

Perspective

Bridging Lab and Industry
with Flow ElectrochemistryNour Tanbouza,¹ Thierry Ollevier,¹ and Kevin Lam^{2,*}

SUMMARY

A revitalization of organic electrosynthesis has incited the organic chemistry community to adopt electrochemistry as a green and cost-efficient method for activating small molecules to replace highly toxic and expensive redox chemicals. However, many of the critical challenges of batch electrosynthesis, especially for organic synthesis, still remain. The combination of continuous flow technology and electrochemistry is a potent means to enable industry to implement large scale electrosynthesis. Indeed, flow electrosynthesis helps overcome problems that mainly arise from macro batch electro-organic systems, such as mass transfer, ohmic drop, and selectivity, but this is still far from being a flawless and generic applicable process. As a result, a notable increase in research on methodology and hardware sophistication has emerged, and many hitherto uncharted chemistries have been achieved. To better help the commercialization of wide-scale electrification of organic synthesis, we highlight in this perspective the advances made in large-scale flow electrosynthesis and its future trajectory while pointing out the main challenges and key improvements of current methodologies.

INTRODUCTION

The electrification of organic synthesis has been ignited by chemical industries steering toward the integration of sustainable chemical processes (Pletcher and Walsh, 1993; Cardoso et al., 2017; Atobe et al., 2018; Leech et al., 2020; Pletcher et al., 2018). This push for sustainability has emerged from the increasing global awareness of climate change and the realization of a need to shift toward processes that can sustain themselves, while keeping up with the modernization of industry and a fast-paced economy (McElroy et al., 2015; Adams et al., 2013). This mindset comes hand-in-hand within the academic chemistry community—not only as a goal for sustainability but also as a chance for innovation and revolutionizing the way we approach and re-imagine chemical methodologies (Roschangar et al., 2018). A perfect example of how green and sustainable chemistry is translating into emerging methodologies is the recent rise of new studies using organic electrosynthesis (Yan et al., 2017; Yoshida et al., 2008).

When it comes to academia, over the past couple of decades, a resurgence of organic electrosynthesis has been observed after its long negligence in organic synthesis. Previously, organic electrosynthesis was a niche area of research and conducted almost exclusively by specialists in electrochemistry and thought of as “outdated” for application in organic synthesis. The following are the main reasons for electrochemistry being placed at the very bottom of an organic chemist’s toolbox: (1) its disconnection from organic synthesis when taught in undergraduate and graduate courses to chemists and chemical engineers (mainly taught as a subfield to analytical and physical chemistry) instead of being incorporated into organic chemistry lectures and demonstrated in complementary laboratory classes; (2) lack of resources for cell assembly in synthetic chemistry laboratories; (3) prohibitive costs of some electrode material; (4) limited compelling and general electrochemical reactions reported in the literature (Kingston et al., 2019; Kawamata and Baran, 2020). So, these factors make it difficult for many organic chemists to set up and optimize electrochemical reactions and have very much contributed to electrosynthesis being “outside” of traditional synthetic organic chemistry.

Despite these challenges, the search for synthetic methodologies that are better, simpler, and cheaper have made scavenging these niche fields and venturing into new areas of research outside a single expertise an emerging theme for innovation (Gomollon-Bel, 2019; Capaldo et al., 2019). In addition,

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<https://doi.org/10.1016/j.isci.2020.101720>



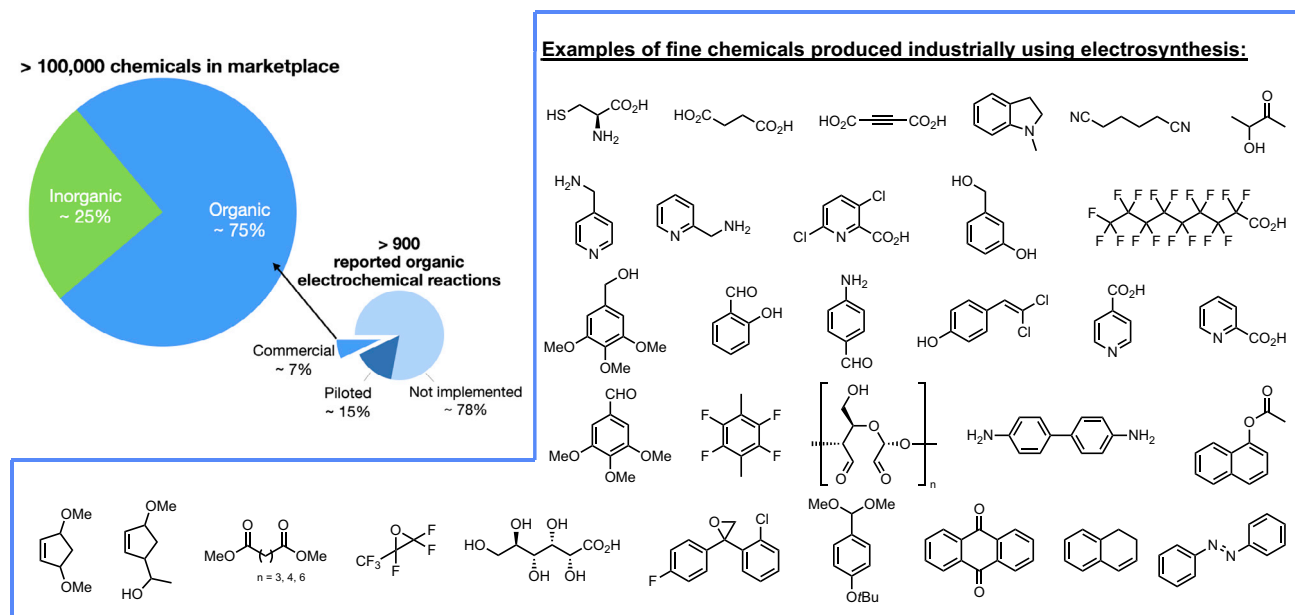


Figure 1. Overview of Fine Chemicals Produced through Electrochemical Processes in Industry

