

Electrochemistry – Escaping Stoichiometric Redox Reagents

Introduction

Redox chemistry is ubiquitous throughout organic chemistry since control of the oxidation state of carbon and heteroatom within chemical structures is vital to the construction of both simple and complex organic compounds. Aside from elegant reactions where the oxidant or reductant are directly incorporated into the final product, reactions often require stoichiometric amounts of external oxidant and reductant, reducing the atom economy, increasing the cost, and the environmental impact of the process. While there are proposed solutions utilizing molecular oxygen as a “green” oxidant, this introduces new concerns such as the safety of oxygenated environments and organic solvents, or the stability of intermediates in oxygen.^{1,2} Currently there aren’t similarly low environmental impact reducing agents available.

Electrochemistry offers the potential to eliminate both stoichiometric chemical oxidant or reductant. By utilizing electrons directly as the oxidant or reductant, we can perform these reactions in an easily controlled manner, potentially offering fewer side-reactions.

Electrochemical oxidations

Electrochemical oxidation is a well-studied area with the classic Kolbe electrolysis being one of the earliest published examples of organic electrochemistry. Its utility is highlighted in several reviews including a recent one by Ackermann examining how organic electrochemistry can be used in late stage functionalizations of medicinal compounds.³

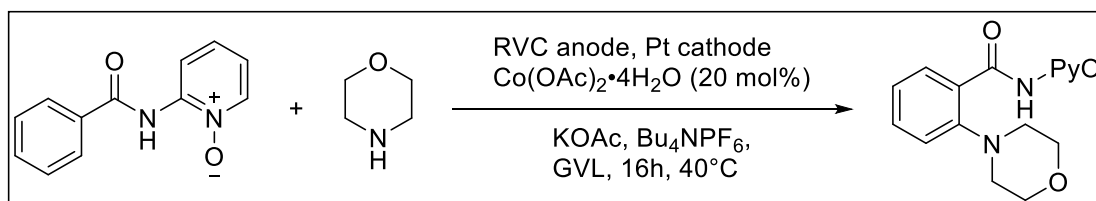
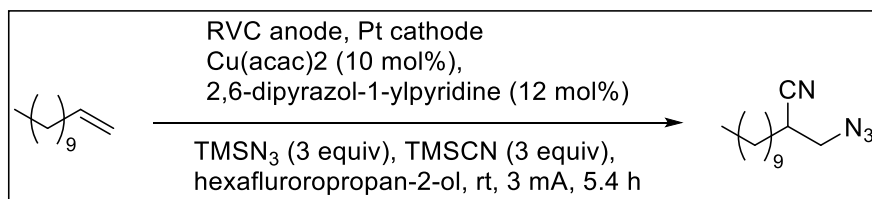
We can arrange oxidations into two broad categories, direct electrochemical oxidation, and indirect electrochemical oxidation. Direct oxidation is the oxidation of the substrate at the anode that consequentially results in the product formation, an example would be the Kolbe electrolysis. Meanwhile indirect oxidation involves the regeneration of a catalyst which then goes on to complete the desired chemistry. This has the advantage of utilizing well established chemistries of redox agents while avoiding the need for stoichiometric quantities.

Recently, indirect oxidations are of particular interest since they can facilitate asymmetric reactions to occur through the control of a chiral catalyst. Here we review some recent publications that we believe to be of interest.

Difunctionalization of alkenes is a useful synthetic technique that allows complexity in a molecule to be rapidly introduced.

