



High-Throughput Electrochemistry: State of the Art, Challenges, and Perspective

Alfie Wills, Sylvain Charvet, Claudio Battilocchio, Christopher Scarborough, Katherine Wheelhouse, Darren Poole, Nessa Carson, Julien Vantourout

► To cite this version:

Alfie Wills, Sylvain Charvet, Claudio Battilocchio, Christopher Scarborough, Katherine Wheelhouse, et al.. High-Throughput Electrochemistry: State of the Art, Challenges, and Perspective. Organic Process Research and Development, 2021, 25 (12), pp.2587-2600. 10.1021/acs.oprd.1c00167 . hal-03867466

HAL Id: hal-03867466

<https://cnrs.hal.science/hal-03867466>

Submitted on 25 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

High-Throughput Electrochemistry: State of the Art, Challenges, and Perspective

Alfie G. Wills,^a Sylvain Charvet,^b Claudio Battilocchio,^c Christopher C. Scarborough,^c Katherine M. P. Wheelhouse,^d Darren L. Poole,^{a*} Nessa Carson,^{e*} Julien C. Vantourout^{*b}

^aMedicinal Chemistry, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, United Kingdom.

^bUniv Lyon, Université Lyon 1, CNRS, INSA, CPE-Lyon, ICBMS, UMR 5246, Bâtiment LEDERER, 1 rue Victor Grignard, 69622 Villeurbanne cedex, France.

^cResearch Chemistry, Syngenta Crop Protection, Schaffhauserstrasse 101, CH-4332 Stein, Switzerland.

^dChemical Development, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, United Kingdom.

^eSyngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, United Kingdom.

*Email: julien.vantourout@univ-lyon1.fr; nessa.carson@syngenta.com; darren.l.poole@gsk.com

ABSTRACT: Electrochemical transformations involve complex parameter interactions, from universal chemistry variables such as solvent and reagents, to specialist factors including electrode material and current density. Hence, development of a robust and scale-independent electrochemical reaction can currently be a challenge. High-throughput experimentation (HTE) is an enabling method for reaction optimization and robustness testing. Here, we provide an industrial and academic perspective on the state of the art of the combination of HTE with electrochemical reaction optimization for applications including scaleup. We then present our vision for a future of HTE reducing barriers to wide adoption of electrochemistry across the field of chemical synthesis.

Keywords: *Electrochemistry – High-throughput – Technology – Method development*

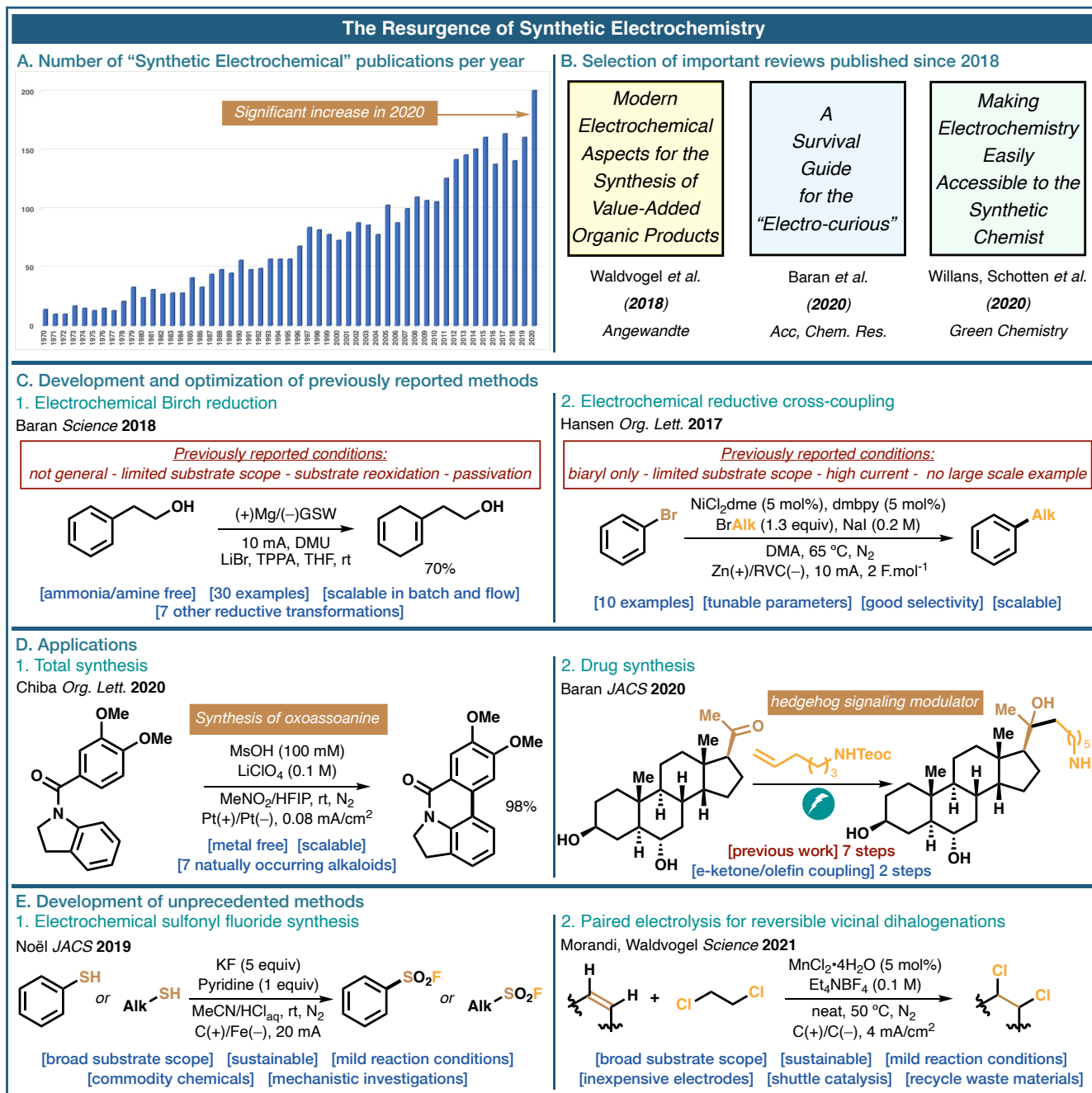
INTRODUCTION

High-throughput experimentation (HTE) is an enabling technology, involving running multiple designed experiments rapidly or in parallel to evaluate many combinations of variables more efficiently than in one-at-a-time fashion, allowing rapid acquisition of data for decision-making, and often incorporating the use of laboratory automation.¹ It enables fast testing of multidimensional hypotheses and high-risk, high-reward possibilities that would be impractical to explore one at a time.² HTE is commonly employed in pharmaceutical and agrochemical discovery and process development for everything from optimizing reaction conditions (e.g. solvents, catalysts, reagents, or reaction parameter

ranges)³ and robustness⁴ to studying extractions⁵ and developing crystallizations.⁶ Recent reports describe the development of photoreactors suitable for high-throughput optimization of photochemical transformations, enabling screening of different controlled wavelengths, modulating of light intensity and control of temperature whilst evaluating different reaction components.⁷ Not only does this enable more rapid screening of photochemical reactions, it also enables determination of key parameters crucial to robustness, reproducibility, and process understanding.⁸ A system to enable high-throughput optimization of conditions for electrosynthesis reactions, including pertinent variables such as electrode materials, voltage, etc., would be similarly powerful. We review the state of the art of high-throughput electrochemistry devices through the lens of potential applications to small molecule research and development. Although high-throughput analytical electrochemistry has been widely explored,⁹ this perspective focuses on high-throughput electrochemistry dedicated to reaction optimization and parallel small molecule synthesis.

THE RESURGENCE OF SYNTHETIC ELECTROCHEMISTRY

The recent commercialization of standardized electrochemical equipment has generated a resurgence of interest for the development of novel electrochemical transformations. Indeed, over the past few years, the number of reported novel electrochemical methods is constantly increasing and more than 200 papers were published in 2020 (Figure 1A).¹⁰ This significant increase was accompanied by the disclosure of several key reviews that allowed the practitioners to familiarize themselves



inspired by the work of Périchon (Figure 1C, 2).¹⁴ This transformation is of high interest as it finds applications in both medicinal and process chemistry. While the initially reported conditions were limited to the formation of biaryl compounds and were not scalable, the new protocol that allows for the use of alkyl halide coupling partners usefully expanded the scope of the reaction. In addition, the reaction parameters can now be easily tuned, and the transformation was easily scaled up without stoichiometric amounts of reducing metal such as Zn or Mn powders.

Optimized synthetic electrochemical reactions have also been developed in the context of total synthesis (Figure 1D, 1). In 2020, the group of Chiba disclosed an intramolecular electrochemical C(sp²)-H cross-coupling and dehydrogenative indole synthesis which was applied to the synthesis of natural pyrrolophenanthridone alkaloids including oxoassoanine.¹⁵ Interestingly, both the generation of a strong electrophilic radical cation and the benzylic oxidation of the same electron-rich indoline moiety were induced at the anode, but with excellent selectivity. Finally, it was also demonstrated that electrochemistry can considerably facilitate and accelerate drug discovery by replacing useful methods with more user-friendly protocols. As an example, Baran and coworkers readily synthesized tertiary alcohols from ketones in a complementary fashion to the use of Grignard reagents (Figure 1D, 2).¹⁶ Reversal of the polarity of the ketone under electrochemical conditions produced an excellent nucleophilic radical that was able to react with unactivated alkenes. The steroid example presented in Figure 1D highlights the enabling nature of the reaction for multi-step synthesis. These examples clearly demonstrate how synthetic electrochemistry can dramatically accelerate reaction development and simultaneously impact several chemical fields.

As depicted in Figure 1E, the resurgence of synthetic electrochemistry has also motivated several groups to

develop unprecedented transformations with significant applications. In 2019, the Noël group reported the electrochemical synthesis of both aryl and alkyl sulfonyl fluorides from ubiquitous thiol or disulfide starting materials in the presence of KF as fluoride source (Figure 1E, 1).¹⁷ Notably, no additional oxidants nor catalysts were required, and the mild reaction conditions afforded a broad substrate scope. This synthetic electrochemical method represents a novel approach for the synthesis of highly desirable sulfonyl fluorides and should find applications in both academic and industrial settings. More recently, Morandi, Waldvogel, and coworkers assembled an electrochemically assisted shuttle system for the simple and scalable interconversion of alkenes and vicinal dihalides (Figure 1E, 2).¹⁸ The reaction was demonstrated in a simple undivided cell equipped with inexpensive graphite electrodes under mild conditions. One of the major applications described in the paper is the full dechlorination of lindane (a hexachlorinated persistent pollutant found in polluted soils) to benzene using simple alkene acceptors. This electrochemical approach is a step forward to the direct remediation of lindane-contaminated soils.

