Organic electrosynthesis amps up the potential for synthetic innovation, while technological advances decrease the resistance for entry into this electrifying field

By Matthew Hartle, Ph.D.

Abstract

Organic electrochemistry is an area that is receiving more attention as chemists face pressures to synthesize more complex molecular targets in a more efficient fashion. The pressure comes from many corners including a desire to develop processes that are greener and more sustainable while producing significantly fewer toxic wastes and a reduction in manufacturing costs. It helps that many electrochemical processes are safer to operate and can be inherently linked to renewable energies. While innovations in beaker-scale electrolysis[1] have opened the field to the typical organic bench chemist, a technology gap exists for scaling the reactions to the production level.[2] Here we review several recent organic transformations that could either scale to larger flow-cell type systems or require further optimization in parallel with scale-up, as examples where the technology gap could be bridged. The Electrosynthesis Company is well-positioned to bridge the gap that exists between the bench and commercialization.

A technology gap exists in scale-up of organic electrochemistry

Reduction and oxidation are a short topic in the typical college organic chemistry class. Redox topics are relegated to the reduction of multiple bonds to alkenes or alkanes and the oxidation of oxygen groups to form carboxylic acids. Graduate-level organic chemistry classes also tend to follow the typical idea of organic chemical transformations being substitutions, eliminations, and concerted mechanisms without a deep description of reductions and oxidations of each process beyond hydrogenations or heterogeneous oxidations. Despite this, regular traditional oxidation and reduction chemistry is integral to organic synthesis from pharmaceutical development to carbohydrate synthesis.[3] Electrochemistry in organic synthesis is rarely mentioned.

The current problems facing organic electrochemistry are not an absence of reproducibility which earned organic chemists' skepticism in the past. Instead, the technique suffers from a lack of understanding and a gap in technology that simplifies it for the traditional bench chemist, graduate researcher, or retrosynthetic analyst. The introduction of IKA's ElectraSyn 2.0 addresses this for early-stage reaction development.[1] The simple stir-plate device has made testing electrochemical reactions much simpler and consistent as an undivided beaker cell, removing the barrier for a chemist to try the technique on various leads.

The academic literature has responded to this simplification, with a staggering number of reviews published in the past few years to engender growth in organic electrochemistry.[4–13] The interest has manifested itself in the formation of research centers as well.[14] Multiple labs now focus on electrochemical transformations in organic synthesis. C&EN, the magazine of the American Chemical Society, published a feature piece on organic electrochemistry in 2017,[15] and featured it in the "Reactions of the Year" retrospective.[16] Using the *Web of Science* database,[17] the number of publications published within the search topic "organic electrochemistry" followed the same general trend as "chemistry" until 2013 when the number of papers published significantly diverges from the historical trend (Figure 1). Still, the industrial adoption of electrochemical methods lags the academic explosion.