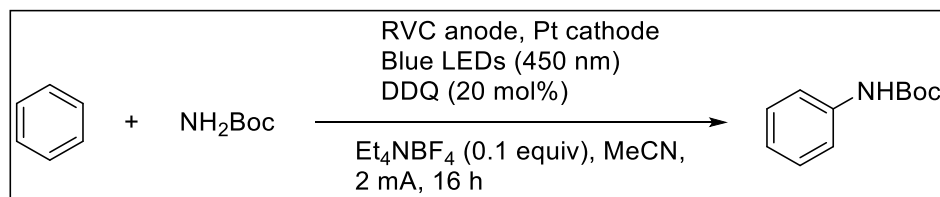
Many make use of

transition metal catalysts to facilitate the reaction, and it is possible to use chiral ligands to introduce asymmetry to the molecule. While some examples are fully catalytic, some require the use of a sacrificial oxidant to regenerate the catalyst to close the catalytic loop. Zheng and Xu recently reported an azidocyanation difunctionalization reaction that proceeds electrochemically without the need for a sacrificial oxidant.⁴ A reticulated vitreous carbon (RVC) anode, and a platinum cathode were employed in an undivided system. Copper (II) is used as the catalyst, which is unsurprising since it is a popular catalyst for this type of functionalization. Trimethylsilyl azide and trimethylsilyl cyanide are the two reagents that are incorporated into the molecule. It is proposed that the azide ion can be oxidized at the anode to an azide radical that will go on to attack the terminal alkene. The new radical then coordinates to the copper (II) catalyst, forming a copper (III) complex including the cyanide ion as a ligand. This complex reductively eliminates to the final product, and the resulting copper (I) ion is oxidized back to the copper (II), closing the catalytic cycle. Alkyl alkene substrates are normally found to be less active than aryl alkenes or dienes in these types of reaction, this is illustrated by the control reaction run without electricity not seeing any product formation. Something that makes this report stand out is the inclusion of a gram scale synthesis and further functionalizations displaying the reaction's utility. The authors were able to make 1.8 grams of the desired product with a 75% yield and only using 1.5 F/mol of charge, which indicates that there is a potential for scaling the reaction further.



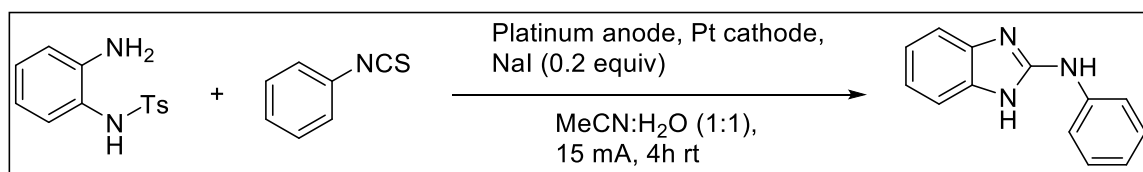
Other transition metal catalysts such as cobalt can also be refreshed using electricity. Sauermann et al. make use of this technique to allow cobalt to be used catalytically in the amination of aromatic rings. Cobalt (III) carboxylate can displace a hydrogen atom from the aromatic ring, forming a cobalt (IV) complex with one carboxylate, the nitrogen in the amide bond and the oxygen in the pyridine oxide group on the amide. The carboxylate can be displaced by a secondary amine which will then insert itself into the cobalt-carbon bond, forming a new carbon-nitrogen bond. Finally in a reductive elimination step the cobalt is expelled from the product as cobalt (I) where it must undergo a two-electron oxidation to cobalt (III) to become active again. The process shows modest to good yields, with a range between 50-85%, and the faradic efficiency appears to be around 50%. The missing charge and material aren't accounted for in the text; however, it may be presumed that a lot of the charge is lost to side reactions at the anode since there are several components of the reaction that can be oxidized, such as the quaternary amine salt used as a base, or the acetate additive. These side reactions may also be highlighted by the need for a low current

density. The initial experiments reported the current density at about 2.7 mA/cm², though since the anode is a three-dimensional high surface area material the current density is likely much lower than that. When lowering the current density further to 1.67 mA/cm² the yield of the reaction increased, suggesting that there are several side-reactions occurring that are reducing the yield of the reaction. Despite these drawbacks, this is interesting work since both electron rich and poor aromatic rings can be used, as long as the amide group with a pyridine oxide is present. Additionally, they made use of γ -valerolactone as the solvent. This solvent is interesting as it is easily derived from cellulose digestion, making it a potentially renewable solvent.



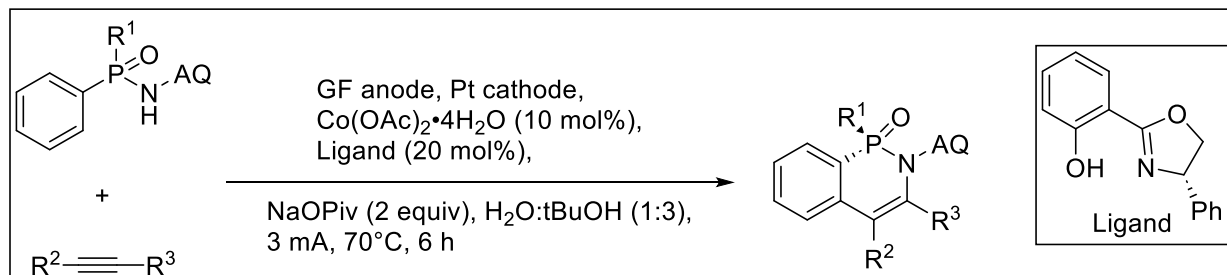
Electro and photochemistry are often placed at odds against one another as different groups invest into the