SYNTHETIC ELECTROCHEMISTRY ENABLES GREENER PROCESSES

Sustainable transformations have been an influential goal for the chemical industries in recent years, in the drive to minimize environmental impact. For example, since 2007, the ACS Green Chemistry Industry Pharmaceutical Roundtable has identified several key areas of synthetic chemistry and aspirational reaction types that would result in more efficient pharmaceutical processes and production, a number of which may benefit from the application of electrochemistry.¹⁹

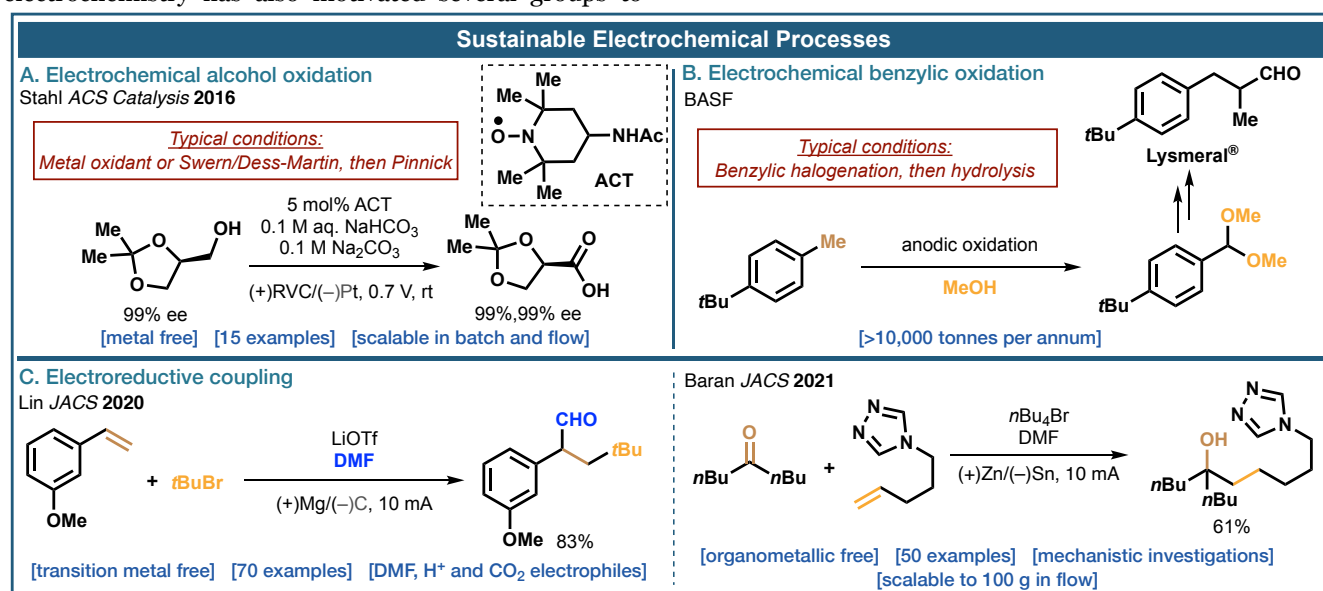


FIGURE 2. Examples of sustainable alternatives through electrochemistry.

Synthetic electrochemistry has a number of positive impacts on chemical process sustainability.²⁰ Electrons are an essentially massless reagent, replacing the need for stoichiometric (and often environmentally dubious) oxidants or reductants.²¹ Additionally, the “greenness” of these processes is expected to increase yet further as society moves from the use of fossil fuels toward more renewable and sustainable sources of electricity. Numerous literature examples of electrochemical oxidations and reductions provide alternatives to traditional stoichiometric reagents: too many to cover in this perspective. Two pertinent examples include the electrochemical Birch reduction (Figure 1C.1), and the 4-acetamido-TEMPO mediated oxidation of alcohols and aldehydes to carboxylic acids developed by Stahl and coworkers, which both provide a mild alternative to classical methods employing stoichiometric metal- or chlorine-containing oxidants (Figure 2A).²²

Typically, electrochemical reactions take place at or close to ambient temperature,²³ negating the cost and high energy consumption required for heating or cooling on scale. Ambient temperature also provides further environmental and safety benefits, namely reducing the risk of corrosion, reactor failure, and accidental release.¹⁹ A key, industrially-relevant example of electrochemistry enabling lower process temperature is the oxidation of toluene derivatives to benzaldehydes at a carbon anode conducted by BASF. Compared to the traditional approach of high-temperature chlorination followed by hydrolysis, the lower temperature and choice of methanol as reagent and solvent together provide a clear sustainability benefit (Figure 2B).²⁴ In two recent examples, the groups of Lin and Baran independently published electroreductive functionalizations of olefins, conveniently effecting transformations traditionally conducted at cryogenic temperatures with organometallic reagents (Figure 2C).^{18,25}

One difference between an electrochemical reaction and a standard chemical reaction is the requirement for a supporting electrolyte species to reduce the resistance of the electrochemical cell. While many electrolytes employed in organic electrosynthesis are cheap and readily-available (e.g. alkali metal halides), others such as tetraalkylammonium salts can be expensive. Also, many common electrolytes are incompatible with standard industrial wastewater treatments used, detracting from the sustainability of an electrochemical process – although recovery and recycling of the electrolyte can minimize costs and improve sustainability.²⁶ Another method to reduce quantities of electrolyte is to conduct the reaction in a flow cell, where small interelectrode distances reduce resistance between the electrodes, minimizing or even removing the need entirely for a supporting electrolyte.²⁷

THE ADVANTAGES OF ELECTROCHEMICAL SYNTHESIS IN FLOW

Flow electrochemical reactors may also provide many additional benefits in carrying out electrochemical

reactions. These include improving mass transfer, and thus improving the reaction rate where the electrochemical reaction is not charge transfer-limited. This can be achieved in two ways in flow electrochemical cells: either by the introduction of static mixers to intensify mass transport, or by the use of flow microreactors with small interelectrode gaps, decreasing the time taken for a species in solution to diffuse to the electrode of interest.²⁶ Conducting electrochemical reactions in flow also facilitates the careful control of reaction temperature due to the more efficient heat exchange in flow systems, which can have a positive impact on reaction selectivity and on leading to more controlled and reproducible results upon scaling.²⁸ As most electrochemical flow reactors use the electrodes as two of the walls of the flow cell, there is an inherent increase in the surface area of the electrode relative to the reactor volume, which further improves reaction efficiency.^{26,28}

Numerous electrochemical flow reactors and microreactors have been reported,^{26,28,29} and a number are also commercially available.³⁰ Given the benefits of scaling electrochemical reactions in flow, it is clear that the ability to perform high-throughput experimentation in a flow microreactor, and a full understanding of the electrochemical parameters, could have significant benefits in taking a process from conception through to reactions on a multigram or even kilogram scale, without the requirement for extensive reoptimization.

AN IDEAL ELECTROCHEMICAL HIGH-THROUGHPUT SCREENING APPARATUS

The optimization of conditions for a given chemical transformation can be an arduous task even in the absence of electricity, and the addition of unique electrosynthesis-associated variables significantly increases the complexity of the variable space. Beyond “typical” factors involved in optimization of a chemical transformation (temperature, concentration, solvent, additives, *etc.*), variables unique to electrochemistry include:

- Cell geometry
 - o Batch cell geometry (e.g. shape, volume, electrode size(s), interelectrode distance)
 - o Flow cell geometry (e.g. laminar *vs.* turbulent flow, interelectrode gap, presence/absence of a heat exchanger)
- Cell type
 - o Undivided cell
 - o Divided cell
 - Nature of the dividing material (e.g. glass frit, cation or anion exchange membrane)
- Material of the anode
- Material of the cathode
- Current density (not easily calculated or controlled with non-plate electrodes like RVC or metal foam electrodes)
- Mixing in the inter-electrode region (liquid-solid interface and fluid dynamics in the gap)
- Nature and concentration of supporting electrolyte

- Electrode surface modification over time

The parameter space of electrosynthesis is therefore highly complex, underpinning HTE as an ideal approach.

Do the needs of an electrosynthesis HTE kit depend on the nature of the research? When approaching electrosynthesis, a chemist may be interested in either applying a known transformation to their substrate of interest, or possibly developing a novel transformation. Within these two approaches, the availability of the starting material is a key factor: is the starting material easily accessed on multi-gram scale (e.g. commercially available or part of a process development campaign), or is the starting material precious and scarce (e.g. late in a total synthesis, or an advanced intermediate in a medicinal or agrochemical synthesis campaign)? Thirdly, with modern interest in machine-learning applications for the development of reactivity models, would it not be best to regularly screen a wide array of conditions across an array of chemically-diverse substrates to generate a reactivity model? Despite the numerous scenarios requiring electrosynthesis studies, the goals of an electrosynthesis HTE kit unify under this concept of reactivity models. That is, even when repeating a single literature transformation, a desirable outcome is to collect sufficient data on the target of interest and other chemically-diverse targets to address future needs from that reaction, instead of repeating the studies when a new substrate of interest arises. Hence, the generation of a large dataset is invaluable for any new transformation, whether known for related substrates or novel, and such an effort would address each scenario above if the full dataset could be generated rapidly from a small amount of substrate, perhaps no more than 100 mg.

A complicating aspect of electrosynthesis is that translation of results from one cell to another is not often straightforward. This can inhibit uptake of electrosynthesis by the community because of challenges in reproducibility without common equipment, and when all parameters are not accurately described. For example, mixing is highly complex in an electrosynthesis reactor, while also being important for processes like electrochemistry that occur at solid-liquid interfaces. Mixing depends on factors such as interelectrode distance, the electrode surface area (poorer mixing toward the center of the interelectrode region) and bubble and heat generation (related to current density). Furthermore, when transitioning from batch to flow, mixing changes significantly owing to the nature of flow (laminar *vs.* turbulent) and the generation of volumes of gas commensurate with reactor volume. Finally, production-scale electrosynthesis generally occurs in flow in galvanostatic mode, at higher current densities than are possible in small batch reactors owing to heat generation, and on scales where turbulent mixing is normative. On the other hand, promoting turbulent mixing in very small-scale flow cells with significant gas generation is a major challenge, meaning that scaling up between different flow reactors is not straightforward. Nonetheless, it is our view that the most general electrosynthesis HTE kit would run in flow with turbulent mixing to enable smooth

translation to higher scales. Also, in the transient periods before and after steady state concentrations are reached in galvanostatic flow electrochemistry, undesired reactivity such as overoxidation is enhanced, when the full current is applied to a small fraction of the reaction mixture.³¹ Since the steady state period is short on very small scales, potentiostatic mode is preferred for very small-scale flow HTE. However, galvanostatic conditions are often preferred in batch, regardless of scale, due to a simpler setup and greater reliability and reproducibility.^{28,32}

Finally, electrode fouling can cause reproducibility challenges if the electrodes are not properly treated between usage, so an ideal electrosynthesis HTE kit would make use of small, disposable, and inexpensive electrodes.

The technical challenges of achieving an ideal electrosynthesis HTE kit are significant:

- Turbulent flow on microliter scales in electrochemical flow cells with an array of disposable electrodes that manages rapid pressure changes due to gas formation
- Independent electrical control of each cell, where potentially hundreds of cells are needed to effectively map the variable space across a range of diverse substrates
- Divided cells testable with an array of different membrane materials
- Miniaturization of reliable reference electrodes to allow for precise potentiostatic electrolysis

Similarly, for operational simplicity and material conservation, HTE reactions will ideally be conducted on <300 μ L volume in batch and yet lower in flow, to run as many concomitant reactions as possible. For example, high-throughput photoredox chemistry in flow has been conducted down to nanoliter scale.^{7c} With these desired characteristics in mind, we next evaluate state-of-the-art flow and batch electrochemistry screening kits, which highlights the remaining unsolved challenges.

