictated by the substrate's functional groups and further physical parameters complicate the prediction of the interfacial electron-transfer step. To circumvent the kinetic inhibition associated with the heterogeneous charge transfer, mediated electrosynthesis has been developed as a valuable approach, employing a redox mediator to transfer the charge in a homogeneous fashion.[6] In this case, the redox mediator is often only responsible for the charge transfer and largely does not alter the innate substrate reactivity.

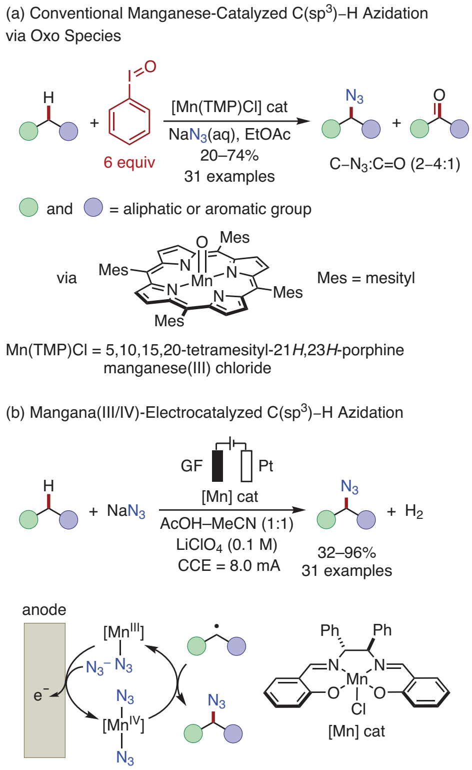
Metal catalysis has emerged as a transformative tool for overcoming the inherent substrate chemo- and regioselectivity, and has enabled the cleavage of otherwise inert bonds. In this context, the selective activation of omnipresent C–H bonds has arguably become one of the most vibrant research arenas within the last two decades.[7] The recent merger of the two approaches—electrochemistry and C–H activation—has led to unmatched levels of resource economy[8] and catalyst selectivity control (**Scheme 2**, Part (a)).[9,10] Thus, direct bond formations can be enabled by full catalyst control, as was recently exemplified by the enantioselective pallada-electrocatalyzed C–H olefination (Scheme 2, Part (b)).[11] Likewise, the combination of electrochemical oxidation with asymmetric Lewis acid catalysis has recently been shown to be a potent and sustainable method for efficient oxidative coupling reactions.[12] Furthermore, very recent reports have supported the notion that electrochemical redox control of the key catalyst–substrate complex can enable novel reaction mechanisms that conventional chemical charge carriers do not facilitate, such as oxidation-induced reductive elimination in cobalta- or nickela-electrocatalyzed C–H activation under mild conditions.[13,14]

The beneficial features of metalla-electrocatalysis are not limited to redox reactions. Indeed, isohypsic and reductive cross-coupling reactions have benefited equally from electrochemically induced single-electron-transfer steps.[15] However, these transformations often suffer from the requirement of sacrificial electrodes, thus compromising the aforementioned advantages of electrosynthesis. Here, specific electrode material design and the application of alternating current hold the potential to address these challenges.[16,17]

A recent study of the mangana-electrocatalyzed azidation of inert secondary, tertiary, and benzylic $C(sp^3)$–H bonds clearly demonstrated that electrocatalysis outperformed simple (electro)synthesis and chemical oxidants in terms of chemo- and regioselectivity.[18,19] While conventional reaction design employs chemical oxidants such as iodosobenzene to generate the high-valent manganese(V)oxo species, these oxo intermediates result in undesirable oxygenation reactions (**Scheme 3**, Part (a)).[18] In sharp contrast, the developed manganese(III/IV) electrocatalysis manifold minimizes undesirable side reactions



Scheme 2. Merging of Electrochemistry and C–H Activation. *(Ref. 9–11)*



Scheme 3. Rethinking Established Concepts on Catalyst-Guided C–H Functionalization. *(Ref. 18,19)*

and delivers the desired azide products with only hydrogen gas as byproduct (Scheme 3, Part (b)).[19] The robustness and versatility of this concept were validated by highly selective late-stage C–H azidations of bioactive and pharmaceutically relevant compounds in the absence of photochemical irradiation.[20]