advancements in technologies, such as flow and batch reactors (Cardoso et al., 2017), and in-line analysis equipment (Carter et al., 2010), have highly contributed to the uptake of electroynthesis. Electrode material has also gained sophistication whether in terms of electrode material as observed with the increased availability of boron-doped diamond electrodes, which enable a wide potential window for electrochemical reactions (Lips and Waldvogel, 2019), or in terms of engineering 3D or rotating electrodes (Mohle et al., 2018). As a result, the past 40 years or so have driven an exponential increase in research in organic electrochemistry as a means to replace chemical reagents, replace thermal processes, or discover new forms of chemical activation. Also, the current research is aiming toward more approachable and relatable setups and processes to promote it as less of a “black box” and more of an accessible and everyday tool for organic synthesis. It is becoming more common to use standard electrolysis cells, with some of them even being commercially available and completely standardized, and this resolves issues with variable electrochemical setups from lab to lab (Yan et al., 2018). Hence, it is receiving much more well-deserved value and appreciation as a tool in organic synthesis.

Over a few decades, the academic community has been able to pick up the pace with now over 900 organic electrochemical reactions being reported, while including many breakthroughs in achieving hitherto inaccessible transformations (Yan et al., 2017). Albeit the booming uptake of organic electroynthesis in academia, industries have been slow in incorporating these new methodologies into their processes. Out of all the electrochemical processes reported, a rough 7% of them have been commercialized and 15% piloted (Figure 1) (Sequeira and Santos, 2009). This is a negligible figure when compared with the number of processes in the chemical manufacturing industry. Currently, there are over 100,000 chemicals available in the marketplace (Agam, 2012; Botte, 2014) with roughly 75% of them being organic compounds (European Chemical Industry Council, 2017; American Chemical Society, nd, 2020; Blanco et al., 2019). To better understand the reasons behind this gap, it is important to note that an industry exists to meet the needs of society while making a profit and sustain itself over a long period. To do so, it will want to use low-cost technologies that convert the cheapest option of raw material and energy sources into the desired product (Pletcher and Walsh, 1993).

For an electrolytic step to be incorporated into the manufacturing route of a certain product, it must be convincing in economic terms, logistics, and the industry’s long-term vision. So, it is important to note that, in most cases, a chemical process will consist of a complex sequence of several stages or steps. This means that each step that will go into a synthetic plan will be assessed in a bigger picture point of view. If at least one of those steps is an electrochemical one, it means that it could be easily coupled

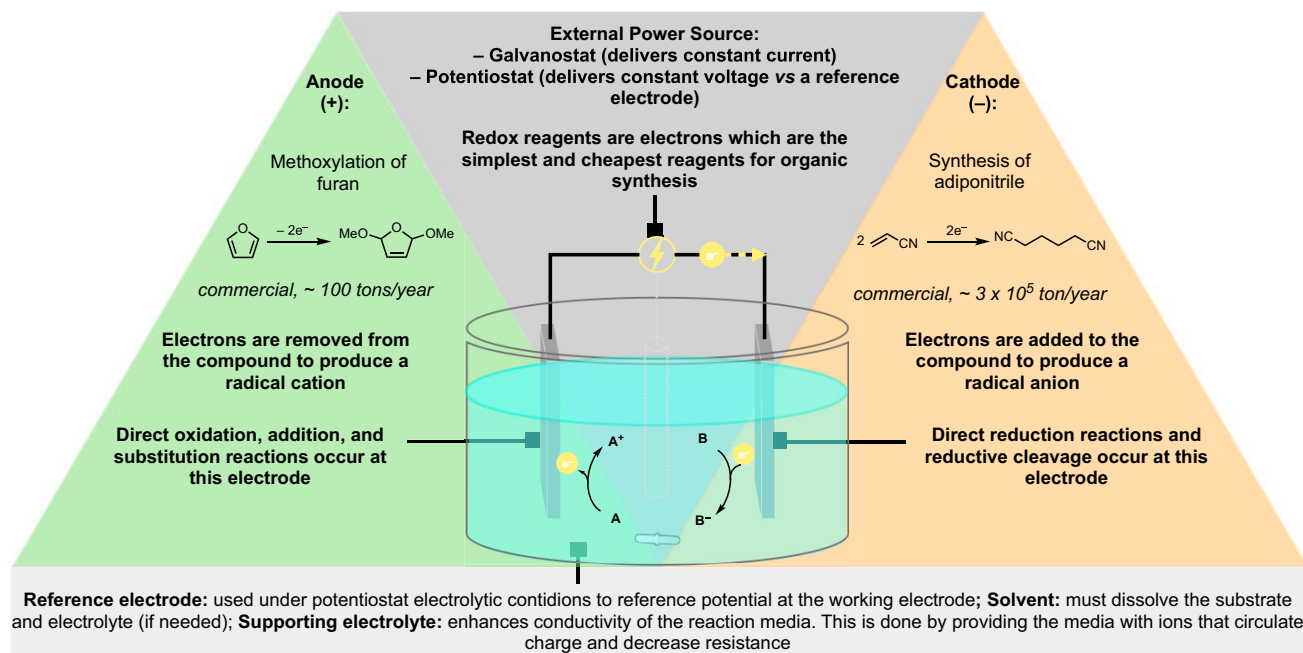


Figure 2. Fundamental Concepts Relevant to Understanding Organic Electrosynthesis