infrastructure required to research one or the other. Several groups recognize that the two techniques can be used in a complimentary manner, allowing access to previously challenging transformations. Hou et al. present one such reaction. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) can be used to functionalize arenes by shining blue light on the reaction in the presence of carbamates.⁵ This converts the DDQ to the reduced hydroquinone which renders it inactive in the reaction. Other groups make use of external oxidants to regenerate DDQ, however Hou et al show that it is possible to regenerate DDQ at the anode of an electrochemical cell. This eliminates the use of a stoichiometric oxidant and renders the process far more economical. This process is limited by the oxidation potential of the arenes; when it is too high, they are unable to be oxidized by the photoexcited form of DDQ. Faradic efficiency is respectable with the two-electron process requiring 2.4 F/mol, resulting in yields of 80-90%. The gram-scale synthesis resulted in a yield of 65%, and a faradic efficiency of less than 50%, indicating that there is still work to be done to be able to scale this process. Likely the simple glass beaker cell with blue LED lights needs further development.



Another useful function of anodic oxidation is regenerating iodine from iodide, reducing stoichiometric amounts of the toxic halogen to catalytic amounts. Additionally, iodide salts are relatively easier to handle than iodine. A recent example of this was reported by Nguyen et al. in their work creating N-substituted 2-aminobenzimidazoles.⁶ Here, they cyclize o-phenyldiamines with isothiocyanates by using iodine as a mediator in the desulfurization of the thiourea intermediate. The reduced iodide can then be oxidized back to iodine at the platinum anode. Yields are good to excellent with a range of 60-97%, electron deficient anilines appear to work better than electron rich ones. The current density of 6 mA/cm² is low with a faradic efficiency of around 50%. A current density is this low indicates that higher current densities are detrimental to the yield. It might be worth examining three-dimensional electrodes to increase the current to industrially useful values

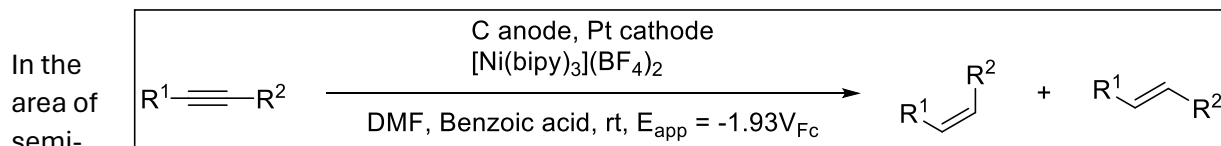
without increasing the current density to maintain selectivity. Something that may need to be accounted for in this process is the creation of base from the hydrogen evolution reaction. Since there is no acid being produced at the anode, assuming an efficient reaction, then the pH of the electrolyte is going to gradually increase over time and potentially cause side reactions of the starting material and the product.



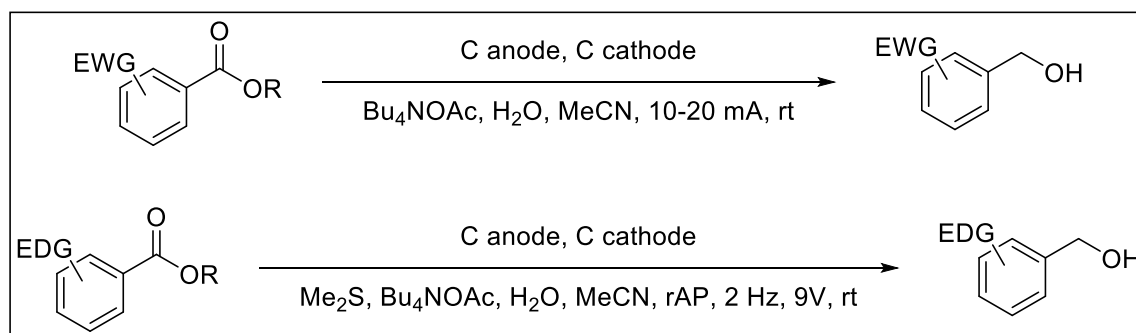
Chiral catalysis is sometimes thought of as the holy grail of organic synthesis due to its difficulty and utility in areas such as medicine. The added success parameter of enantioselectivity often makes or breaks a project as achiral processes are often cheaper and more developed. Enantioselective catalysis in an electrochemical setting faces further challenges as the ligands typically used in classical organic settings make use of anhydrous conditions and poorly conductive organic solvents, often the inclusion of any water can destroy the expensive chiral catalyst used in the process. This makes it difficult to apply the developed chiral processes to an electrochemical setting. In 2023 Liu et al published an exciting process that makes use of a cobalt chiral catalyst that is regenerated via electrooxidation.⁷ Compounds with phosphorus chiral centers are seen throughout nature and have uses in medicine and beyond as chiral ligands. The ability to act as a ligand does make their synthesis difficult as they often deactivate the metal catalysts that are being used to synthesize. Liu et al identified cobalt as a metal that can avoid this issue and examined how it could be used in C-H activation. The study of cobalt in this manner is not as robust as, for example, platinum or palladium since it is less active in comparison. Upon screening several Salox ligands one candidate was carried forward through the other optimization steps (see above.) They found that the chiral catalyst offered good yield with excellent enantioselectivity despite being used in aqueous and aerobic conditions, which are often detrimental to enantioselective catalysts. While the temperature of 70 °C is a little high for enantioselective reactions, it was found that similar yields were possible at room temperature, albeit the reaction running for a much longer time span. The current density examined is very low at 1.5 mA/cm² though the faradic efficiency is acceptable, being calculated in the region of 60%. When the anode was changed to use planar platinum rather than graphite felt the yield of the reaction dropped dramatically. It is unclear whether this is due to the drastic increase in current density, if the geometry of the electrode plays a significant role in the mass transfer of the catalyst to the electrode, or if platinum is merely worse at regenerating the catalyst than graphite. Despite these problems in the reaction Liu et al have shown an extensive scope of the reaction, and a gram scale synthesis with 89% yield and 99% enantiomeric excess. Due to the high value nature of the product, the lower, but reasonable Faradic efficiency can be forgiven. There is still plenty of value in examining ways to improve the current efficiency and density should the process need to be scaled.

