ACS ORGANIC & INORGANIC Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Perspective

The Future of Electro-organic Synthesis in Drug Discovery and Early Development

Published as part of ACS Organic & Inorganic Au special issue "Electrochemical Explorations in Organic and Inorganic Chemistry".

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Cite This: ACS Org. Inorg. Au 2024, 4, 571−578
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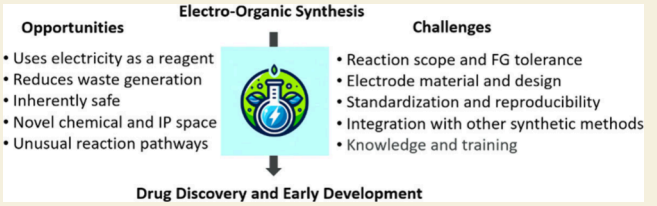
ABSTRACT: Electro-organic chemistry presents a promising frontier in drug discovery and early development, facilitating novel reactivity aligned with green chemistry principles. Despite this, electrochemistry is not widely used as a synthesis and manufacturing tool in drug discovery or development. This overview seeks to identify key areas that require additional research to make synthetic electrochemistry more accessible to chemists in drug discovery and early development and provide potential solutions. This includes expanding the reaction scope, simplifying rapid scale-up, developing electrode materials, and improving knowledge transfer to aid reproducibility and increase the awareness of electrochemistry. The integration of electro-organic synthesis into drug discovery and development holds the potential to enable efficient, sustainable routes toward future medicines faster than ever.



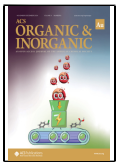
KEYWORDS: *electro-organic synthesis, electrochemistry, drug discovery, sustainability, perspective, medicinal chemistry, drug development*

The formation and breaking of chemical bonds necessitates the transfer of electrons. While traditional organic chemistry relies on chemical reagents for this purpose, electro-organic chemistry aims to employ electricity to facilitate oxidations and reductions. Through this approach, electro-organic chemistry combines organic chemistry principles with electrochemical methods to promote and regulate organic reactions. The main advantage of electro-organic synthesis lies in its ability to complement traditional chemical approaches, offering more selective and milder routes toward reactive intermediates that are often difficult to obtain using conventional reagents. This approach enables the discovery of novel transformations and chemotypes, thereby optimizing the synthetic routes of complex molecules, conserving time and materials.[1−4]

The ability to access novel and often unusual reactivity makes electrochemistry an exciting proposition for discovery and also process chemists within the pharmaceutical sector.[5−7] Furthermore, electro-organic chemistry holds promise in significantly reducing waste generation by circumventing the necessity for stoichiometric reagents. This is an important consideration as an increasing number of pharmaceutical companies are committed to accelerating the transition to net zero health systems.[8] In 2020, AstraZeneca announced their Ambition Zero Carbon with the aim to reduce emissions from lab to patient by 90% by 2045. To achieve this, drug discovery and early development must evolve by embracing and applying innovative synthetic techniques.

Electro-organic chemistry presents a compelling proposition in the realm of sustainable chemical synthesis, particularly due to its adherence to green chemistry principles.[9] By harnessing electricity to drive reactions, this methodology not only minimizes the use of traditional, potentially hazardous chemicals but also mitigates associated risks to human health and the environment. As it keeps improving, electro-organic chemistry has the potential to make drug discovery and development more efficient, sustainable, and innovative. However, there are still some challenges to overcome.[10] This perspective aims to illuminate both challenges and opportunities for electro-organic chemistry in the field of drug discovery and early development (Figure 1).

Received: September 3, 2024
Revised: November 1, 2024
Accepted: November 7, 2024
Published: November 16, 2024



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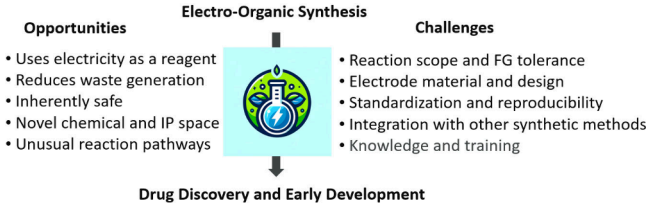


Figure 1. Opportunities and challenges of electro-organic chemistry in drug discovery and early development.