with a subsequent transformation without the need to remove any redox reagents, that would have been present otherwise, or even potentially enabling divergent synthesis to favor selected reactions to proceed by tuning electrochemical conditions. Some limitations that might be holding back the vast incorporation of these new organic electrochemical reactions into a commercial setting could be overcome by increased research using electrochemical flow cells. Continuous flow chemistry is a long-existing technology that has been rapidly making its way through many industries, with the most recent being the pharmaceutical sector (Malet-Sanz and Susanne, 2012; Bogdan and Dombrowski, 2019). Replacing batch reactions, whether chemical, thermal, or electrochemical, by a continuous flow process has shown to be capable of mitigating many pitfalls with large-scale batch reactions that include, and are not limited to, problems with heat runaway, mixing, and mass transfer. A major advantage that comes with running reactions in continuous flow is that academics can mimic reactions and develop them in a setting that is very similar to industry. Another important factor to emphasize research on flow electrochemistry is that almost all industrial electrochemical processes use flow cells (Sequeira and Santos, 2009; Atobe et al., 2018). In this perspective, we will provide readers with an overview of general concepts of organic electrosynthesis and organic flow electrosynthesis while discussing their current standing in academia and industry. We will disclose recent vital milestones that organic electrosynthesis has allowed to overcome and a critical overlook on the use of electrochemical flow cells in industry.

CHALLENGES IN ORGANIC ELECTROSYNTHESIS

For any chemical reaction to occur, a driving force must be present to initiate it and, in analogy to using a catalyst, electrochemistry is a way of activating molecules but by the addition or removal of electrons. Activation, generally speaking, occurs at the surface of electrodes and hence is regarded as a heterogeneous chemical reaction, by a single electron transfer (SET) process that converts the substrate into a reactive intermediate that ultimately gives rise to the desired product (Pletcher, 1984). Any electrolytic cell is composed of at least two electrodes, connected by a power source, which act as a cathode and an anode. At the anode, an electron is abstracted from a compound (Figure 2A), then oxidized into a carbocation/radical intermediate (Figure 2A⁺), and hence direct oxidation, addition, or substitution reactions can occur. Contrariwise, at the cathode, direct reduction reactions and reductive cleavage occur via the intake of an electron to produce a carbanion/radical (Figure 2B⁻). Either the cathode or anode is referred to as the working electrode, *i.e.* the electrode at which the reaction of interest is happening, and the other is referred to as the counter electrode. Then, to maintain charge balance in the bulk of the solution, electrons must pass from anode to cathode via an external electric circuit; hence, a mechanism for charge transport between

the two electrodes must exist. The movement of ions through the solution, or separator in the case of a divided cell, allows the maintenance of charge neutrality. Thus, the solution must be conductive enough to allow the transport of ions. The conductivity is dependent on many parameters, such as the dielectric constant of the solvent used, the types and concentration of supporting electrolyte, the distance between the two electrodes (inter-electrode gap), and the temperature. Conductivity is easily achieved for electrolysis under aqueous conditions; however, organic reactions are not usually feasible in water. In some cases where reactions can tolerate water, a practical alternative is the use of a biphasic or emulsion aqueous/organic mixtures in which organic droplets are dispersed in an aqueous media (Marken and Wadhawan, 2019). Mostly, organic electrosyntheses are done in organic solvents containing supporting electrolytes that offer enhanced conductivity. Reactions can be run either in galvanostatic mode, where the cell is given a constant current and voltage changes and adapts to the set current, or under potentiostatic mode, where the potential of the cell is kept constant by referencing the working electrode to an additional electrode (*i.e.* reference electrode) and current decreases following a negative exponential function. Applications in organic electrosynthesis mainly depend on galvanostatic operations that have a simpler setup, while still being capable of carrying out desired reactivity (Pletcher, 1984).

Organic electrosynthesis is re-emerging as an attractive approach for conducting organic reactions in an environmentally responsible manner (Blanco et al., 2019; Petti et al., 2019). When it comes to academia, organic electrosynthesis can be considered as a viable and better way of conducting oxidation and reduction reactions with higher yields, selectivity, and purity (Yan et al., 2017). Many of the advantages of organic electrosynthesis have been summed up in different reports that have shown its potency and features as a play-and-go equipment, and this has encouraged it as a go-to tool when it comes to academic research (Yan et al., 2017, 2018; Kingston et al., 2019; Yoshida et al., 2008; Cardoso et al., 2017; Capaldo et al., 2019; Chang et al., 2020; Leech et al., 2020). Also, the search is always on for innovating new processes in organic chemistry. We want reactions that are better, faster, and new. Using electrons as reagents can be considered as inherently greener and cheaper than any other chemical reagent because 1 mol of electrons can have a little-to-no footprint and could cost a few pennies—not to forget the shift toward more economic and sustainable electricity sources that makes this field all the more worthwhile to develop.

Electrochemical reactions are considered mild as they can be often done at ambient temperature and under atmospheric pressure. On the contrary to common perception around electrochemistry being harsh and presumably unselective, reactions can be controlled and reaction selectivity can be tuned by the nature of electrodes, the potential at the working electrode, and the nature of the electrolyte (Pletcher, 1984). Also, as in any traditional organic chemical reaction, the degree of transformation can be controlled by tuning charge consumption. Pivotal developments in the field, such as the Kolbe electrolysis (Kolbe, 1847) and increased accessibility to standardized and off-the-shelf cells (Kawamata and Baran, 2020), have encouraged the adoption of electrosynthesis as a versatile tool in organic synthesis and helped it move out of being a niche area of research. This increase in research is still, however, limited despite its obvious benefits. The preconception and stigma that surround electrochemistry is a major contributor to this phenomenon, and the “easiness” of opting for a chemical substitute makes the venture less and less worthwhile. Still, the innate benefits are being increasingly embraced by synthetic chemists in both academia and industry as a means for innovation, but this remains in its very early ages.

