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Enhancing electrochemical reactions in organic synthesis: the impact of flow chemistry

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Utilizing electrons directly offers significant potential for advancing organic synthesis by facilitating novel reactivity and enhancing selectivity under mild conditions. As a result, an increasing number of organic chemists are exploring electrosynthesis. However, the efficacy of electrochemical transformations depends critically on the design of the electrochemical cell. Batch cells often suffer from limitations such as large inter-electrode distances and poor mass transfer, making flow cells a promising alternative. Implementing flow cells, however, requires a foundational understanding of microreactor technology. In this review, we briefly outline the applications of flow electrosynthesis before providing a comprehensive examination of existing flow reactor technologies. Our goal is to equip organic chemists with the insights needed to tailor their electrochemical flow cells to meet specific reactivity requirements effectively. We also highlight the application of reactor designs in scaling up electrochemical processes and integrating high-throughput experimentation and automation. These advancements not only enhance the potential of flow electrosynthesis for the synthetic community but also hold promise for both academia and industry.

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Introduction

Organic electrosynthesis is a centuries old field that exploits the most direct source of electrons, electricity, to forge new bonds. This field enables electrochemists to develop greener synthetic pathways by bypassing the need for hazardous/toxic chemical oxidants and/or reductants.^{1–5} and by achieving scalable reactivity that would otherwise not be attainable.^{6,7} Batch reactors in electrosynthesis have largely benefited from numbers of innovations to improve the robustness and versatility of electrosynthesis.⁸ Recent efforts have been made to standardize electrolysis reactors to reduce the amount of non-characterized reactors permeating the literature. This has promoted the field to be a suitable complementary method to photocatalysis or two electron chemistry at large.⁹

Electrochemical reactions offer highly efficient synthetic routes as the applied potential or number of electrons exchanged can be “dialed-in” using a potentiostat.¹⁰ Indirect electrolysis offers an alternative way to enhance or alter selectivity by careful consideration of the redox mediator.¹¹ However, electrochemistry inherently involves heterogeneous processes, requiring effective mass transfer from the bulk to the electrode surface. The large inter-electrode distance (IED) and the poor mixing of batch electrolysis reactors reduces the faradaic efficiency (FE),¹² making scale-up of batch electrolysis reactors challenging and often limiting the yields. Therefore, switching to flow electrolysis reactors enables to drastically increase the electrode surface to volume ratio resulting in an improved efficiency.¹³ Additionally, the small interelectrode distances in microreactors reduces the Ohmic drop, enabling to reduce the amount of the usually costly supporting electrolyte.¹⁴ These advantages make flow electrosynthesis reactors the ideal candidates for optimizing electrosynthetic transformations and potentially transferring them on an industrial scale.^{15–17} Additionally, continuously improving reactor designs enables the chemist to

Electrochemistry and Flow electrochemistry in organic chemistry since 1985

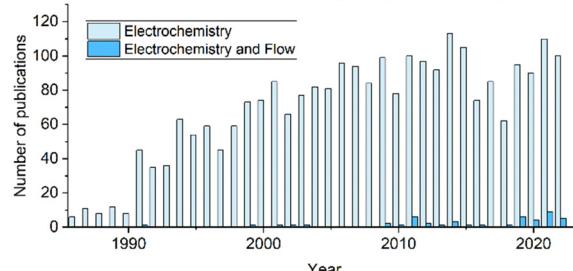


Fig. 1 Literature gap between the use of electrosynthesis and electrochemistry in flow. The plotted data was obtained using the term “Electrochemistry” or “Electrochemistry” and “Flow” as queries in the Organic Synthesis category of Web Of Science advanced search on March 15th 2024.¹⁸

overcome the traditional limitations of flow reactors by being able to handle slurries, using gases as reagents, merging the use of light and electricity to broaden the scope of reactions achievable in flow.

Given the advantages of flow electrosynthesis over batch in scaling-up and optimizing electrochemical transformations, it is intriguing to see how under-exploited the use of microfluidics for electrosynthesis has remained (Fig. 1).

Arguably, organic electrosynthesis is still hindered by its perception as a black box and the need for sophisticated setups,^{19,20} making it less likely to be used in routine reactivity screening. Moreover, as flow chemistry requires an additional expertise, it can be challenging to successfully merge it with an electrosynthetic process. However, plenty of resources on the basics of electrochemistry,^{10,21–24} flow chemistry and even flow electrochemistry are now available.^{25–28} So, in order to lower the entry barrier to flow electrosynthesis, we believe that there should be a stronger focus on the key tool for such endeavors: the flow electrochemical reactor. In this review we henceforth



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Timothy Noël

Timothy Noël is a Full Professor and Chair of Flow Chemistry at the University of Amsterdam, where he focuses on the delicate synergy between synthetic organic chemistry and technology. He has received several awards for his research in flow chemistry, including the DECHEMA prize (2017), the Hoogewerff Jongerenprijs (2019), the IUPAC-ThalesNano prize (2020), the KNCV Gold Medal (2021), the ACS Sustainable Chemistry & Engineering Lectureship Award (2022), and the ChemSocRev Pioneering Investigator Lectureship (2023). He was also named a Fellow of the Royal Society of Chemistry in 2024. In addition, he serves as Editor-in-Chief of the Journal of Flow Chemistry, as president of the Flow Chemistry Society and is a co-organizer of #RSCPoster.



aim to assist organic chemists in transferring their electrochemistry in flow by providing a rationale for choosing a reactor design among the various options available in the literature.

Assessing whether flow is the way to go for your electrosynthetic process

The positive impact of implementing an electrochemical processes in flow is non negligible. Beyond the benefits for the electrochemical system itself mentioned afore (improved robustness, mass transfer, reduced ohmic drop, scalability), flow chemistry can provide workarounds for the constraints of a given reactivity.²⁹ First of all, the use of flow inherently allows for easier multistep processes, specifically when the required intermediates can be degraded under electrochemical conditions, or when the electro-generated intermediate is short-lived and needs to be readily trapped or quenched.¹² Moreover, regardless of the selected reactor design, the flow type can be adapted to the nature of the reaction mixture. As an example, when dealing with liquid biphasic mixtures, a segmented flow is better suited to maximize the mass transfer that would be otherwise drastically hindered in batch.^{30,31} Another strategy is to purposefully separate the two phases, using a “parallel laminar flow”, to differentiate the redox processes undergone by the reagents.³²

However, one must be aware, that the use of a flow reactor brings additional complexity to the process. Beyond the basic knowledge of flow chemistry required, challenges may arise that traditional organic chemists are not always familiar with, such as: picking a flow reactor design to use and/or the added sophistication of the electrochemical setup (*i.e.*, engineering aspects of flow chemistry). Therefore, one must ensure whether the benefits in terms of reactivity outbalance the added complexity (Fig. 2).

In this review, we provide an overview of the various electrochemical reactor designs developed in recent years to accommodate different types of synthetic organic chemistry. The nature of the reaction mixture (homogeneous *vs.* heterogeneous) often

determines the type of flow reactor required. We also explore more specialized branches, such as electrophotocatalysis, which necessitates dedicated designs to enable simultaneous access to photons and electrons. Additionally, we describe the opportunities for scaling flow electrochemistry and implementing electrochemical reactors in high-throughput experimentation and automated platforms.

Tailoring the reactor to the reactivity

Parallel plate flow reactors

Synthetic electrochemists interested in the advantages of continuous flow often start with parallel plate reactors. These reactors comprise several main components: (i) a spacer with a carved flow channel that directs the liquid flow between the electrodes. (ii) Two isolation layers surrounding the spacer to accommodate the electrodes. (iii) A main body that secures all components in place. The design of having parallel electrodes promotes a uniform current density and potential distribution, enhancing the selectivity and reproducibility of the reaction. The straightforward geometry of parallel plate reactors simplifies its assembly and the machining of various electrode materials.

Conversion in parallel plate reactors can be optimized by choosing between single pass (continuous) or recirculation (semi-batch) modes.³³ In single pass operation, achieving high conversion necessitates fine-tuning current densities and flow rates. This optimization can be complicated by gas evolutions (such as hydrogen), which create erratic flow velocities and zones of infinite electrical resistance due to the presence of gas bubbles.³⁴ Despite these challenges, the primary benefit of this mode is shorter reaction times, which typically enhance the selectivity profile of the chemical process. In the recirculation mode, the reaction mixture is held in a batch vessel and circulated over the electrodes using a pump, passing multiple times until complete conversion is achieved. This mode allows for a more compact setup and higher flow rates, which facilitates the removal of gas bubbles from the electrode surface. However, a notable drawback is the prolonged exposure of the product to the electrodes, potentially resulting in the formation of unwanted byproducts.

Parallel plate reactors are prominently featured in flow electrochemistry literature, and are valued for their low cost, straightforward design, ease of operation and maintenance, and notably, their high modularity. For example, these reactors can function in either divided or undivided cell configurations simply by incorporating a membrane into the reactor stack. The interelectrode distance can be precisely adjusted by altering the thickness of the spacer. Modifications to the liquid path created by the spacer, such as adding curves, can enhance mixing without necessitating significant changes to the cell design. This adaptability makes parallel plate reactors ideal for simple scale-up processes, which can be achieved by connecting multiple units in series or by stacking several electrode pairs in a “numbering up” approach. Additionally, owing to extensive research in the field of redox-flow batteries, the mass

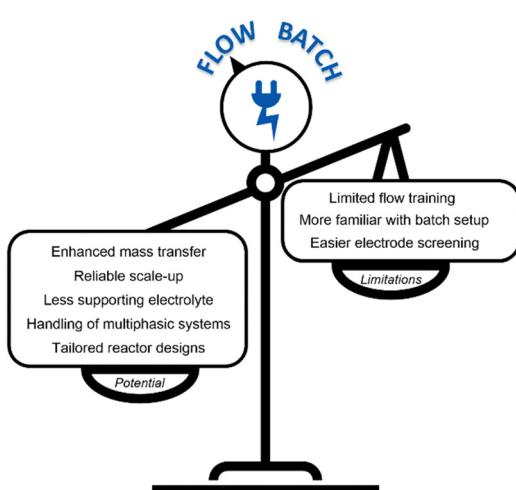


Fig. 2 Balancing the pros and cons of using a flow technology.



transport phenomena and concentration gradients in such electrolyzers are well understood.

Although several commercial parallel plate reactors are available, none has yet become the “gold standard” for flow electrosynthesis, unlike the batch reactor Electrasyn 2.0 developed by IKA. While commercial reactors are generally more expensive than homemade designs, they offer increased reproducibility and require less engineering and design expertise, enabling rapid initiation of experimental work. However, a significant drawback of commercial setups is their limited flexibility; users are confined to the reactor’s design, making

it challenging to tailor the system to specific experimental needs.

