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The Role of Synthetic Organic Electrochemistry in the Technological Revolution of Pharmaceutical Industry

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Abstract: Electrochemistry is significantly contributing to the technological revolution of organic synthesis, where the implementation of different techniques has garnered innovative and scalable synthetic methodologies. This article explores the impact of synthetic organic electrochemistry in the pharmaceutical and agrochemical industry. Key examples in high throughput experimentation, medicinal chemistry, discovery process chemistry, and process chemistry are presented, highlighting the relevance of electrochemistry in the advancement of organic synthesis, and driving innovation in the fine chemical industry.

Keywords: Electrochemistry · Flow chemistry · Research and development

Dr. Gabriele Laudadio received his PhD in chemistry from Eindhoven University of Technology in 2020. After a brief experience as a postdoctoral fellow and group leader at the University of Amsterdam, he joined the Scripps Research Institute as a Hewitt Foundation Fellow. Currently, Dr. Gabriele Laudadio is a University Assistant (Principal Investigator) at the University of Graz. His research is primarily focused on the application of technology in the field of organic chemistry, with a specific emphasis on the synergistic use of electrochemistry and flow chemistry in synthetic methodologies.

1. Technological Revolution of Organic Synthesis

Organic chemistry plays a pivotal role in the discovery and development of new bioactive compounds for agricultural and medicinal applications.[1–3] The ability to access complex structures that can fit into a specific three-dimensional pocket of a peptide or receptor is a crucial characteristic of such bioactive molecules.[4,5] Over the past decades, the synthesis of these compounds has witnessed remarkable progress, driven by tangible advancements in synthetic methodologies with high selectivity and broad functional group tolerance.[6,7] Despite these impressive achievements, the field of organic synthesis has faced stagnation due to the inherent limitations of chemical reactivity. The reliance on stoichiometric oxidants and reductants has hindered the advancement of certain areas, such as single-electron transfer reactions and sustainable synthesis.[8,9] A paradigm shift occurred when the scientific community realized that intrinsic chemical behavior could be harnessed through alternative approaches, previously explored but often underestimated, delivering energy through unconventional means. In particular, the use of photons and electrons emerged as a valuable and sustainable alternative to certain reagents, offering a milder and more controllable approach to redox reactions. The integration of traditional organic chemistry with technologies like photochemistry and electrochemistry has inaugurated a new era of molecular design and synthesis, expanding the retrosynthetic horizons to a more intuitive single-electron disconnection logic.[10–14] Furthermore, the adoption of these approaches unveiled new intriguing reactivity patterns that could not be achieved otherwise (Fig. 1A).

The advent of these exciting opportunities gave rise to multidisciplinary challenges, primarily concerning the scalability of these processes. Efforts from various research groups have demonstrated that implementing photo- and electrochemical reactions in flow reactor technology offers a powerful and scalable alternative to standard batch techniques.[15–17] In electrochemical systems, the small interelectrode gap typical of flow electrochemical devices ensures efficient conductivity, enabling highly selective transformations while minimizing electrolyte consumption (Fig. 1A).[18]

Additionally, the high surface-to-volume ratio enhances mass transfer, making flow reactors an ideal environment for multiphasic electrochemical reactions (*e.g.* gas-liquid, liquid-liquid).[19] These advantages have led to a highly reproducible and scalable approach that has significantly advanced the application of electrochemistry over the years.[20]

2. From Batch to Flow: Matching the Right Reactor to Every Electrochemical Reaction

Breakthroughs in electrochemical reactor technology have rapidly led to the development of various devices tailored for different applications. The introduction of commercially available, standardized equipment marked the beginning of a new era for electrochemistry. Systems such as the IKA Electrasyn 2.0 and IKA Flow provided user-friendly, certified devices, particularly valuable for industrial applications (*vide infra*).[21,22] Simultaneously, numerous homemade electrochemical flow reactors emerged, demonstrating their utility in synthetic methodology and process intensification. These systems enabled the use of inexpensive materials and customizable reactor designs, facilitating systematic exploration of key reactor parameters (*e.g.* surface area, interelectrode spacing, *etc*.).[23–25]

By the late 2010s, the field had access to robust batch and parallel-plate electrochemical cells capable of handling reactions from ~10 mg to decagram scales (Fig. 1B, 2 and 3). The remarkable progress achieved in this short time fueled further advance-