Taking into consideration all the advantages of an electrified chemical manufacturing industry from an economic and sustainability viewpoint, there is still slow incorporation of organic electrosynthesis (Sequeira and Santos, 2009). Electrosynthesis has a long-standing history in industry and some make up some of the largest scale chemical processes and have withstood time to remain commercial until today. Organic electrosynthesis was popularized by M. M. Baizer at Monsanto before shifting to academia (Baizer, 1990). On the other hand, many electrochemical processes that are being piloted have failed to reach commercialization and even some already-commercialized processes are being discontinued (Cardoso et al., 2017). So, it is important to have a grasp on the reasons behind both the successes and struggles of scaling and commercializing electrochemical processes. This understanding could deliver a larger pool of highly viable options that industries would more frequently pick up. Looking at the successful commercialized electrochemical processes, good examples are the current commercial preparations of dimethoxycyclopentene and adiponitrile, which are done on hundreds to megaton scales annually (Sequeira and Santos, 2009). These are commodity and low-cost chemicals that are produced non-stop year-round, and hence the smallest increase in efficiency and the cost of electrons really count. No chemical process can come close to the

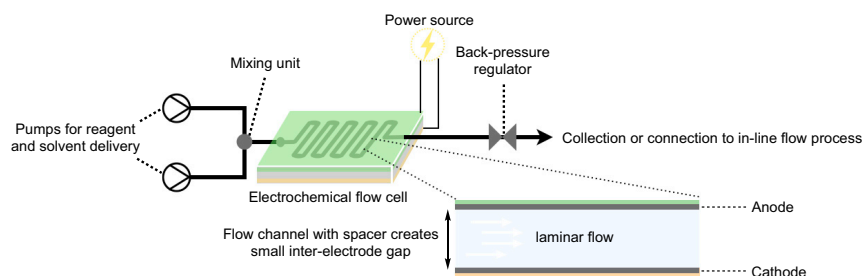


Figure 3. Basic Components of an Electrochemical Flow Setup

efficiency, economy, and sustainability of electrochemistry in these cases. Here, an organo-electrochemical method must produce the desired chemical from the cheapest raw material and equipment, while being superior in selectivity and highly scalable. However, when it comes to fine or specialty chemicals, industries including medicinal and radiochemistry will still welcome reactions using stoichiometric reagents even if they use expensive and toxic transition metals, as long as they are easily manufactured and are well understood by process chemists. So, in this scenario, innovation and the simplicity of methods that produce high-value molecules are key.

For any chemical transformation, moving productivity from laboratory scale to pilot and production scale is a challenge. However, for electrochemical reactions, scaling up a batch process is formidably challenging, as the cell voltage and energy costs would dramatically go up when the interelectrode gap increases. For this, industrial electrochemical cells are almost exclusively flow cells that offer high electrode surface area to reaction volume ratio (Pletcher et al., 2018; Pletcher and Walsh, 1993). That, with the narrow inter-electrode gap, enable reactions that are faster and reach higher current with lower concentrations of supporting electrolyte.

CONTINUOUS FLOW CHEMISTRY AND FLOW ELECTROSYNTHESIS

Flow chemistry is a technology that enables faster, safer, and reproducible routes to make high-purity products and demonstrates significant potential as synthetic tool (Hartman et al., 2011; Glasnov, 2016). When it comes to chemical synthesis using flow chemistry, its setup is quite modular, but its key elements are the following five components: reagent and fluid delivery system (usually pumps), mixing unit, reactor/flow cell, pressure regulator, and collection unit (Figure 3) (Plutschack et al., 2017). A flow reactor can decidedly vary in type according to application. A few examples include chip reactors, coil reactors, tube-in-tube (for gas reagents), reactors containing static mixers, and column reactors for supporting heterogeneous reagents. All these can be tailored and tweaked around as seen fit for application. In addition to the main five components of a flow setup, there is the infinite option of modules that can be easily coupled for carrying out complex synthetic sequences and processes (Baxendale et al., 2009; Tsubogo et al., 2015; Britton and Raston, 2017). The main advantage to flow chemistry is the possibility of carrying out multi-step syntheses by adding several reactors in series with the option of in-line quench or purification systems (Godin et al., 2017; Deadman et al., 2013). Even in the most complicated of setups, a flow system can be monitored and assessed in real-time via analytical instrumentation, such as IR and UV-Vis, which is most advantageous for system automation and high throughput analysis (Musio et al., 2017; Reizman and Jensen, 2016; Isbrandt et al., 2019).

Principally, a continuous electrochemical flow synthesis is carried out by continuously pumping a solution of reactants into a flow reactor (usually in a laminar flow mode) where mass transfer along electrodes is achieved by diffusion, created by a concentration gradient from the reaction progress, and migration of the charged species in a potential field (Noël et al., 2019). The electrodes are separated by spacers that can vary from mm to μm scale. This narrow distance is proportional to the solvent/electrolyte system's resistance and is hence highly advantageous. Inside the reactor, reaction conditions, such as temperature and pressure, are controlled, and the stream of product is either carried into a second reactor or displaced into a collection unit (Rehm, 2020). The amount of time reactants spend in a flow reactor is defined by residence time and is a factor of flow rate and reactor volume (residence time = flow rate \times volume). Reaction scale is a matter of the amount of material injected or, in other words, how long material was allowed to flow into the reactor. Hence, a flow synthesis can be envisioned across the sequential scaling routes of laboratory-

scale/discovery-stage scale, pilot plant, and full-scale commercial production, while combining improvements in process intensification and optimization (Hartwig et al., 2014). With a continuous flow process withholding the same basic operational concepts across different reaction scales, a wall is broken between the sectors at all scales.