Using the ElectraSyn Flow from IKA, Ackermann *et al.* developed a rhodium-electrocatalyzed annulation strategy to synthesize isoquinolines (3), as depicted in Fig. 3(A).³⁵ This reactor design offers convenience since the rectangular electrodes do not require drilling for microfluidic connections, simplifying the electrode screening process. This ease of machining is particularly advantageous for working with brittle electrode materials. Initially, the reaction was conducted in a batch setup using a graphite felt (GF) anode and a platinum

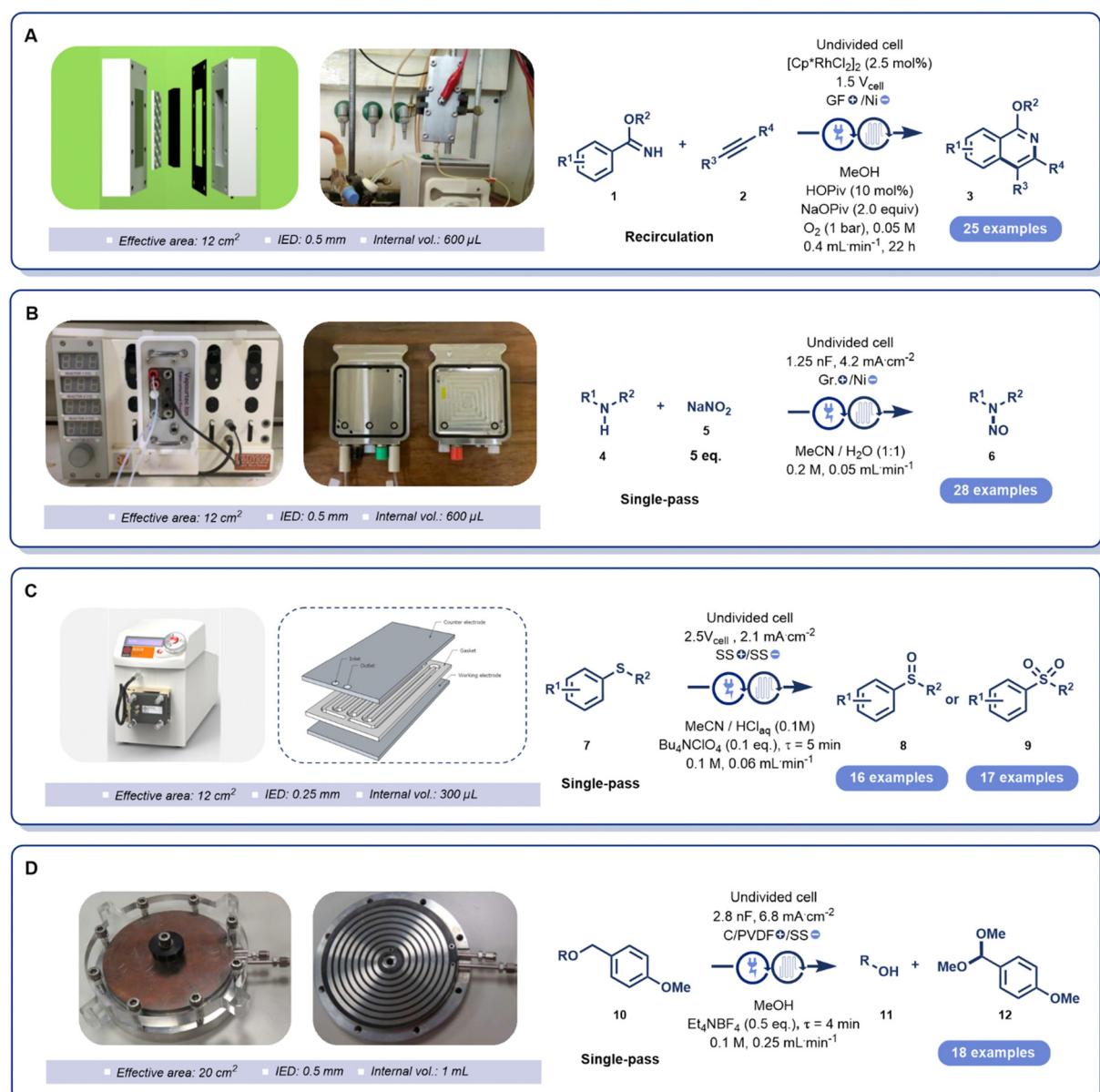


Fig. 3 Representative examples of recent electrosynthetic transformations that benefited from a translation to flow using a commercially available parallel plate reactor design. (A) Rhodaelectrocatalysis by Ackermann *et al.* Reproduced from ref. 35 with the permission of the American Chemical Society. (B) *N*-Nitrosation of secondary amines by Wirth *et al.* Reproduced from ref. 38 with the permission of Wiley-VCH GmbH. (C) Selective oxidation of thioethers to sulfoxides or sulfones by Noël *et al.* Reproduced from ref. 39 with the permission of the Royal Society of Chemistry. (D) Electrochemical deprotection of *p*-methoxybenzyl ethers by Brown *et al.* Reproduced from ref. 40 with the permission of the American Chemical Society.



cathode. Transitioning to flow, Ackermann and co-workers replaced the platinum cathode with a nickel plate and the carbon plate anode. These initial materials provided by IKA yielded poor results, prompting the team to modify the anode's PTFE compartment to accommodate a porous graphite anode with a turbulence promoter, enhancing mass transfer within the reactor. The annulation process proved more effective in recirculation mode, with reaction times being optimally adjusted using in-line NMR to monitor conversion. Although examples of flow-based asymmetric electrosynthetic processes remain limited,¹⁷ the ElectraSyn Flow setup was used by Ackermann *et al.* to develop an atroposelective, electrocatalyzed C–H annulation with allenes to yield C–N axially chiral compounds. The reaction could be successfully implemented in single-pass flow without supporting electrolyte and allow for straightforward decagram production of the target compound demonstrating its industrial potential.³⁶ The ElectraSyn Flow has also proven convenient for various simple transformations and can be equipped with a Nafion membrane for divided cell electrolyses.³⁷

The setup from Vapourtec Ltd, known as the Ion electrochemical reactor, can either be integrated as a module into an existing Vapourtec flow system or operated independently. It features a screw mechanism to apply even pressure, ensuring the system is properly sealed. This reactor is a notable commercial option because it can operate across a wide range of temperatures (from -10°C to 100°C) and pressures (up to 5 bar). Wirth and colleagues utilized this reactor for a streamlined *N*-nitrosation of secondary amines (**4**) using sodium nitrite (**5**) as an economical source of nitrite ions, as illustrated in Fig. 3(B).³⁸ This method improves functional group compatibility by avoiding the strong acids required in traditional approaches. Conventional electrochemical nitrosations are often restricted to low-solubility nitrite salts like $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, which could lead to clogging in parallel plate reactor designs. Wirth and co-workers demonstrated that in the homogeneous mixture the nitrite ion is oxidized, generating NO^+ and NO_3^- , both of which interact with the amine. This complex is then deprotonated by hydroxide ions produced from water reduction at the cathode, yielding the product. Significantly, the authors enhanced the process by coupling electrosynthesis with an in-line acidic extraction to purify the compound directly, fully leveraging the potential of flow synthesis.

The Asia Electrochemistry Flow Chemistry system, developed by Syrris Ltd, offers controlled temperatures ranging from 0°C to 60°C and pressures up to 5 bar. A key advantage of this reactor is its ease of assembly, as the parallel plate stack does not require specialized tools, and the inclusion of a built-in power supply makes the setup compact. However, a standalone version of this reactor is not available. This commercial setup was utilized by Noël *et al.* for the oxidation of thioethers (**7**), as shown in Fig. 3(C).³⁹ The oxidation process to sulfoxides (**8**) or sulfones (**9**) is highly selective when the cell potential is carefully controlled. Additionally, the application of continuous flow facilitated the rapid screening of various flow rates and cell potentials, optimizing mass transfer and selectivity, which

are essential for achieving full conversion in a single-pass reactor.

The Ammonite 8, developed by the groups of Brown and Pletcher and commercialized by Cambridge Reactor Design Ltd, distinguishes itself from other commercial parallel plate reactors with its impressive 1-meter-long channel, which facilitates high conversions in single-pass mode and boosts productivity.⁴¹ However, the range of available electrode materials is limited, with options including stainless steel for the cathode, and carbon and copper for the anode. Additionally, the reactor's design mandates the use of a grooved cathode, complicating manufacturing and precluding the use of brittle electrode materials such as glassy carbon and boron-doped diamond. Despite these limitations, if a chemical transformation is compatible with the Ammonite series, scaling up is simplified through the availability of a larger version, the Ammonite 15, which features a 2-meter-long channel. Brown, Pletcher and co-workers utilized both the Ammonite 8 and 15 for the electrochemical deprotection of *para*-methoxybenzyl ethers (**10**) to the corresponding free alcohols (**11**), as shown in Fig. 3(D).⁴⁰ The benzylic position of the protecting group is efficiently oxidized and attacked by methanolate, generated by the reduction of the solvent at the cathode, resulting in the deprotected alcohol. Demonstrating the scalability of the process, the Ammonite 15 achieved nearly a 10-fold increase in productivity under optimal flow electrochemical conditions.

The widespread use of parallel plate flow reactors can largely be attributed to their straightforward manufacturing, which has led to the development of numerous "home-made" designs. This flexibility allows electrochemists to customize their reactors to achieve optimal reactivity. Consequently, the remainder of this section will concentrate on exploring reactor designs that employ unique approaches to maximize the potential of their electrochemical processes. Wirth and co-workers have significantly advanced flow electrosynthesis by developing a 3D printed parallel plate reactor that operates at room temperature.⁴² The use of 3D printing enables rapid manufacturing, prototype testing, optimization, and allows for a highly customizable reactor design at a reduced cost. Similarly, Lam *et al.* designed another 3D-printed reactor that is adaptable to any power supply and can be integrated with an Electrasyn 2.0.⁴³ More recently, Barecka and colleagues demonstrated the potential for even greater accessibility by creating a versatile 3D-printed reactor that costs less than \$5, suitable for general electrosynthesis, CO_2 reduction, electroplating, and electrophotochemical reductions.⁴⁴

In general, 3D printing dramatically broadens the possibilities for electrosynthetic chemists, offering precise control over reactor volume, mixing properties, and membrane configurations for divided cells,⁴⁵ using their 3D-printed design, which features an FEP spacer that can be tailored into any channel design to optimize mass transfer, the group of Wirth successfully synthesized benzothiazoles (**14**) (Fig. 4(A)).⁴⁶ This catalyst- and electrolyte-free process facilitates the convenient production of heteroaromatic scaffolds through a dehydrogenative C–S bond formation, believed to involve thioamide oxidation followed by cyclization to produce the desired heteroarene.



