

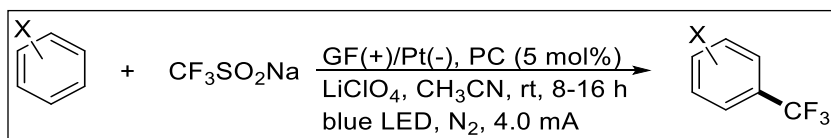
Unlocking New Potential using Photoelectrochemistry in Organic Synthesis

Introduction

Photocatalysis and electrochemistry have long been useful tools in organic synthesis. These techniques allow for transformations under mild conditions without the use of stoichiometric reagents; however, by combining these two well-studied techniques it is possible to uncover previously inaccessible reactions. By using a photocatalyst to perform chemical transformations followed by the electrochemical regeneration of the catalyst, the need for strong chemical oxidants or reductants is removed, along with the possibility for unwanted electrochemical reactions due to the relatively low potential required.¹ Some of these reactions have even been demonstrated in a flow-cell capacity, enabling the ability for potential scale-up to industrial production. Limitations currently exist in these chemical processes like the use of organic solvents that make it difficult to scale. However, companies such as the Electrosynthesis Company are uniquely positioned to help bridge that gap thanks to a deep understanding of both research lab, and industrial plant processes.

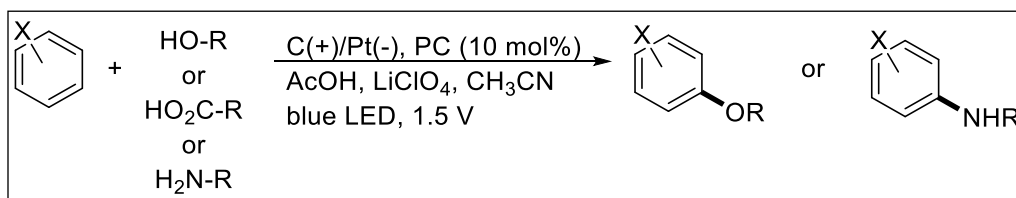
Below are a series of recent reports on the use of photoelectrochemistry in organic synthesis that demonstrate the combined use of photocatalysts with electrochemistry to perform previously difficult reactions, as well as issues that must be overcome before these techniques could be implemented for large-scale use.

C-H Activations – Photocatalytic Oxidation

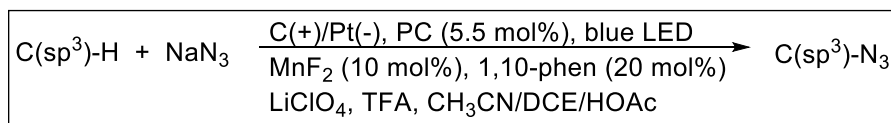


C-H activation reactions are of great interest in organic synthesis due to their ability to open functionalization of relatively inert bonds; however, these reactions typically require the use of transition metal catalysts. The use of a photocatalyst (PC) can replace the need for these transition metals, with electrochemical regeneration of the photocatalyst allowing for mild reaction conditions and no stoichiometric chemical redox reagents. A list of the chemical structures of all photocatalysts described in this article is contained in the supplemental information. Qiu et al sought to combine photocatalysis and electrochemistry in the trifluoromethylation of non-activated aryl C-H bonds due to their use in medicinal and pharmaceutical chemistry.² The reaction set-up consisted of a graphite felt anode and platinum plate cathode, using a blue LED to activate the [Mes-Acr⁺]⁺ClO₄⁻ PC in a sealed glass undivided cell under N₂. The PC is activated by the blue light and undergoes a single electron transfer (SET) reaction with the Langlois reagent (CF₃SO₂Na), generating the CF₃ radical. This radical can be added to the aryl ring, with Mes-Acr⁺ then oxidizing the ring. After deprotonation, aromaticity is reestablished and the trifluoromethylated product is generated. The PC is regenerated via oxidation

at the anode, with reduction of protons occurring at the cathode to produce H₂. This reaction was demonstrated on several different arene ring-containing compounds, with yields reaching a high of 85% with mesitylene as the substrate. The reaction was also performed in a flow-cell apparatus with a nickel cathode and transparent tubing to allow for illumination. Yields for the mono-trifluoromethylation of mesitylene reached 76%. Despite the use of organic solvents (MeCN) and relatively low Faradaic efficiency (36%), this process has potential to scale up given its demonstrated use in flow and robust tolerance of starting materials.