RECENT HISTORY AND STATE OF THE ART OF FLOW ELECTROCHEMICAL SCREENING EQUIPMENT

Flow electrosynthesis has evolved rapidly in the last decade, with many suppliers making flow cells with diverse functions available. Flow cells can lead to much improved electrosynthetic performance, due to the narrow electrode gap and the ability to run reactions under pressure and improve mixing. Despite the many advances, there is no full practical solution which can yet be directly applied to HTE.³³ However, there are some efficient designs which represent steps toward the “holy grail” of a flow cell to address HTE needs.

Waldvogel and coworkers have pioneered not only the resurgence of batch electrochemistry, but also of flow.

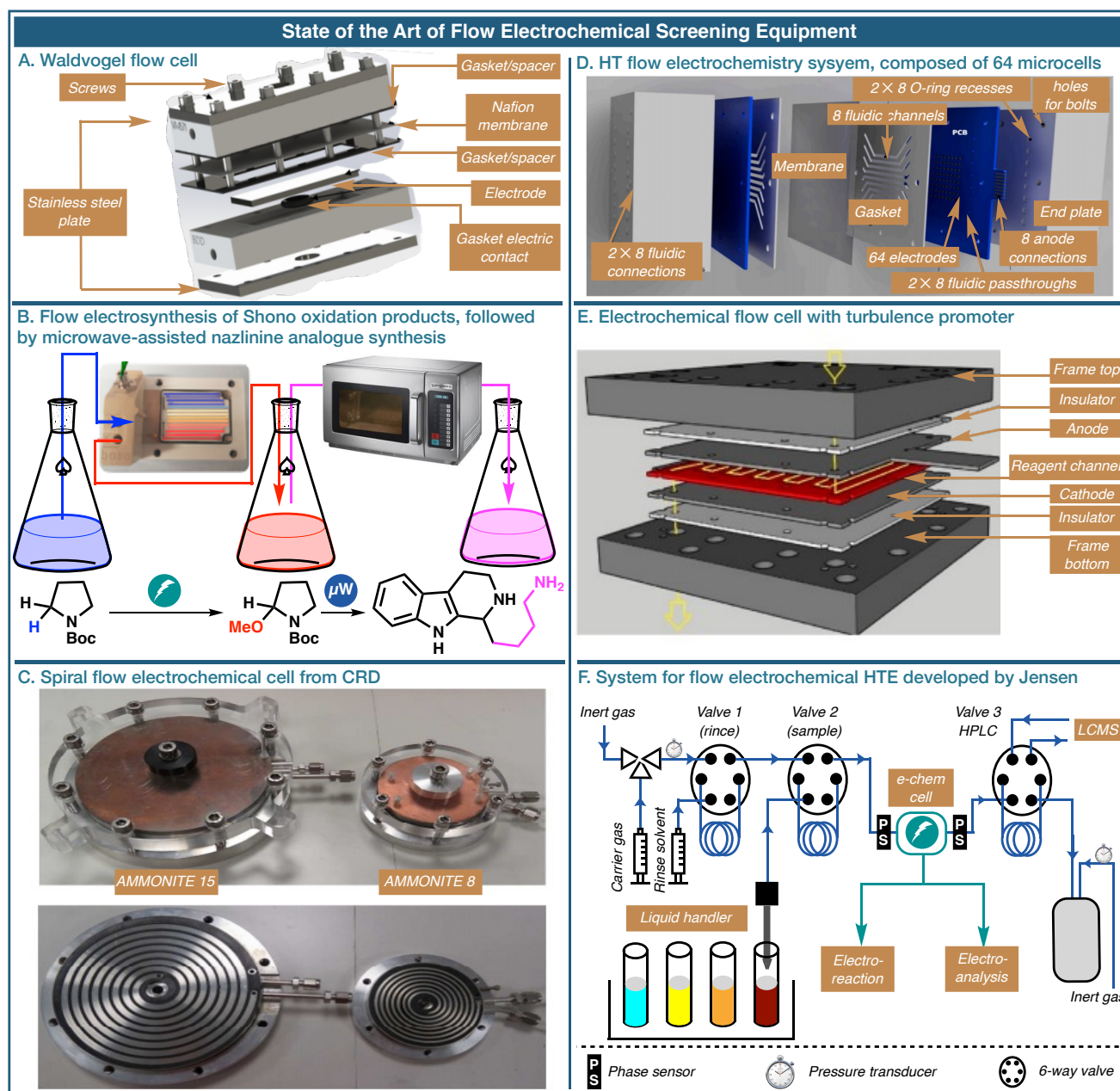


FIGURE 3. State of the Art of flow electrochemical screening equipment. (A) Reprinted with permission from *Org. Process Res. Dev.* **2017**, *21*, 771–778. Copyright 2017 American Chemical Society; (C) Reprinted with permission from *Org. Lett.* **2017**, *19*, 2050–2053. Copyright 2017 American Chemical Society. (D) Creative Commons images reproduced from *Catalysts* **2020**, *10*, 1165; (E) Reprinted with permission from *Ind. Eng. Chem. Res.* **2020**, *59*, 7321–7326. Copyright 2020 American Chemical Society.

Their recent paper reports an extremely modular flow cell (Figure 3A).³⁴ This cell allows easy adjustment of interelectrode distance, as well as facile replacement of electrodes, with the possibility to switch between divided or undivided cell formats. The electrode material is thermally positioned into a Teflon piece, allowing the use of expensive and nonmachinable electrode materials like boron-doped diamond or glassy carbon. The flexible cell design creates opportunities for chemists, including those with lesser practical experience in flow chemistry, and competes with classical preparative approaches in terms

of performance and productivity. A drawback of the cell is mixing within the flow channel, where flow is laminar and gas generation is not controlled. Ley and his group have been pushing the boundaries of enabling technologies in the last 15 years, particularly with flow chemistry.³⁵ In one recent work, they demonstrate how flow electrochemistry can be utilized to generate molecular diversity.³⁶ A commercially-available system (i.e.: Syrris electroflow cell) was used to perform a Shono oxidation on a series of derivatives, before telescoping the reaction output to generate nazlinine analogues (Figure 3B). The

commercial system used for this work is a flexible setup, which is useful for lab research applications.

Another interesting application was reported by Richard Brown and coworkers in collaboration with AstraZeneca and Eli Lilly, using a system developed and commercialized by Brown: the Ammonite, a spiral-shaped electrochemical flow cell with narrow interelectrode gap (Figure 3C).³⁷ Here, the authors explore the electrochemical deprotection of *p*-methoxybenzyl ethers in MeOH solution, using an undivided electrochemical flow reactor. Notably, this method avoids the need for chemical oxidants, and the electrolyte can be recovered and reused. High conversions were obtained from several substrates in a single pass, albeit so far in the literature largely being performed with a “one factor at time” approach.

Hilton, Lam, and coworkers have also described a low-cost, 3D-printed electrosynthesis flow cell, that interfaces with the IKA commercial ElectraSyn 2.0 system (*vide supra*).³⁸ This system allowed them to improve their previously-developed methoxymethyl-protection of aliphatic alcohols³⁹ by eliminating the need for a supporting electrolyte, and avoiding overoxidation of substrates such as benzylic alcohols.

One recent work by Schouten et al. describes one of the very few literature reports to create a HTE flow electrochemical system for the screening of electrode materials used for electrosynthesis in electrochemical parallel plate reactors (Figure 3D).⁴⁰ The reactor is composed of 64 microflow cells that can be operated in different configurations, allowing screening of 64 different anode/cathode combinations, with the systems separated by a membrane. The authors go some way to addressing the dissimilarity between small-scale screening setups and larger-scale flow cells as well as the scalability of the setup to yet larger setups: to obtain a system amenable to scaleup, the authors miniaturize and further parallelize the parallel plate reactors to form a matrix of flow cells that can be run at industrial current densities.

Industrial colleagues from Syngenta have described the design of an electrochemical flow cell that provides excellent mixing by incorporation of a turbulence promoter in the flow channel, which enables high current densities to be achieved on research-relevant scales (≤ 1 g, up to 10 g scale; Figure 3E).⁴¹ The use of high current densities is a very relevant factor relating to potential for scalability and brings value when it comes to translating an electrochemistry concept from small scale process research toward the development environment. The cell design embeds a turbulence promoter and cooling layers, and was operated with a current density of 1000 mA/cm² for the oxidative dimethoxylation of furan.

Work by Jensen and coworkers describes a microfluidic platform that enables automated THE for electroorganic synthesis at a 15- μ L scale (Figure 3F).⁴² Two THE modules are demonstrated: rapid electrochemical condition screening for a radical–radical cross-coupling reaction on micro-fabricated,

interdigitated electrodes, and measurements of kinetics for mediated, anodic oxidations using microliter-scale cyclic voltammetry.

RECENT HISTORY AND STATE OF THE ART OF BATCH ELECTROCHEMICAL SCREENING EQUIPMENT

In addition to flow electrochemical screening equipment, the batch approach has also been developed and different techniques have emerged offering the practitioners several options when running a high-throughput screening campaign. These can be separated into systems using many electrodes and one electrolyte, one electrode and many electrolytes, or full screening capabilities with many electrodes and many electrolytes. Here, the term ‘electrolyte’ refers to a reaction solution that is physically separated from neighbouring solutions, and should not be confused with a ‘supporting electrolyte’, an additive that may or may not be present.

Many electrodes, one electrolyte

Initial research into a high-throughput approach to electrochemistry focused on the synthesis and analysis of libraries of modified electrode surfaces. The first report details the combinatorial synthesis of an electrode array containing 645 unique alloys of platinum group metals with the aim of developing an optimal electrocatalytic surface for methanol oxidation.⁴³ Catalytic activity was determined using a pH-dependent fluorescent dye to identify areas of low pH on the surface of the array, indicative of methanol oxidation. This was followed by a more general method using a computer-automated screen to allow direct serial electrochemical analysis of organosulfur monolayers on a 64-electrode array.⁴⁴ These early methods are examples of ‘many electrode, one electrolyte’ systems in which multiple electrode surfaces are submersed in a single electrolyte, forming one electrochemical cell (Figure 4A). This is advantageous as it simplifies the electrochemical equipment required for the screen and allows it to be scaled relatively easily. The principal disadvantage for synthesis of this format is the inability to screen electrolytes, the components of which constitute most of the independent variables of a reaction that are desirable to screen. A many electrodes, one electrolyte method has also been applied to the high-throughput synthesis of conducting polymers *via* electrochemical polymerization.⁴⁵ This allows for their combinatorial synthesis on a 96-electrode array followed by high-throughput analysis of the relevant electrochemical properties. In a more recent example, a high-throughput screen of a library of 60 glassy carbon electrodes covalently modified with Ru(II) or Zn(II) complexes was used to identify an optimal surface modification for NADH oxidation.⁴⁶ Other examples of many electrodes, one electrolyte methods outside of reaction optimization include the synthesis of addressable microelectrode arrays pioneered by Moeller.⁴⁷ This technique allows site selective functionalization of individual microelectrodes in the array with proteins or other small molecules that can then be used in biological