Electrochemical Reductions

The area of electrochemical reduction is generally underdeveloped, a major exception being the adiponitrile process in nylon manufacturing, with many recent studies being focused on the reduction of carbon dioxide to more useful materials such as formates, carbon monoxide, or short chain alkanes. For an overview of that particular topic see review by Lu and Jiao.⁸ Below we have selected several recent papers focused on the replacement of chemical reductants by cathodic electrochemistry.

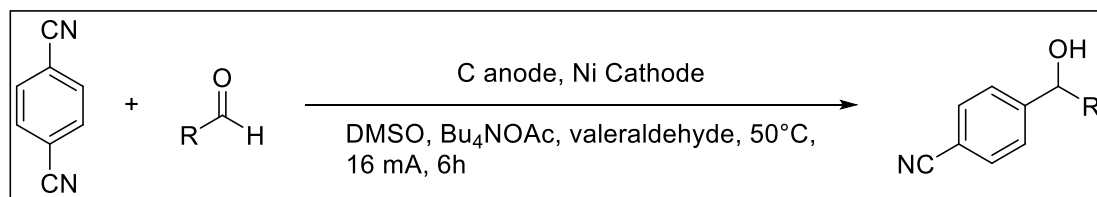


hydrogenation, the space for hydride free reduction had been underdeveloped until recently. In 2022 Lee et al. published work showing an electrochemical semi-hydrogenation of alkynes to Z alkenes can be achieved using a nickel based homogenous catalyst.⁹ While the yields are only moderate across the chosen scope of the research, and the faradaic efficiency is poor, there are several aspects of this process that show promise for the future. Nickel being an earth abundant metal, and the simplicity of the Bipyridine ligand offer economic advantages over precious metal heterogenous catalysis. Furthermore, the potential for ligand design in the process could be a simple avenue for improving both the yield and selectivity of the process. Other aspects of the process that will need further development before being able to be scaled industrially would be the necessity to use DMF as the solvent, whether the reaction must be completely water free, and can the cathode material be scaled to larger sizes. The solvent choice and water tolerance will likely be improved via ligand design, with ligands that give more stable complexes in the presence of water being ideal.



Fatty esters are abundant in nature; however, their corresponding alcohol must often be produced chemically, using stoichiometric reductants such as lithium aluminum hydride. There exists a space that calls for fatty esters to be reduced using environmentally friendly methods, which Zhang et al. have shown can potentially be filled by electrochemistry.¹⁰ In their report they make use of carbon felt electrodes to reduce benzylic esters to their benzylic alcohol counterparts. They identified several challenges with this process, first that the alcohol product can often be oxidized at the anode in an undivided cell. This can be addressed by using a divided cell with a membrane separating the catholyte from the anode, however this can result in new problems such as chemical