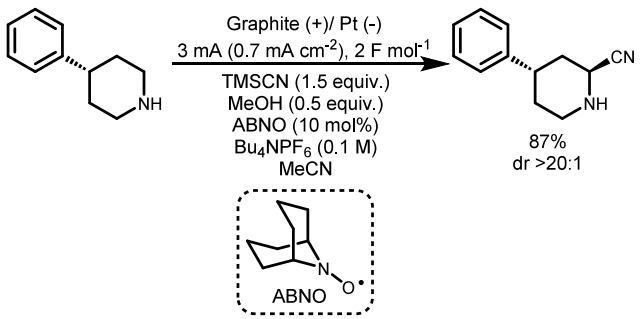
REACTION SCOPE AND FUNCTIONAL GROUP COMPATIBILITY

The range of reactions that can be effectively carried out using electro-organic methods has expanded greatly but is still somewhat limited compared to traditional synthetic methods.[11] Robust reactions and procedures are highly sought after by the discovery chemist, due to the limited time and amount of material that is usually available. Developing new reactions and expanding the scope of existing electrochemical transformations is crucial for broader adoption in drug discovery, which lays the foundation for drug development in the future.

Research should be conducted to expand the scope of electro-organic reactions, discovering new methodologies that are applicable to a wider range of substrates. Many drugs and intermediates contain sensitive functional groups, such as cyano- or nitro-groups, which are sensitive to reduction and may not be compatible with electrochemical conditions.[12] Ensuring compatibility with a wide range of functional groups is essential for the success of electro-organic chemistry in drug synthesis. This includes an honest appraisal of a reaction's scope. Knowing the limits of a reaction is important, and it is encouraging to note that more groups are starting to highlight substrates that did not perform well in their publications. The inclusion of negative results will also enable the development of predictive models.[13,14]

The use of different catalysts and mediators should be explored with the aim of enhancing the efficiency and selectivity of electro-organic reactions. Mediated electrolysis can often avoid problems with functional group compatibility, as well as providing other benefits such as reduced electrode fouling and improved mass balance.[2,15−19] For example the Stahl group have employed nitroxyl radicals to act as mediators, selectively oxidizing saturated nitrogen heterocycles and enabling their functionalization with nucleophiles (Scheme 1).[20] By using a mediator the reaction can be performed at a lower potential, allowing a wider range of functional groups to be tolerated.[21] In this case the stereoselectivity is substrate controlled.

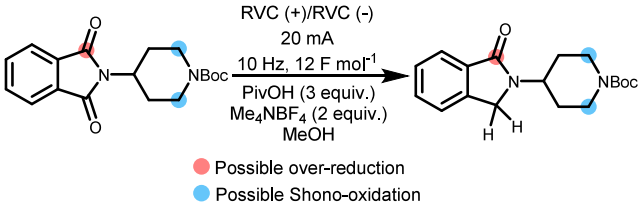
Scheme 1. Cyanation of Piperidines, Developed by the Stahl group, Uses Nitroxyl Mediators to Allow a Lower Potential to Be Used[20]



Comparatively little work has been focused on enantioselective electrochemistry.[22] Given the ubiquity of chiral centers in drug molecules, further development in this area would be highly beneficial. This would likely involve the use of chiral mediators or ligands to direct the asymmetric electro-synthesis of molecules.[23,24]

Approaches like alternating current electrolysis,[25−27] microflow or bipolar electrosynthesis are being further explored to solve issues in selectivity, mass-transfer, and scalability.[28] A thorough mechanistic understanding of reactions is required to decide when such techniques are beneficial. An example by the Baran lab employs rAP (rapid alternating polarity) to achieve good selectivity in the reduction of cyclic imides to lactams, avoiding Shono-oxidations or over-reduction. Here, the electrodes switch polarity every 50 ms, to suppress side reactions (Scheme 2).[29]

Scheme 2. Alternating Polarity Was Used by the Baran Group[29] to Minimize Competing Reactions When Performing a Reductive Deoxygenation



SCALABILITY

The ability to perform initial scale up reactions (for example, 100−1000 mg) quickly is crucial for drug discovery projects.[30] Although electrochemistry has been widely used in the bulk chemical industry, scaling up is far from trivial. Issues such as electrode fouling, heat generation, and mass transfer limitations must be carefully considered.