There is an introduced factor of relatability because a flow synthesis combines aspects of both organic synthesis and chemical engineering, which is key for better communicating and understating the advantages and disadvantages of the process at hand. The synergy of synthetic chemistry and chemical engineering is rarely achieved in an academic setting and could be pivotal for driving better academic-industrial collaborations. This can be achieved by, first and foremost, a shift in perspective to eliminate prejudice of stepping beyond the boundaries of a field of expertise. Second, the inherent advantages of chemists and chemical engineers working on the same bench should be better recognized and encouraged by both societies. Last, the lack of contact between the two should be addressed by a better presence of chemical engineers in chemistry events, such as conferences, department gatherings, and panel discussions, and vice versa to spark conversations of potential collaborations.

Even though a continuous flow process is not a new technology—on the contrary, it has been around for decades and is the basis of the petrochemical industry in extracting crude material all the way to refining and bulk product synthesis—the use of flow cells for organic synthesis has only recently gained traction in academia (Pletcher et al., 2018). The pursuit for innovative and sustainable chemical processes in organic synthesis can attribute the grand attraction toward flow chemistry, and this is because reactions feature high selectivity and reproducibility while reducing costs, energy and solvent consumption, and carbon footprint. Various chemical manufacturing industries have opted for flow systems and, recently, the pharmaceutical industry has started incorporating flow chemistry (Bogdan and Dombrowski, 2019; Hughes, 2020). To further encourage the use of flow chemistry in the pharmaceutical sector, in the CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries) a green flag was awarded to reactions in flow, which adds to a metric toolkit for the evaluation of reaction sustainability and its “green credential.” (McElroy et al., 2015). Besides, flow synthesis has been praised for its contribution to the twelve principles of green chemistry and rated by IUPAC as one of the top ten chemical innovations that will change our world and that is because of its contribution to the UN sustainability goals by responsible consumption and production (Gomollon-Bel, 2019). Also, it exhibits high potential for decentralizing chemical production, which is vital especially for developing countries to enable access to a variety of commodities. This is a prime socioeconomic advantage where a commodity chemical or even a pharmaceutical can be made on-site without the hindrance of the cost and space of a huge infrastructure. So, using small flow reactors that can be easily transported enables countries, that have limited chemical manufacturing capabilities, to adopt this low-cost technology for local manufacture, which could possibly lead to better access to key medicines for the underprivileged (de Souza and Watts, 2017).

Flow synthesis is becoming increasingly appreciated among academic researchers for its innate advantages of enhanced mass and heat transfer, reliable scalability, and inherent safety. As such, there is a mounting push from academia and industries to adopt this technology. Hence, a combination of two emerging technologies in organic synthesis—flow chemistry and electrochemistry—could seem like the answer for creating a bridge between both sectors.

An electrochemical flow cell would, in the simplest and most common of arrangements, have two plate electrodes facing each other, and the reaction solution would flow into a channel created by isolating spacers. A flow cell in this type of setup is in parallel electrode configuration. Parallel electrodes configuration is characterized by facile fabrication and exhibits uniform potential and current distribution, which attributes its wide applicability for organic electrosynthesis (Atobe et al., 2018). Other configurations have been reported, such as interdigitated electrode configuration in which arrays of microscopic electrodes are either metal-sputtered or screen-printed onto a plate; this configuration results in high current due to reduced thickness of the solution’s diffusion layer and has been widely used in conducting sensors (Wehmeyer et al., 1985) and amperometric detectors (Aoki et al., 1987) but also applied in the electrochemical methoxylation of furan and epoxidation of propylene (Belmont and Girault, 1994; Belmont and Girault, 1995). Also, serial electrode configuration flow cells, which have chip-like electrodes in a single segment arrangement, are applied mostly for chemical and biochemical analyses, such as determination of glucose in soft drinks (Cerqueira Ferreira et al., 2013), but is rarely used for organic

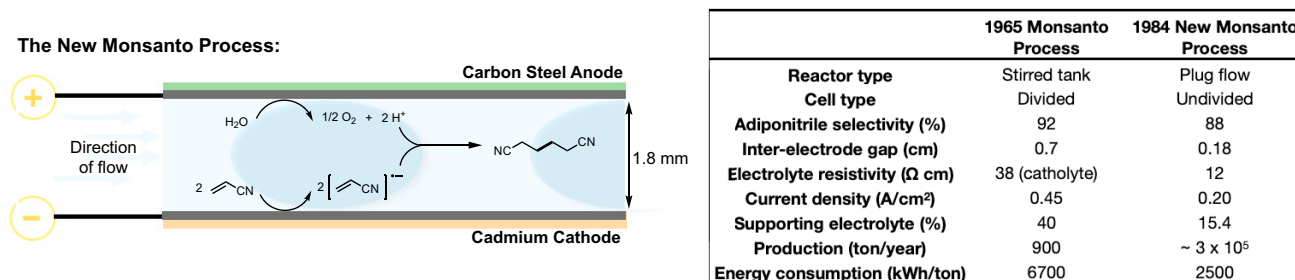


Figure 4. The Advantages of Flow Electrosynthesis to the Monsanto Process

Schematic highlighting the “New Monsanto” Process (left); table comparing the “old” 1965 and “new” Monsanto Process (right)

electrosynthesis due to their low productivity, which is explained by the limited contact area with the electrodes, but it has been found useful for the anodic cyanation of pyrene for overcoming its limitation of overoxidation (Ueno et al., 2004).