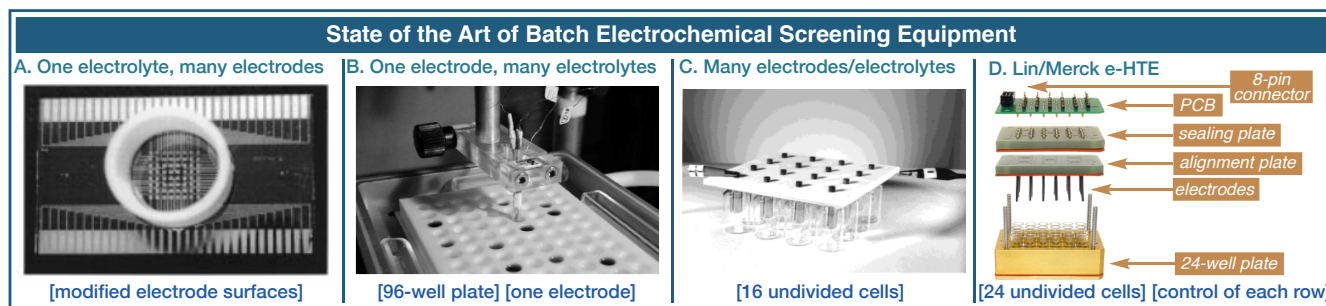


FIGURE 4. State of the Art of batch electrochemical screening equipment. (A) Reprinted with permission from *Anal. Chem.* **1999**, 71, 4369–4375. Copyright 1999 American Chemical Society; (B) Reprinted with permission from *Electrochim. Acta* **2005**, 50, 2753–2762. Copyright 2004 Elsevier Ltd; (C) Reprinted with permission from *J. Comb. Chem.* **2000**, 2, 5545–5549. Copyright 2000 American Chemical Society (D) Creative Commons images reproduced from ChemRxiv (CC-BY-NC-ND 4.0).

assays. Numerous reactions have been adapted for these functionalizations including electrochemically enabled Wacker oxidation, Suzuki-Miyaura coupling and reductive amination.^{47–49} The selective reaction of individual electrodes in a single electrolyte is ideal for the synthesis of functionalized electrode arrays; however, it is not directly applicable to the high-throughput screening of electrochemical reaction conditions.

One electrode, many electrolytes

A fully-automated screening platform for high-throughput electrochemical analysis has been developed using an alternative, one electrode, many electrolyte approach for high-throughput chemical analysis (Figure 4B).⁵⁰ The setup consists of a 96-well plate acting as an array of electrochemical cells, and a single three-electrode probe that can be inserted consecutively into each cell to obtain cyclic voltammograms. While first being used to build structure-activity relationships for conducting polymers, this analytical method has also been applied to the automated screening of Ru(II) hydrogenation catalysts.⁵¹ In addition to cyclic voltammetry, this system has been adapted for the microscale electrochemical synthesis of combinatorial compound libraries including iminoquinol ethers and triazolopyridinium ions, as well as the electroreductive coupling of α,β -unsaturated esters and allyl bromides.⁵² These compounds were synthesized on 200- μ L reaction scale in a microtiter plate, with reaction progress monitored by steady state voltammetry and product formation screened by HPLC-MS. These methods can be classified as ‘one electrode, many electrolytes’ systems in which a conserved bundle of electrodes is introduced to each cell in a sequential fashion, followed by cyclic voltammetry or preparative electrolysis. This approach allows the high-throughput screening of many electrolyte samples in a single plate and is better suited to screening reaction conditions than a many electrode, one electrolyte method. Another significant advantage of this system is the successful miniaturization of the cells, enabling the screening of a large number of reactions using a small amount of material. Limitations of this format include the increased time it takes to run a screen due to the consecutive nature of the reactions as well as the relative difficulty of screening different electrode materials. The reuse of

electrodes between reactions also has the potential to introduce electrode passivation and cross-contamination between cells.

Many electrodes, many electrolytes

A third paradigm of high-throughput electrochemistry was established during Yudin and coworkers’ development of a spatially addressable electrolysis platform (SAEP) for the combinatorial electrosynthesis of α -alkoxy carbamates, amides, and sulfonamides.⁵³ The platform was constructed using a 4×4 array of stainless steel cathodes and graphite anodes, each contained within a Teflon or glass vessel, giving a 16-well plate of individual electrochemical cells. The electrodes were then connected in parallel to allow galvanostatic electrolysis from a single power source. This is the first example of a many electrode, many electrolytes approach, in which each set of electrodes is contained within their own electrolyte, forming a set of independent electrochemical reactions (Figure 4C). This format has the significant advantage of allowing variation of both the electrode material and the constituents of the electrolyte in a single screen. It also permits simultaneous electrochemical reaction of different substrates, making it well-suited for library synthesis.⁵⁴ Another literature example of a many electrode, many electrolytes method is an electrochemical microtiter plate (eMTP) designed for parallel spectroelectrochemical measurements.⁵⁵ A 24-well plate was used to house 8 cells, each containing 1 mL of electrolyte and three electrodes suspended from a circuit board lid. The cells of the eMTP were connected to an 8-channel potentiostat, allowing independent potentiostatic control of each cell. A proof-of-concept study demonstrated the ability to conduct cyclic voltammetry and chronoamperometry using the device and the eMTP was subsequently applied to the screening of cytochrome P450 monooxygenase mutants and reaction conditions for electroenzymatic synthesis.⁵⁶ A more advanced system, designed specifically for electrosynthetic screening, has been developed by Waldvogel and coworkers. This consists of eight Teflon cells housed in a steel block for temperature control during electrolysis.⁵⁷ In this “Screening System”, the cells are designed for facile changing of electrodes between reactions and can accommodate up to 6 mL of reaction mixture. The setup

is typically controlled with an 8-channel DC power source allowing galvanostatic control of each cell independently. Alternatively, it can be run potentiostatically using an 8-channel potentiostat. This system can also accommodate six divided cells, making it a singular example of high-throughput screening capability for divided electrolysis. This system has been used to develop methodologies including oxidative cross-coupling of electron-rich aromatics,⁵⁸ reductive dehalogenation,⁵⁹ and deoxygenation,⁶⁰ as well as the electrochemical dehydration of aldoximes to nitriles.⁶¹ The most recent development in batch high-throughput electrosynthesis has been reported as a preprint by the group of Lin in collaboration with Merck. The authors present a 24-well, plate-based system (called HTe-Chem) constructed from a commercially-available, high-throughput photochemistry reactor (Figure 4D). This format makes it compatible with automated reagent addition systems and existing high-throughput analytical equipment, further expediting the setup and subsequent analysis of reaction screens. It features widely-available, parallel, cylindrical rod electrodes that are readily interchanged to allow for screening of electrode material. The individual cells have a reaction volume of 200 – 600 μL , the smallest so far in high-throughput organic electrosynthesis, and a notable improvement on existing systems. In addition, the authors propose that the design is theoretically scalable to a 96-well format without major design modifications. The housing block allows for temperature control and is compatible with both magnetic and tumble stirring, while a silicon rubber gasket functions as a septum for each cell,

limiting solvent evaporation and enabling reactions to be conducted under inert conditions. A 6×4 vial arrangement with each row of cells connected in series allows screening of four distinct currents or potentials across the plate. A disadvantage of this setup is that failure of one cell causes the whole row to fail, and so a 'skipper pin' has been developed to bypass individual cells. This also allows for crucial, no-electricity control experiments to be conducted concurrently with electrochemical reactions. The HTe-Chem has been applied to various transformations and showed a 2.2% standard deviation in yield across the plate with no impact from vial position in a proof-of-concept study. Finally, basing the system on a photochemistry reactor allows light to be delivered to the cells, further increasing the scope of the device. One disadvantage is that small-diameter rod electrodes make the use of reticulated electrode materials like RVC and nickel foam challenging. That being said, this newly-disclosed device fulfills the majority of the requirements for the ideal high-throughput electrochemistry system, and commercialization of a reactor of this type would represent a significant step toward accessible, high-throughput reaction development in organic electrosynthesis.⁶²

IKA enabled simplification of electrochemistry

Although organic electrochemistry has been used for many years to improve or develop chemical reactions, the lack of intuitive electrochemical equipment limited the uptake of this useful technique. The development of

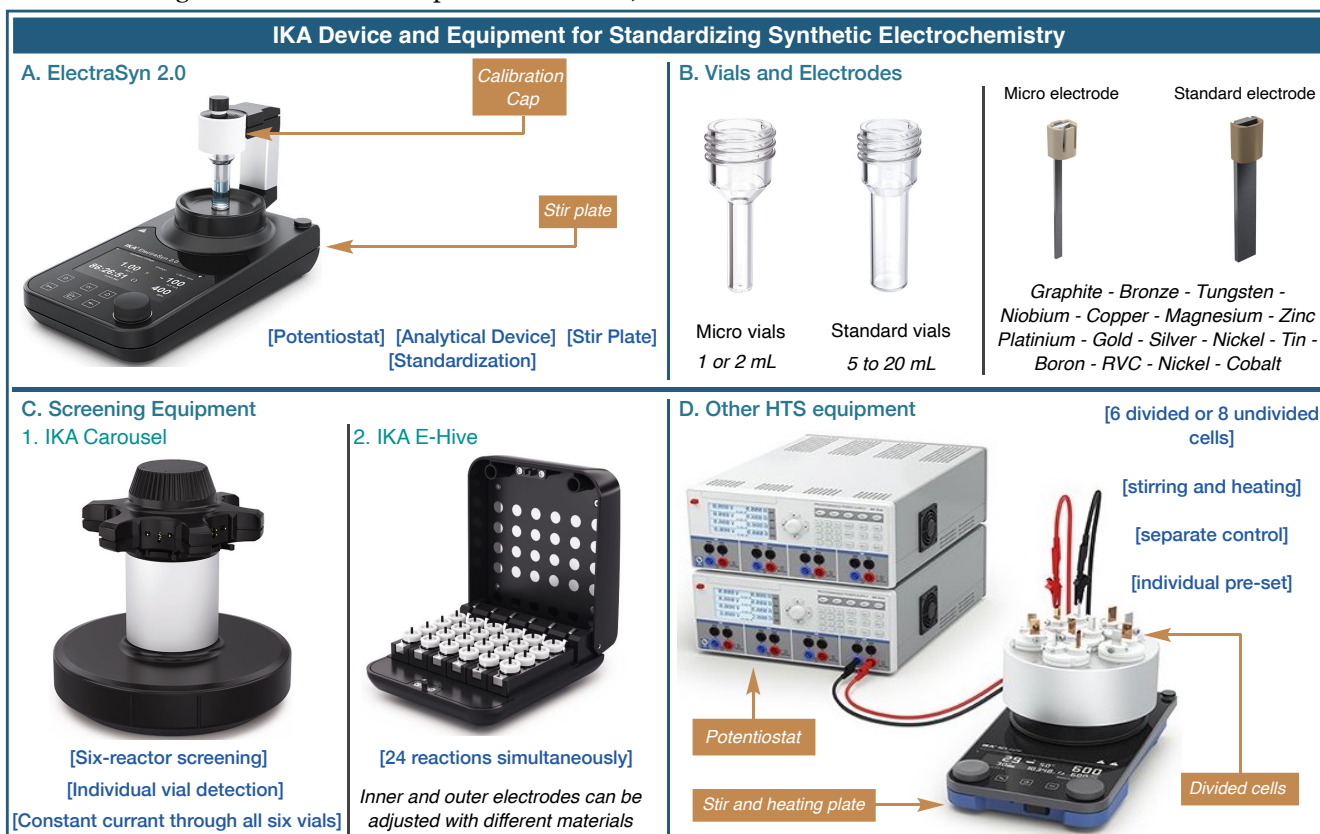


FIGURE 5. IKA equipment for standardizing synthetic electrochemistry.