Large electrode surface areas are required to increase the throughput of a reaction. When operating at a "medium scale" (1000 mg, for example) batch scale-out approaches are a quick way of achieving a larger surface area. Beyond this flow reactors are an obvious solution and interesting in the phase of early drug development (Figure 2), whether they are used in single pass or a recirculating setup.[31,32] Flow reactors can overcome challenges like heat transfer (an issue that increases when operating at high current densities), or mass-transfer limitations.[33−35] The lower interelectrode gap of flow cells can help to abstain from supporting electrolytes, reducing the environmental impact, and simplifying the work up.[5]

Another related issue with throughput is the current density. Many reactions are reported with low current densities, presumably as a result of poor functional group tolerance when operating at higher currents.[10,36] While this might not be too much of an issue at a small scale, a low current density can result in long reaction times once a reaction is scaled up. The development of reactions that can be performed at high current densities (20−50 mA cm^{-2}, for example), would be highly beneficial. The use of mediators may be helpful in achieving this.

Collaborations should be encouraged between engineering and industrial chemistry experts to design and implement

https://doi.org/10.1021/acsorginorgau.4c00068
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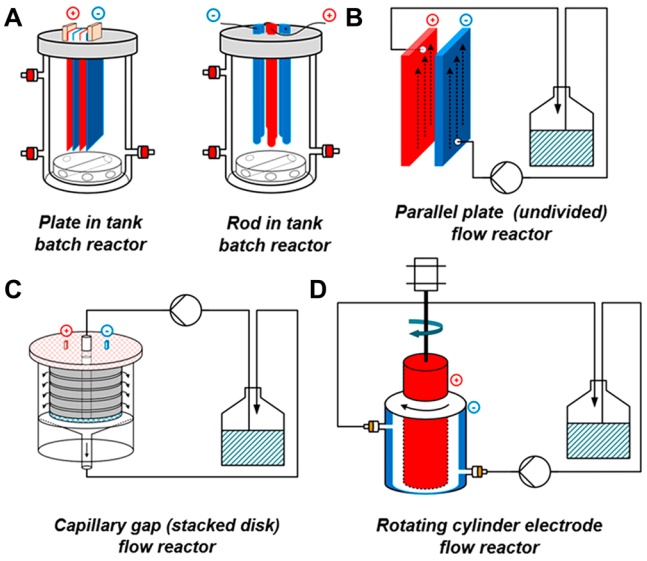


Figure 2. Types of reactors used to scale up electrochemical reactions. (A) Batch reactors. (B) Parallel plate reactor. (C) Capillary gap reactor. (D) Rotating cylinder reactor. Adapted from *Org. Process Res. Dev.* **2024**, *28*, 338−366.[32] Copyright 2024 American Chemical Society.

scalable electrochemical reactors. These reactors should be easy to use and well characterized to enable the rapid scale up of reactions. These reactors must be commercially available as development and manufacture are frequently outsourced.

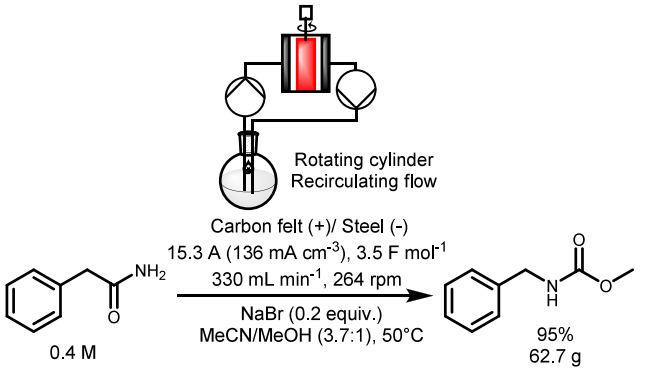
As electrochemistry is heterogeneous, good mass transfer is likely to be important in these reactors and will probably be an important parameter to control when scaling up reactions.[37] There are some commercial reactors which report similar mass transfer coefficients when scaled up (ElectroCell and C-Tech innovation).[38,39]

The ability to handle solids/slurries would be beneficial as many API intermediates exhibit poor solubility and the volume of solvent makes a large contribution toward the environmental footprint of a reaction.[35,40] Currently most commercial reactors are incapable of handling solids, although the Kappe and George groups have tried to address this through the development of rotating cylinder and Taylor vortex reactors (Figure 2, D). These have the bonus of decoupling the mass transfer from the residence time.[41,42]

