

Exploring the Reach of Organic Electrochemistry

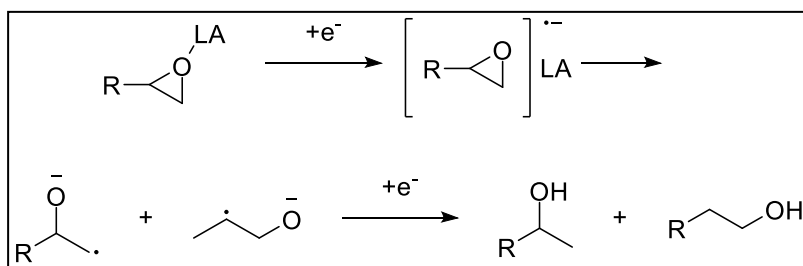
Introduction

Organic electrochemistry continues to enjoy a renaissance as more groups investigate its ability to perform selective transformations without the use of stoichiometric chemical oxidants, metal catalysts, or high energy precursors. Since our previous review by Matthew Hartle, research groups have prevailed to further expand the organic electrochemistry toolkit.¹ Furthermore, there has been renewed interest by major industry players who see electrochemistry's potential to use renewable electricity sources as an increasingly more economical pathway to essential products. The gap between academia and industry continues as while new processes develop in lab-based environments, they often scale poorly due to low current densities, faradic efficiencies, and the use of hazardous solvents. Companies such as the Electrosynthesis Company are uniquely positioned to help bridge that gap thanks to their deep understanding of both research lab, and industrial plant processes.

Below are a series of recent organic electrochemical reports that reflect the potential for these techniques, and the current shortcomings that require addressing before applying them to an industrial setting.

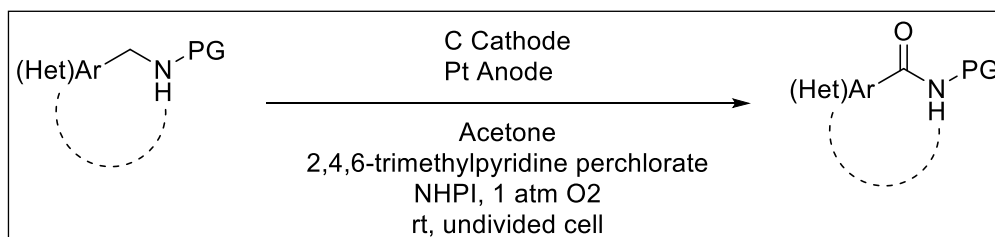
Transformations

Anti-Markovnikov addition is a classic textbook reaction taught to students to illustrate the importance of ionic pathways in organic mechanisms. Typical Markovnikov alcohols are easily formed from alkenes using



halogen acids, the anti-Markovnikov products are more difficult to access and require the use of boranes to achieve. Huang et al, describe an electrochemical process that can form the anti-Markovnikov alcohol products from epoxides and furans.² The conditions are mild, working at ambient temperature and pressure, and the only additives are lithium chloride, which acts as a Lewis acid and electrolyte, methyl urea, the source of protons for the transformation, and (pyrrolidino)phosphoramidate, which serves as both a co-solvent and an agent which suppresses the electrodeposition of lithium and magnesium on the cathode surface. They describe a wide scope of benzylic and allylic epoxides that form the anti-Markovnikov products, as well as several cyclic ethers that also undergo the transformation. The scope is limited in that epoxides and ethers not found in the benzylic or allylic positions result in Markovnikov product formation. Additionally, the current density is low, resulting in long reaction times and low concentrations, this is likely due to

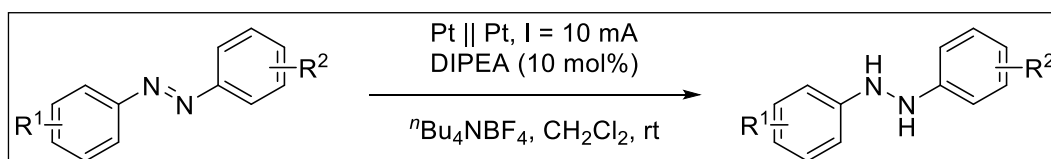
limitations of the lab set up, where they are using a poorly conductive solution and a wide electrode gap of 1 cm. Nitrile and nitro groups were tolerant of the process which indicates that this process has potential to be a valuable tool in multi-step synthesis.