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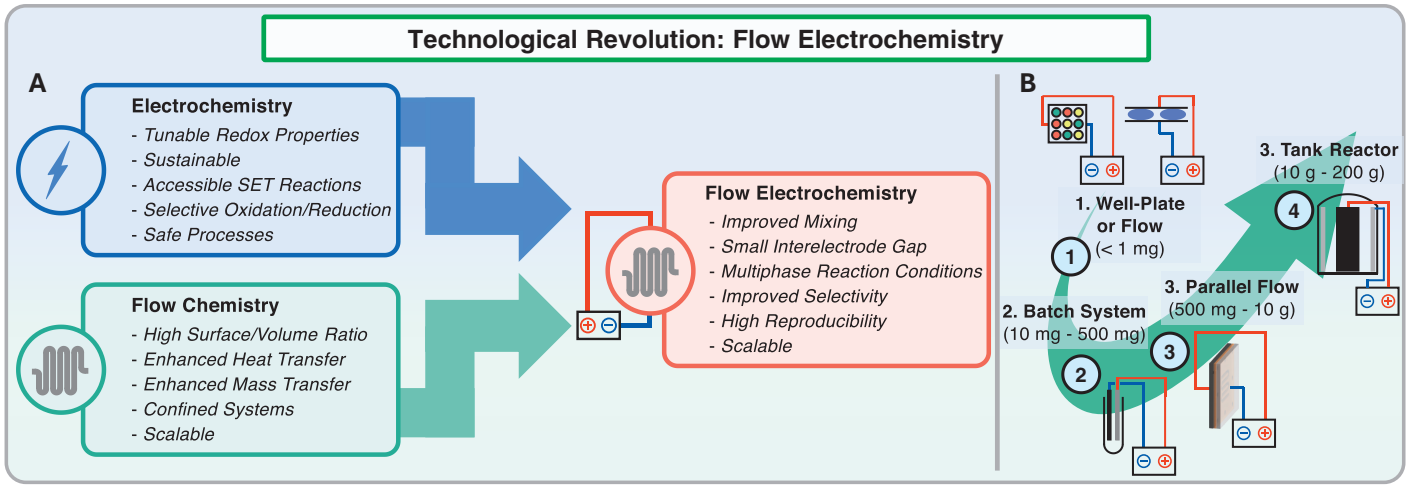

Fig. 1. Technological revolution of organic synthesis. A. Features of flow electrochemistry; B. Reactor designs across different reaction scales.

ments in both chemistry and engineering, driving research efforts to bridge existing gaps and maximize the potential of electrochemistry. The missing pieces of the puzzle were reactor designs that could accommodate both small-scale (<1 mg) and large-scale (>10 g) processes.

Small-scale electrochemical platforms are crucial for high-throughput experimentation (HTE), which plays a key role in reaction condition screening and compound library generation.[26] However, the development of such a system was hindered by the challenge of electrode miniaturization, which complicated the fabrication of a well-plate-style electrochemical reactor. To address these limitations, two main strategies have emerged (Fig. 1B, 1): i) continuous-flow and slug-flow electrochemical systems, often integrated with automated platforms and fraction collectors, enabling the use of minimal material for library generation and optimization studies;[27] ii) miniaturized systems designed to accommodate microelectrodes for parallel screening.[28] Recently, an elegant wireless approach has been proposed to further advance HTE in electrochemistry. Specifically, the Lin group introduced photoelectronic devices that enable wireless electrochemical screening on standardized, commercially available parallel plates (SPECS), leveraging electrode activation *via* low-energy irradiation.[29]

Large-scale electrochemical synthesis has also witnessed rapid advancements, pushing scalability into the kilogram range. Traditionally, electrochemical scale-up has relied on plate- or rod-in-tank batch designs.[30] However, the adoption of parallel-plate flow reactors has significantly enhanced scalability due to the fixed relationship between electrode surface area and reactor volume (Fig. 1B, 4). Despite these advantages, parallel-plate cells are constrained to homogeneous reaction mixtures, as solid byproducts or suspensions could lead to clogging. To overcome these limitations, alternative reactor designs such as spinning electrode reactors have been explored (*vide infra*).[31,32]