The proficient fusion of electrosynthesis and photoredox catalysis, called electrophotocatalysis, has recently enabled the functionalization of strong bonds through the generation of unmet redox potential windows.[21-23] Further promising concepts in electrocatalysis include flow-electrosynthesis[24] and bioelectrocatalysis.[25]

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Tjark H. Meyer studied chemistry at the Georg-August-Universität Göttingen and obtained his M.Sc. degree in 2016 under the supervision of Prof. Dr. L. Ackermann. During his graduate studies, he joined the group of Prof. Stephen P. Thomas at the University of Edinburgh for a four-month research stay, and he later had an industrial internship at Bayer AG, Wuppertal. In 2017, he started his doctoral studies in the group of Prof. Dr. L. Ackermann. His current research is focused on synthetic organic electrochemistry, with a major interest in combining metal-catalyzed C–H activation with electrocatalysis.

Lutz Ackermann studied chemistry at the Christian-Albrechts University Kiel and obtained his Ph.D. degree in 2001 with Prof. Dr. Alois Fürstner at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. He was a postdoctoral fellow with Prof. Robert G. Bergman (UC Berkeley) before initiating his independent research in 2003 at the Ludwig-Maximilians University München, supported within the Emmy Noether Program of the Deutsche Forschungsgemeinschaft. In 2007, he became full professor at the Georg-August-Universität Göttingen, where he served as the Dean of Research and Dean of Chemistry as well as the director of the Wöhler Research Institute for Sustainable Chemistry (WISCh). The development of novel concepts for homogeneous catalysis and their applications to sustainable organic synthesis, late-stage peptide diversification, and molecular imaging are among his current main research interests.

VICTOR SNIECKUS[1]

(August 1, 1937—December 18, 2020)

By: Sharbil J. Firsan, Ph.D.
Editor, *Aldrichimica Acta*

Professor Victor Snieckus, Emeritus Alfred R. Bader Chair of Organic Chemistry at Queen's University in Kingston, ON, Canada, passed away peacefully at his daughter's cottage in the Kawarthas, ON, surrounded by loving family members.[2,3] A polyglot and an ever-optimist, nothing captures his work ethic better than what he told his son and daughter a week before he died (while he was receiving treatment for his grave illness), "Ok, let's get this over with so I can get back to work."

A friend to many, those who knew him well can attest to him being unpretentious, down-to-earth, and witty sometimes even to the point of being mischievous. His love of family, wine, jazz, and his obsession with physical fitness were only matched by his passion for chemistry, which he dedicated his life to studying. As Professor Cathleen Crudden, a colleague at Queen's, put it, "Victor was a bright light in the area of organic chemistry. His passion for chemistry and people was evident for anyone who knew him, and for anyone who saw him talking chemistry at a conference into the wee hours of the night."

With a career spanning over 50 years first at the University of Waterloo and then at Queen's, Snieckus was a prodigious researcher who oversaw the training and graduation of hundreds of students who went on to have successful careers of their own. While best known for his fundamental contributions to our understanding of Directed Ortho Metalations (DoMs), he also made significant contributions in other areas of chemical synthesis that together earned him wide acclaim and recognition in the form of numerous awards and fellowships. Dr. Thomas Colacot, a good longtime friend and scientific collaborator, summed up Professor Snieckus best, "Vic was an outstanding scientific leader, highly passionate about chemistry, and a gentleman who was eminently approachable, had a knack for connecting with people at all levels, and developed a unique style of delivering scientific talks with great humor."

We, at Merck KGaA, Darmstadt, Germany, recognize and honor Professor Snieckus's dedication and contributions to scientific research, and would like to offer our sincere condolences to his daughter Naomi and son Darius and the rest of the family. His unbridled enthusiasm for chemistry, his ability to easily connect with people, and his humor will be sorely missed. Rest in peace!

Professor Victor Snieckus.
Photo courtesy Naomi Snieckus.

(1) I am grateful to the following individuals for reviewing and commenting on an early draft of this piece: Dr. Ben Glasspoole (Merck KGaA, Darmstadt, Germany) and Ms. Naomi Snieckus (daughter).