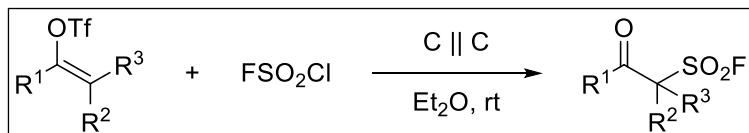
Benzamides are a common feature of natural products and drug-like molecules, and Bai et al offer a

method with the potential to be used during the later stages of a total synthesis program.³ They describe an oxidation of the benzylic carbon alpha to the nitrogen that can be carried out under ambient temperature in an oxygen environment. The graphite anode is run at a low current density of 0.55 mA/cm², resulting in long reaction times. Whilst a wide scope is described there does appear to be a selectivity issue where oxidation can occur on other carbons alpha to the nitrogen atom. Additionally, when non-amide protecting groups were used on the amine no reaction occurred indicating that the carbonyl of the amide has some sort of activating effect on the benzylic hydrogens. Faradic efficiencies appear to be moderate with approximately 2-3 F/mol being used during the reaction. In addition to these challenges, the cathodic reaction appears to be HER from collidine, and since this is an undivided system an oxygen-hydrogen mixture will be forming throughout the reaction leading to a potentially hazardous situation. Since it doesn't appear that much investigation has been done to reduce the amount of oxygen needed for the process, it would be interesting to see if the 1 atm of oxygen could be reduced to avoid the formation of explosive gas mixtures.

Hydrogenations are commonly seen in synthesis, but industrial processes often



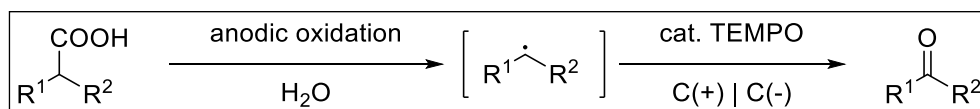
use high pressures and temperatures, and large quantities of hydrogen gas. Electrochemical hydrogenations offer pathways to reduce these factors. Zhou et al have developed a process to reduce azobenzene compounds utilizing dichloromethane as a hydrogen source.⁴ The process is interesting as it proposes a mechanism that involves both the anode and cathode to be directly involved. At the cathode the azobenzene is reduced forming a charged radical with which it can abstract protons from the positively charged dichloromethane radical. They found that this dichloromethane species could be formed directly, the anode would become fouled. Instead, catalytic amounts of diisopropylethylamine are used which to form a redox cycle with the anode and dichloromethane, producing the dichloromethane radical cations. Several areas of the process need development, the current density is low, the faradic efficiency is poor at nearly 4 F/mol, and while the risks of explosion are reduced, a significant amount of dichloromethane is used. Additionally, the waste carbon radical may polymerize which will result in problems down the line if the process is scaled to high enough concentrations.



β -keto sulfonylfluorides are highly versatile chemical building blocks that can be derivatized into a number of useful chemicals as well as being

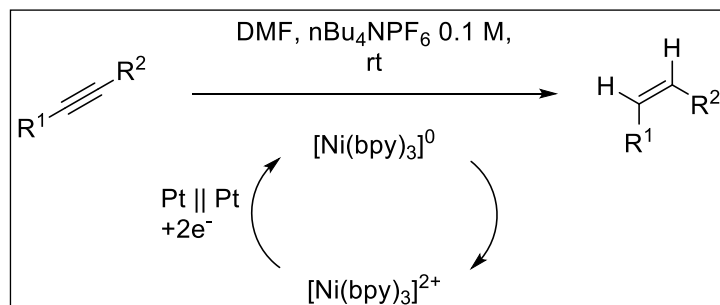
used in Sharpless' sulfur fluoride exchange click reactions. Unfortunately, making these has previously required a sacrificial magnesium anode, limiting their industrial potential. Feng et al have developed an electrochemical process that avoids the use of a sacrificial anode as well as the need for a pure oxygen atmosphere.⁵ Utilizing fluoro sulfonyl chloride, vinyl triflates can be converted to β -keto sulfonylfluorides using economical graphite carbon electrodes, and tetrabutylammonium phosphates as an electrolyte. The scope presented is wide, with a variety of terminal and internal vinyl triflates being used, though there's a marked drop in the reactivity of fully substituted alkenes. Since the process was reported to be run at a constant 15 V the faradic efficiency isn't clear, though the current density is likely to be low considering the conductivity of dichloromethane solutions. There are also two potentially hazardous stoichiometric byproducts being produced in the form of sulfur dioxide and fluoroform. In an industrial setting these byproducts may have some utility so capture of both is likely to be worthwhile.