A rotating cylinder reactor was used by the Kappe group in collaboration with a team from MSD to facilitate a Hofmann rearrangement (Scheme 3).[43] NaBr, which acts as a mediator, is poorly soluble in organic solvents and by using a rotating cylinder reactor the presence of solids was able to be accommodated. The use of graphite felt as an anode was essential, with the 3D electrode giving improved selectivity, possibly due to operating at a lower current density (as a result of a larger surface area). This enabled a good throughput due to the high overall current. Furthermore, the interelectrode distance in the small batch reactor which they used for optimizing conditions was the same as in the rotating cylinder reactor, reducing the amount of time and material required to scale up the reaction.

Where the reaction of interest is a reduction, a sacrificial reductant would be preferable to a sacrificial anode. Although they may be permissible when working at a small scale, sacrificial anodes should be avoided once a reaction begins to be scaled up.[44] The production of large quantities of zinc,

Scheme 3. Rotating Cylinder Reactor Was Used by the Kappe Group and MSD to Scale up a Hofmann Rearrangement[43]



magnesium or aluminum waste is not practical or desirable on scale, not least due to the challenges with handling solids.[45] There have been several publications developing methods using amines, silanes and thioethers as sacrificial reductants, as well as the hydrogen anode technology although more work is required to assess their compatibility with existing reductive electrochemistry.[29,46−50]

While it may be desirable to avoid divided cells, in part due to the additional electrolyte required, they may be beneficial under certain circumstances particularly if the counter electrolyte could be reused in subsequent batches.[3] The use of membranes adds extra complexity, especially as most membranes have been designed for aqueous systems and often exhibit reduced performance when used with organic solvents.[51] More research on the effects of organic solvent systems on membranes would be beneficial, along with the development of membranes for use in organic electrochemistry.

Solvent is an incredibly important contributor to the environmental impact of a process because it makes up such a large proportion of the reaction mixture. “Greener” solvents should be utilized wherever possible, not only in the reaction, but also in the work up.[52] Similarly, experimentalists should try to reduce the amount of solvent required. The use of halogenated solvents should be avoided, due to their toxicity or persistent nature. The amount of halogenated additives, such as HFIP, should be reduced or eliminated where possible.[52] Development of alternative, greener additives would be highly beneficial.

ELECTRODE DESIGN AND MATERIALS

The choice of appropriate electrodes and materials for electrochemical cells is critical. Developing cost-effective, durable and sustainable electrodes that can withstand a variety of reaction conditions and are capable of selective electron-transfer is an ongoing challenge.[53]

There have been many publications looking at materials developed for the bulk chemical industry, but very few consider electrodes for organic transformations.[53] Investment should be made in the development of novel electrodes and materials that are cost-effective, durable, and selective for various electrochemical transformations. Many metals and alloys with improved stability or unique properties like leaded bronze, tantalum or molybdenum are being tested in electrosynthesis. Boron doped diamond (BDD) and leaded

https://doi.org/10.1021/acsorginorgau.4c00068
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bronze are already broadly applied at a small scale.[54,55] BDD can offer improvements with regards to electrode robustness, while leaded bronze is often used to promote reductions as it has a very high hydrogen evolution overpotential. Although popular on a small scale (Figure 3), platinum and glassy carbon electrodes tend to be used less often when reactions are scaled up, with cheaper electrodes such as graphite and stainless steel being more popular.[32,53]

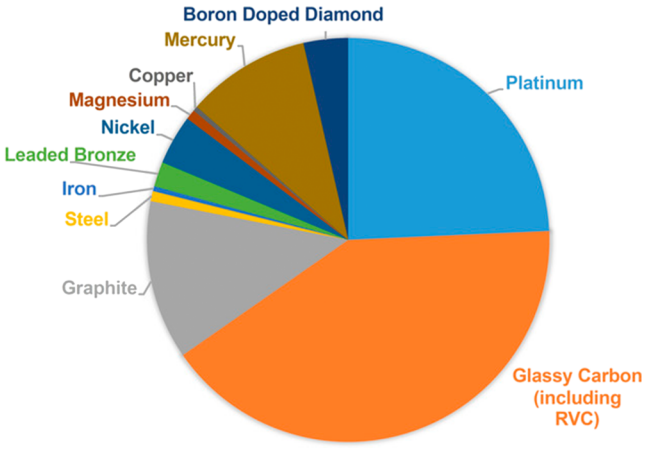

Figure 3. Materials used as anodes or cathodes in synthetic electrochemistry between 2000 and 2017. Reproduced with permission from *Angew. Chem. Int. Ed. Engl.* **2020**, *59*, 18866−18884[53] under creative commons licensing CC-BY 4.0.