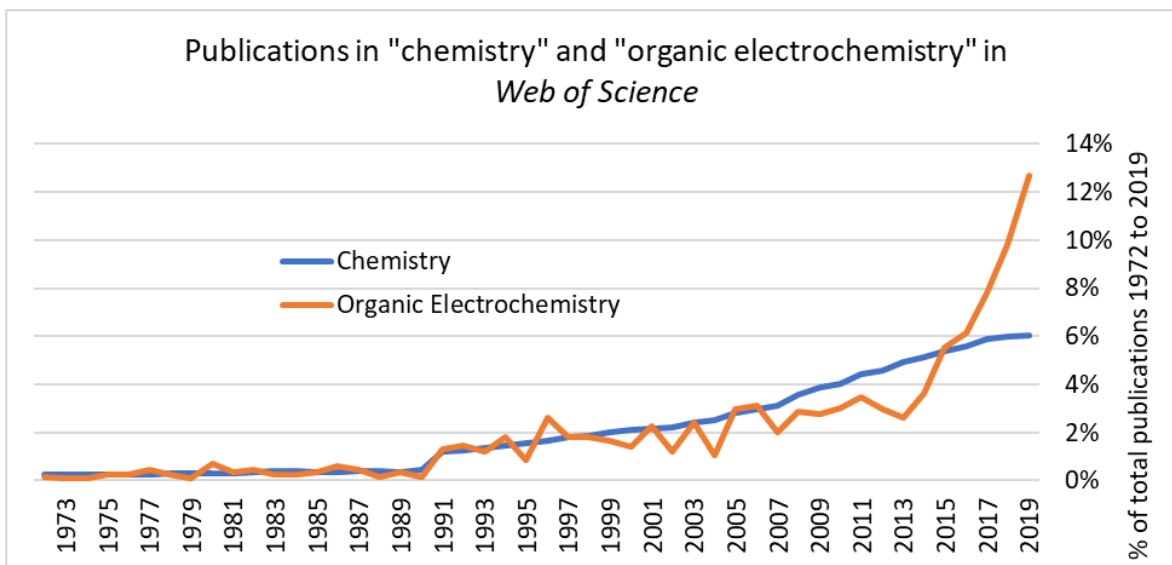Publications in "chemistry" and "organic electrochemistry" in *Web of Science*

Figure 1. Graph showing the growing trend of organic electrochemistry articles published compared to chemistry articles from 1972 through 2019 using the "Web of Science" database. Citation Report graphic is derived from Clarivate Analytics Web of Science. © Copyright Clarivate Analytics 2020. All rights reserved.

Industrial chemists continue to face pressure to produce more complex products and perform increasingly challenging synthesis in a more sustainable, chemo-selective fashion. Electrochemistry is interesting to industrial chemists and process scientists for its ability to be linked more directly to renewable energy, decrease in toxic reagent use, increased safety over many traditional techniques, and close alignment with the 12 principles of green chemistry.[18] Still, the bridge between industry and academia is lacking, as an update in C&EN addressing the scale-up concerns of process chemists highlights.[2]

The C&EN article emphasized a technology gap that exists when applying electrochemical techniques learned from small-scale beaker cells to the multi-kilo scale. Bethany Halford points out in the article that "…process chemists who want to do electrochemistry face an equipment gap. The ElectraSyn 2.0 works well for small-scale syntheses, and chemists have dedicated equipment for doing electrochemistry on a large scale. Working in the space in between can be a challenge," when speaking with Novartis chemist Max Ratnikov.

The Electrosynthesis company can meet this technology gap for scale-up, with multiple decades of experience in electrochemical development. Here we present a selection of recently published electrochemical transformations that are accessible for scaling to multi-kilo quantities or require some optimization at the gram scale concomitant with scale-up. Importantly, electro-synthetic chemistry is an excellent option to consider when requiring highly specific transformations that are tolerant of other functional groups, if step reductions that decrease the amount of waste generated are desired, and when alternative traditional synthetic methods are exhausted or costly. Electrochemistry is not inherently difficult or scary and can provide a simple and practical solution.

Scale-up is best performed in flow cells

Even with the wide range of demonstrated molecules by various academic groups, the work is done in custom-built beaker cells. The reported yields in these systems likely represent the lowest

possible. In the initial scaling of a bench reaction, transitioning from the milligram scale to gram scale in a flow reactor is an important first step. A flow reactor is more representative for scale-up of electrochemical reactions, and in our experience produces similar results to that of a multi-kilo pilot plant. A flow-cell system can run in a single-pass configuration or rapidly recirculate the reactant past the electrodes with minimal conversion-per-pass. The rapid flow regime enhances mass transport to the electrode, and typically results in better efficiency, while slower flow rates may be beneficial for the accumulation of reactive intermediates that quench upon leaving the cell. Additionally, alternative electrodes may prove more suitable in a flow cell system such as high surface area forms of carbon, in which the electrolyte is forced to flow through the electrode, rather than past it.