3. Synthetic Organic Electrochemistry in the Pharmaceutical Industry

Fundamental chemical and engineering advancements in electrochemistry have garnered significant interest from fine chemical companies (Fig. 2).[33] On one hand, the development of robust and broadly applicable synthetic methodologies (often complementary to photochemical approaches) has found promising applications in medicinal and discovery process chemistry.[34] On the other hand, the sustainability, cost-effectiveness, and scalability of electrochemical reactions have been recognized by process chemistry and agrochemical communities as a viable alternative to conventional chemical transformations.[20]

This section highlights key industrial applications and collaborations between academic and industrial research groups across different scales. Given the breadth of this topic, readers are encouraged to refer to comprehensive reviews that systematically cover the various aspects of synthetic organic electrochemistry for a more in-depth perspective.[12,18,21,30,35]

3.1 *High Throughput Experimentation*

In the early stages of an industrial campaign, the development of bioactive compounds requires access to a broad range of molecular structures, enabling a prompt evaluation of pharmaceutical properties for key fragments. Versatile and robust synthetic methodologies are essential to expedite molecular assembly and test a wide variety of moieties.[4] High-throughput experimentation (HTE) systems have significantly accelerated structural diversification, offering a rapid and efficient technology to assess preliminary studies and identify promising chemical spaces for further exploration.[36]

Many chemical companies have adopted electrochemical HTE platforms, leveraging both batch and flow systems, particularly in Ni-electrocatalyzed C–C, C–N, and C–O cross-couplings (Fig. 3, Top). In collaboration with Biogen and Chemveda, Baran and coworkers employed the commercial e-Hive system to assess Ag/Ni electrocatalytic reactivity, developing a systematic approach to synthesize complex unnatural amino acids from aspartic and glutamic acid and (hetero)aryl halides.[37] Similar applications were reported by Sanofi in collaboration with the Waldvogel group[38,39] and Chiesi Pharmaceuticals.[40] Likewise, the Discovery Chemistry team at MSD, in collaboration with the Watson and Sevov groups, successfully utilized the HT*e*-Chem system[41] to optimize a Ni-electrocatalyzed C–C coupling between alkyl pyridinium salts and (hetero)aryl bromides.[42]

Beyond these batch-system explorations, pharmaceutical companies have also embraced automated flow systems, leveraging existing literature to streamline electrochemical methodologies. In collaboration with Merck KGaA, our group developed a slug-based electrochemical platform for optimizing Ni-electrocatalyzed C–N coupling, applied in the synthesis of E3 ligase binder analogs.[43] At Janssen, Jones, Carvalho, and coworkers introduced an electrochemical platform for C–N and C–O cross-coupling, employing an alternating polarity approach.[44] This system was validated by testing challenging structures from the chemistry informer libraries.[45]