The current literature has lots of data for H_2, O_2 and Cl_2 evolution in the context of electrode selection,[53] no doubt as a result of the historic leaning of electrochemistry toward the bulk chemical industry and wastewater treatment. Currently, electrode choice involves a lot of educated guesswork and ultimately the screening of different materials. It would be useful to have the overpotentials with different materials for some common organic reactions of interest (e.g., TEMPO oxidation) to aid electrode selection.

STANDARDIZATION AND REPRODUCIBILITY

Achieving consistent and reproducible results across different laboratories is a common challenge in electro-organic chemistry.[6] Standardization of reaction conditions and protocols is necessary to facilitate broader adoption and acceptance within the synthetic chemistry community.

Information-sharing and collaboration should be encouraged within the scientific community to improve the reproducibility and reliability of electrochemical methods. To this end we welcome the ACS's relatively recent guidelines for reporting electrochemical reactions and hope that other publishers follow suit.[56] Standardized protocols for electro-organic reactions, including reaction conditions, the reactor (with dimensions if not commercially available), electrode materials, and analytical methods should be established.

Electrode materials and cleaning procedures should be accurately reported given the electrode surface is of high importance.[6] Accurate reporting should include the material composition and supplier or manufacturing process. Current density is important for transferring reactions between reactors[37] but it is often not reported. Where constant current conditions are employed, the current density should be given. In instances when the surface area is difficult to determine (e.g., 3D electrodes) it would be helpful to know the volume of electrode in solution in addition to the current applied, as a minimum.[43]

Reactors must be well-characterized to enable the smooth transfer of reactions between them. In the case of batch reactors this should include the physical dimensions and the stirring rate used, as well as type, size or shape of stirring bar or stirrer.[6] For flow reactors this should include physical dimensions as well as residence time distributions when used in single pass and mass transfer coefficients whether used in a single pass or recirculating set up. These details are relatively easy to obtain experimentally and should be available from manufactures for commercial reactors or reported in publications for homemade reactors.[57]

Efforts toward standardization have been made by for example the Baran, Waldvogel and Willans laboratories, by commercializing easy-to-use equipment like the IKA ElectraSyn, the IKA Screening-Kit or the Asynt ElectroReact (Figure 4).[58,59] Equipment for high throughput experimentation has been developed by the Lin group and is available as the HTe⁻Chem from Analytical Sales.[60]