These electrochemical flow cells are becoming increasingly popular and have demonstrated high capability to overcome limitations posed by conventional “batch” electrochemical processes. The small inter-electrode gap is incredibly useful to electrochemical reactions in organic solvents because it significantly reduces resistance, *i.e.* reduces the concentration of supporting electrolyte and could even eliminate its need, and this leads to a cleaner process that is more economic (price of electrolyte, extraction- and purification-related pricing) and reduces waste. Most importantly, the flow electrochemical step can be much easily coupled with a subsequent flow reaction in series. Also, facile and controlled generation of radicals and highly reactive intermediates that can be safely made and consumed *in situ* allows accessing uncharted chemistries (Britton and Raston, 2017). Heat runaway can be easily managed in a flow system when compared with macro batch electrochemical cells that can lead to more controlled and reproducible electrochemical reactions upon scale-up. The characteristic of flow syntheses offering a high surface area to reaction volume ratio is pivotal especially when one of the reactants is a heterogeneous reagent as in an electrochemical process because in this setup there is a large electrode area to reactor volume ratio that can make a reaction proceed, with increased mass transfer leading to better selectivity and reduced reaction times, *i.e.* higher product output. Most importantly, flow electrosynthesis is paving way for innovation and cross-disciplinary collaboration by allowing researchers to go after reactor design and commercialization (Folgueiras-Amador et al., 2020; Murray et al., 2019; Kirkaldy et al., 2018). The Ammonite electrolysis cells have come about from the collaborative work of R. Green, R. Brown, and D. Pletcher with Cambridge Reactor Design Ltd. (Green et al., 2016). It is a commercial large electrolysis flow cell designed for multigram scale syntheses composed of a spiral flow channel sandwiched in between carbon polymer and stainless-steel electrodes and separated by a polymer spacer (Author Anonymous, nd, 2020). The performance of the flow cell was exemplified by various reactions, such as the methoxylation of *N*-formylpyrrolidine and deprotection of PMB (*para*-methoxybenzyl) ethers (Green et al., 2016, 2017).

Flow electrosynthesis has shown high industrial potential, and this can be exemplified by the “new Monsanto” process for the electrosynthesis of adiponitrile (Figure 4) (Danly, 1984). The Monsanto process is the electrochemical hydrodimerization of acetonitrile into adiponitrile, which is a precursor of nylon 6–6, and has been produced in 0.34 million tons/year in 2010, making it the largest industrial electrochemical process. The early batch process in 1965 used a divided cell with lead/lead oxide electrodes and a catholyte mixture of 16% acetonitrile, 16% adiponitrile, 40% tetraethylammonium ethylsulfate, and 28% water. Each cell was applied with 12 V and resulted in a cathode current density of 0.4–0.6 A/cm^2 leading to 92% selectivity in adiponitrile. The annual production of 900 tons used a total cell current of 2870 A and consumed 6700 kWh/ton. The process then went through multiple stages of development to reach the now-used second-generation or “new Monsanto” process in 1984 that enables comparable selectivity and implements an undivided flow cell with electrodes made of carbon steel sheets and cadmium-plated faces. The reaction mixture is an emulsion of acetonitrile and adiponitrile in water containing 0.4% hexamethylene-bis(ethyl dibutylammonium), 15% disodium hydrogen phosphate. The interelectrode gap has been reduced from 0.7 cm to 2 mm and thus a significant cutback in the amount of needed supporting electrolyte (40%–15.4%) and its type allowed more straightforward isolation by simple extraction followed by distillation. Adiponitrile production currently exceeds 300,000 tons/year and this flow process has led to

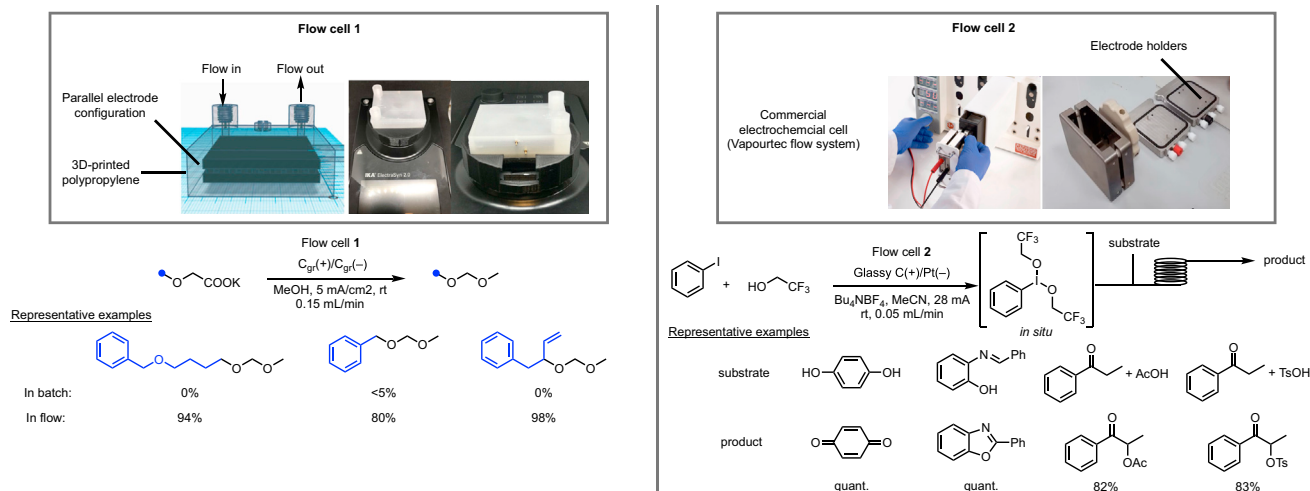


Figure 5. Examples in Advancements in Flow Electrosynthesis

Electrochemical methoxymethylation of alcohols (left); electrochemical *in situ* generation of hyper iodine species (right). Figures were reproduced with permission from Van Melis et al., 2019; Elsherbini et al., 2019 Wiley (2020).

a 37% drop in energy consumption to 2500 kWh/ton (Pletcher and Walsh, 1993). Thus, the choice here to invest into an electrochemical flow setup of such a high-demand commodity chemical has resulted in a simpler cell design that uses cheaper electrode material and offers the same range in selectivity but with a huge cutback in the amount of electrolyte and energy consumption. This investment significantly advanced the process as a whole, made it more sustainable, and considerably improved its economic standpoint to keep up with modern-day production scales.