compatibility with the membrane, complication of the cell design and added costs from the new consumable. Another issue with reducing benzoic esters is that electron donating groups on the aromatic ring can make it harder to be reduced, resulting in a loss of current efficiency as hydrogen is evolved instead. To combat these problems, two separate strategies were developed depending on whether there was an electron withdrawing group (EWG) or an electron donating group (EDG) on the aromatic ring. To combat oxidation of the alcohol products with EWGs they made use of quaternary ammonium acetate salts to ensure that water was oxidized in the OER before the alcohol was. This resulted in some success with yields generally being moderate at 50-75%. However, when compared to the reaction without water included that resulted in complex mixtures of products and only a small amount of the desired product, there is a clear improvement. To allow for reductions of benzylic esters with EDGs on the aromatic ring a slightly more complex strategy was employed. The first change was to switch from DC electrolysis to rapidly alternating polarity (rAp) electrolysis. This method, highlighted by Baran's group in 2021 as a method for chemoselective electrolysis allows you target certain groups on a molecule for electrolysis depending on their relative reaction rate.¹¹ Additionally dimethylsulfide was included as an additive in the reaction. Due to the kinetics of electron transfer using this technique it is possible to perform the oxygen evolution reaction at the electrode in the positive peak-to-peak voltage stage, so the reducing agent dimethylsulfide is included to balance the charge. Not including DMS resulted in poorer yields. The yields of the scope containing EDGs were moderate to good, with the majority of tested compounds falling in the 60-80% isolated yield range. Additionally, they tested some of the benzoic acid esters that had EWGs but performed poorly under DC conditions, rAp allowed these compounds to form the desired products in moderate yields.

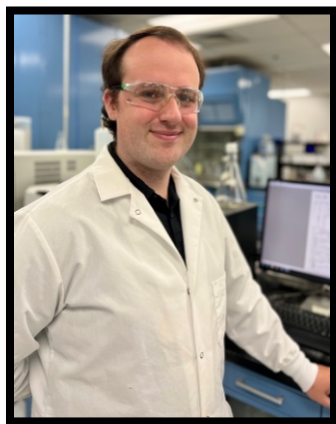


While developing a paired electrosynthesis reaction to create valuable alcohols, Zhang et al. displayed a reductive arylation of aldehydes and ketones.¹² 1,4-cyanobenzene can be reduced at a nickel cathode to make a reagent that can couple either nucleophilically or radically to an aldehyde or ketone. The electrolyte is made up of tetrabutylammonium acetate in DMSO, with valeraldehyde as an additive. The valeraldehyde reacts with the cyanide formed during the reaction to render it benign. The scope of this aspect of the reaction is fairly broad, with electron rich benzaldehydes appearing to grant better yields than electron poor benzaldehydes. Ketones reacted similarly with many examples having yields higher than 90%. By using cathodic reduction to initiate the reaction, Zhang et al. are able to avoid the use of complex metal catalysts or stoichiometric reductants. Additionally, this method is far more tolerant of functional groups than traditional Grignard reactions. Taking their work further, Zhang et al. showed that you can use benzyl alcohols instead of aldehydes or ketones and still form the desired product. Due to the cell being undivided, the benzyl alcohol can be oxidized to a benzyl aldehyde, before reacting with the reduced 1,4-dicyanobenzene. This paired electrolysis has a net oxidation state change of zero, with either one or two electrons being used at both the anode and the cathode depending on the final route. This sort of paired electrolysis where both the anode and cathode are working is rare and displays the merit

of this method. The large scale electroreduction reaction worked well with a 94% yield of the desired product. There was less success with the paired electrolysis reaction at only 64% yield, indicating that there may be competing side reactions at the anode. Faradic efficiency is low at around 55%, which is often seen with these benchtop reactions. Furthermore, something that may hinder industrial scale up is the reliance on DMSO as a solvent, DMA had a lower yield and is more toxic so a poor alternative. A wider solvent could possibly improve the process to make it more economically viable.

Conclusion

As more groups see the potential of using electrochemistry to control the redox processes within their reactions, we see the field of literature expanding. This shows that not only do we not need to rely on stoichiometric amounts of toxic metals and chemicals to perform these transformations, but we can also have greater control over those processes and open avenues to target compounds that were previously unavailable. While there are few paired electrochemical processes it should be noted that the side product of many oxidation reactions is hydrogen at the counter electrode. Hydrogen has potential as a chemical of value itself as we move forward towards a hydrogen economy. There are still challenges to be faced on scaling from the lab to industrial scale, notably current densities, solvents, and air sensitivity, these challenges are merely hurdles that can be jumped by further investment in the research and development of these processes.



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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