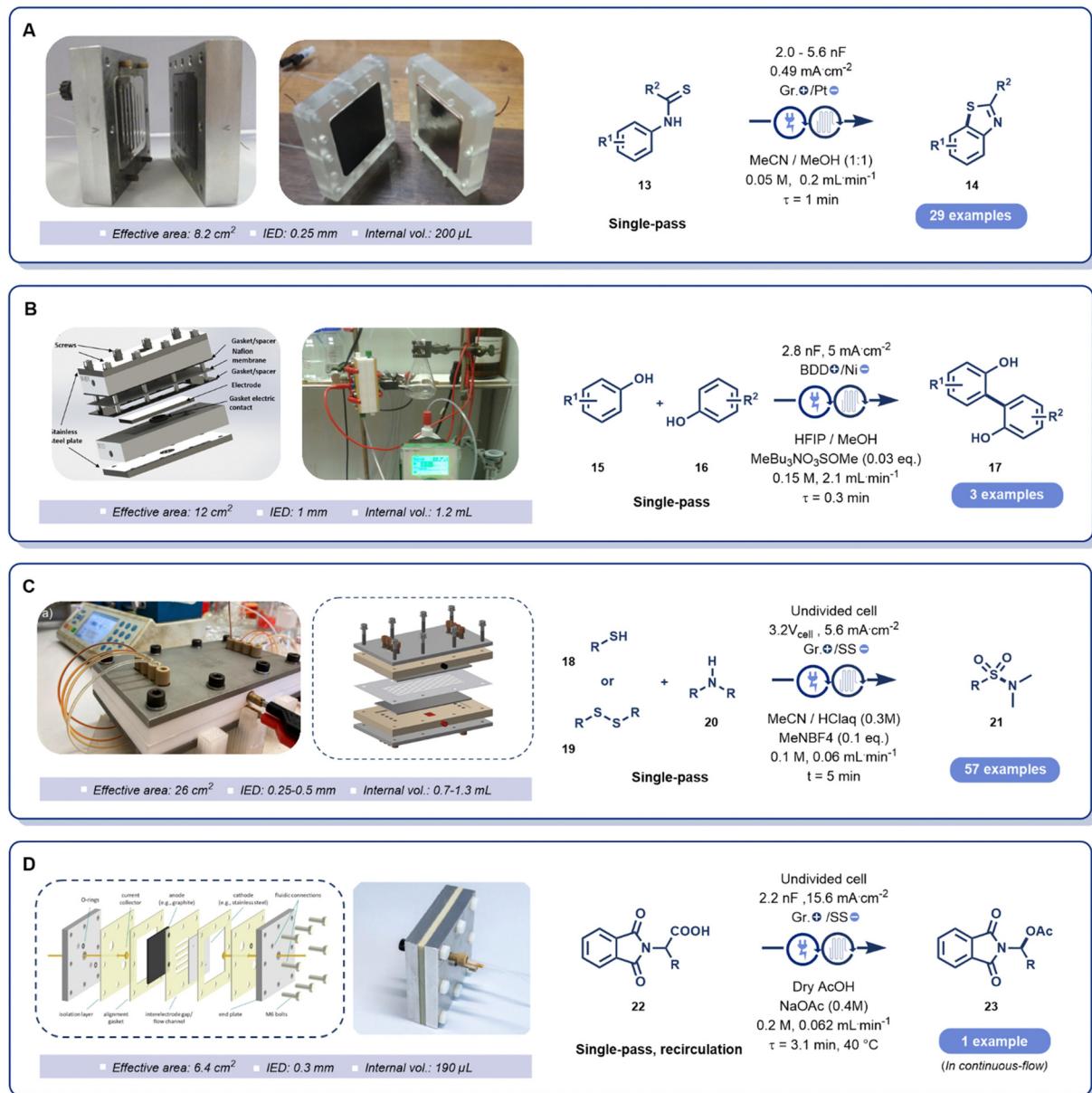


Fig. 4 Representative examples of recent electrosynthetic transformations that benefited from a translation to flow using home-made parallel plate reactor design. (A) Benzothiazole synthesis by Wirth *et al.* Reproduced from ref. 42 with the permission of Wiley-VCH Verlag GmbH & Co. KGaA. (B) Dehydrogenative cross-coupling of phenols by Waldvogel *et al.* Reproduced from ref. 47 with the permission of the American Chemical Society. (C) Electrosynthesis of sulfonamides by Noël *et al.* Reproduced from ref. 49 with the permission of Springer Nature. (D) Decarboxylative acetoxylation of aminoacids by Cantillo *et al.* Reproduced from ref. 50 with the permission of Wiley-VCH GmbH.

Moreover, this reaction was effectively scaled up to a 13 mmol scale using the same reactor setup. To date, the number of electrosyntheses producing organic compounds in a divided cell flow reactor remains relatively rare. Addressing this limitation, the Waldvogel group has introduced a reactor design that can operate in both divided and undivided electrolysis modes.⁴⁷ As a proof of concept in divided cell mode, they performed oxime oxidation to nitrile N-oxide using a Nafion 324 membrane. Expanding upon this, Waldvogel *et al.* developed a scaled-up version of the reactor, which was successfully applied to a phenol–phenol coupling-type reaction, as shown in

Fig. 4(B). This reactor design achieved a maximum productivity of approximately 3.5 g h⁻¹, demonstrating its efficacy and potential for broader applications in flow electrosynthesis.⁴⁸

To enhance the throughput of the parallel plate reactor, Noël and colleagues designed their cell with independent channels that can be configured in parallel or series.⁴⁹ This modular approach allows for easy adjustment of reactor volume or enhancement of throughput without the need to construct a new reactor. To validate the effectiveness of their design, it was benchmarked against the commercial flow electrolysis cell from Syrris, yielding comparable results. This flexibility has

made the reactor versatile for various applications in both undivided^{30,51–53} and divided setups,⁵⁴ and each channel can be independently used to quickly screen different parameters. The reactor was employed in the development of an electro-synthetic method for producing sulfonamides from thiophenols (17) and amines (19) (Fig. 4(C)). A recent example from Ošeka *et al.* demonstrated the flow telescoped synthesis of vicinal diamines using the electrochemical generation of aziridines and a subsequent ring-opening reaction with nucleophiles, showcasing the practical utility of this reactor.^{55,56}

The reactor developed by Cantillo *et al.* is designed by laser cutting technology, which reduces the costs typically associated with computer numerical control (CNC) machining.⁵⁰ They demonstrated the effectiveness of this design with a proof-of-concept reaction, *i.e.* the decarboxylative acetoxylation of amino acids (21) (Fig. 4(D)). They also showed that the flow anodic process used with this reactor is more mass-efficient and atom-economical than traditional synthetic methods for producing these compounds 22. The examples discussed highlight that parallel plate flow reactors are favored for relatively simple reaction mixtures, such as homogeneous and monophasic systems. However, these reactors are less effective with gas reagents and products; the minimal inter-electrode distance can impede the electrochemical process at localized spots where gas bubbles are formed or accumulated.³⁴ Additionally, handling slurries in these reactors is problematic due to the risk of clogging.

Rotating cylinder electrode reactors (RCER)

Parallel plate reactors are recognized for their simplicity, modularity, and availability either through purchase or as home-made setups. However, a major limitation of this design is the requirement for all reagents, products, and side-products to be fully soluble. Many reactions, both in traditional organic chemistry and in electrosynthesis, involve solid catalysts, insoluble salts, or products precipitating out. These solid particles can lead to blockages in the reactor, necessitating that the entire assembly be disassembled and cleaned before operations can continue.⁵⁷

Seminal reports on “rotating cylinder cells” initially focused on their application in metal extraction.^{58,59} Recently, these spinning electrode reactors have been adapted for organic synthesis.⁶⁰ The enhanced mixing provided by the rotating electrode overcomes typical limitations encountered with parallel plate cells, such as fouling and clogging.^{23,61} Additionally, in gas-forming electrochemical reactions, the rotation facilitates faster detachment of gas bubbles, which remain relatively small, thereby reducing Ohmic drops.⁶² The excellent and adjustable rotation of the electrode leads to improved mixing efficiency, achieving high conversions in a single pass. Furthermore, the rotation limits the thickness of the double layer, allowing for higher current densities at the same cell potential—essentially, achieving higher throughput without compromising functional group compatibility.

To address the limitations of flow electrosynthesis confined to homogeneous solutions, Cantillo, Kappe, and co-workers

developed a rotating electrode reactor designed for large-scale reactions involving slurries.^{63,64} The model reaction chosen to test this setup was the reagent-free side-chain cleavage of cortisone (24).⁶³ The transformation was facilitated using graphite anode rotating at 300 rpm paired with a static stainless steel cathode, operating in recirculation mode at a flow rate of 200 mL min⁻¹, processing a total of 1 liter of cortisone slurry (Fig. 5(A)). The reaction was successfully completed with an isolated yield of 94%, largely due to the improved mixing efficiency of the electrolysis cell compared to previous batch experiments.

George *et al.* described an adaptation of a rotating cylinder electrochemical reactor that maintains high efficiency in environments with significantly increased viscosity—approximately 5.5 times that of THF.⁶⁵ The implemented model reaction was an electrochemical Birch reduction of naphthalenes (26) (Fig. 5(B)) utilizing an aluminum cylinder as both the stator and sacrificial anode, and a stainless steel cylinder as the rotor.⁶⁶ The small IED and strong rotation generate Taylor vortices within the liquid flow, significantly enhancing mass transfer.

The use of rotating electrode reactors represents a powerful tool for organic electrochemists, with ongoing discoveries that continue to expand their applications, including potential reactions with gases like CO₂, CH₄, and CO.^{67,68} Currently, the main limitation of these reactors is the sparse literature, which restricts the range of explored reactivities. This gap in research also contributes to the limited availability of these reactors from commercial suppliers.

Electrophotocatalytic reactors

Over the past decade, there has been a significant increase in the use of photocatalytic transformations in organic synthesis, largely due to the ability of photocatalysts to harness light energy to access reactive intermediates under mild conditions. The development of electrophotocatalysis (EPC) merges electrochemical and photocatalytic methods, facilitating the creation of super-oxidants and super-reductants and enabling catalyst regeneration.⁶⁹ However, integrating electrochemistry with photocatalysis presents substantial challenges in reactor design, necessitating the simultaneous arrangement of electrodes and effective illumination of the reaction medium. Achieving a synergy between electron and photon delivery is essential for effective electrophotocatalytic processes. Common hurdles in photochemistry, such as light attenuation, and in electrochemistry, like ohmic drop, can be addressed through the use of miniaturized systems. Microreactor technology has proven effective in maximizing photon delivery close to the electrode surfaces. Currently, flow electrophotocatalysis primarily involves simpler molecules like CO₂ or formic acid, using transparent electrodes made of fluorine-doped tin oxide glass coated with photocatalysts such as TiO₂.⁷⁰ Recently, electro-photocatalytic flow reactors have been constructed and used for synthetic applications. Guo, Xia *et al.* successfully utilized such a setup to carry out a C(sp³)-H borylation reaction in continuous flow.⁷¹ The reactor operates in single-pass mode and is composed of two graphite electrodes with grooves, set 2 mm