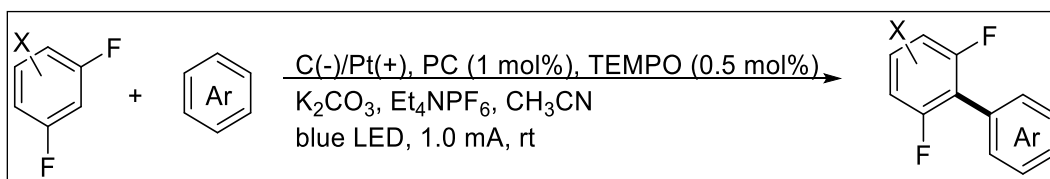
Another photoelectrochemical C-H activation reaction has been demonstrated by Huang et al.³ The PC 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as a photochemical oxidant in the hydroxylation and amination of arene rings. Using a carbon anode and platinum cathode in an undivided cell with illumination by blue LED, the photoexcited DDQ oxidizes the arene ring, allowing reaction with the nucleophile. After a second oxidation and deprotonation, the product is generated. The reduced DDQ is then regenerated via oxidation at the anode, with protons being reduced at the cathode at a cell voltage of 1.5 V. This reaction was demonstrated using water as the nucleophile as well as several other hydroxyl and amino containing molecules to form several different aryl ethers, amines, esters, and amides. Not only was this reaction performed using several different nucleophiles, but it also appeared to work on a variety of substrates as well, with yields of up to 85%. This transformation was demonstrated in a flow-cell setup on the model substrate benzene with water as the nucleophile. The flow-cell achieved up to 65% yield, with the difference between glass-cell and flow-cell likely coming from the shorter exposure to light when in the flow set-up. Since the PC is exposed to the LED for a shorter duration before cycling through the flow apparatus, it is likely that there is less activation and therefore a lower amount of product generated, necessitating longer run times in flow. Even with this decrease in photocatalytic efficiency, the scale-up capability of flow makes it worth exploring these transition metal catalyst and stoichiometric redox reagent free C-H activation reactions.



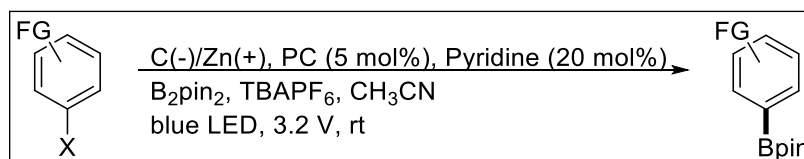
In addition to the activation of sp²-hybridized C-H bonds, C-H activation reactions on sp³ carbon centers can be achieved using photoelectrochemistry. The addition of azides to the carbon-hydrogen backbone of complex molecules is important due to the diversity of functional groups that can be obtained such as reduction to amines or the reaction with alkynes via click chemistry to form complex heterocycles. Chemical amination of carbon atoms usually involves stoichiometric oxidizing agents, leading to the generation of waste. By performing the reaction photoelectrochemically, this can be removed leading to more environmentally friendly production of desirable C-N bond containing molecules. Niu et al have recently discovered a photoelectrochemical strategy for azide insertion

using manganese as a catalyst and various organic molecules such as DDQ as the PC.⁴ The reaction occurs via excitation of the PC followed by hydrogen atom transfer from the substrate to the PC, generating a carbon radical on the substrate and a reduced PC radical species, which is regenerated via oxidation at the carbon anode. Simultaneously, azide coordinates with the Mn(II). In addition to electrochemical regeneration of the PC, the Mn(II) is oxidized to Mn(III), generating a neutral azide radical. The azide radical can then subsequently react with the carbon radical to form a C-N bond: inserting azide into a sp^3 -hybridized carbon. This reaction is different than the C-H activations previously described: not only in that it occurs on a sp^3 carbon, but also that the electrochemical component is used for more than just regeneration of the PC. The reaction was tested on a variety of substrates with the highest yields (up to 96%) occurring on tertiary carbons, presumably due to the stability of the radical vs. a primary or secondary carbon radical. While this reaction also uses organic solvents and has only been demonstrated in small batch-cell setups, the ability to remove waste from potentially large-scale production of desirable molecules makes this one of great interest for further study, particularly if it can be performed under aqueous conditions.