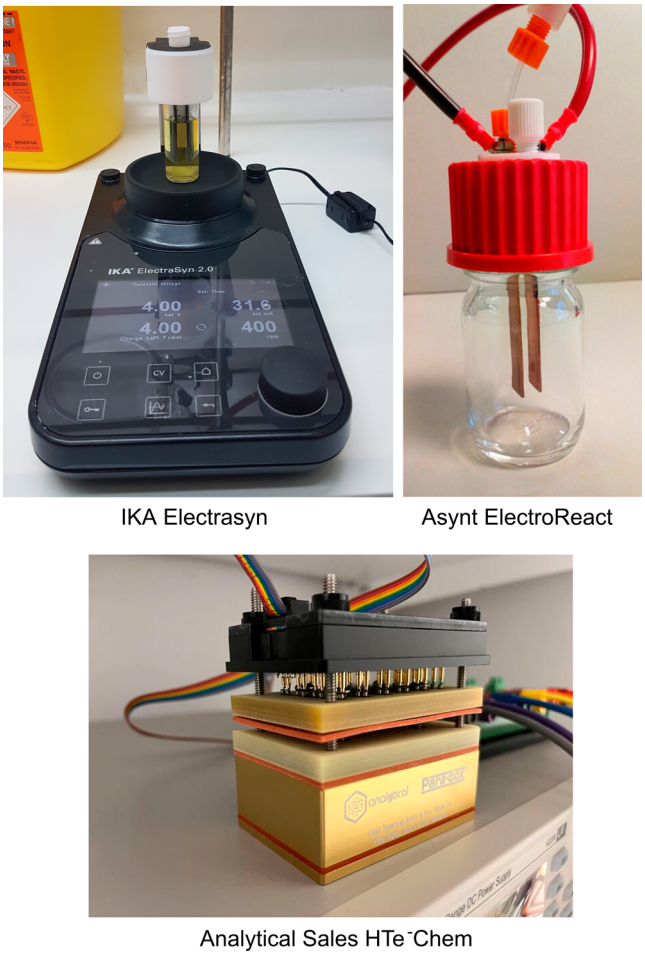

Figure 4. Commercial batch reactors for electrosynthesis. Image of Asynt ElectroReact reproduced from *Org. Process Res. Dev.* **2020**, *24*, 1084−1089.[58] Copyright 2020 American Chemical Society.

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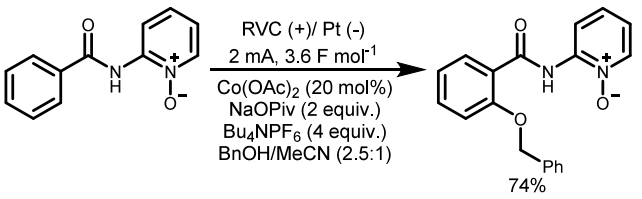
INTEGRATION WITH OTHER SYNTHETIC METHODS

Drug dicovery and development often require the use of multiple synthetic methods. Integrating electro-organic chemistry seamlessly with other synthetic techniques is a challenge that needs to be addressed for its widespread adoption in pharmaceutical research. Interdisciplinary collaborations should be fostered between electrochemists and experts in other synthetic methods to develop integrated approaches for drug synthesis.

The compatibility of electro-organic chemistry with established methodologies, such as organometallic and transition-metal catalysis should continue to be explored.[17] The Ackermann group for example has looked at incorporating electrochemistry with C−H activation protocols to further improve the functional group tolerance and make their transformations more sustainable.[23] One example from the Ackermann group uses cobalt as a mediator for C−H oxygenation, a transformation that only proceeded under electrochemical conditions (Scheme 4).[61]

Scheme 4. Electrochemical Cobalt Catalyzed C−H Oxygenation Developed by the Ackermann Group[61]



The combination of photochemistry and electrochemistry enables the formation of radical species that would be impossible to form using other techniques. This can enable challenging transformations to be performed under relatively mild conditions. As a more recent synthetic method, this area has lots of opportunities for development.[62]

The combination of electrosynthesis and biocatalysis is another relatively recent field. The electrochemical regeneration of biomimetic cofactors or coenzymes can reduce costs directly or through simplifying work ups.[63,64] Plenty of opportunities exist for increasing the scope and robustness of these systems.[65]

High-throughput library synthesis is a staple of modern drug discovery, often utilizing advances in automation. Although the HTe⁻Chem can perform parallel reactions to great effect in a plate format, it is difficult to see how this could be automated further due to the fragile nature of small electrodes. Some groups have started to develop automated electrochemical flow set-ups, which can be used for reaction optimization or library synthesis when paired with an autosampler.[66−69] Careful validation of these set ups is required to ensure that the electrode surfaces remain active. In some cases, cleaning procedures may be required to ensure that the electrodes remain active and false negative results are avoided.

KNOWLEDGE AND TRAINING

Incorporating electrochemical methods into the synthetic chemist's toolbox requires a solid understanding of electro-organic chemistry principles. Training chemists in this field and disseminating knowledge about its applications and limitations is crucial for its successful implementation. Educational programs and workshops should be developed to train synthetic chemists in the principles and applications of electro-organic chemistry. Training courses are available online, for example by the Stahl and Rafiee groups, offering virtual short courses[70] or by David Cantillo.[71]

Universities have typically taught electrochemistry from an analytical perspective. While these skills are undoubtably useful for the synthetic chemist, institutions should also incorporate preparative electrochemistry as part of undergraduate studies. There are a number of accessible reviews[72−77] and undergraduate style experiments available to help with this.[78]

Within companies, an awareness of electrochemistry and its applications should be fostered, even if only in the broadest