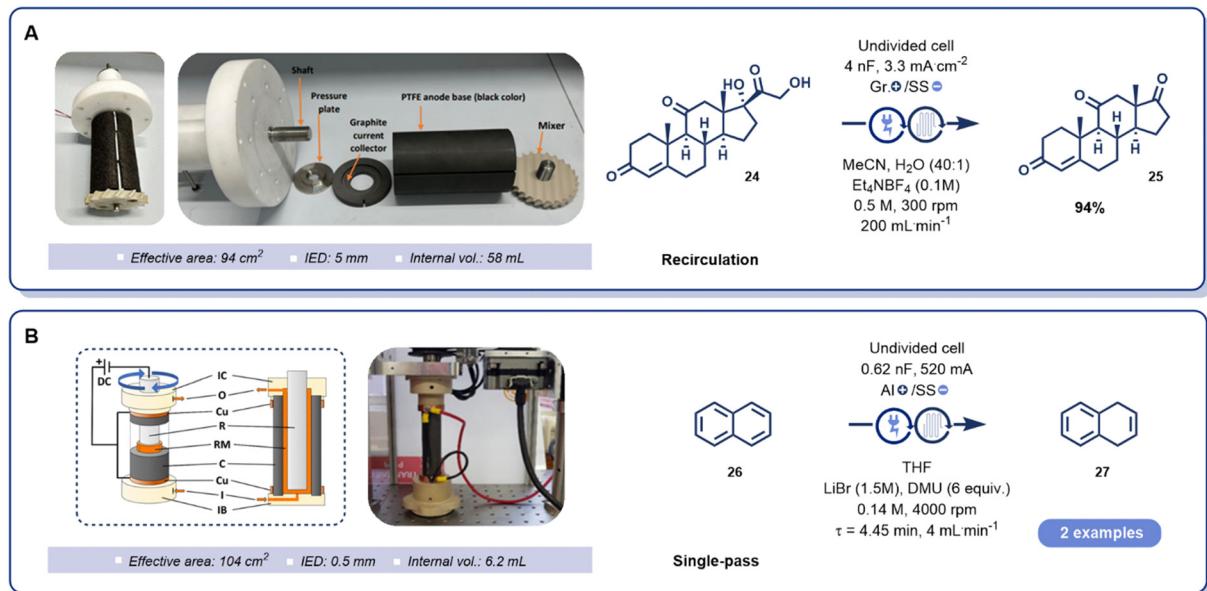


Fig. 5 Representative examples of recent electrosynthetic transformations that benefited from a translation to flow using a rotating cylinder electrode reactor design: (A) oxidative C–C bond cleavage of cortisone using a spinning electrode. Reproduced from ref. 64 with the permission of the American Chemical Society, Copyright 2024. (B) Electrochemical Birch reduction using a continuous-flow electrochemical Taylor vortex reactor. Reproduced from ref. 65 with permission of the American Chemical Society Copyright 2024.

apart, and encased by a translucent quartz window within an aluminum-PTFE body. In this process, the electrochemical and photochemical components collaborate to generate chlorine radicals, which abstract hydrogen atoms from the unactivated C(sp³)-H bond of **28**. The radical intermediate is subsequently captured by B₂(cat)₂ (**29**), leading to the formation of the borylated product (**30**). Despite the reactor's robust performance in handling a 20 mmol scale single-pass reaction, its small size and the specific chemistry involved constrain the system's throughput to 0.41 mmol h⁻¹ (Fig. 6(A)).

Reek, Noël *et al.* used a fluorine-doped tin oxide glass with deposited platinum nanoparticles as the transparent electrode in their electrophotocatalytic flow reactor.⁷² The graphite anode is set at a narrow gap of 0.1–0.5 mm, creating ideal channels for both photo- and electrochemistry. In this setup, the combined electrochemical and photochemical activation modes generate chlorine radicals that perform hydrogen atom transfer, leading to C(sp³)-H functionalization. The resulting carbon-centered radicals are then captured by a *N*-nucleophile (**32**). This reactor is effectively scalable in a single-pass mode up to a 5 mmol scale, achieving productivities of up to 1 mmol h⁻¹, and demonstrating a reaction scope that includes 20 examples (Fig. 6(B)). Heugebaert *et al.* utilized a fluorine-doped tin oxide glass window similar to the approach used in other electrophotocatalytic flow reactors.⁷³ In their design, the electrodes are spaced at a distance of 0.25–0.5 mm, forming narrow serpentine channels optimal for flow electrophotocatalysis. The team employed this setup for *N*-arylation reactions, using a trisaminocyclopropenium radical dication (TAC) as the electrophotocatalyst. This catalyst acts as a super-oxidant in a single-pass regime. When compared to traditional batch

processes, this reactor achieved a remarkable 300-fold increase in space-time-yield under electrolyte-free conditions, and the throughput was enhanced to 0.04 mmol h⁻¹ of **35** (Fig. 6(C)). This demonstrates a significant improvement in efficiency and productivity over batch methods.

The integration of light as a reagent in electrosynthesis opens up new possibilities for synthetic organic chemists by expanding the range of reactivities that can be accessed. Various methods have been developed to effectively deliver both electrons and photons to the reaction mixture, enabling desired chemical transformations. However, the field of flow electrophotocatalysis is still emerging, and the reactor designs discussed provide foundational examples for future innovations aimed at expanding reactivity and enhancing efficiency in this promising area.

Gas-fed electrochemical reactor

The utilization of gases as cheap, abundant, atom-efficient, and versatile synthetic reagents is well-recognized in synthetic chemistry. However, their application is complicated by gas-to-liquid mass transfer limitations, making flow technology an ideal solution for handling such gases.⁶⁷ Although there are some successful examples reported in the literature,⁷⁴ the use and generation of gases in flow electrochemistry present distinct challenges. In batch processes, gas bubbles can detach and be removed from the electrode surface due to gravity,⁷⁵ but in the confined space of a flow reactor, these gases are trapped. This entrapment creates a significant barrier for ion transport, effectively halting the electrochemical process.³⁴ This is particularly problematic in reactions that generate hydrogen, where a substantial volume of gas can accumulate, leading to



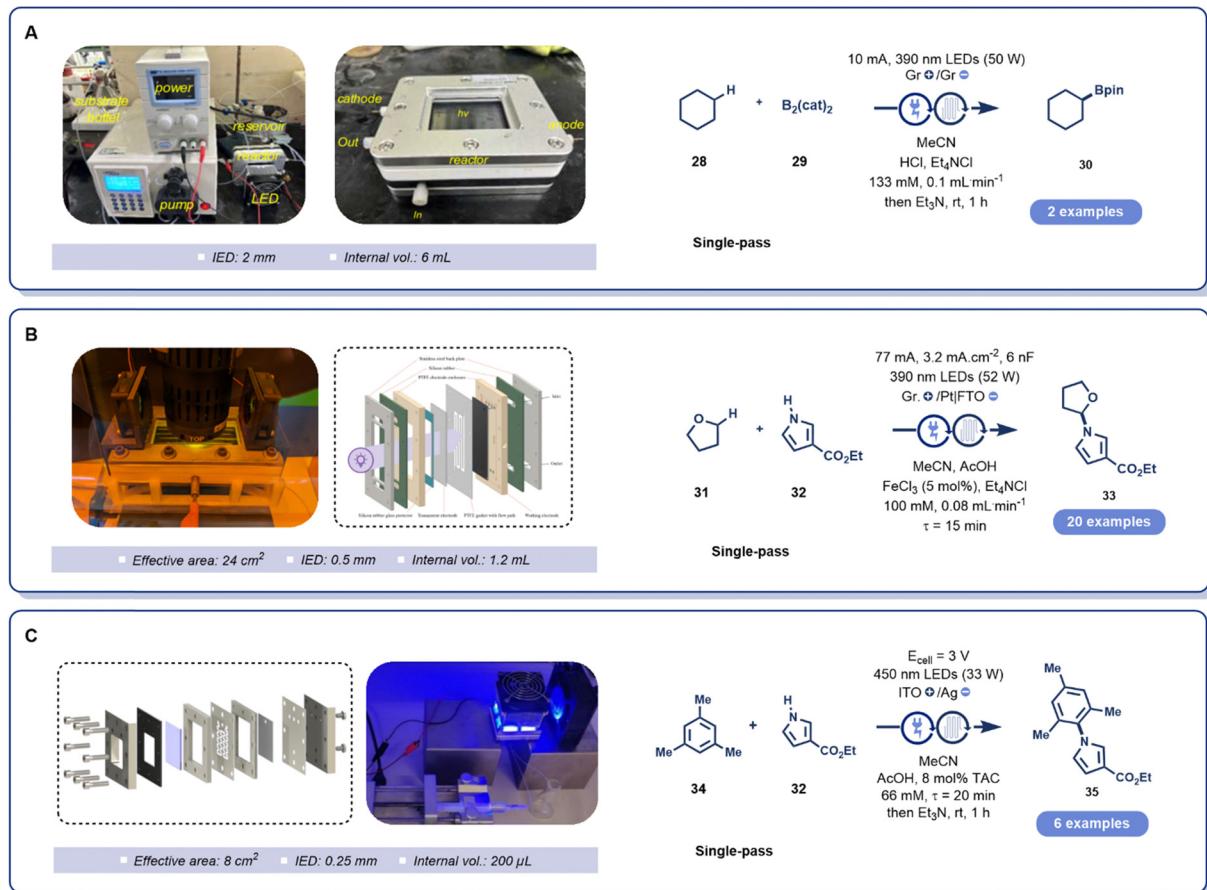


Fig. 6 Examples of recent electrophotocatalytic transformations in continuous flow (A) C(sp³)–H borylation by Guo, Xia *et al.* Reproduced from ref. 71 with the permission of Springer Nature (B) N-alkylation by Reek, Noël *et al.* Reproduced from ref. 72 with the permission of Wiley-VCH GmbH. (C) N-Arylation by Heugebaert *et al.* Reproduced from ref. 73 with the permission of Springer Nature, copyright 2023.

inefficient use of the electrochemical reactor. To overcome the challenges associated with gases in continuous-flow electrochemical reactions, reactors equipped with gas diffusion electrodes (GDEs) have been developed. It is important to note that the terminology used to describe gas-fed reactors varies across publications and has evolved over time. In this work, we use the term “gas-fed reactor” to refer to reactors where gaseous reagents are separated from the liquid phase and introduced through a gas diffusion electrode (GDE). GDEs comprise a porous gas diffusion layer (GDL) and a catalyst layer (CL), facilitating electrochemical reactions at the gas–liquid interface. GDE-based cells offer a robust solution to the issues of gas diffusion limitation and high electrical resistance encountered in traditional reactor designs. By enhancing diffusion and reducing resistance, GDEs achieve higher conversion rates and faradaic efficiencies compared to conventional electrocatalytic electrodes. When paired with continuous-flow systems, GDEs significantly improve mass transfer, thereby increasing the overall productivity.^{76–80}

Although gas diffusion electrode (GDE) reactors have been in use for decades, their application has primarily been confined to producing small molecules from gases, fuel cells, and the degradation of pollutants through the *in situ* production of hydrogen peroxide (H₂O₂).