Aryl Halide Coupling Reactions – Photocatalytic Reduction

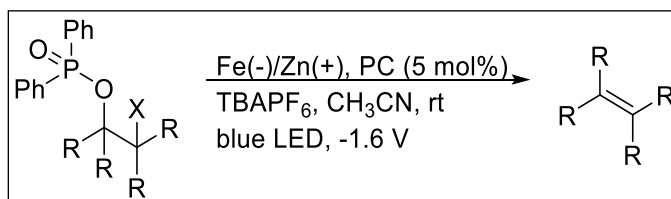


In addition to C-H activation reactions, photoelectrochemistry can be used to generate C-C bonds via radical anion formation from fluorinated arenes via a paired electrolysis mechanism. Chen et al have developed a technique to selectively arylate polyfluoroarenes using *N,N*-Bis(2,6-diisopropylphenyl)perylene3,4,9,10-bis(dicarboximide) (PDI) as a PC and TEMPO as a redox catalyst.⁵ The reaction begins via the reduction of PDI at the carbon cathode followed by the photoexcitation of the reduced PC with visible light. This catalyst reacts with a polyfluorinated substrate by reducing it via SET. The reduced substrate can then react with TEMPO that had been oxidized at the platinum anode to form a radical arene. This can then react with the second arene reactant to form a biaryl radical that is oxidized by additional oxidized TEMPO, generating a biaryl cation and regenerating the TEMPO. After deprotonation, the biaryl coupled product is formed. The reaction was performed on several different substrates, including both the fluorinated and other non-fluorinated substrate with yields of >90% for some couplings. This demonstrates a reaction that could be favorable in late-stage functionalization of drugs in a green, efficient, and atom-economical manner.



Another coupling reaction from a halogenated starting material is described by Kim et al using DCA as the PC.⁶ In this reaction, dicyanoanthracene (DCA) is reduced at the cathode with Zn oxidation

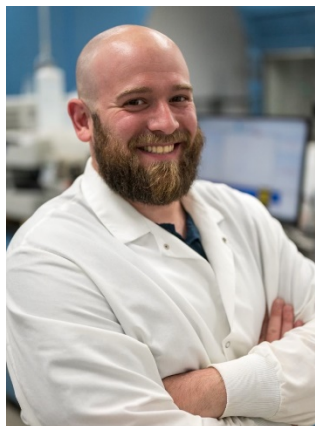
occurring at the anode. The reduction of DCA is followed by photoexcitation to generate the excited reduced PC. This then follows a similar mechanism to the previously described reaction, in which the PC reduces the halogenated substrate which leads to generation of the arene radical that reacts with another substrate. Several substrates were tested with either chlorine or bromine as the halogen leaving group, with various electron donating and withdrawing groups on the arene rings with Bpin being the coupling reactant. Generally, bromine-containing substrates provided higher yields than their chlorine counterparts due to the stability of the bromide over chloride as the leaving group, with the highest yields being >80%. This coupling offers the ability for reactions such as borylations to occur in greater yields and without the use of elements like palladium when compared to traditional coupling reactions.



A final example of using photoelectrochemistry in organic synthesis reactions is the selective C-O cleavage of phosphinated alcohols to carbanions via photocatalysis. Tian et al describe a method to perform these cleavages using ⁿBuo-NpMI as the PC and generating (*E*) double bonds.⁷ The PC is reduced at the cathode and then illuminated with blue light to generate the excited PC. Despite the high redox potential of the various phosphinated alcohol substrates (-2.6 V), the excited photocatalyst has a high enough potential (-2.8 V) to reduce the substrate to a radical anion. The substrate then undergoes cleavage to form the sp³ carbon radical that is reduced further to the carbanion. If there is an adjacent halogen leaving group, an elimination reaction will occur leading to the double bond with (*E*) stereochemistry. This is just another example of performing functional group transformations in a greener, more efficient way using photoelectrochemistry.

Conclusion

As illustrated here, photoelectrochemistry is emerging as a powerful tool in organic synthesis. Translating bench-top lab work to industrial scale processes, however, is a significant challenge. The team at the Electrosynthesis Company possess the knowledge, experience, and facilities that make bridging the gap from laboratory to production possible. If you are interested in the Electrosynthesis Company finding an electrochemical or photoelectrochemical solution to your organic synthesis problem, please contact us at info@electrosynthesis.com.



Michael Clark 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 both organic synthesis and photoelectrochemistry, Dr. Clark received his Ph.D. in Chemistry from the State University of New York at Buffalo in 2023 in the Watson research group studying the synthesis of chalcogenoxanthylum dyes and their use as photocatalysts in the photoelectrochemical generation of hydrogen via water splitting.

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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.

References

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Supplemental Information

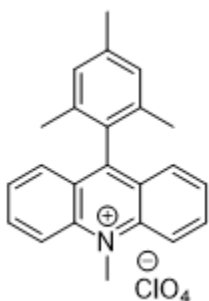


Figure 1: [Mes-Acr⁺]⁺ClO₄⁻

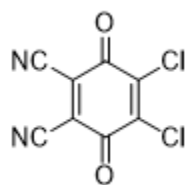


Figure 2: DDQ



Figure 3: PDI

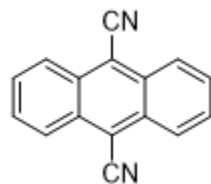


Figure 4: DCA

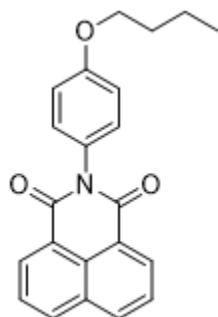


Figure 5: ⁿBuO-NpMI