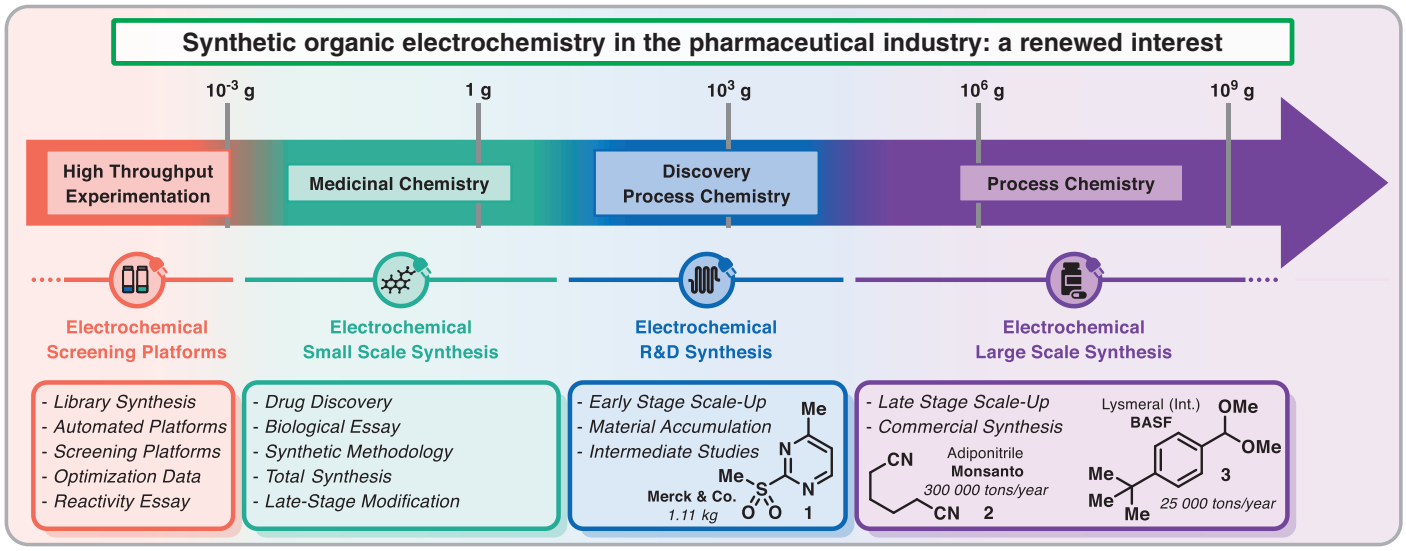

Fig. 2. Applications of synthetic organic electrochemistry in chemical industry across different scales.

The rapid expansion of electrochemical HTE platforms beyond academia underscores their growing importance in the fine chemical industry. These developments highlight the industry's commitment to accelerating and promoting electrochemical transformations, demonstrating the increasing integration of HTE technologies in medicinal and process chemistry.[20]

3.2 *Medicinal Chemistry Applications*

The adoption of electrochemical methodologies in medicinal chemistry holds great potential for the modular synthesis of key intermediates and promising bioactive scaffolds.[33] In this context, electrochemical technology must offer unique reactivity or enable a shortened synthetic sequence. As the sustainability argument does not constitute a primary driver at the drug discovery stage, these features are essential to facilitate practitioners in a technological transition that would otherwise be difficult to achieve.[34]

Instead, medicinal chemists prioritize highly versatile reactions that facilitate the rapid synthesis of diverse analogs essential for comprehensive biological assay studies. In essence, electrochemistry is typically employed when traditional methods fail to access the target molecule or when it provides a more expedite route to a broad range of analogues. Several literature examples highlight these advantages of electrochemical methodologies (Fig. 3, Center). For instance, in collaboration with Genentech, the Lin group developed an intuitive yet powerful electrochemical desaturation of substituted amines followed by a fluorination reaction.[46] This late-stage functionalization strategy enables the efficient decoration of highly substituted amines, demonstrating its potential as an innovative tool for compound diversification in medicinal chemistry.

At Bristol Mayer Squibb, the adoption of Ni-electrocatalyzed $C(sp^3)$–$C(sp^2)$ couplings enabled the selective synthesis of challenging bromophenol intermediate **6** for the synthesis of KRAS inhibitors.[47] More recently, the Stahl group, in collaboration with GSK, reported a manganese-mediated sulfide oxidation strategy, significantly expanding the applicability of electrochemistry for this synthetic transformation.[48] Finally, in partnership with Eli Lilly, Cantillo and coworkers developed an elegant $C(sp^3)$–$C(sp^3)$ electrochemical cross-coupling utilizing alkyl bromides and tosylates as widely accessible precursors for the synthesis of complex, medicinal chemistry relevant molecules.[49]

With their complementary reactivity and high degree of reaction control, electrochemical synthetic methodologies are gaining increasing attention in medicinal chemistry. The pharmaceutical industry anticipates that the continued advancement of synthetic organic electrochemistry will unlock new opportunities for innovative chemical transformations, further justifying the growing number of collaborations in this field.[33]

3.3 *Discovery Process Chemistry Applications*

With the advent of more refined and complex workflows in the area of drug development, pharmaceutical companies have established Discovery Process Chemistry departments, which operate at the interface between the late-stage drug discovery and final manufacturing process.[50] These teams work in synergy with enabling technology departments, providing critical insights into the early scalability of synthetic routes. Alongside continuous-flow systems, electrochemical technologies have already been integrated in pharmaceutical campaigns, enabling the synthesis of key intermediates over the decagram scale.[35] This approach has also found fertile ground in the academic environment, where researchers focused their attention on the development of scalable synthetic methodologies beyond gram-scale productivity.[18] Tackling this scientific challenge requires expertise beyond synthetic organic chemistry,[34] involving chemical engineering,[21] material science,[51] and physical chemistry.[52] This multidisciplinary effort has led to innovative reactor designs or deeper investigations into mass-transfer and fluid dynamics of electrochemical systems different to standard batch cells.[19,53]