While there are a few reports in the literature of their use in organic synthesis,^{81–84} there is still a significant gap in fully understanding and exploiting their potential in this area. In 2010, Kenis *et al.* developed a pioneering microfluidic reactor that serves as an invaluable tool for rapidly assessing various catalysts and conditions (Fig. 7(A)).⁸⁵ This reactor design is adapted from a fuel cell previously developed by their group and facilitates the reduction of CO₂ into formic acid. In this process, gaseous CO₂ is channelled through a separate chamber and reduced at the catalyst layer (CL) to produce formic acid. On the anodic side, oxygen generated from the oxidation of water is released through the GDE anode into the open air. The two GDEs are separated by a 1.5 mm thick poly(methyl methacrylate) (PMMA) sheet with a 0.5 × 2 cm window where the electrolyte is flowing. Both electrodes are tunable and can be coated with specific catalysts as required. This innovative reactor design has demonstrated effective conversion of CO₂ into formic acid, achieving high faradaic efficiency (89%) and energetic efficiency (45%), with a current density of 100 mA cm⁻². The microfluidic setup also offers significant advantages for analytical purposes, particularly due to its ability to operate under continuous flow and adjust conditions flexibly, facilitating inline analysis. This makes it a



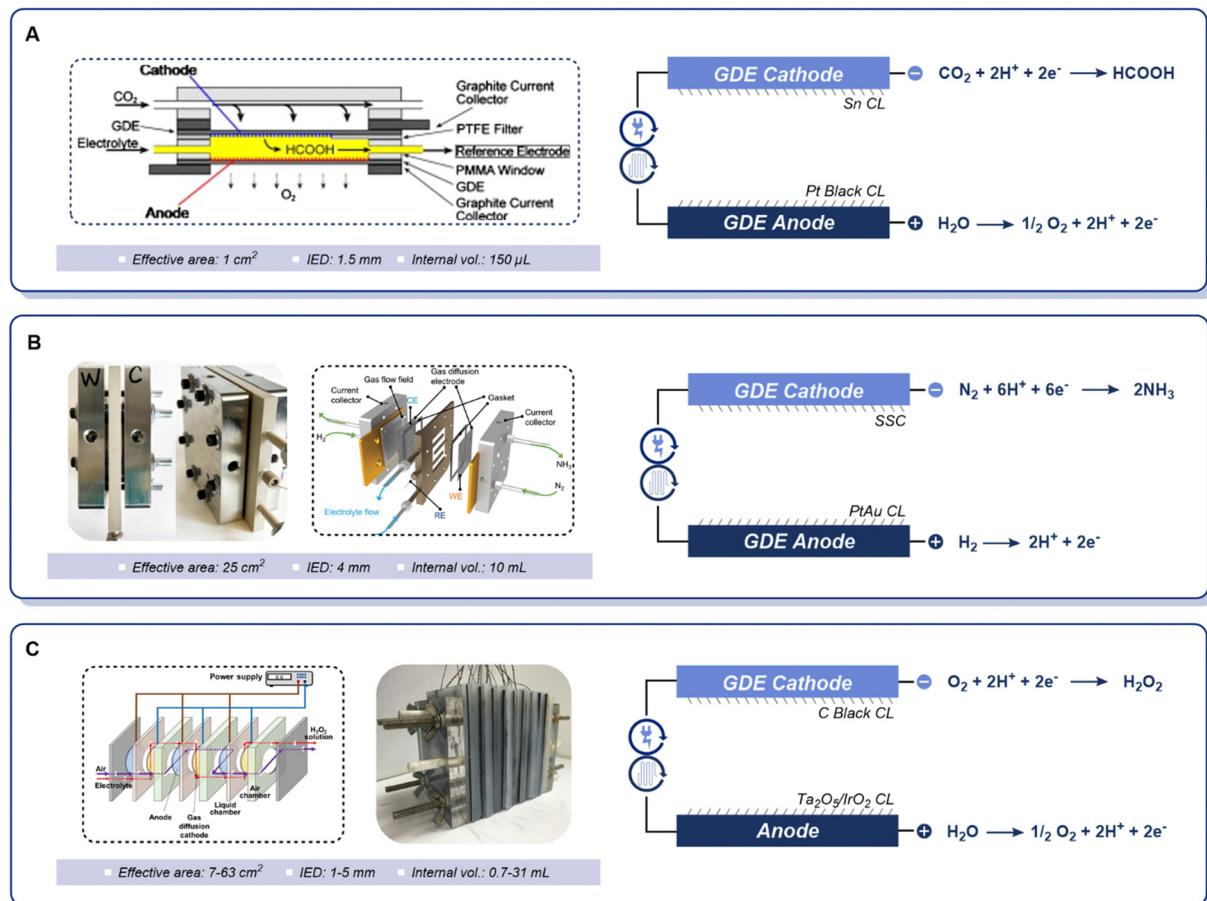


Fig. 7 Representative examples of electrochemical transformations involving gases in continuous flow (A) CO_2 reduction by Kenis *et al.* Reproduced from ref. 85 with the permission of IOP Publishing, copyright 2010. (B) Ammonia synthesis by Nørskov, Chorkendorff *et al.* Reproduced from ref. 86 with the permission of The American Association for the Advancement of Science, copyright 2023. (C) Hydrogen peroxide synthesis by Liu *et al.* Reproduced from ref. 87 with the permission of Elsevier, copyright 2017.

powerful tool for screening reaction conditions and new catalysts. However, the reactor design limits its scalability and, consequently, its potential industrial application, due to its sensitivity to pressure and low volume capacity.

In a recent development from 2023, Nørskov, Chorkendorff and co-workers⁸⁶ introduced a reactor design aiming to address the economic and environmental challenges associated with traditional ammonia production, notably the large energetic footprint of the Haber–Bosch process.^{88,89} The authors have designed a continuous-flow reactor that pairs hydrogen oxidation with lithium-mediated nitrogen reduction (Li-NRR) to efficiently produce ammonia (Fig. 7(B)). In this configuration, gases are supplied to the gas diffusion electrodes (GDEs) *via* a serpentine gas flow field covering an effective area of 25 cm^2 . The setup includes two stainless steel cloth (SSC) GDEs, which are spaced apart by a 4 mm thick gasket. Through this gasket flows a mixture of lithium salt, ethanol, and tetrahydrofuran, facilitating the reaction. This innovative approach represents a significant step forward in the quest for more sustainable and economical ammonia production methods. The well-developed flow reactor described can be coupled with a water splitting

reactor to supply hydrogen. Remarkably, this system achieves a record-high faradaic efficiency of up to 61% and an energetic efficiency of 13%, marking a significant advancement in the continuous-flow synthesis of ammonia *via* lithium-mediated nitrogen reduction (Li-NRR). However, the current density applied in this study— 6 mA cm^{-2} —is still far below industrial standards, highlighting a key area for improvement and further research.

In recent years, numerous research efforts have been focused on developing electrochemical methods for the *in situ* production of hydrogen peroxide.^{90,91} However, these methods often face challenges such as high energy consumption, modest production rates, and low concentrations. In response to these limitations, Liu *et al.*⁸⁷ developed a novel stacked electrosynthesis reactor (SER) a novel stacked electrosynthesis reactor (SER) aimed at enhancing both the productivity and energy efficiency of H_2O_2 *in situ* generation (Fig. 7(C)). The SER comprises several electrode pairs stacked with varying spacing. Each electrosynthesis unit within the reactor includes a liquid chamber, a gas chamber, a gas diffusion cathode, and a titanium anode coated with IrO_2 or Ta_2O_5 . The number of units is modular, ranging from one to



nine pairs, with adjustable spacing between them. This design allows gas and liquid phases to flow through different paths within the reactor, converging at the GDE surface in each unit where the electrochemical reaction occurs. It provides a large specific ($7\text{--}63\text{ cm}^2$) area with minimal inter-electrode spacing (1–5 mm), significantly enhancing productivity with a maximum rate of $1929 \pm 51\text{ mg L}^{-1}\text{ min}^{-1}$. This rate is considerably higher—ranging from 160 to 3215 times greater—than those reported for other reactors prior to this study. The design's specified features also help reduce internal resistance and, consequently, the applied voltage, which leads to decreased energy consumption. Although these results are promising, the reactor volume and hydrogen peroxide concentration produced still do not meet industrial standards. Nonetheless, these findings offer encouraging prospects for future research, pointing towards potential enhancements that could bridge the gap to industrial applicability.

As shown in this section, gas-fed reactors outperform many other designs that utilize gases, offering superior mass transfer, faradaic efficiency, and scalability. However, several challenges remain. Current designs do not fully meet industrial standards, which require high current densities and low cell voltages. Additionally, gas diffusion electrodes (GDEs) often require costly catalysts and complex manufacturing processes, and are prone to flooding, *i.e.* excess liquid blocking the pores of electrodes, that can severely impair gas flow and reaction performance. In conclusion, while the application of gas-fed reactors is currently limited to simpler organic compounds and proof-of-concept models, they demonstrate significant potential for advancing gas/liquid electrosynthesis.

Reactor designs for industrial and high-throughput electrosynthesis

Scaling up flow electrosynthesis

To fully harness the transformative power of organic electrochemistry for producing both commodity and fine chemicals, scaling up electrosynthetic reactions is crucial. This scaling-up requires the development of robust, cost-effective, highly productive, and safe processes, along with access to a diverse array of reactor technologies in terms of scale and design.¹² Achieving this necessitates meticulous consideration of electrode materials, supporting electrolytes, and reactor configurations to optimize productivity while maintaining selectivity and ensuring long-term stability of reactor operation. Addressing challenges such as electrode fouling, mass transport limitations, and reaction stability is critical, underscoring the importance of process reliability and sustainability in electrochemical synthesis.⁹²

While laboratory-scale flow-based setups suffice for small-scale production, meeting industry demands necessitates more robust and reliable scale-up processes. This challenge is not unique to electrochemistry but is also prevalent in continuous microflow chemistry.

Scaling up flow reactors involves strategies such as numbering up and sizing up, each with its own advantages and drawbacks.^{93,94} Internal and external numbering up strategies provide avenues for parallelization, but careful attention must be paid to ensure uniform flow distribution, especially in multiphase reactions. Extending reactor length maintains a constant surface-to-volume ratio but raises concerns about

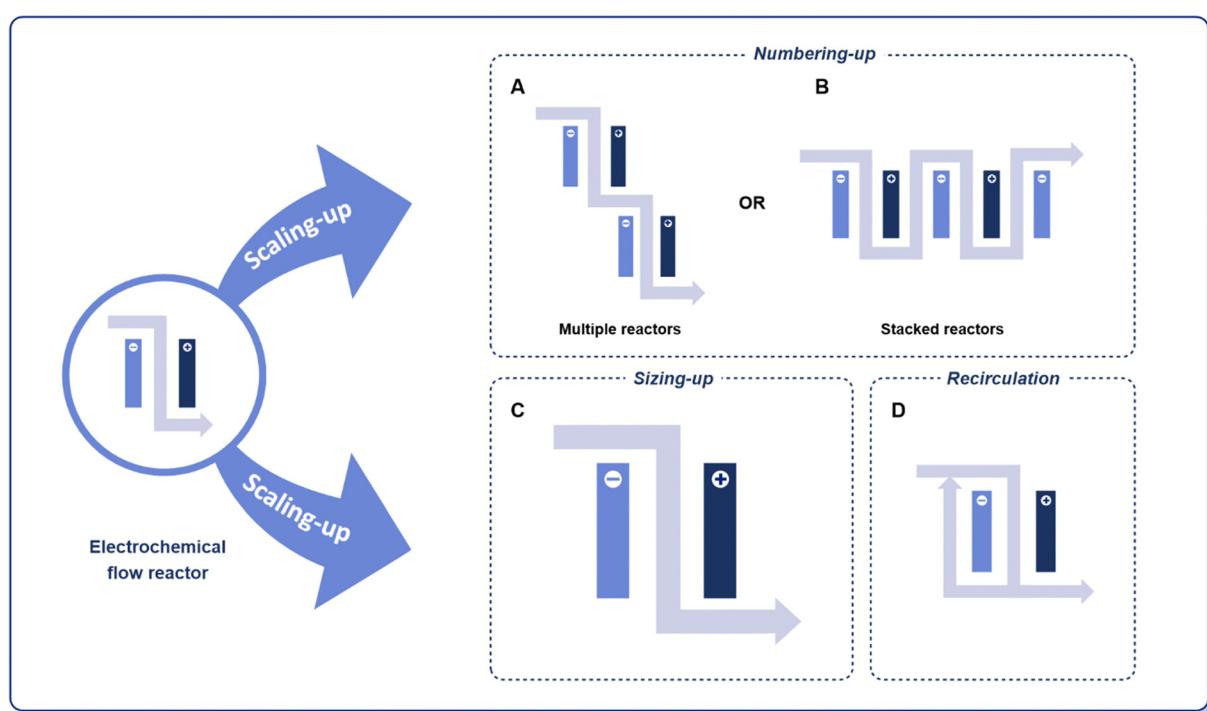


Fig. 8 Scale-up strategies for electrochemical flow reactors: (A) numbering up by using multiple reactors. (B) numbering up by using multiple stacked electrode units. (C) sizing up and (D) recirculating flow.