standardized and user-friendly equipment was needed to create a resurgence of the electrochemical field.⁶³ Therefore in 2018, IKA developed a new electrochemical product in collaboration with Phil Baran: the “ElectraSyn 2.0” (Figure 5A).⁶⁴ ElectraSyn 2.0 combines three devices in one: (1) a stir plate, (2) a potentiostat, and (3) analytical capabilities; avoiding complicated multi-equipment setups (computer, potentiostat, cables, separate stir plate, *etc.*) to simply run electrochemical reactions. In addition, consumables such as vials and electrodes have been standardized to allow the practitioner to reproduce reported reactions without hardship. IKA provides two types of vials: micro and standard (Figure 5B). Micro vials can contain volumes from 1 to 2 mL while standard vials start from 5 up to 20 mL allowing for different scales. In addition, the diversity of electrodes, in both size (micro or standard) and material offers access to a broad range of reactivity. Although ElectraSyn 2.0 represented an important advance for the field of synthetic electrochemistry, the biggest drawback remained that reactions could only be carried out one at a time. To overcome this limitation, IKA developed several screening equipment (Figure 5C) for performing parallel reactions: the “IKA carousel” and the “IKA e-Hive”. The first transforms ElectraSyn 2.0 from a single reactor to the six-reactor Screening System, with individual vial detection and a constant current or voltage through all six vials in series. The second provides a constant-voltage screening platform for a maximum of 24 parallel reactions, but with no individual control. An important feature of this device is that inner and outer electrodes of different materials may be screened. IKA also decided to commercialize the aforementioned electrochemical Screening System which can stir and heat up to eight undivided cells or six divided cells simultaneously and individually (Figure 5D).

Despite IKA’s efforts to render electrochemistry accessible to anyone, much remains to be done especially from a high-throughput experimentation standpoint. Indeed, the IKA Carousel or IKA e-Hive do not provide heating options, which considerably limits their range of reactive chemistry. Additionally, a limitation of the e-Hive is that the cathode surface is twenty times larger than the anode, which necessitates electrode size to be reoptimized for scaleup. Furthermore, only constant voltage can be used. Finally, the device features an opaque case, preventing its use with photochemical apparatus. For parallel synthesis or reaction optimization, the most broadly desirable option seems to be the IKA Screening System: the main constraints being that only a maximum of eight reactions can be performed at once, and that a minimum reaction volume of milliliters is required.

Use of batch high-throughput electrochemistry outside organic synthesis

Outside organic synthesis, the prevailing format for electrochemical high-throughput screening is many electrode, one electrolyte systems, which have been used to screen electrode materials and surface modifications for battery,⁶⁵ fuel cell,⁶⁶ and sensing⁶⁷ applications. One example of screening potentially amenable to organic

electrosynthesis comes from a high-throughput screen of electrolyte additives to improve the performance of Li ion batteries.⁶⁸ In this many electrode, many electrolyte method, 96-well microplates were used with a liquid-handling dispenser and a 96-channel electrochemical analyser to screen samples containing combinations of Li salts. Battery components (anode, cathode, and separator) were placed in each well along with 100 μ L of electrolyte to create a plate where 96 individual cells could then be analysed by intermittent pulse amperometry. The use of a robotic arm to fully automate the process gave a throughput of 400 samples/day and allowed the authors to rapidly identify the optimum combination of Li salts with a high degree of accuracy. The miniaturization and automation demonstrated by this method has enabled a throughput exceeding that achieved using existing many electrode, many electrolyte systems in organic electrochemistry. However, adaptation from an electrochemical analyser to a device capable of preparative electrolysis in each well could be a challenge and a barrier to adoption for reaction development. Furthermore, while the robotic arm greatly increases throughput, the associated cost and large footprint could be prohibitive in some settings.

Screen printed multielectrode sensor arrays are another technology that has enabled high-throughput electrochemical screening outside organic synthesis. These arrays were first designed to detect nucleic acids in multiple samples after polymerase chain reaction amplification,⁶⁹ and have since been applied to the detection of other biomolecules.⁷⁰ The arrays generally consist of 96-well plates containing two carbon electrodes that have been screen printed onto a printed circuit board. In addition to biomolecule detection, screen printed multielectrode arrays have been adapted for the high-throughput screening of enzyme libraries generated from directed evolution.^{71,72} In these systems, the electrodes in each well are covered with 35–200 μ L of electrolyte, and the enzymatic activity determined using intermittent pulse amperometry. This many electrode, many electrolytes approach has been used to select enzymes for biofuel cells⁷¹ and synthetic biology,⁷² as well as the screening of enzyme inhibitors.⁷³ Screen printed multielectrode arrays have also been developed in a three-electrode format to allow more precise control over electrode potential.⁷⁴ These techniques also have the advantage of enabling electrochemistry to be conducted on a smaller scale and with higher throughput than current electrosynthetic methods. Their application to organic synthesis would require consideration of the power source used to control the array as well as the possible requirement for the anode and cathode to be collocated at the bottom of the well, something that would not be consistent with the parallel electrode setup used in preparative electrolysis. Screen printed electrodes are used extensively for sensing applications including pharmaceutical and biological assays,⁷⁵ however their use in organic electrosynthesis is limited. The few available examples involve the use of interdigitated platinum electrodes, screen printed on alumina and applied to the mediated oxidation of feedstock chemicals.⁷⁶ Screen

printed electrodes have a relatively small surface area. While this is advantageous for sensing applications where microliter quantities of analyte may be required, it is a limitation for preparative electrolysis during organic synthesis. Secondly, screen printed electrodes are generally less robust than electrodes made of a bulk material, requiring frequent replacement. Interestingly, these qualities support their use in high-throughput screening of organic electrochemical reactions where both microliter reaction scale and single-use electrodes are desirable. Developments in the field have also led to the commercial availability of screen-printed electrode materials commonly used for organic synthesis, including platinum, carbon, boron-doped diamond, and nickel,⁷⁷ and those resistant to organic solvents.⁷⁸

SUMMARY AND OUTLOOK

The parameter space of electrochemical reactions includes not only classical reaction optimization variables such as solvent, reagents, and reagent loadings, but also specialized factors such as electrode material and current density. Careful consideration and exploration of these is particularly important for scaleup of electrochemical processes. High-throughput experimentation is a valuable, enabling capability for the rapid generation of data to optimize and ensure robustness of reactions within this complex parameter space. Presently, features such as disposable electrodes, independent electrical control of individual cells, and microliter-scale flow experiments are possible. The HTE-Chem system recently developed by the Lin group, featuring readily-interchanged electrodes and low reactor volumes in a familiar format suitable for automated reagent dispensing is a particularly welcome advance that forges an accessible path for high-throughput organic electrochemistry. Alternative modalities such as flow electrochemistry combined with automated liquid handling techniques provide yet further opportunities for rapid screening of both chemical and electrochemical parameters down to microliter scale, with significant recent advances having been reported in this area. The possibility of disposable, screen printed electrodes for organic electrochemistry has not been well-explored but presents another intriguing possibility for the future. High-throughput electrochemistry could allow inherently-scalable optimization of electrochemical processes, enabling trust in electrochemistry from discovery stage chemistry onward, while simultaneously facilitating rapid development of new reactions and access to new areas of chemical space. We believe that these encouraging technological developments herald a future of reduced barriers to electrochemistry at all stages within the pharmaceutical and agrochemical industries.

AUTHOR INFORMATION

Corresponding Authors

*julien.vantourout@univ-lyon1.fr

*nessa.carson@syngenta.com

*darren.l.poole@gsk.com

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ORCID

Claudio Battilocchio: 0000-0002-4601-8527

Nessa Carson: 0000-0002-2769-1775

Sylvain Charvet: 0000-0003-1612-9338

Darren L. Poole: 0000-0001-5050-5996

Christopher C. Scarborough: 0000-0001-7714-1643

Julien C. Vantourout: 0000-0002-0602-069X

Katherine M. P. Wheelhouse: 0000-0002-1963-1465

NOTES

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support for this work was provided by the CNRS, French Ministry of Research and the University of Lyon I. A. G. W. thanks the GlaxoSmithKline/University of Strathclyde Collaborative PhD program and the EPSRC for funding via Prosperity Partnership EP/S035990/1. S. C. thanks the ICBMS for a Master fellowship.

REFERENCES

- a) Mennen, S. M.; Alhambra, C.; Allen, C. L.; Barberis, M.; Berritt, S.; Brandt, T. A.; Campbell, A. D.; Castañón, J.; Cherney, A. H.; Christensen, M.; Damon, D. B.; de Diego, J. E.; García-Cerrada, S.; García-Losada, P.; Haro, R.; Janey, J.; Leitch, D. C.; Li, L.; Liu, F.; Lobben, P. C.; MacMillan, D. W. C.; Magano, J.; McInturff, E.; Monfette, S.; Post, R. J.; Schultz, D.; Sitter, B. J.; Stevens, J. M.; Strambeanu, I. I.; Twilton, J.; Wang, K.; Zajac, M. A. The Evolution of High-Throughput Experimentation in Pharmaceutical Development and Perspectives on the Future. *Org. Process Res. Dev.* **2019**, *23*, 1213–1242. b) Carson, N. Rise of the Robots. *Chem. Eur. J.* **2020**, *26*, 3194–3196. c) Shevlin, M. Practical High-Throughput Experimentation for Chemists. *ACS Med. Chem. Lett.* **2017**, *8*, 601–607. d) de Vries, J. G.; de Vries, A. H. M. The Power of High-Throughput Experimentation in Homogeneous Catalysis Research for Fine Chemicals. *Eur. J. Org. Chem.* **2003**, 799–811. e) Welch, C. J. High throughput analysis enables high throughput experimentation in pharmaceutical process research. *React. Chem. Eng.* **2019**, *4*, 1895–1911.
- a) Pan, J. Y. Engineering Chemistry Innovation. *ACS Med. Chem. Lett.* **2019**, *10*, 703–707. b) Allen, C. L.; Leitch, D. C.; Anson, M. S.; Zajac, M. A. The power and accessibility of high-throughput methods for catalysis research. *Nature Catal.* **2019**, *2*, 2–4.
- a) Pitzer, L.; Schäfers, F.; Glorius, F. Rapid Assessment of the Reaction-Condition-Based Sensitivity of Chemical Transformations. *Angew. Chem. Int. Ed.* **2019**, *58*, 8572–8576. b) Perera, D.; Tucker, J. W.; Brahmabhatt, S.; Helal, C. J.; Chong, A.; Farrell, W.; Richardson, P.; Sach, N. W. A platform for automated nanomole-scale reaction screening and micromole-scale synthesis in flow. *Science* **2018**, *359*, 429–434.
- a) Richardson, J.; Ruble, J. C.; Love, E. A.; Berritt, S. A Method for Identifying and Developing Functional Group Tolerant Catalytic Reactions: Application to the Buchwald-Hartwig Amination. *J. Org. Chem.* **2017**, *82*, 3741–3750. b) Collins, K. D.; Glorius, F. A robustness screen for the rapid assessment of chemical reactions. *Nature Chem.* **2013**, *5*, 597–601.