The fundamental advantages of using continuous flow chemistry for organic electrosynthesis have been applied for a wide variety of electrochemical techniques and has received significant research interest during a time of peaking resurgence of both organic electrosynthesis and flow synthesis. As a result, many studies have reported the use of flow reactors in chemical synthesis and impressive cell designs, and innovative chemical processes have been disclosed and also extensively reviewed. To better advocate the usefulness and potency of flow electrosynthesis, reports that show the accessibility and economic viability of opting for a flow setup are important to highlight and show how reactivity could be highly affected and triggers more curiosity to continue exploring this area. This can be showcased through work by K. Lam et al. for the flow electrochemical methoxymethylation of alcohols, which significantly improved the previously reported method in batch (Figure 5) (van Melis et al., 2019). The undivided electrochemical flow cell and complete setup was made of low-cost 3D-printed material, and the flow cell was printed in parallel electrode configuration using graphite electrodes under galvanostatic conditions and did not even use any pumps where solutions were simply delivered with pressurized air, thus making it more accessible and economic for researchers who are still skeptic in investing in a commercial flow system. Under traditional batch electrolysis conditions, anodic methoxymethylation suffers from drawbacks that include low current efficiency, which is a result of overoxidation of the MOM ether product, in addition to the need of high amounts of supporting electrolyte to increase solution conductivity to reach desired current levels. Hence, a flow process that significantly reduces the interelectrode gap down to 2 mm allows desired current levels to be reached without any supporting electrolyte. In addition to this environmental and economic advantage, drawbacks of overoxidation have been overcome in a flow setting, and even easily oxidizable benzylic substrates are high yielding in the desired ether. This could be explained by a variety of factors: one would be the minimum residence time of the solution in the electrochemical cell, so the product leaves the cell before the chance of further oxidation; another would be the nature of the flow regime that is laminar and hence reduces the contact of the ether product with the anode due to selective oxidation into the carbocation intermediate followed by its diffusion closer to the cathode where it is less likely to undergo subsequent oxidation, *i.e.* selective wetting of electrodes.

One of the big pictures of flow chemistry is its use for multi-step synthetic processes by coupling various reactors in one system that leads to complex molecules. Complex organic compounds, especially those

relevant to specialty chemicals, such as the pharmaceutical industry, are comprised of several individual synthetic and purification steps. These processes are normally energy and solvent consuming and not to mention time- and labor-exhaustive. Thus, continuous flow offers the option of merging steps of a total synthesis into a single, streamlined, and automated flow configuration. This approach reduces the need for a quench or purification to be executed separately and would be executed in-line and this could offer great safety and economic benefit. Multi-step syntheses in flow are especially relevant to reactions that produce highly reactive intermediates. These species and even any other toxic and hazardous compound could be generated *in situ* in highly controlled conditions and directly injected into the next reactor for the desired subsequent reaction. T. Wirth *et al.* have employed this strategy to make unstable hypervalent iodine reagents in flow, which were used in subsequent in-line reactions all in one flow setup (Elsherbini *et al.*, 2019). This approach has allowed tapping into the reactivity of these highly unstable yet incredibly versatile reagents. In this work, the anodic oxidation of iodobenzene in an undivided flow cell of glassy carbon/platinum electrodes with trifluoroethanol gives the corresponding hypervalent iodine species in high yields while avoiding its degradation. The reaction is coupled to a second reactor to conduct oxidation chemistry, heterocycle synthesis, acetoxylation, and tosyloxylation (Figure 5).

There is no question that when looking into reports using flow electrochemistry, a series of advantages to batch conditions have been observed. Even when starting flow conditions could not produce desired reactivity, the modularity of flow chemistry has allowed chemists to outmaneuver setbacks (Noël *et al.*, 2019). For instances when a reaction necessitates a divided electrochemical cell, flow cells can be adapted to allow the integration of membranes and create that needed setup. When laminar flow mode is disruptive to an electrochemical process, this has been solved by creating flows with toroidal/turbulent vortices induced by multiphase flow patterns to eliminate circumstances of extremely low mass transfer to the electrodes. This modularity in addition to the discovery of new electrode material makes this field a gold mine for accessing innovative and new reactivity (Kawamata and Baran, 2020). So, if flow electrochemistry is so great and potent, then why has it been so sluggish for wide application and commercialization? If electrochemical processes in industry are almost exclusively based on flow cells, then why these emerging flow technologies are not making it to commercialization? Also, in the opposing sense, if academic researchers exploring organic electrochemistry know that a batch process would be almost impossible to scale and appeal to industries, then why are studies not investigated in a flow setup more often? No matter how you put it, it is evident that barriers are preventing the use of flow electrochemistry despite many of its inherent advantages.

When it comes to academia, the problem with the slow adoption of flow electrochemistry could be attributed to it being considered as a “black box in a box.” If a synthetic chemist has never used organic electrochemistry or flow chemistry, the chances that a combination of such “ambiguous” tools could be considered are extremely low. It would require time investment to learn and master the basics of electrochemistry, flow chemistry, and the combination of the two. Learning one and not the other would not suffice and one cannot directly jump to learning flow electrochemistry because flow chemistry itself is not a self-sufficient research area and an understanding of electrochemistry in batch is key (Maljuric *et al.*, 2020). So, for flow electrochemistry to pick up better traction it has to be hand-in-hand with an improved appreciation of batch organic electrochemistry. Once a grasp is held on organic electrochemistry, a flow version is far from as simple as translation of batch conditions into a flow setup. In most cases, changes in conditions or even a complete redesign of the process are needed, so a better understanding of fluid dynamics and engineering aspects, such as steady-state conditions and liquid flow velocity, creates another limitation (Gerardy *et al.*, 2018). In academia at least, at the end of the day, money talks and the exorbitant prices for commercial flow equipment and lab space hinder application and divert interested research groups to opt for home-made setups that could result in reproducibility problems and are not as practical (Wegner *et al.*, 2011).