Significantly, the optimization procedures undertaken in the different studies use a systematic and logical approach, like how optimization would be conducted for a traditional stirred-pot reaction. Further application of physical-organic principles help guide the selection of electronic auxiliaries (adding electron-withdrawing groups to phthalimides to enhance its acidity in the catalytic cycle) and extend to the solvent selection, additive addition, and electronic parameters such as current density and flow rate.[19]
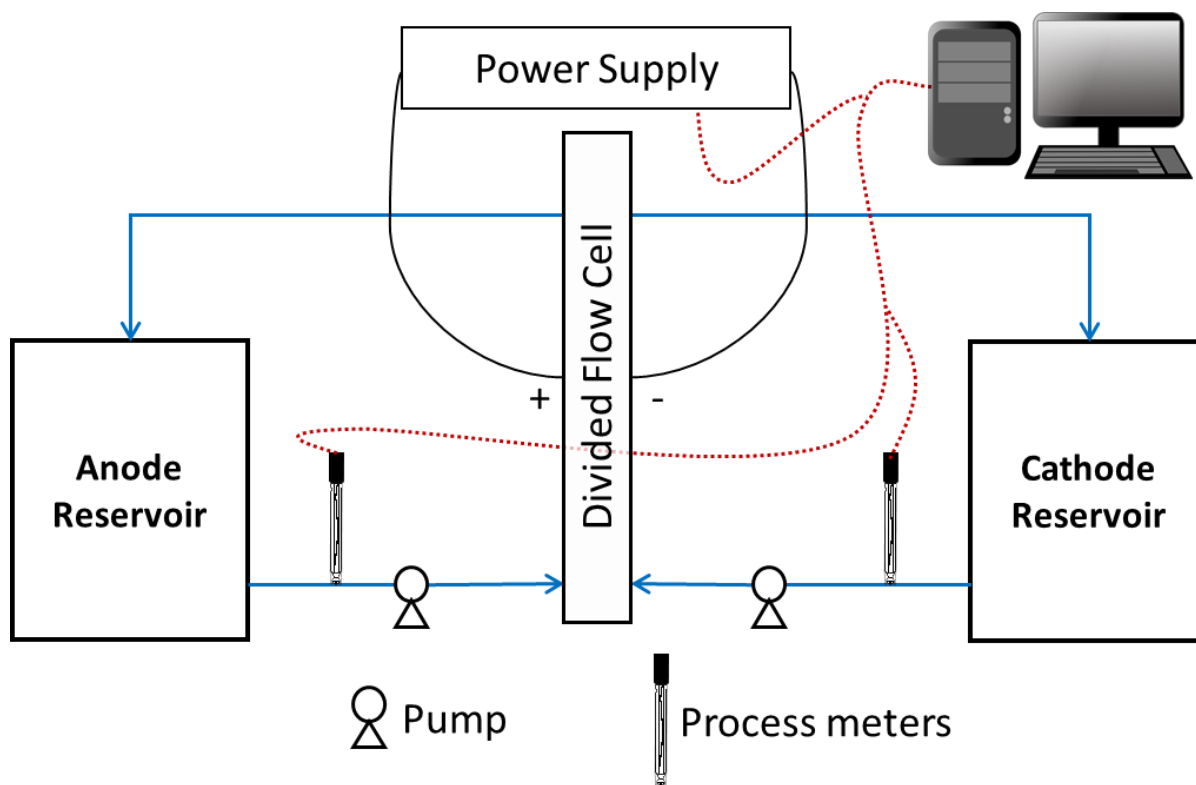

Figure 2. A simple divided flow cell schematic showing separate reservoirs. The entire setup can be monitored. The cell design itself depends greatly on the synthetic application and is connected to a DC-current power supply that is computer controlled.