pressure drops, while enlarging reactor diameters (and thus the inter-electrode distance) can introduce ohmic drop issues and

can impact flow dynamics and heat transfer.⁹⁵ Nonetheless, innovations in novel reactor designs, leveraging process

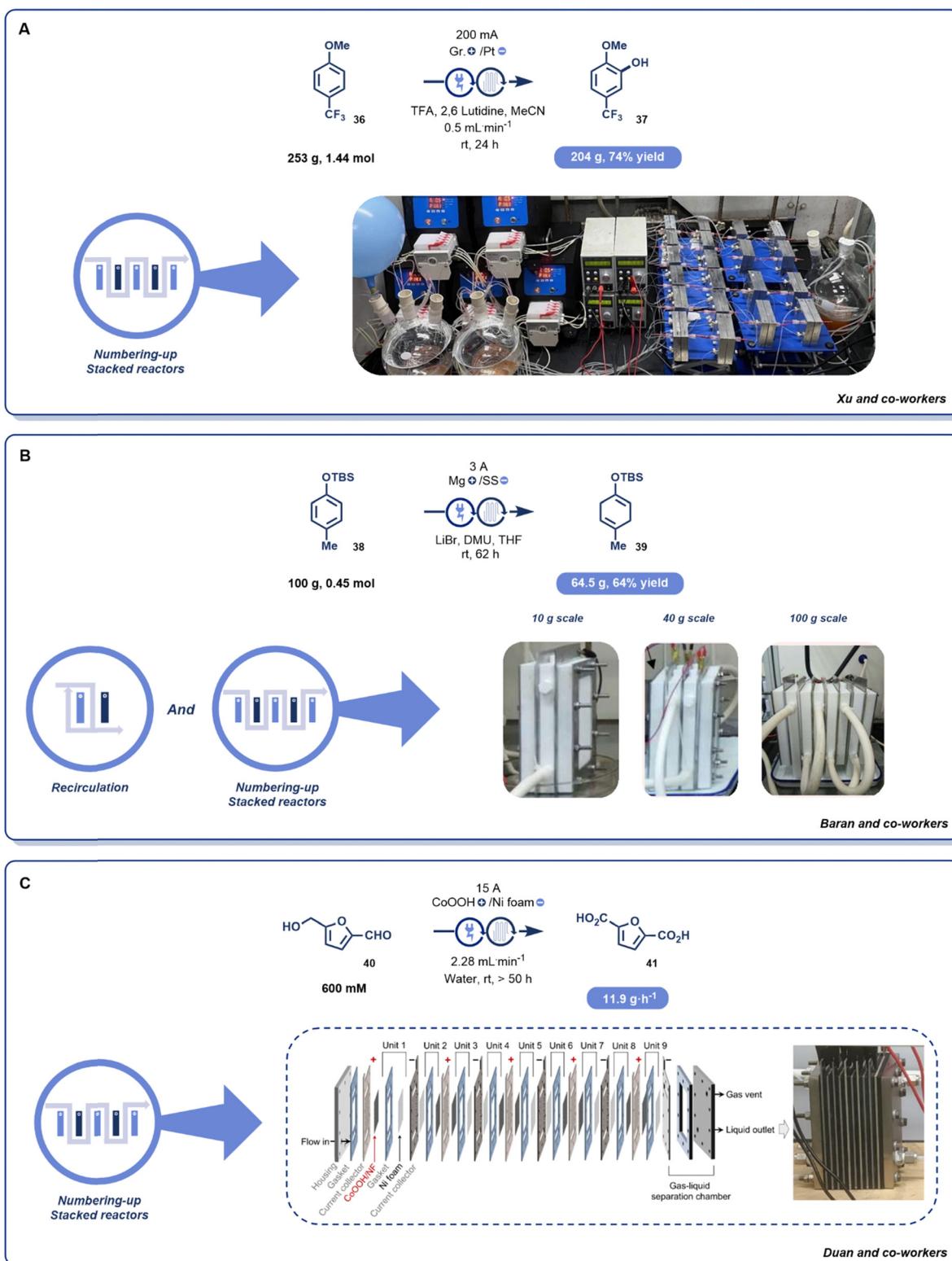


Fig. 9 Numbering-up scale-up strategies for electrochemical flow transformations: (A) electrochemical aromatic hydroxylation by Xu et al. Reproduced from ref. 98 with the permission of Springer Nature. (B) Electrochemical Birch reduction by Baran and co-workers Reproduced from ref. 4 with the permission of AAAS, copyright 2019. (C) Electrochemical HMF oxidation by Duan et al. Reproduced from ref. 100 with the permission of Springer Nature.

intensification principles, present promising solutions for overcoming scalability limitations and boosting productivity in both custom-made and commercial reactor setups (Fig. 8). To enhance the scalability of electrochemical transformations in continuous flow, the Xu group adopted the numbering-up strategy.^{96,97} They employed 20 parallel-plate undivided flow reactors arranged in parallel, achieving product formation within a single-pass regime. This strategy has been successfully implemented across various electrosynthetic methodologies by the same group, facilitating the production of desired oxidation products on a 100 g scale. A notable example of this approach is the electrochemical aromatic C–H hydroxylation, where the process was scaled up to a 250 g scale, corresponding to 1.44 mol of **37** (Fig. 9(A)).⁹⁸ As another notable example, Xu *et al.* implemented a large-scale electrochemical C–H phosphorylation of arenes, yielding 55 g of product using two reactors in parallel (*i.e.*, numbering-up strategy).⁹⁹

Baran *et al.* implemented a stacked, undivided reactor configuration incorporating flat electrodes with alternating

polarities.^{101,102} Although categorized as a numbering-up, this methodology ensures the scaling up of processes within a single reactor. By integrating a stacked reactor design, recirculating the reacting solution from a reservoir, and employing high flow rates, they demonstrated the feasibility of achieving 100 g scale-ups for both oxidative and reductive electrochemistry.

Notably, they successfully executed a 100 g scale electrochemical Birch reduction using this cost-effective reactor setup in a recirculatory fashion (Fig. 9(B)).⁴

Similarly, the Duan group employed a stacked, undivided reactor composed of 9 parallel units to establish a scalable electro-oxidative approach for synthesizing valuable chemicals derived from biomass. Remarkably, they devised a method to convert hydroxymethylfurfural (HMF, **40**) into 2,5-furandicarboxylic acid (FDCA, **41**) within a single-pass regime, achieving a productivity of 11.9 g h⁻¹. (Fig. 9(C)).¹⁰⁰

The Process Research & Development group at Merck & Co., Inc. envisioned a scaling-up solution using sized-up stacked reactors.¹⁰³ Demonstrating the efficacy of this approach, they

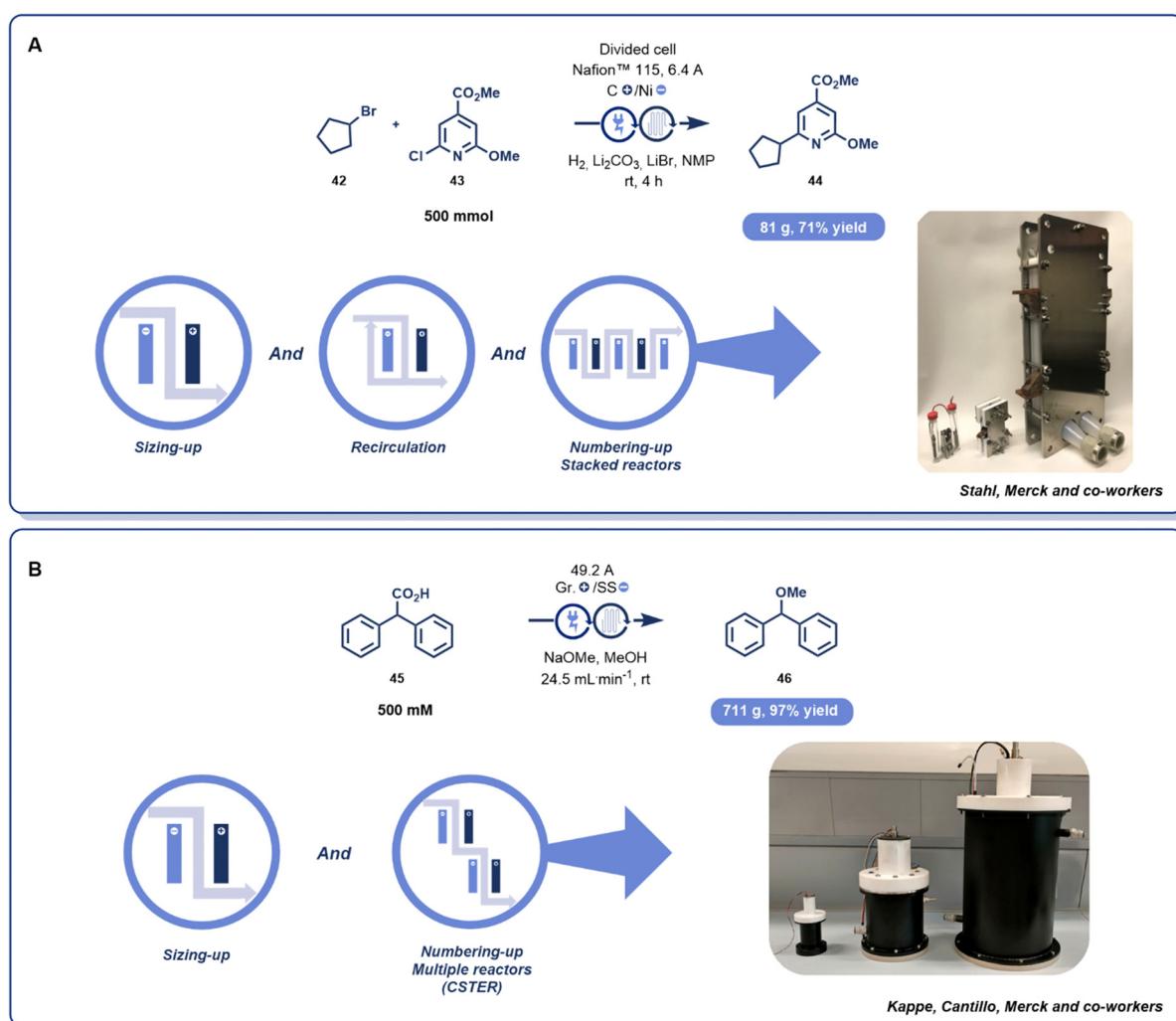


Fig. 10 Other scale-up strategies for electrochemical flow transformations: (A) electrochemical cross electrophile coupling by Weix, Root, Stahl *et al.* Reproduced from ref. 104 with the permission of Springer Nature, copyright 2023. (B) electrochemical decarboxylative methoxylation by Kappe, Cantillo *et al.* Reproduced from ref. 105 with the permission of the American Chemical Society.

showcased that by upscaling the flow reactor using a 1600 cm² anode enabled the production of 1.11 kg of the desired oxidized product in less than 18 hours in a recirculation mode.