One of the most striking examples of successful electrochemical scale-up was reported by Bottecchia, Lehnherr, and coworkers from Merck & Co. (MSD) for the oxidation of the sulfide **7** (Fig. 3, Bottom).[54] A thorough mechanistic study of the chlorine-mediated reaction led to the identification of the optimal electrode material for the synthesis of the sulfone **1** on a kilogram scale reaction employing a stacked electrode recirculation setup.[54] Another transformation of high interest is the Ni-electrocatalyzed $C(sp^3)$–$C(sp^2)$ coupling, whose scalability can be challenging, depending on the reaction conditions. In collaboration with Pfizer, the Weix group investigated the scalability of this process, identifying key parameters to enhance the reaction productivity. Employing two flow cells in parallel, compound **10** was successfully synthesized on a multigram scale.[55]

Electrochemical reactions can also be scaled up using tank reactor designs where various electrode arrangements have been shown to enable significant process intensification. For instance, a rod-in-tank apparatus was successfully applied by the Waldvogel

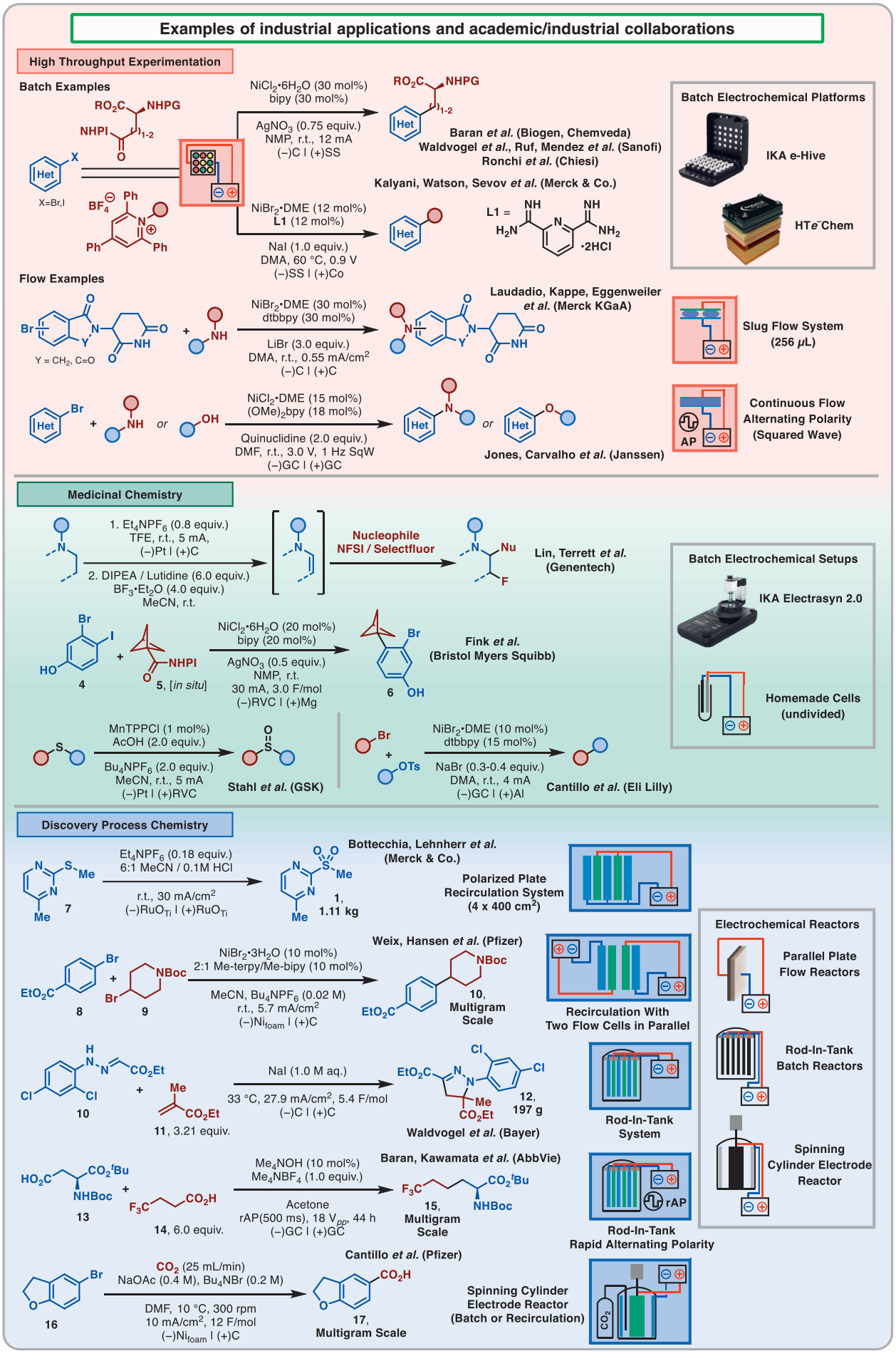

Fig. 3. Examples of electrochemical reactions developed in an industrial setting (internal projects or collaborations with academic research groups). Top: High throughput experimentation; Center: Medicinal chemistry; Bottom: Discovery process chemistry.

group in collaboration with Bayer for the synthesis of mefernpyr-diethyl **12**, a herbicide safener. This setup, employing graphite electrodes, allowed the construction of the pyrazoline core on a 0.5 mol scale (~200 g).[56] Another noteworthy application of rod-in-tank reactors was presented by Baran, Kawamata, and co-workers in collaboration with AbbVie, utilizing a Kolbe coupling employing a rapid alternating polarity (rAP) approach.[57] Using this reactor equipped with glassy carbon rods, a 25 gram scale synthesis of the fluorinated unnatural amino acid **15** was carried out.[58]

Recently, other versatile reactor designs have been explored to overcome scalability limitations, particularly for heterogeneous and multiphasic mixtures, where flow scale-up is often compromised by clogging in parallel plate reactors. One of the most promising solutions is the Spinning Cylinder Electrode Reactor (SCER), which features a rotating electrode that guarantees intimate mixing between different phases and facilitates scale-up through a seamless transition from batch to recirculation or reactor cascade mode.[32]