N-oxide mediators for selective C-H functionalization and oxidation

The functionalization and utilization of C-H bonds represent a large range of chemical reactions from arene cross-couplings through Friedel-craft acylation. Allylic oxidation especially features in a wide range of natural products and pharmaceuticals to form enones and allylic alcohols. Despite its common occurrence, most traditional synthetic methods for this transformation still use highly toxic reagents or expensive catalysts.[20] The synthetic applicability of allylic oxidation can be further hindered by other reactive functional groups due to the poor selectivity of a chosen oxidant. The lack of specificity limits the technique to early-stage development. Late-stage development is hindered by several electrophilic centers that the oxidation introduces. These problems highlight the perpetual need for late-stage functionalization of complex molecules.

Electrochemistry provides a unique solution to the identified problems as described by the Baran group from The Scripps Research Institute.[21] An electro-auxiliary organic catalyst mediates the electrochemical oxidation. The redox mediator is cycled between the anode and alkene, requiring deprotonation from an endogenous base each cycle (Figure 3). It is important to note that the cathodic counter-reaction is identified as hydrogen generation (and implies hydroxide formation) that neutralizes the pyridinium. After the first one-electron oxidation, the allylic radical is trapped by an oxygen donating peroxide before decomposing to the desired product. The electrochemical method not only removes the use of toxic metals from the reaction but increases the overall process greenness score from ~35% using a chromium or ruthenium oxidant to 56%, in part by using a mostly aqueous system. Importantly, the Baran group used a process of systematic changes to optimize the reaction just as traditional organic synthetic work would.

Figure 3. The proposed electrochemical catalytic mechanism for allylic oxidation. R is a tetrachloro phthalide *N-oxide*.[21]

Figure 4. Catalytic mechanism of electrochemical TEMPO oxidation. TEMPO is first oxidized at the anode to the oxoammonium. This then undergoes a nucleophilic attack at the nitrogen before rearrangement and generation of the hydroxylamine before anodic oxidation back to the starting TEMPO free-radical.

The strategy of using N-oxyl mediators is not uncommon in electrochemical reactions and extends to alcohol oxidation by TEMPO.[22–24] TEMPO cycles between the anode and alcohol with great selectivity over other functional groups present in the molecule (Figure 4). Unlike the tetrachloro-phthalimide, TEMPO reactions can take place in completely aqueous systems (due to solubility),
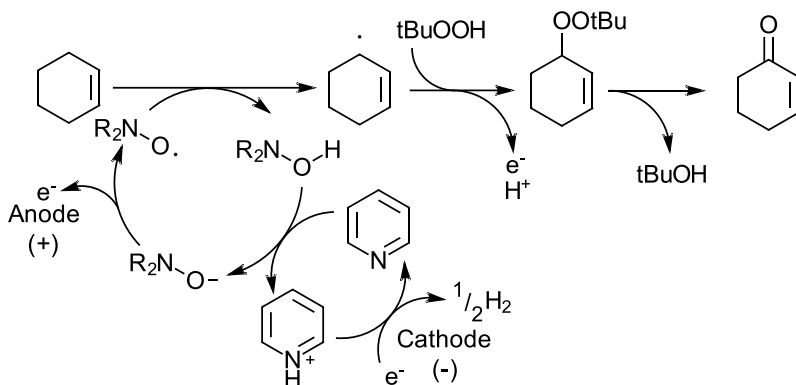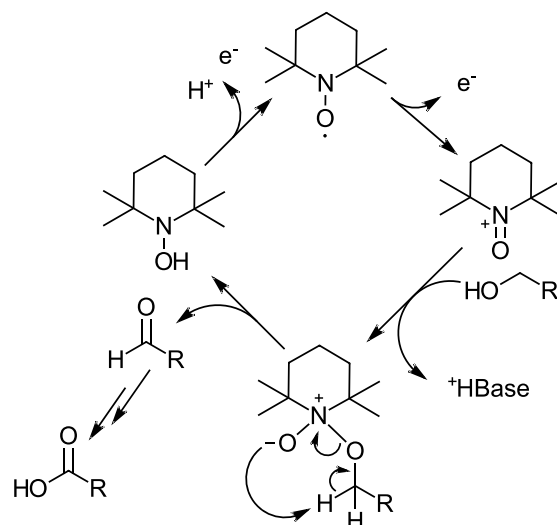
and do not require additional base if the pH of the solution is kept above 3; however, the electrochemical reaction becomes mass transfer controlled above pH 7. This is important since it allows the counter-reaction to be hydrogen formation. The applicability of the TEMPO mechanism away from external additive and oxidants makes it attractive as a mediator, and the catalyst can be recovered with an azeotropic distillation of water.