- (5) a) Selekman, J. A.; Tran, K.; Xu, Z.; Dummeldinger, M.; Kiau, S.; Nolfo, J.; Janey, J. High-Throughput Extractions: a New Paradigm for Workup Optimization in Pharmaceutical Process Development. *Org. Process Res. Dev.* **2016**, *20*, 1728–1737. b) Dzakovich, M. P.; Hartman J. L.; Cooperstone, J. L. A High-Throughput Extraction and Analysis Method for Steroidal Glycoalkaloids in Tomato. *Plant Sci.* **2020**, *11*, 767.
- (6) a) Qiu, J.; Stevens, J. M. High-Throughput Classical Chiral Resolution Screening of Synthetic Intermediates: Effects of Resolving Agents, Crystallization Solvents, and Other Factors. *Org. Process Res. Dev.* **2020**, *24*, 1725–1734. b) Alvarez, A. J.; Singh, A.; Myerson, A. S. Polymorph Screening: Comparing a Semi-Automated Approach with a High Throughput Method. *Cryst. Growth Des.* **2009**, *9*, 4181–4188. c) Alsenz, J.; Kansy, M. High throughput solubility measurement in drug discovery and development. *Adv. Drug Deliv. Rev.* **2007**, *59*, 546–567.
- (7) a) Bonfield, H. E.; Mercer, K.; Diaz-Rodriguez, A.; Cook, G. C.; McKay, B. S. J.; Slade, P.; Taylor, G. M.; Ooi, W. X.; Williams, J. D.; Roberts, J. P. M.; Murphy, J. A.; Schmermund, L.; Kroutil, W.; Mielke, T.; Cartwright, J.; Grogan, G.; Edwards, L. J. The Right Light: *De Novo* Design of a Robust Modular Photochemical Reactor for Optimum Batch and Flow Chemistry. *ChemPhotoChem* **2020**, *4*, 45–51. b) Bissonnette, N. B.; Ryu, K. A.; Reyes-Robles, T.; Wilhelm, S.; Tomlinson, J. H.; Crotty, K. A.; Hett, E. C.; Roberts, L. R.; Hazuda, D. J.; Willis, M. J.; Oslund, R. C.; Fadeyi, O. O. Design of a Multiuse Photoreactor To Enable Visible-Light Photocatalytic Chemical Transformations and Labeling in Live Cells. *ChemBioChem* **2020**, *21*, 3555–3562. c) Sun, A. C.; Steyer, D. J.; Allen, A. R.; Payne, E. M.; Kennedy, R. T.; Stephenson, C. R. J. A droplet microfluidic platform for high-throughput photochemical reaction discovery. *Nature Commun.* **2020**, *11*, 6202. d) Pimparkar, K.; Yen, B.; Goodell, J. R.; Martin, V. I.; Lee, W.-H.; Porco, Jr., J. A.; Beeler, A. B.; Jensen, K. F. Development of a Photochemical Microfluidics Platform. *J. Flow Chem.* **2011**, *1*, 53–55.
- (8) a) Grainger, R.; Heightman, T. D.; Ley, S. V.; Lima, F.; Johnson, C. N. Enabling synthesis in fragment-based drug discovery by reactivity mapping: photoredox-mediated cross-dehydrogenative heteroarylation of cyclic amines. *Chem. Sci.* **2019**, *10*, 2264–2271. b) Grainger, R.; Whibley, S. A Perspective on the Analytical Challenges Encountered in High-Throughput Experimentation. *Org. Process Res. Dev.* **2021**, *25*, 354–364. c) Sezen-Edmonds, M.; Tabora, J. E.; Cohen, B. M.; Zaretsky, S.; Simmons, E. M.; Sherwood, T. C.; Ramirez, A. Predicting Performance of Photochemical Transformations for Scaling Up in Different Platforms by Combining High-Throughput Experimentation with Computational Modeling. *Org. Process Res. Dev.* **2020**, *24*, 2128–2138.
- (9) a) de la Mora, J. F.; VanBerkel, G. J.; Enke, C. G.; Cole, R. B.; Martinez-Sanchez, M.; Fenn, J. B. Electrochemical processes in electrospray ionization mass spectrometry. *J. Mass Spectrom.* **2000**, *35*, 939–952. b) Blades, A. T.; Ikonomou, M. G.; Kebarle, P. Mechanism of electrospray mass spectrometry. Electrospray as an electrolysis cell. *Anal. Chem.* **1991**, *63*, 2109–2114. c) VanBerkel, G. J.; Quirke, J. M. E.; Tigani, R. A.; Dilley, A. S.; Covey, T. R. Derivatization for electrospray ionization mass spectrometry. 3. Electrochemically ionizable derivatives. *Anal. Chem.* **1998**, *70*, 1544–1554. d) Tang, S.; Chen, H.; Yan, X. On-Demand Electrochemical Epoxidation in Nano-Electrospray Ionization Mass Spectrometry to Locate Carbon-Carbon Double Bonds. *Angew. Chem. Int. Ed.* **2020**, *59*, 209–214.
- (10) The graphic describe in Figure 1A was created with CAS SciFinder using the key word “synthetic electrochemical”.
- (11) For a selection of reviews: a) Kärkäs, M. D. Electrochemical strategies for C-H functionalization and C-N bond formation. *Chem. Soc. Rev.* **2018**, *47*, 5786–5865. b) Moeller, K. D. Using Physical Organic Chemistry to Shape the Course of Electrochemical Reactions. *Chem. Rev.* **2018**, *118*, 4817–4833. c) Horn, E. J.; Rosen, B. R.; Baran, P. S. *ACS Cent. Sci.* **2016**, *2*, 302–308. d) Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S. R. Electrifying Organic Synthesis. *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619. e) Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angew. Chem., Int. Ed.* **2018**, *57*, 6018–6041. f) Meyer, T. H.; Choi, I.; Tian, C.; Ackermann, L. Powering the Future: How Can Electrochemistry Make a Difference in Organic Synthesis? *Chem* **2020**, *6*, 2484–2496.
- (12) Kingston, C.; Palkowitz, M. D.; Takahira, Y.; Vantourout, J. C.; Peters, B. K.; Kawamata, Y.; Baran P. S. A Survival Guide for the “Electro-curious”. *Acc. Chem. Res.* **2020**, *53*, 72–83.
- (13) Peters, B. K.; Rodriguez, K. X.; Reisberg, S. H.; Beil, S. B.; Hickey, D. P.; Kawamata, Y.; Collins, M.; Starr, J.; Chen, L.; Udyavara, S.; Klunder, K.; Gorey, T. J.; Anderson, S. L.; Neurock, M.; Minter, S. D.; Baran, P. S. Scalable and safe synthetic organic electroreduction inspired by Li-ion battery chemistry. *Science* **2019**, *363*, 838–845.
- (14) Perkins, R. J.; Pedro, D. J.; Hansen, E. C. Electrochemical Nickel Catalysis for sp^2 – sp^3 Cross-Electrophile Coupling Reactions of Unactivated Alkyl Halides. *Org. Lett.* **2017**, *19*, 3755–3758.
- (15) Okamoto, K.; Chiba, K. Electrochemical Total Synthesis of Pyrrolophenanthridone Alkaloids: Controlling the Anodically Initiated Electron Transfer Process. *Org. Lett.* **2020**, *22*, 3613–3617.
- (16) Hu, P.; Peters, B. K.; Malapit, C. A.; Vantourout, J. C.; Wang, P.; Li, J.; Mele, L.; Echeverria, P.-G.; Minter, S. D.; Baran, P. S. Electroreductive Olefin–Ketone Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 20979–20986.
- (17) Laudadio, G.; Bartolomeu, A. de A.; Verwijlen, L. M. H. M.; Cao, Y.; de Oliveira, K. T.; Noël, T. Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride. *J. Am. Chem. Soc.* **2019**, *141*, 11832–11836.
- (18) Dong, X.; Roeckl, J. S. L.; Waldvogel, S. R.; Morandi, B. Merging shuttle reactions and paired electrolysis for reversible vicinal dihalogenations. *Science* **2021**, *371*, 507–514.
- (19) a) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaksh, A.; Zhang, T. Y. Key Green Chemistry Research Areas—a Perspective from Pharmaceutical Manufacturers. *Green Chem.* **2007**, *9*, 411–420. b) Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Weiberth, F. J. Key Green Chemistry Research Areas from a Pharmaceutical Manufacturers’ Perspective Revisited. *Green Chem.* **2018**, *20*, 5082–5103.
- (20) Matthews, M. A. Green Electrochemistry. Examples and Challenges. *Pure Appl. Chem.* **2001**, *73*, 1305–1308.
- (21) Horn, E. J.; Rosen, B. R.; Baran, P. S. Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method. *ACS Cent. Sci.* **2016**, *2*, 302–308.
- (22) Rafiee, M.; Konz, Z. M.; Graaf, M. D.; Koelman, H. F.; Stahl, S. S. Electrochemical Oxidation of Alcohols and Aldehydes to Carboxylic Acids Catalyzed by 4-Acetamido-TEMPO: An