In collaboration with Pfizer, Cantillo and co-workers employed the SCER for the reductive carboxylation of aryl halides, circumventing the need for sacrificial anodes. The triphasic mixture, consisting of partially soluble sodium acetate, DMF solution, and CO_2 gas, was subjected to electrochemical conditions in the rotating cylinder reactor, leading to the multigram scale synthesis of carboxylic acid.[59] The integration of advanced technologies in electrochemistry has been crucial for the development of scalable and reliable synthetic methods, that have already been adopted in the fine chemical industry. These achievements in discovery process chemistry highlight the potential for further investigation, paving the way for a sustainable transition from research to industrial production.

3.4 *Process Chemistry Applications*

Electrochemical synthetic processes have been employed in the fine chemical industry since the 1950s, leveraging large-scale electrochemical cell technology originally developed for other applications.[60,61] This adaptation enabled the commercial production of various chemicals, often replacing hazardous, stoichiometric reagents with inexpensive electricity, making these processes both cost-effective and sustainable (Fig. 4).[62]

One of the most successful examples is the cathodic synthesis of adiponitrile **2** *via* the reductive dimerization of acrylonitrile. This process, pioneered by Monsanto, produces approximately 300,000 tons per year of the monomer using a plug-flow electrochemical reactor equipped with carbon steel anodes and cadmium cathodes under high current density conditions.[19,35]

Similarly, BASF employs electrochemistry for the large-scale production of numerous commodity chemicals. Among them, the anodic oxidation of 4-butyltoluene to 4-*t*-butylbenzaldehyde dimethyl acetal **3** is one of the most significant electrochemical processes, yielding 25,000 tons per year of this key intermediate for Lysmeral, a widely used fragrance in cosmetics and detergents. While detailed process conditions remain undisclosed, it is known that the acetal undergoes hydrolysis followed by distillation for isolation of the desired intermediate.[61]

With the resurgence of interest in synthetic organic electrochemistry, new challenges in process intensification and pilot-plant transfer are emerging. First, the high dilution of common electrochemical reactions poses a productivity problem, especially when non-benign solvents are required (*e.g.* DMF, DCM, *etc.*).

Furthermore, the use of large quantities of supporting electrolyte, necessary to ensure good conductivity, are perceived as detrimental in terms of atom efficiency and green metrics, discouraging the application of these protocols at pilot scale. Another key consideration is the toxicity and cost of the redox reagents involved. Inexpensive and benign oxidants or reductants (*e.g.* bleach, thiosulfates) are often difficult to replace with electrochemical alternatives unless a clear cost or efficiency advantage is demonstrated.