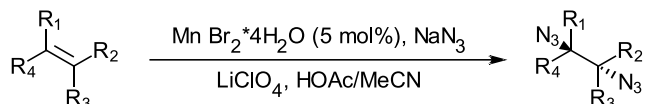## Diamination of alkenes via electrochemistry is more sustainable and safe

Figure 5. General scheme for diazidation of alkenes. Carbon anode, platinum cathode, 22°C

The vicinal diamine functionality is common to many active pharmaceutical ingredients and homogeneous catalyst ligand scaffolds. As such, significant effort has been put into designing synthetic pathways to access the increased functionality these structures provide. Reaction conditions are typically highly specialized, and no broad approach is yet available to incorporate diamines, unlike 1,2-diol formation. The methods that do exist habitually require the stoichiometric addition of expensive heavy metals, chemical oxidants, or complex nitrogen mediators that lack broad substrate scope.

A report from the Lin group addresses the gap in amine installation using electrochemical oxidation to install 1,2-diazides across doubles bonds (Figure 5).[25] The reaction requires a small amount of manganese to catalyze the reaction pathway in a predominantly organic solvent. An initial radical is generated on the azide, which oxidizes and coordinates to manganese.[26] The metal complex then undergoes addition to the alkene, generating an organic radical. After addition, the organic radical terminates by addition to a second manganese coordinated azide, and the metal re-oxidizes at the anode.

Of course, one of the main components of the Lin reaction is sodium azide, which introduces an entirely new set of hazards. The Xu group further reduced the hazard of nitrogen incorporation by using an organic redox mediator (tris(2,4-dibromophenyl) amine) and sulfamides to effectively incorporate nitrogen functionalities in a diastereoselective manner. The use of a sulfamide allows the nitrogen to be pre-functionalized prior to incorporation into the alkene backbone (Figure 6). This unique reactivity and breadth of chemical functionality allow the synthetic organic chemist to incorporate a broad range of amine functionality to the molecule. After the addition of the sulfamide, deprotection affords the desired amines.
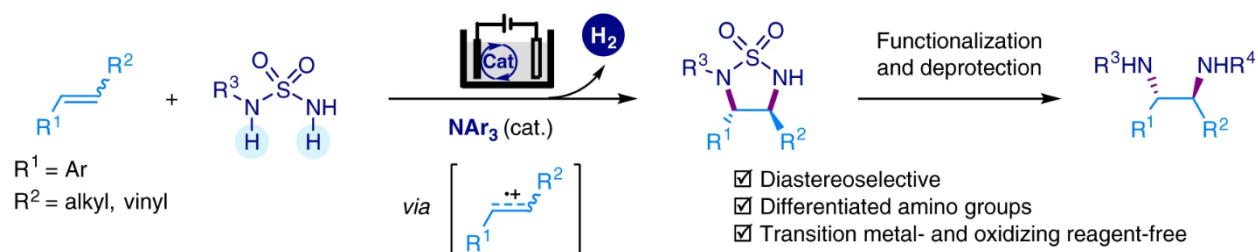

Figure 6. Stereoselective amination of alkenes with differentiated amino groups from Cai, C., Shu, X. & Xu, H. Practical and stereoselective electrocatalytic 1,2-diamination of alkenes. Nat Commun 10, 4953 (2019). https://doi.org/10.1038/s41467-019-13024-5 used under Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

Developing this reaction required optimization of solvent selection and incorporation of various activating agents. While the authors did not investigate the mechanism in detail, they point out that the two key additives could be coordinating as a Lewis acid-base adduct to produce a stronger proton-donor in solution and decreasing the cathodic proton reduction potential. Decreasing the reduction potential protects the substrates or products. The reaction chemistry is conducted under an inert atmosphere; however, the authors did not test the tolerance of the reaction for water or oxygen. Taking the postulated advantage of excess proton allowing for a cleaner cathode reaction, added water would be helpful in the electrochemical cell. The key postulated intermediate is a carbocation that could undergo rapid internal cyclization, so water would likely not interfere with product formation.