The Kolbe electrolysis is a classic organic



electrochemical reaction where carboxylic acids are oxidatively decarboxylated, and the consequential radicals coupled together. The decarboxylative process can also be used as a pathway to alkyl radicals that can be derivatized in many ways beyond radical termination coupling reactions. For example, the Hofer-Moest electrolysis results in the formation of alcohols. Meng et al take the Hofer-Moest process and modify it for the formation of ketones and aldehydes from carboxylic acids.⁶ 2,4,6-collidine is used as a base and tetrabutylammonium chlorate as a supporting electrolyte. The addition of a catalytic amount of TEMPO allows for the Hofer-Moest alcohol to be immediately oxidized to either an aldehyde or a ketone. The TEMPO is regenerated by the anode, avoiding the need for stoichiometric amounts of chemical oxidant. The scope presented is extensive, though somewhat sparse in alkyl chains, likely due to solubility issues in water. Interestingly several common medicinal compounds successfully underwent the process indicating the process's utility in late-stage synthesis. However, the Faradic efficiency is fairly low at <25%, this may be able to be improved with more development of the cell.

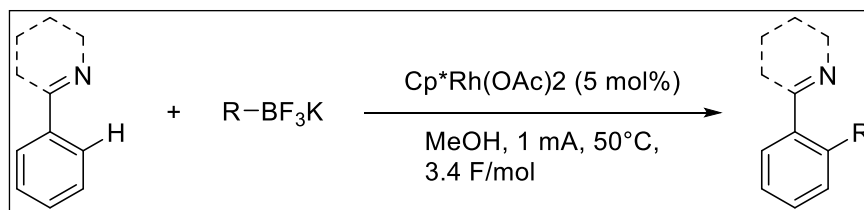
Catalyst Regeneration



In addition to directly reducing compounds for hydrogenation, electrochemistry can be used to regenerate transition metal complexes to make their use catalytic. Lee et al report one such process where they perform semi-hydrogenation of alkynes to alkenes using a nickel (II) complex.⁷ Yields are generally good, with several

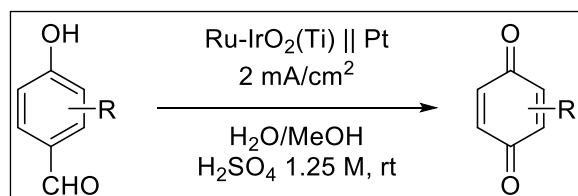
results in the high 80-90% range. Faradic efficiencies were reported and appear to be moderate, with one outlier at above 90%. The use of benzoic acid as a proton source avoids the need for hydrogen gas to be used, making the process desirable from a scaling-up viewpoint. One of the major drawbacks for this process however is the use of DMF as a solvent. Due to the toxicity of this solvent further work would need to be conducted to examine if more benign solvents would be able to be used in this process.

Yang et al report a method that eliminates the need for stoichiometric chemical oxidants in rhodium coupling reactions.⁸ This process is limited since a nitrogen heteroatom in the molecule is required to direct the rhodium to displace the aryl proton. Interestingly, instead of going through direct reductive elimination, the rhodium complex must first go through further oxidation by the anode of the cell before being able to form a new carbon-carbon bond using alkylboron species. This indicates that the electrochemical process is doing more than just recycling the catalyst. Additionally, the aryl species appear to need to be electron rich as electron withdrawing groups tend to lower the rate of the reaction. To demonstrate the utility of the reaction, several biologically relevant heterocycles were subjected to the process with good results, offering insight on how this could be used in methylation of pharmaceutical compounds.