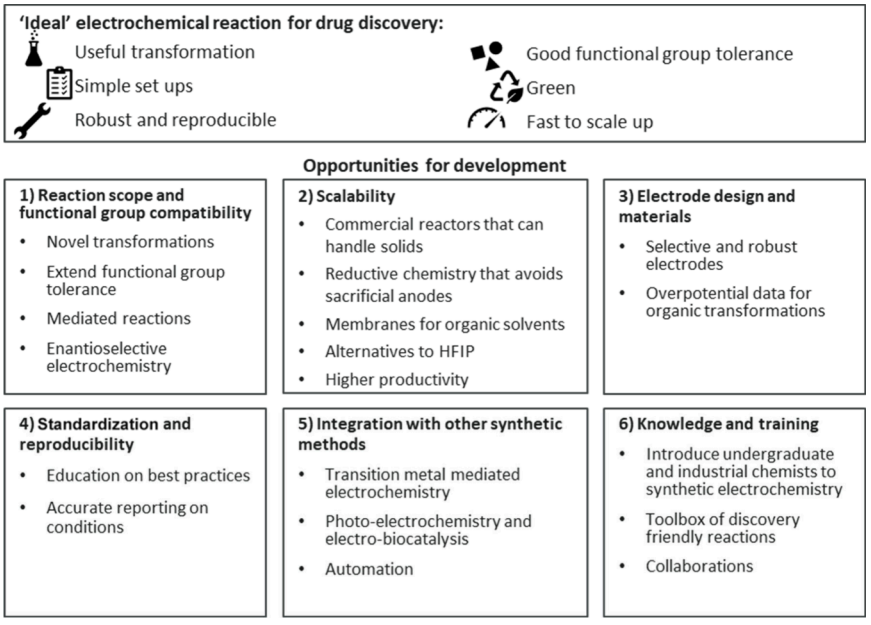


Figure 5. Ideal electrochemical reaction for drug discovery and opportunities for development.

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sense, so that opportunities can be identified. This could be provided in the form of a tutorial-style lecture from a guest academic or internally developed training material. A "toolbox" of useful and robust reactions, along with their limitations would be highly beneficial. This would aid the "nonelectrochemist" in identifying useful opportunities and thereby reduce the barrier to adoption.

Collaboration between academia and industry should continue to be encouraged to facilitate the transfer of knowledge and expertise. This could be through industrially funded projects or more informally at conferences. Cross-pharma collaboration should be maintained, helping to address challenges such as scaling up reactions and developing industry standards, with particular respect to the requirements for regulatory submissions. As electrochemistry has been used as a synthetic tool within the bulk chemical industry for decades interactions between this industry sector and the pharmaceutical sector would be invaluable given the experience of bulk chemical companies with large scale electrolysis.

CONCLUSION

In conclusion, electro-organic chemistry offers discovery chemists the ability to synthesize molecules via alternative and complementary routes. This has the potential to allow access to new compounds through electrochemical transformations and reduce the environmental impact of making APIs. For electrochemistry to be widely adopted by discovery chemists, electrochemical reactions must be robust, procedurally simple, and synthetically useful.

Although great progress has been made in recent decades,[1,3] there remain a number of challenges which we have outlined. Some, like the standardization of equipment, are "solved" problems that require education and training to make the solutions widely known to nonexperts. Others, such as the development of new reactions, provide exciting opportunities for researchers to collaborate and develop interesting chemistry that will have a very real impact on how future medicines are made (Figure 5).

The reticence of experimentalists to adopt synthetic electrochemistry is not a new phenomenon, although electrochemistry is perhaps not as difficult as people think with Tuck noting in 1979 that "an ignorance of the detailed electrochemistry, and even of such fundamental parameters as E_0, need be no bar to the use of electrochemical methods in nonaqueous solvents in preparative chemistry".[79] Thankfully the barrier to adoption is lower than ever and it is our hope that as electro-organic chemistry becomes more accessible its use within drug discovery will become more widespread.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article.

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‖H.R.S. and J.L.R. contributed equally. CRediT: **Hamish Robert Stephen** conceptualization, project administration, resources, visualization, writing - original draft, writing - review & editing; **Johannes Ludwig Röckl** conceptualization, project administration, resources, visualization, writing - original draft, writing - review & editing.

Notes

The authors declare the following competing financial interest(s): Both authors are employees of Astrazeneca.

ACKNOWLEDGMENTS

We acknowledge the kind help and proof-reading of this manuscript by our colleagues Magnus J. Johansson, Rhona Cox, Matthew Burns, and Emma Robertson.

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