Electrochemical reductions provide milder Birch reduction conditions

The Birch reduction is an inherently difficult reaction to perform in a traditional set-up, let alone industrially, due to the need for liquid ammonia, pyrophoric lithium or sodium metal, and cryogenic temperatures. The reaction develops a classic blue color in solution as electrons become "solvated." To the electrons, an aromatic ring and proton-donating alcohol are slowly added, resulting in the formation of unconjugated cyclohexadiene. Importantly, the aromaticity of the compound is broken in a massively uphill thermodynamic event. It is the use of these toxic and hazardous compounds that limits the wide use of the reaction in industrial-scale preparations.

Electrochemistry inherently involves the use of single-electron transformations, but in a much more controlled manner than the Birch reduction's "solvated" electrons. An electrochemical reduction with similar selectivity is very attractive, as it would remove the inherently toxic ammonia and dangerous use of lithium. An interdisciplinary team lead by Phil Baran, Shelley Minteer, and Matthew Neurock developed a technique that utilizes a sacrificial anode with a dimethylurea proton source, and an overcharge additive inspired by Li-ion battery technologies.[27] The reaction is conducted at or near room temperature, allowing for scalable Birch reductions. The hazards of the traditional Birch reduction are eliminated while maintaining the substrate scope and selectivity of the classic reaction. The group further shows that other dissolving-metal reactions are viable under the same conditions (Figure 7).
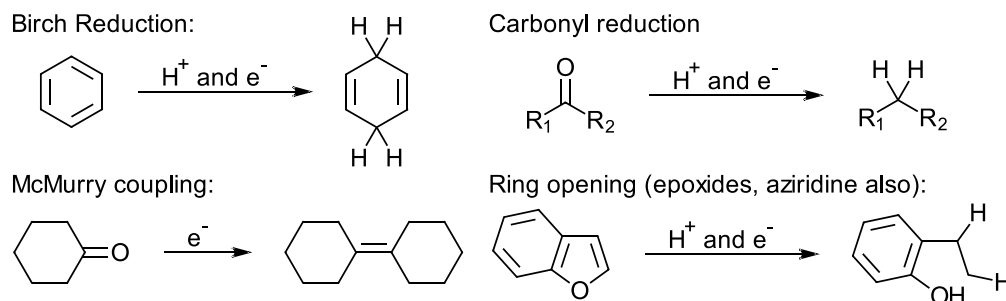

Figure 7. Simplified synthetic schemes for electrochemical reactions as developed by the Baran group.

The study highlights the systematic changes in optimizing the reaction. Careful observation of deposits on the cathode turned out to be lithium metal. The addition of an overcharge protectant commonly used in lithium-ion batteries prevented this potentially hazardous deposition. A further

interesting step was to reduce the size of the cathode and enhance its current density relative to the anode, thereby enhancing the selectivity of the reaction. While understanding why this modification is effective remains unknown, this step has significant implications for reactor design when considering the large-scale application.