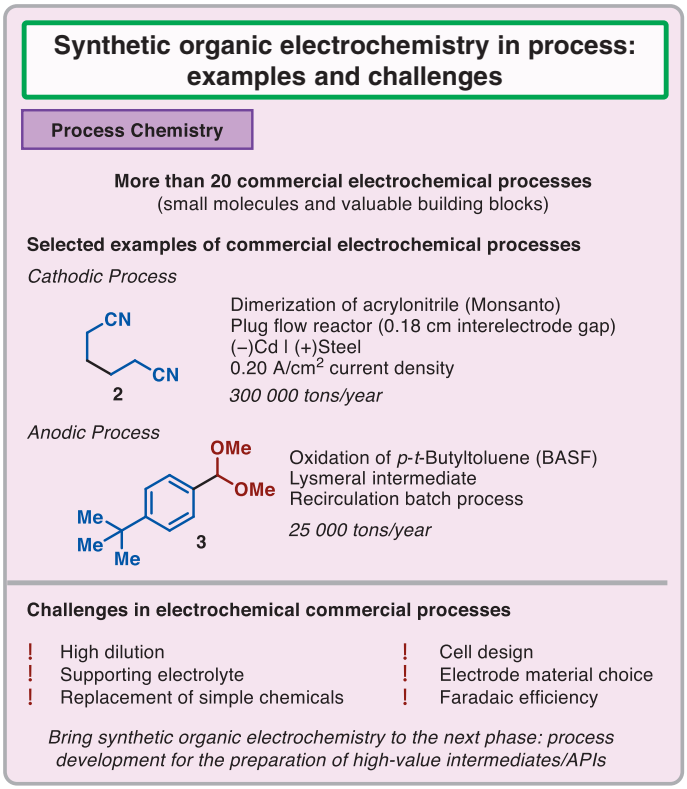

Fig. 4. Examples of electrochemical commercial processes. Challenges in moving electrochemical transformation in process setting.

From a reactor design perspective, several engineering aspects must be addressed when evaluating electrochemical processes for scale-up. Electrode material selection is critical, as chemical stability and durability influence process feasibility.[51] Sacrificial anodes, while useful, pose challenges due to material complication in the downstream processing (*e.g.* emulsion formations), making compatible sacrificial oxidants the preferred alternative.[63] Other essential factors such as heat exchange, Faradaic efficiency, and reaction kinetics must also be optimized for successful scalability.

The advent of flow electrochemistry presents a promising solution, offering enhanced control over reaction conditions and minimizing many of these limitations, paving the way for the successful scale-up of innovative electrochemical transformations.[18]

4. Conclusions and Outlook

While synthetic organic electrochemistry is gaining increasing attention from both academia and industry, it is clear that the field must expand in several key directions. Despite the remarkable advancements highlighted in this manuscript, electrochemistry is still far from being fully integrated into mainstream synthetic methodologies. Many fundamental challenges remain, and addressing these will be crucial to ensure its widespread adoption across diverse application areas.[20]

In the realm of high-throughput experimentation (HTE), the focus is shifting toward automated and self-driven platforms that integrate chemistry with artificial intelligence.[64] Over the past few years, seminal studies have demonstrated the potential of AI-driven electrochemical systems,[65–68] yet more comprehensive and application-oriented platforms are needed to validate their utility in real-world industrial settings. These advancements will further accelerate the adoption of electrochemistry in pharmaceutical research.

In medicinal chemistry, continuous innovation in reactivity and synthetic strategies is essential to expand the toolbox for bioactive compound synthesis. Electrochemistry offers unique opportunities to streamline access to complex molecular scaffolds, reinforcing the need for useful implementation of this technology in drug discovery.[34]

For discovery process chemistry, understanding the scalability of electrochemical reactions by evaluation of different approaches is fundamental. A systematic approach is needed to categorize different transformations, enhance their predictability, and assess their feasibility for scale-up. Furthermore, there is a pressing need for the development of innovative reactor technologies capable of overcoming mass-transfer and kinetic limitations. A tailor-made reactor design will be necessary to enable the efficient scale-up of challenging electrochemical reactions.[69]

In process chemistry, a stronger collaboration between academia and industry is essential to extend electrochemical manufacturing beyond commodity chemicals, incorporating it into the synthesis of complex active pharmaceutical ingredients (APIs). Bridging this gap will be a decisive step in realizing the full potential of electrochemical methodologies in large-scale synthesis.[30]

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