- Alternative to “Anelli” and “Pinnick” Oxidations. *ACS Catal.* **2018**, *8*, 6738–6844.
- (23) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008**, *108*, 2265–2299.
- (24) a) Steckhan, E.; Arns, T.; Heineman, W. R.; Hilt, G.; Hoormann, D.; Jörisen, J.; Kröner, L.; Lewall, B.; Pütter, T. Environmental Protection and Economization of Resources by Electroorganic and Electroenzymatic Syntheses. *Chemosphere* **2001**, *43*, 63–73. b) Degner, D. Organic Electrosyntheses in Industry. In *Electrochemistry III*; Topics in Current Chemistry; Springer, 1988; Vol. 148, pp 1–95.
- (25) Zhang, W.; Lin, S. Electroreductive Carbofunctionalization of Alkenes with Alkyl Bromides via a Radical-Polar Crossover Mechanism. *J. Am. Chem. Soc.* **2020**, *142*, 20661–20670.
- (26) Noël, T.; Cao, Y.; Laudadio, G. The Fundamentals Behind the Use of Flow Reactors in Electrochemistry. *Acc. Chem. Res.* **2019**, *52*, 2858–2869.
- (27) a) Gütz, G.; Stenglein, A.; Waldvogel, S. R. Highly Modular Flow Cell for Electroorganic Synthesis. *Org. Process Res. Dev.* **2017**, *21*, 771–778. b) Folgueras-Amador, A.; Philipps, K.; Guilbaud, S.; Poelakker, J.; Wirth, T. An Easy-to-Machine Electrochemical Flow Microreactor: Efficient Synthesis of Isoindolinone and Flow Functionalization. *Angew. Chem. Int. Ed.* **2017**, *56*, 15446–15450. c) Maljuric, S.; Jud, W.; Kappe, C. O.; Cantillo, D. Translating Batch Electrochemistry to Single-Pass Continuous Flow Conditions: an Organic Chemist's Guide. *J. Flow Chem.* **2020**, *10*, 181–190.
- (28) Tanbouza, N.; Ollevier, T.; Lam, K. Bridging Lab and Industry with Flow Electrochemistry. *iScience*, **2020**, *23*, 101720.
- (29) a) Pletcher, D.; Green, R. A.; Brown, R. C. D. Flow Electrolysis Cells for the Synthetic Organic Chemistry Laboratory. *Chem. Rev.* **2018**, *118*, 4573–4591. b) Perry S. C.; Ponce de León, C.; Walsh, F. C. Review—The Design, Performance and Continuing Development of Electrochemical Reactors for Clean Electrosynthesis. *J. Electrochem. Soc.* **2020**, *167*, 15525. c) Atobe, M.; Tateno, H.; Matsumura, Y. Applications of Flow Microreactors in Electrosynthetic Processes. *Chem. Rev.* **2018**, *118*, 4541–4572. d) Elsherbini, M.; Wirth, T. Electroorganic Synthesis under Flow Conditions *Acc. Chem. Res.* **2019**, *52*, 3287–3296.
- (30) a) The Ammonite Family of Electrolysis Cells <https://www.cambridgereactordesign.com/ammonite/ammonite.html> (accessed Mar 30, 2021). b) Asia FLUX Electrochemistry Module <https://www.syriss.com/modules/asia-flux-electrochemistry-module/> (accessed Mar 30, 2021). c) ElectraSyn Flow <https://www.ikaprocess.com/en/Products/Electro-Organic-Synthesis-Systems-cph-45/ElectraSyn-flow-csb-ES/> (accessed Mar 30, 2021). d) Ion electrochemical reactor – features <https://www.vapourtec.com/products/flow-reactors/ion-electrochemical-reactor-features/> (accessed Mar 30, 2021).
- (31) Maljuric, S.; Jud, W.; Kappe, C. O.; Cantillo, D. Translating Batch Electrochemistry to Single-Pass Continuous Flow Conditions: An Organic Chemist's Guide. *J. Flow Chem.* **2020**, *10*, 181–190.
- (32) Schotten, C.; P. Nicholls, T.; A. Bourne, R.; Kapur, N.; N. Nguyen, B.; E. Willans, C. Making Electrochemistry Easily Accessible to the Synthetic Chemist. *Green Chem.* **2020**, *22*, 3358–3375.
- (33) Pletcher, D.; Green, R. A.; Brown, R. C. D. Flow Electrolysis Cells for the Synthetic Organic Chemistry Laboratory. *Chem. Rev.* **2018**, *118*, 4573–4591.
- (34) Gütz, C.; Stenglein, A.; Waldvogel, S. R. Highly Modular Flow Cell for Electroorganic Synthesis. *Org. Process Res. Dev.* **2017**, *21*, 771–778.
- (35) For a selection of original manuscripts and reviews: a) Ley, S. V.; Chen, Y.; Robinson, A.; Otter, B.; Godineau, E.; Battilocchio, C. A Comment on Continuous Flow Technologies within the Agrochemical Industry. *Org. Process Res. Dev.* **2021**, *25*, 713–720. b) Fitzpatrick, D. E.; Maujean, T.; Evans, A. C.; Ley, S. V. Across-the-World Automated Optimization and Continuous-Flow Synthesis of Pharmaceutical Agents Operating Through a Cloud-Based Server. *Angew. Chem. Int. Ed.* **2018**, *57*, 15128–15132. c) Fitzpatrick, D. E.; Battilocchio, C.; Ley, S. V. Enabling Technologies for the Future of Chemical Synthesis. *ACS Cent. Sci.* **2016**, *2*, 131–138. d) Ingham, R. J.; Battilocchio, C.; Fitzpatrick, D. E.; Sliwinski, E.; Hawkins, J. M.; Ley, S. V. A Systems Approach towards an Intelligent and Self-Controlling Platform for Integrated Continuous Reaction Sequences. *Angew. Chem. Int. Ed.* **2015**, *54*, 144–148. e) Ley, S. V.; Ingham, R. J.; O'Brien, M.; Browne, D. L. Camera-enabled techniques for organic synthesis. *Beilstein J. Org. Chem.* **2013**, *9*, 1051–1072. f) Lange, H.; Carter, C. F.; Hopkin, M. D.; Burke, A.; Goode, J. G.; Baxendale, I. R.; Ley, S. V. A breakthrough method for the accurate addition of reagents in multi-step segmented flow processing. *Chem. Sci.* **2011**, *2*, 765–769. g) Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. Multistep synthesis using modular flow reactors: Bestmann–Ohira reagent for the formation of alkynes and triazoles. *Angew. Chem. Int. Ed.* **2009**, *48*, 4017–4021. h) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. Fully Automated Continuous Flow Synthesis of 4,5-Disubstituted Oxazoles. *Org. Lett.* **2006**, *8*, 5231–5234.
- (36) Kabeshov, M. A.; Musio, B.; Murray, P. R. D.; Browne, D. L.; Ley, S. V. Expedient Preparation of Nazlinine and a Small Library of Indole Alkaloids Using Flow Electrochemistry as an Enabling Technology. *Org. Lett.* **2014**, *16*, 4618–4621.
- (37) Green, R. A.; Jolley, K. E.; Al-Hadedi, A. A. M.; Pletcher, D.; Harrowven, D. C.; De Frutos, O.; Mateos, C.; Klauber, D. J.; Rincón, J. A.; Brown, R. C. D. Electrochemical Deprotection of *Para*-Methoxybenzyl Ethers in a Flow Electrolysis Cell. *Org. Lett.* **2017**, *19*, 2050–2053.
- (38) van Melis, C. G. W.; Penny, M. R.; Garcia, A. D.; Petti, A.; Dobbs, A. P.; Hilton, S. T.; Lam, K. Supporting-Electrolyte-Free Electrochemical Methoxymethylation of Alcohols Using a 3D-Printed Electrosynthesis Continuous Flow Cell System. *ChemElectroChem* **2019**, *6*, 4144–4148.
- (39) Luo, X.; Ma, X.; Lebreux, F.; Markó, I. E.; Lam, K. Electrochemical methoxymethylation of alcohols – a new, green and safe approach for the preparation of MOM ethers and other acetals. *Chem. Commun.* **2018**, *54*, 9969–9972.
- (40) Becker, R.; Weber, K.; Pfeiffer, T. V.; van Kranendonk, J.; Schouten, K. J. A Scalable High-Throughput Deposition and Screening Setup Relevant to Industrial Electrocatalysis. *Catalysts* **2020**, *10*, 1165.
- (41) Lehmann, M.; Scarborough, C. C.; Godineau, E.; Battilocchio, C. An Electrochemical Flow-Through Cell for Rapid Reactions. *Ind. Eng. Chem. Res.* **2020**, *59*, 7321–7326.
- (42) Mo, Y.; Rughoobur, G.; Nambiar, A. M. K.; Zhang, K.; Jensen, K. F. A Multifunctional Microfluidic Platform for High-Throughput Experimentation of Electroorganic Chemistry. *Angew. Chem. Int. Ed.* **2020**, *59*, 20890–20894.