Another interesting implication in this work is that the magnesium anode is sacrificially oxidized. The counter electrode's reaction must always be considered, particularly in the scale-up of novel electrochemical transformations. Using a sacrificial anode has two main implications when considering scale-up: reactor lifetime and oxygen evolution. First, is that the anode will need to change eventually, and this will need to be a simple procedure in the reactor design. Changing the anode could be replacing a sleeve of Mg or electrodeposition to rebuild the layer. Second, is that if there is no or limited oxygen evolution, reducing the overall hazards of the reactor when using a flammable aprotic solvent (such as THF). Flow-cell designs that readily come to mind would be of a pipe design where the anode is a hollow magnesium tube and the cathode is a galvanized steel rod, unlike the plate-and-frame type cells demonstrated by the Baran group. Another alternative cell design is the "pencil-sharpener electrochemical cell" which allows the anode to be electrochemically eroded in a conical shape like a pencil sharpening. The advantage of this cell is that the Mn rod could be gravity-fed into the electrochemical cell.[28]

While not ideal for what most chemists think when considering electrochemistry (entirely aqueous, highly conductive solutions, etc.), this reaction method stands to find considerable use in the implementation of a wide range of industrial processes. Electrochemistry itself can be linked to more sustainable and safer processes, and this synthetic scheme removes the hazards and difficulties of pyrophoric metals and toxic gases at cryogenic temperatures. Overall, these improvements allow for the safer scale-up of otherwise difficult to obtain products.

The Electrosynthesis Company can bridge the scale-up gap

Academic labs will continue to push the boundaries of novel chemical reactions. Even so, the Electrosynthesis company has experience in electrochemical development work and is well-positioned to test the feasibility of a given reaction or further optimize conditions for scale-up. There are now convenient platforms for undivided beaker cells to screen electrochemical conditions for the bench chemist; however, it does have limitations that the Electrosynthesis Company can address. For example, in every electrochemical reaction, both electrode reactions must be considered. If a functional group of the starting material or product is susceptible to oxidation or reduction it could react at the counter-electrode. Dividing the cell with a membrane can prevent this undesired reactivity. Membrane selection is not intuitive and may dramatically change the operational parameters of the cell. If a chemical reaction appears to be low-yielding, or difficult in an undivided beaker cell, the Electrosynthesis Company can test the feasibility in a divided arrangement and provide advice on scaling the reaction or identifying where difficulties are likely to arise.

While bench chemists look to electrochemistry for its novel chemical reactions, process chemists look to scale the formation of an identified molecule from the bench scale to the multi-kilo pilot and ton production scales. There is a significant gap in the scale-up of an electrochemical process from the bench scale to the pilot and beyond. The Electrosynthesis Company has significant experience and expertise in taking the next step from the beaker reactions. Stirred beaker cells are like running small scale screening experiments to get an idea of what works. These experiments are useful but are ultimately insufficient to determine if the transformation is applicable on a larger scale. The Electrosynthesis Company is here to help process chemists decrease the resistance for entry into this electrifying field. The Electrosynthesis Company specializes in confidential contract R&D and process development. Projects have included halogenation/dehalogenation, deacetoxylation, decarboxylation, oxidative methoxylation, coupling reactions, and various other functional group reductions and oxidations.

Matthew Hartle is a Research and Development Scientist at Electrosynthesis Company. His research interests focus on the application of electrochemical techniques to small molecule and carbohydrate synthesis and modification. His professional skills include air and water free synthetic techniques, organic and organometallic small molecule synthesis, purification, and identification, mechanism elucidation, and handling of toxic reagents and gases. His research contributed to 9 peer-reviewed publications and 8 professional presentations. Dr. Hartle received his Ph.D. in Chemistry from the University of Oregon in 2016 in the Pluth research group studying the binding of H_2S to biologically relevant metal and non-covalent scaffolds. Contact Dr. Hartle at info@electrosynthesis.com.

The Electrosynthesis Company has experience in developing and scaling-up electrochemical synthetic transformations. Synthetic experience ranges from mg-scale condition screening in glass beaker cells to flow-cell optimization on the 10-100's of grams through piloting up to 500+ kg continuous batch flow reactions. The team at Electrosynthesis is capable of process optimization at both lab and pilot scales. Furthermore, The Electrosynthesis company has broad experience in industrial electrochemistry successfully demonstrating the scale-up of synthetic reactions, redox flow batteries and membrane separation processes from laboratory to pilot and production. The Company operates from 25,000 sq. ft of well-equipped lab, pilot and office space.

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