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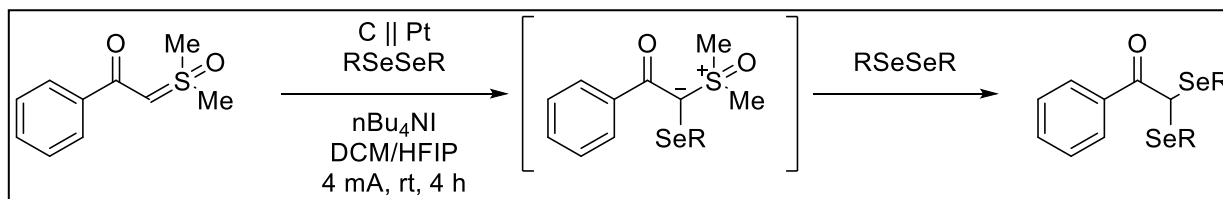
Reducing Harmful Reagents and Improving Atom efficiencies



Sprang et al give an example of how electrochemistry can eliminate the need for transition metal catalysts, or the use of large stoichiometric reagents such as, in this case, Frémy's salt.⁹ They use a carbon electrode to anodically oxidize hydroxybenzaldehydes to benzoquinones.

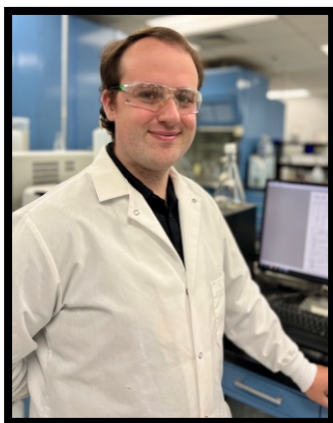
The benefit of the process versus alternative hydrogenations were illustrated. Specifically, the lack of the use of Frémy's salt resulted in a much more atom economical reaction, as well as it being safer with fewer ecological hazards. Compared to a transition metal catalyst the reaction mass

efficiency is greater when using the electrochemical process. The reaction, in acidified methanol, works well with yields greater than 80%, though the faradic efficiency stands to be improved at 4 F/mol. Further, the current density is very low at 3 mA/cm² and would likely need addressing if the process were to be scaled industrially, especially considering the use of expensive ruthenium-iridium oxide electrodes.



Selenium is an element that has had increasingly greater relevance to the pharmaceutical industry, however the ability to incorporate it into molecules is somewhat limited. Xu et al have developed an electrochemical solution that allows for the synthesis of gem-diselenides from sulfoxonium ylides.¹⁰ Conditions are mild with dichloromethane as the primary solvent and hexafluoroisopropanol as a co-solvent. The key component of the reaction is tetrabutylammonium iodide. The iodide is oxidized to iodine at the anode and is then able to react with the sulfoxonium ylide. Simultaneously the diselenide is reduced at the cathode to form organoselenide anions which can then nucleophilically attack the iodoalkane. Further addition of iodide causes dimethylsulfoxide to be eliminated and allows for further nucleophilic attack by organoselenide anions. The Faradic efficiency of this reaction is comparable to other organic electrochemical reactions at 3.6 F/mol, however the current density is still quite low and scaling the reaction will require further study.

As illustrated here, organic electrochemistry continues to offer novel solutions to challenging problems in organic synthesis. Translating bench-top lab work to industrial scale processes, however, is a significant challenge in itself. The team at the Electrosynthesis Company possess the knowledge, experience, and facilities that make bridging the gap from laboratory to factory possible. If you are interested in the Electrosynthesis Company finding an electrochemical solution to your organic synthesis problem, please contact us at info@electrosynthesis.com.



Jonathan Kennedy-Ellis is a Research and Development Scientist at the Electrosynthesis Company. Currently focused on utilizing electrochemical techniques in organic syntheses and scaling up to industrial production levels. With a background in Medicinal Chemistry, and asymmetric catalysis, he is well-versed in a variety of techniques, including but not limited to, air and water-free synthesis, organometallic synthesis, structure determination, analytical science, and multi-step synthesis. Dr Kennedy-Ellis received his Ph.D. in Medicinal Chemistry from the State University of New York at Buffalo in 2022 in the Chemler research group studying three-component asymmetric catalysis.

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The Electrosynthesis Company has experience in developing 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, 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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