In collaboration with the Weix, Root and Stahl groups, the same reactor was adapted into a divided cell, thereby increasing the complexity of the synthetic transformation. They successfully demonstrated that Ni-catalyzed cross-electrophile couplings could be achieved at an 81 g scale within a span of 4 hours (Fig. 10(A)).¹⁰⁴ Kappe, Cantillo *et al.* showcased the scalability of spinning electrode electrochemical reactors.⁶⁴ Through a progressive increase in reactor size, they successfully developed a 1.25 L reactor. Notably, the implementation of a continuous stirred tank electrochemical reactor (CSTER) setup, comprising three reactors in series, facilitated the efficient decarboxylative methoxylation of diphenylacetic acid (**45**) at a scale of 711 g (Fig. 10(B)).¹⁰⁵

Towards high-throughput and autonomous experimentation platforms

The past decades have witnessed substantial progress in synthetic chemistry, with methodologies and techniques enabling faster and more comprehensive exploration of the chemical space. Nowadays, many companies and academic laboratories have developed their own automated and high-throughput platforms to enhance and accelerate reaction discovery, optimization, mechanistic assessment, and more.^{106–109} Automation in laboratories has positively impacted many fields, including

analytics, crystallography, flow chemistry, photochemistry, and flow electrochemistry. The recent development of various reactors and microreactors has created promising perspectives for the field, particularly when combined with automation and high-throughput experimentation (HTE).⁸ In this section we will provide an overview of recent progress made toward high-throughput and autonomous experimentation platforms in flow electrochemistry.

In 2020, Jensen *et al.*¹¹⁰ developed a multifunctional microfluidic platform capable of conducting either electrochemical reactions or electroanalysis on a droplet-scale (15 μ L). The platform is equipped with online HPLC to analyze the reaction outcome (Fig. 11(A)).

The flow cell encapsulates micro-fabricated interdigitated electrodes (IDE) containing 146 platinum cathodes and anodes separated by a 10 μ m gap (Fig. 11(B)). This reactor design offers several advantages; the extremely small inter-electrodes gap provides an excellent conductivity and improves molecular diffusion between cathode and anode. To demonstrate the efficacy of the platform, Jensen *et al.* conducted condition screening using the α -amino C–H arylation as a model reaction. This study was successfully conducted by the platform in 10 hours using 300 μ L of reagents for 20 experiments providing substantial parametric information. To facilitate mechanistic studies, a microliter-scale cyclic voltammetry (CV) flow cell was also designed (Fig. 11(C))), allowing high-throughput electroanalysis of diverse reaction conditions. It is worth mentioning that, in this work, the CV flow cell is not used for monitoring the reaction outcome but directly as a tool to measure kinetic parameters. The device was evaluated by recording cyclic

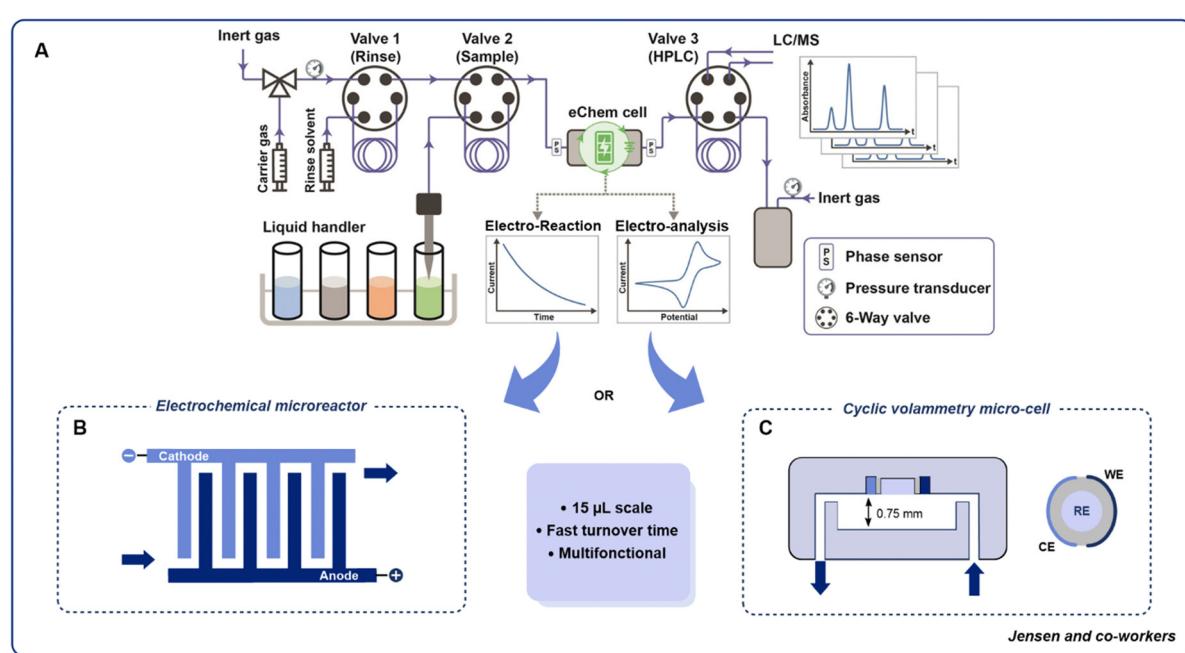


Fig. 11 Overview of the multifunctional microfluidic platform for electrochemical condition screening and kinetic studies by Jensen and co-workers. Reproduced from ref. 110 with the permission of Wiley-VCH GmbH, copyright 2020.



voltammograms of a TEMPO mediated alcohol oxidation reaction at different concentrations. The microliter-scale CV flow cell proved to be accurate and reliable compared to standard-size CV cell. Jensen group developed a microfluidic platform for the high-throughput screening of reaction conditions and kinetic studies while minimizing resource usage. However, the screening of electrochemical parameters can be limited by the use of Pt as the only electrode material. Although the droplet-scale reactor offers many advantages, the microfabrication procedure is complex and its design is difficult to transfer to a larger scale. Additionally, the 10 μm channels are prone to clogging, limiting its use to perfectly soluble reaction media.

More recently, Kappe, Cantillo, Merck and co-workers collaboratively designed a flexible and easy-to-handle electrochemical microreactor for the screening of reaction conditions and statistical analysis.¹¹¹ The flow reactor is part of a platform that includes a power supply, a syringe pump and a fraction collector all operating together in a fully automated manner (Fig. 12(A) and (B)). After collection, all the fractions are analyzed offline by HPLC, and the data collected is then processed with statistical analysis software, resulting in predictive models (Fig. 12(C)). In this design, electrode material is easily interchangeable with commercially-available IKA electrodes or any electrode material machined with the same dimensions. The Hofer-Moest reaction of carboxylic acid 45, as well as 2 oxidations reactions, were evaluated as model reactions. For each reaction, 42 experiments were performed, providing extensive information on the productivity and current efficiency. Finally, the conditions obtained after screening were transferred to a larger electrochemical flow reactor with an identical IED and electrode material. Parameters such as flow rate and

applied current were adjusted to match the current density and charge passed set with the microreactor resulting in similar outcomes.

Another interesting cell design from this collaboration between academia and industry was published in 2023,¹¹² detailing the development of a new flow-through CV cell for real-time inline analysis (Fig. 13(A) and (B)). As highlighted before in the work of Jensen *et al.*, cyclic voltammetry is a powerful analytical technique that can provide quantitative and qualitative data about a reaction. However, its application in continuous-flow systems for inline analysis remains rare. Implementing such technologies for monitoring flow processes and generating real-time reaction data has become the cornerstone for developing automated processes. The cell design emphasizes simplicity, using readily available components; standard 1 mm electrode rods, a 5-port connector, fluidic fittings for the cell body, and a low-cost, open-source potentiostat to power the system. To address issues with continuous electrolyte flow, CV data were recorded using a high potential scan rate (0.4 V s^{-1}) and low-flow rate (70–124 $\mu\text{L min}^{-1}$), resulting in the expected voltammogram. The reliability of the CV flow cell was evaluated by comparing HPLC data from alcohol oxidation reactions with the data obtained with the CV flow cell. The correlation between peak currents obtained with the flow cell and the conversion obtained with HPLC showed an excellent linear fit ($r^2 > 0.977$ for 3 different alcohols, Fig. 13(C)), validating the flow cell as a reliable tool for reaction monitoring. In addition, the assessment of reaction conversion over time revealed consistent trends between the calibrated HPLC and the CV device (Fig. 13(D)). Laudadio, Kappe, Merck and co-workers reported the development of an

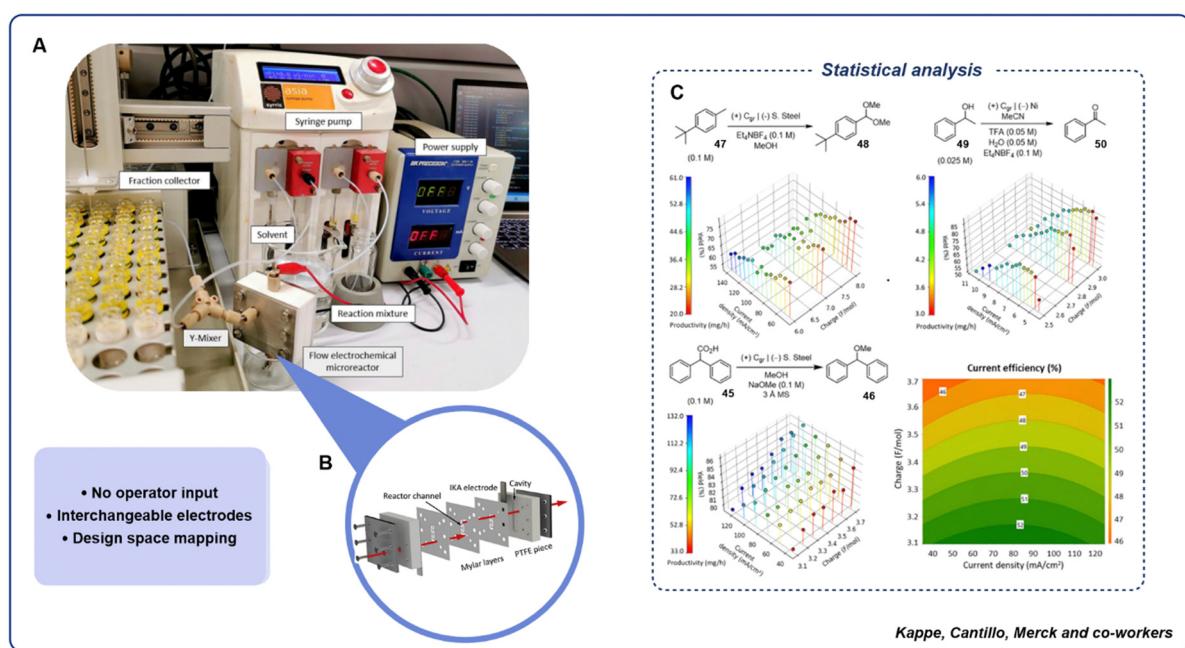


Fig. 12 Overview of the flow electrochemical microreactor for rapid and automated process optimization by Kappe, Cantillo, Merck and co-workers. Reproduced from ref. 111 with the permission from the Royal Society of Chemistry. (A) Photograph of the continuous-flow set-up. (B) Exploded view of the electrochemical microreactor. (C) Results obtained with the automated platform for 3 model reactions.