- (43) Reddington, E. Combinatorial Electrochemistry: A Highly Parallel, Optical Screening Method for Discovery of Better Electrocatalysts. *Science* **1998**, *280*, 1735–1737.
- (44) Sullivan, M. G.; Utomo, H.; Fagan, P. J.; Ward, M. D. Automated Electrochemical Analysis with Combinatorial Electrode Arrays. *Anal. Chem.* **1999**, *71*, 4369–4375.
- (45) Kulikov, V.; Mirsky, V. M. Equipment for Combinatorial Electrochemical Polymerization and High-Throughput Investigation of Electrical Properties of the Synthesized Polymers. *Meas. Sci. Technol.* **2004**, *15*, 49–54.
- (46) Richter, T. V.; Bühler, C.; Ludwigs, S. Water- and Ionic-Liquid-Soluble Branched Polythiophenes Bearing Anionic and Cationic Moieties. *J. Am. Chem. Soc.* **2012**, *134*, 43–46.
- (47) Tesfu, E.; Maurer, K.; Ragsdale, S. R.; Moeller, K. D. Building Addressable Libraries: The Use of Electrochemistry for Generating Reactive Pd(II) Reagents at Preselected Sites on a Chip. *J. Am. Chem. Soc.* **2004**, *126* (20), 6212–6213.
- (48) Hu, L.; Maurer, K.; Moeller, K. D. Building Addressable Libraries: Site-Selective Suzuki Reactions on Microelectrode Arrays. *Org. Lett.* **2009**, *11* (6), 1273–1276.
- (49) Tesfu, E.; Maurer, K.; Moeller, K. D. Building Addressable Libraries: Spatially Isolated, Chip-Based Reductive Amination Reactions. *J. Am. Chem. Soc.* **2006**, *128* (1), 70–71.
- (50) Briehn, C. A.; Schiedel, M.-S.; Bonsen, E. M.; Schuhmann, W.; Bäuerle, P. Single-Compound Libraries of Organic Materials: From the Combinatorial Synthesis of Conjugated Oligomers to Structure-Property Relationships. *Angew. Chem. Int. Ed.* **2001**, *40*, 4680–4683.
- (51) Lindner, E.; Lu, Z.-L.; Mayer, H. A.; Speiser, B.; Tittel, C.; Warad, I. Combinatorial Micro Electrochemistry. Part 4: Cyclic Voltammetric Redox Screening of Homogeneous Ruthenium(II) Hydrogenation Catalysts. *Electrochem. Commun.* **2005**, *7*, 1013–1020.
- (52) a) Märkle, W.; Speiser, B.; Tittel, C.; Vollmer, M. Combinatorial Micro Electrochemistry. *Electrochim. Acta* **2005**, *50*, 2753–2762. b) Schwarz, M.; Speiser, B. Combinatorial Micro-Electrochemistry. Part 5. Electrosynthesis Screening of the Electroreductive Coupling of α,β -Unsaturated Esters and Allyl Bromides in a Room Temperature Ionic Liquid. *Electrochim. Acta* **2009**, *54*, 3735–3744.
- (53) Siu, T.; Li, W.; Yudin, A. K. Parallel Electrosynthesis of α -Alkoxy carbamates, α -Alkoxyamides, and α -Alkoxy sulfonamides Using the Spatially Addressable Electrolysis Platform (SAEP). *J. Comb. Chem.* **2000**, *2*, 545–549.
- (54) Boulou, N.; Walshe, N.; Bradley, M. Polyethers: A Solid-Phase Iterative Approach. *J. Comb. Chem.* **2001**, *3*, 6–8.
- (55) Ley, C.; Zengin Çekiç, S.; Kochius, S.; Mangold, K.-M.; Schwaneberg, U.; Schrader, J.; Holtmann, D. An Electrochemical Microtiter Plate for Parallel Spectroelectrochemical Measurements. *Electrochim. Acta* **2013**, *89*, 98–105.
- (56) Ley, C.; Schewe, H.; Ströhle, F. W.; Ruff, A. J.; Schwaneberg, U.; Schrader, J.; Holtmann, D. Coupling of Electrochemical and Optical Measurements in a Microtiter Plate for the Fast Development of Electro Enzymatic Processes with P450s. *J. Mol. Catal. B Enzym.* **2013**, *92*, 71–78.
- (57) Gütz, C.; Klöckner, B.; Waldvogel, S. R. Electrochemical Screening for Electroorganic Synthesis. *Org. Process Res. Dev.* **2016**, *20*, 26–32.
- (58) a) Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. Metal- and Reagent-Free Highly Selective Anodic Cross-Coupling Reaction of Phenols. *Angew. Chem. Int. Ed.* **2014**, *53*, 5210–5213. b) Elsler, B.; Wiebe, A.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. Source of Selectivity in Oxidative Cross-Coupling of Aryls by Solvent Effect of 1,1,1,3,3,3-Hexafluoropropan-2-ol. *Chem. Eur. J.* **2015**, *21*, 12321–12325. c) Schulz, L.; Enders, M.; Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. Reagent- and Metal-Free Anodic C–C Cross-Coupling of Aniline Derivatives. *Angew. Chem. Int. Ed.* **2017**, *56*, 4877–4881.
- (59) Gütz, C.; Selt, M.; Bänziger, M.; Bucher, C.; Römelt, C.; Hecken, N.; Gallou, F.; Galvão, T. R.; Waldvogel, S. R. A Novel Cathode Material for Cathodic Dehalogenation of 1,1-Dibromo Cyclopropane Derivatives. *Chem. Eur. J.* **2015**, *21*, 13878–13882.
- (60) Edinger, C.; Grimaudo, V.; Broekmann, P.; Waldvogel, S. R. Stabilizing Lead Cathodes with Diammonium Salt Additives in the Deoxygenation of Aromatic Amides. *ChemElectroChem* **2014**, *1*, 1018–1022. b) Edinger, C.; Waldvogel, S. R. Electrochemical Deoxygenation of Aromatic Amides and Sulfoxides: Electrochemical Deoxygenation of Aromatic Amides and Sulfoxides. *Eur. J. Org. Chem.* **2014**, 5144–5148.
- (61) Hartmer, M. F.; Waldvogel, S. R. Electroorganic Synthesis of Nitriles via a Halogen-Free Domino Oxidation–Reduction Sequence. *Chem. Commun.* **2015**, *51*, 16346–16348.
- (62) Rein, J.; Annand, J. R.; Wismer, M. K.; Fu, J.; Siu, J. C.; Klapars, A.; Strotman, N. A.; Kalyani, D.; Lehnher, D.; Lin, S. – Unlocking the Potential of High-Throughput Experimentation for Electrochemistry with a Standardized Microscale Reactor (Version 2). **2021**. ChemRxiv e-Print archive. https://chemrxiv.org/articles/preprint/Unlocking_the_Potential_of_High-Throughput_Experimentation_for_Electrochemistry_with_a_Standardized_Microscale_Reactor/14173538 (accessed Apr 19, 2021).
- (63) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemistry: Calling All Engineers. *Angew. Chem., Int. Ed.* **2018**, *57*, 4149–4155.
- (64) IKA Electrochemistry Kit <https://www.ika.com/fr/Produits-Lab-Eq/Kit-d%27electrochimie-csp-516/> (accessed Apr 19, 2021).
- (65) a) Fleischauer, M. D.; Hatchard, T. D.; Rockwell, G. P.; Topple, J. M.; Trussler, S.; Jericho, S. K.; Jericho, M. H.; Dahn, J. R. Design and Testing of a 64-Channel Combinatorial Electrochemical Cell. *J. Electrochem. Soc.* **2003**, *150*, A1465. b) Jiang, R. Combinatorial Electrochemical Cell Array for High Throughput Screening of Micro-Fuel-Cells and Metal/Air Batteries. *Rev. Sci. Instrum.* **2007**, *78*, 072209. c) Roberts, M. R.; Spong, A. D.; Vitins, G.; Owen, J. R. High Throughput Screening of the Effect of Carbon Coating in LiFePO₄ Electrodes. *J. Electrochem. Soc.* **2007**, *154*, A921.
- (66) a) Lin, X.; Zheng, L.; Gao, G.; Chi, Y.; Chen, G. Electrochemiluminescence Imaging-Based High-Throughput Screening Platform for Electrocatalysts Used in Fuel Cells. *Anal. Chem.* **2012**, *84*, 7700–7707. b) Jiang, R.; Chu, D. A Combinatorial Approach toward Electrochemical Analysis. *J. Electroanal. Chem.* **2002**, *527*, 137–142. c) Osmieri, L.; Mauger, S.; Ulsh, M.; Neyerlin, K. C.; Bender, G. Use of a Segmented Cell for the Combinatorial Development of Platinum Group Metal-Free Electrodes for Polymer Electrolyte Fuel Cells. *J. Power Sources* **2020**, *452*, 227829. d) Smotkin, E. S.; Jiang, J.; Nayar, A.; Liu, R. High-Throughput Screening of Fuel Cell Electrocatalysts. *Appl. Surf. Sci.* **2006**, *252*, 2573–2579.
- (67) a) Simon, U.; Sanders, D.; Jockel, J.; Heppel, C.; Brinz, T. Design Strategies for Multielectrode Arrays Applicable for High-Throughput Impedance Spectroscopy on Novel Gas Sensor Materials. *J. Comb. Chem.* **2002**, *4*, 511–515. b)

- Koplin, T.; Siemons, M.; Océn-Valéntin, C.; Sanders, D.; Simon, U. Workflow for High Throughput Screening of Gas Sensing Materials. *Sensors* **2006**, *6*, 298–307. c) Potyrai, R. A.; Mirsky, V. M. Combinatorial and High-Throughput Development of Sensing Materials: The First 10 Years. *Chem. Rev.* **2008**, *108*, 770–813. d) Kosugi, K.; Hasegawa, Y.; Uchida, H. Light-Addressable Amperometric Sensor with Counter and Working Electrodes of the Same Material. *IEEE Trans. Elec. Electron. Eng.* **2021**, *16*, 478–485.
- (68) Matsuda, S.; Nishioka, K.; Nakanishi, S. High-Throughput Combinatorial Screening of Multi-Component Electrolyte Additives to Improve the Performance of Li Metal Secondary Batteries. *Sci. Rep.* **2019**, *9*, 6211.
- (69) Wojciechowski, M.; Sundseth, R.; Moreno, M.; Henkens, R. Multichannel Electrochemical Detection System for Quantitative Monitoring of PCR Amplification. *Clin. Chem.* **1999**, *45*, 1690–1693.
- (70) a) Piermarini, S.; Micheli, L.; Ammida, N. H. S.; Palleschi, G.; Moscone, D. Electrochemical Immunosensor Array Using a 96-Well Screen-Printed Microplate for Aflatoxin B1 Detection. *Biosens. Bioelectron.* **2007**, *22*, 1434–1440. b) Koehne, J. E.; Marsh, M.; Boakye, A.; Douglas, B.; Kim, I. Y.; Chang, S.-Y.; Jang, D.-P.; Bennet, K. E.; Kimble, C.; Andrews, R.; Meyyappan, M.; Lee, K. H. Carbon Nanofiber Electrode Array for Electrochemical Detection of Dopamine Using Fast Scan Cyclic Voltammetry. *Analyst* **2011**, *136*, 1802.
- (71) Abdellaoui, S.; Noiriél, A.; Henkens, R.; Bonaventura, C.; Blum, L. J.; Doumèche, B. A 96-Well Electrochemical Method for the Screening of Enzymatic Activities. *Anal. Chem.* **2013**, *85*, 3690–3697.
- (72) a) Abdellaoui, S.; Bekhouche, M.; Noiriél, A.; Henkens, R.; Bonaventura, C.; Blum, L. J.; Doumèche, B. Rapid Electrochemical Screening of NAD-Dependent Dehydrogenases in a 96-Well Format. *Chem. Commun.* **2013**, *49*, 5781. b) Aymard, C.; Bonaventura, C.; Henkens, R.; Mousty, C.; Hecquet, L.; Charmantray, F.; Blum, L. J.; Doumèche, B. High-Throughput Electrochemical Screening Assay for Free and Immobilized Oxidases: Electrochemiluminescence and Intermittent Pulse Amperometry. *ChemElectroChem* **2017**, *4*, 957–966.
- (73) Aymard, C. M. G.; Halma, M.; Comte, A.; Mousty, C.; Prévot, V.; Hecquet, L.; Charmantray, F.; Blum, L. J.; Doumèche, B. Innovative Electrochemical Screening Allows Transketolase Inhibitors to Be Identified. *Anal. Chem.* **2018**, *90*, 9241–9248.
- (74) a) Fantuzzi, A.; Mak, L. H.; Capria, E.; Dodhia, V.; Panico, P.; Collins, S.; Gilardi, G. A New Standardized Electrochemical Array for Drug Metabolic Profiling with Human Cytochromes P450. *Anal. Chem.* **2011**, *83*, 3831–3839. b) Mu, S.; Wang, X.; Li, Y.-T.; Wang, Y.; Li, D.-W.; Long, Y.-T. A Novel Screen-Printed Electrode Array for Rapid High-Throughput Detection. *Analyst* **2012**, *137*, 3220. c) Erlenkötter, A.; Kottbus, M.; Chemnitz, G.-C. Flexible Amperometric Transducers for Biosensors Based on a Screen Printed Three Electrode System. *J. Electroanal. Chem.* **2000**, *481*, 82–94.
- (75) a) Ozcelikay, G.; Karadurmus, L.; Kaya, S. I.; Bakirhan, N. K.; Ozkan, S. A. A Review: New Trends in Electrode Systems for Sensitive Drug and Biomolecule Analysis. *Crit. Rev. Anal. Chem.* **2020**, *50*, 212–225. b) Taleat, Z.; Khoshroo, A.; Mazloun-Ardakani, M. Screen-Printed Electrodes for Biosensing: A Review (2008–2013). *Microchim. Acta* **2014**, *181*, 865–891. c) Beitollahi, H.; Mohammadi, S. Z.; Safaei, M.; Tajik, S. Applications of Electrochemical Sensors and Biosensors Based on Modified Screen-Printed Electrodes: A Review. *Anal. Methods* **2020**, *12*, 1547–1560.
- (76) a) Belmont, C.; Girault, H. H. Coplanar Interdigitated Band Electrodes for Electrosynthesis: Part II: Methoxylation of Furan. *J. Appl. Electrochem.* **1994**, *24*, 719–724. b) Shi, Z.; Wu, S.; Lipkowski, J. Coadsorption of Metal Atoms and Anions: Cu upd in the Presence of SO_4^{2-} , Cl^- and Br^- . *Electrochim. Acta* **1995**, *40*, 9–15. c) Mengaud, V.; Bagel, O.; Ferrigno, R.; Girault, H. H.; Haider, A. A Ceramic Electrochemical Microreactor for the Methoxylation of Methyl-2-Furoate with Direct Mass Spectrometry Coupling. *Lab Chip* **2002**, *2*, 39.
- (77) Metrohm AG: Swiss-quality products for chemical analysis <https://www.metrohm.com/en-us/> (accessed Mar 27, 2021).
- (78) Zimmer and Peacock screen printed electrodes resistant to organic solvents <http://www.zimmerpeacocktech.com/knowledge-base/faq/spe-resistant-to-organic-solvents/> (accessed Mar 27, 2021).

Table of Contents