(2) For other tributes and details about Professor Snieckus's personal life and circumstances, refer to: (a) Queen's Remembers Professor Emeritus Victor Snieckus. *Queen's Gazette*, December 22, 2020. https://www.queensu.ca/gazette/stories/queen-s-remembers-professor-emeritus-victor-snieckus (accessed Jan 12, 2021). (b) Victor Snieckus (1937–2020). *ChemViews Magazine*, December 21, 2020. https://www.chemistryviews.org/details/ezine/11282662/Victor_Snieckus_1937__2020.html (accessed Jan 12, 2021). (c) Victor Snieckus. *Wikipedia*®, January 6, 2021. https://en.wikipedia.org/wiki/Victor_Snieckus (accessed Jan 12, 2021).

(3) Anne Snieckus, wife of Professor Snieckus, passed away about a year earlier (February 12, 2020). She was a huge part of his professional life and success, who among many other things helped build the community of students around him, the community of The Snieckus Group.

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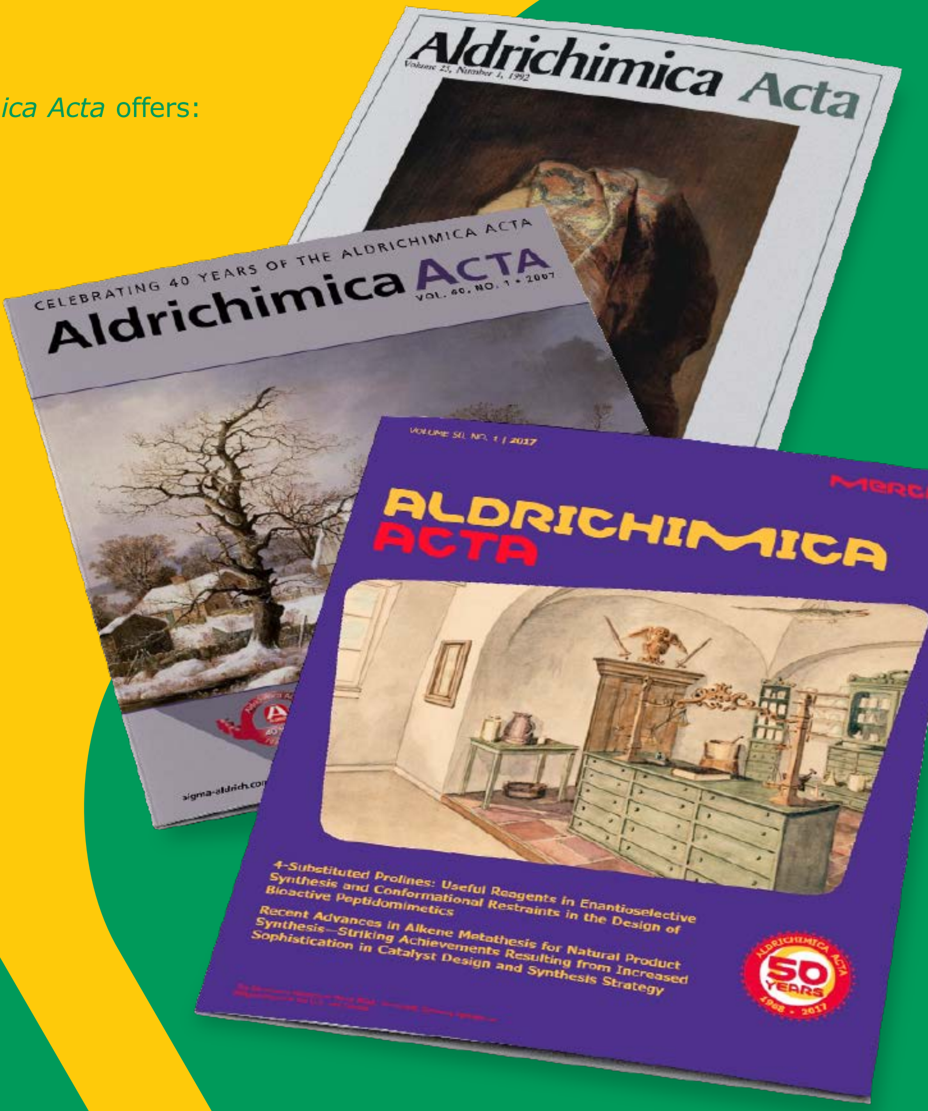

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