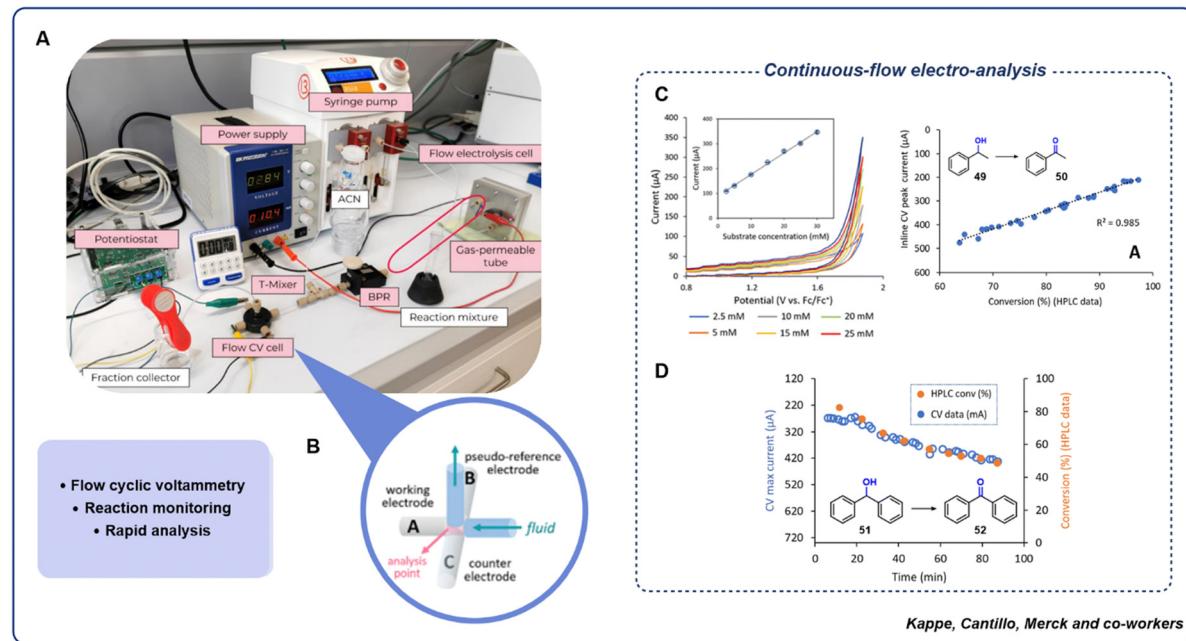


Fig. 13 Overview of the flow-through cyclic voltammetry cell for real-time inline reaction analytics by Kappe, Cantillo, Merck and co-workers. Reproduced from ref. 112 with the permission from the Royal Society of Chemistry. (A) Photograph of the continuous-flow set-up. (B) Schematic representation of the cyclic-voltammetry flow cell. (C) Results obtained by inline CV monitoring for different concentration of 1-phenylethanol **49** and comparison with HPLC data. (D) Comparison of the results obtained by inline CV monitoring and HPLC data, conversion of **51** over time.

automated electrochemical flow platform for reaction optimization and library synthesis (Fig. 14).¹¹³ The platform is divided in 3 modules; reaction mixture preparation, electrochemical reaction and sample collection (Fig. 14(A)). All the modules are controlled by a Python script, enabling the generation of large

datasets without human assistance during the process. This newly developed platform is equipped with a single-pass micro-reactor based on a previous design (Fig. 4(D)).⁵⁰ This flow reactor offers an internal volume of 64 μ L with an IED of 100 μ m, ensuring optimal material consumption and efficient reaction

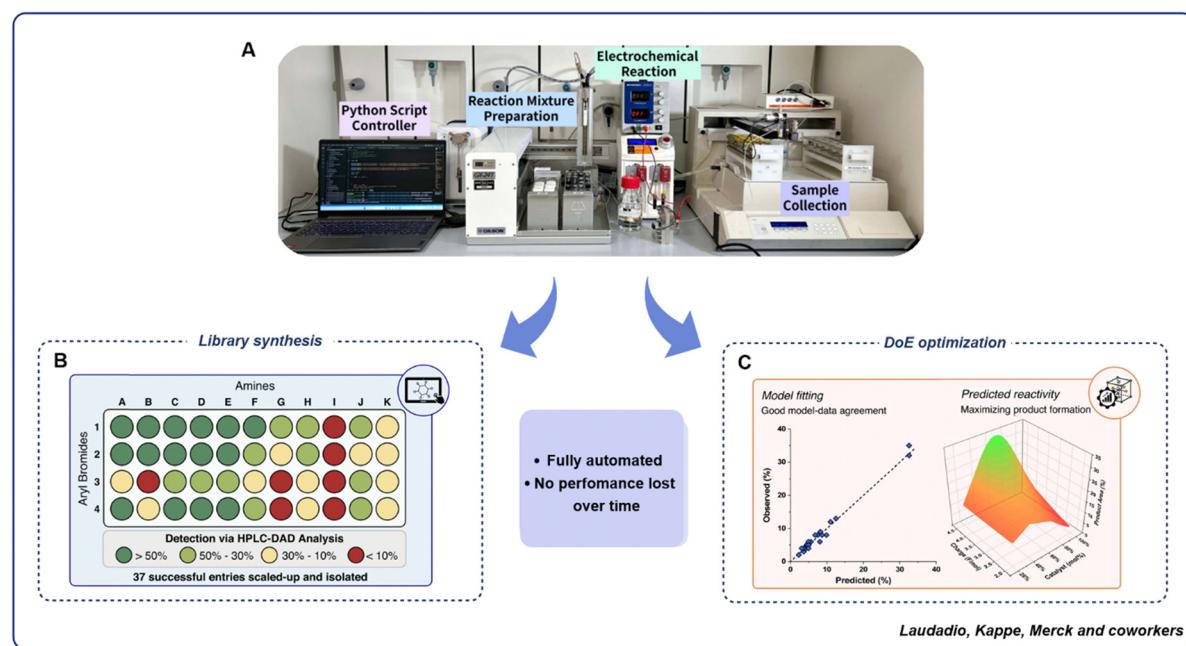


Fig. 14 Overview of the electrochemical flow platform for library synthesis and reaction optimization by Laudadio, Kappe, Merck and co-workers. Reproduced from ref. 113 with the permission from ChemRxiv. (A) Photograph of the platform set-up. (B) Library synthesis results. (C) Model fitting and predicted reactivity obtained from the DoE optimization.



times. With the aim of evaluating the efficacy of the platform, 4 aryl bromides and 11 amines were selected to conduct a C–N Ni catalyzed couplings based on a previously reported work from Baran and co-workers.^{114,115} The platform's robustness was assessed over an extended period, displaying no electrode degradation or fouling, which ensured reliable data collection. Therefore a sequence of 20 entries alternating between two different substrates was conducted. The results showed consistent yields and negligible variation over time, with no cross-contamination. This methodology was then applied to generate a library of 44 protein degrader fragments, which was achieved in only 8 hours of continuous operation and under strictly inert conditions. Out of the 44 experiments, 26 of them showed yields over 30% (Fig. 14(B)). Secondly, reaction optimization was carried out from an unsuccessful datapoint, a DoE (Design of Experiments) optimization was conducted in 4 hours with preset parameters. The results obtained were used in a prediction model (multiple linear regression) that showed excellent agreement ($r^2 = 0.950$) between predicted and observed values (Fig. 14(C)). Finally, the optimized conditions were applied and led to a remarkable 5-fold increase in yield (7% to 35%).

In summary, the recent advancements in high-throughput and automated cell design in flow-electrochemistry announce a transformative era in the field. These innovations, exemplified by the development of user-friendly and flexible electrochemical microreactors, offer significant opportunities for accelerating reaction discovery, optimization, and mechanistic assessment. By automating processes, streamlining analysis and reducing resource consumption, these designs pave the way for enhanced efficiency in chemical research. While some challenges persist (such variable electrode performance and manual electrode exchange), the promising results and demonstrated reliability of these new designs underscore their pivotal role in shaping the future of electrochemistry and chemical research.

Conclusions

This review highlights how conscious reactor design is critical for enabling new synthetic options in electrochemistry. We focused on providing an overview of various electrochemical flow cell designs, detailing the scenarios in which they should be used and their main limitations. In recent years, technological solutions have been developed to efficiently handle gases, manage slurries, and use light as an additional reagent. Additionally, robust flow processes can facilitate the large-scale electrochemical production of high-value compounds. Furthermore, recent reports have demonstrated that electrochemical reactors can be combined with advanced automation protocols and process analytical technology to gather more data, accelerate mechanistic investigations, and carry out reaction optimization and discovery.

Despite significant advancements in novel flow cells, further progress is needed in several areas. A thorough and systematic description of reactor designs is not yet standard practice, with key information such as inter-electrode distance and effective

electrode area often omitted. Additionally, electrode degradation remains a concern for prolonged experiments, especially at the scale-up stage, and hinders high-throughput experimentation and automated screening protocols, as varying reaction conditions over time can result in sub-par data collection.

Looking forward, addressing these challenges will be essential for the continued development and application of electrochemical flow reactors. Standardizing reactor design descriptions and improving electrode durability will enhance the reliability and efficiency of these systems. By doing so, the full potential of electrochemical synthesis can be realized, paving the way for innovative research and industrial applications.

Author contributions

Writing – original draft: M. R., C. V. and D. I. I. wrote the first draft of this review. Formal Analysis: M. R., C. V. and D. I. I. analyzed the literature and selected the discussed papers. Writing – review & editing: T. N. corrected and edited the entire manuscript. Supervision: T. N. and M. R. supervised the progress of this project. Funding acquisition: T. N. acquired the necessary funding to execute this project.

Data availability

This review article does not involve the generation or analysis of new data. All data referenced and discussed in this review are available from the original published studies, which are cited in the text. Therefore, a data availability statement is not applicable.

Conflicts of interest

There are no conflicts to declare.

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