Taking into account an industry perspective, the “black box in a box” comes into play here as well. Yes, electrochemical reactions in industry mainly use flow cells, but they represent an extremely small percentage of chemical processes. Current industrial electrochemical processes are done in flow cells but are not genuinely continuous flow processes and are instead conducted in a semi-batch mode, *i.e.* the electrolyte solution is recirculated through a reservoir and there is no constant stream of product (Pletcher and Walsh, 1993; Pletcher *et al.*, 2018). The reason that these electrochemical flow cells are employed in semi-batch mode is to enable better conversions. When high conversions are achieved after passing through one

cell, this single-pass process is truly continuous. Thus, the development of single-pass flow electrolysis is highly desirable because it enables integration into a continuous sequence with other synthetic steps or workups. So, the likeliness of high availability of trained personnel in truly continuous flow electrosynthesis is still rare especially for industries that have only recently introduced flow systems. Again, as for academia, a cultural change to learn something new and step out of comfort zones is detrimental.

There are also some technical issues with flow synthesis that would seem to hinder its clearance to pilot or commercialization. For example, the arch-nemesis of any continuous process, electrochemical or not, is clogging. Solids that fail to dissolve can create several problems that range from non-uniform flow distribution to extreme pressure buildup. An electrochemical process is highly susceptible to problems of clogging because of electrode fouling or side reactions. Surely one of the most important advantages of using electrolytic flow cells is the small inter-electrode gap that reduced significantly cell resistance; however, that small distance comes to a limit where it could reach the point of creating an electrical arc (Noël et al., 2019). In addition, electrochemical processes tend to produce gases as by-products, such as N₂ or H₂. Unlike batch electrolysis, in a flow setup, these gases do not have any headspace to escape and thus create gas-liquid segments. Such segments might help reactions that need improved mass transfer by increasing turbulence in the liquid phase. However, gas does not conduct electricity and hence gas-liquid segments negatively affect the performance of the flow cell by increasing local current densities (Maljuric et al., 2020; Cao et al., 2021). When it comes to scale-up, several electrochemical cells are stacked together in a filter-press arrangement. However, not only does this strategy need highly complex monitoring but it also means that a large amount of electrode material is needed, which could be limiting in terms of economics, especially for state-of-the-art electrode material (Atobe et al., 2018).

Electrosynthesis is a great option for commodity industries and should be more of a target of academic research but that is not the case. Commodity-producing industries highly value the slightest economic and socioeconomic advantage of an improved chemical technology because the slightest saving counts and any squeeze in improved efficiency is in the scale of kilos and tons per year. This is why these industries are the main users of electrochemical processes. So, while researchers are rushing to celebrate the renaissance of organic electrosynthesis and achieve new reactivities with complex natures and create compounds with extreme complexity and novelty, fundamental reactions and functionalities made via organic electrosynthesis and their demonstration in continuous flow is ignored in comparison. It is important to recognize that as much as it is exciting to forge new and unconventional bonds in organic synthesis to create compounds with high structural complexity, fine chemical and pharmaceutical industries will only invest in it if it exceedingly beats an existing technology because cost and simplicity are less of a concern in those fields. Their objective is to make the marketed product as fast as possible even if the process used is not highly productive. So lastly, to better remedy this gap, the “black box” label has to be overcome. Organic electrosynthesis should become more common practice and less of a niche and that is what we are witnessing today. But also, following in the steps of some universities, hands-on flow chemistry training should become an integral part of undergraduate laboratory training. Most importantly, whether by getting industry scientists and academics to interact more or by adopting flow technology and electrosynthesis, there has to be a sustainable relationship between the two sectors. They should come together more often in building new projects and unifying their goals toward scientific, environmental, and economic growth.

CONCLUSION AND OUTLOOKS

All in all, it is certain that flow electrosynthesis exhibits high potency and is appealing to both academics and industry scientists as a means to scale-up organic electrochemical processes and access novel reactivity. There is mounting interest from both sides for new technologies that use flow chemistry, and organic electrosynthesis is readily making its way through chemical laboratories as a useful synthetic tool. Hence, organic flow electrosynthesis could be the meeting point for enabling better knowledge transfer across the various sectors of this re-surfacing technique. The interdisciplinarity of organic flow electrosynthesis, through a fusion of organic chemistry, electrochemistry, and chemical engineering, is pivotal for enabling chemical innovation. Further developments should focus more on collaborations between the three sectors to address and have a lateral view of the many challenges disrupting commercialization and widespread application. The development of competitive and sustainable electrochemical processes for the manufacture of building blocks, APIs (*i.e.* Active Pharmaceutical Ingredients), and commodities that incorporate flow chemistry are imperative for advancement and continued growth of academia and

manufacturing industries. Truly continuous electrosynthetic processes are still in their early stages of maturity and, with increased examples and application, its robustness and applicability will surely pick up the pace.

ACKNOWLEDGMENTS

N.T. is grateful to the Natural Sciences and Engineering Research Council of Canada for a doctoral award (PGSD3 - 546986–2020) and the Royal Society of Chemistry for a Researcher Mobility Grant (M19- 0357) for funding her visit to work with K.L. and also thanks Dr. Matthew C. Leech (University of Greenwich, UK) for his passionate mentoring in electrosynthesis. T.O. thanks the Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant RGPIN-2017-04272, the FRQNT Centre in Green Chemistry and Catalysis (CGCC) Strategic Cluster FRQNT-2020-RS4-265155-CCVC, and Université Laval. K.L. is grateful to the Engineering and Physical Sciences Research Council (Grant EP/S017097/1) for their financial support and the University of Greenwich.

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