Published in final edited form as:

Angew Chem Int Ed Engl. 2018 April 09; 57(16): 4149–4155. doi:10.1002/anie.201707584.

Synthetic Organic Electrochemistry: Calling All Engineers

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To many students of chemistry, electrosynthesis (the preparation of materials via addition/removal of electrons with the electromotive force) is almost synonymous with the production of bulk chemicals such as aluminum, and caustic soda on megaton scales (Figure 1A). In fact, pictures of gigantic plants are frequently included in textbooks to illustrate the concept of electrolysis.^[1] Electrochemistry has also played prominent roles in analytical chemistry wherein electrolytic reactions of analytes in as low as picogram scales allowed quantitative determination of their concentrations.^[2] Miniaturized and chip-based sensors have been devised for this purpose. Thus, electrochemical processes have been engineered with great fidelity on both large (megaton) and small (picogram) scales. Conversely, between these two extreme ends of the spectrum, electrochemical techniques have never been a regular tool in the armamentarium of synthetic organic chemists working on laboratory scales (Figure 1A). Such scales (1 mg–1 kg) encompass the majority of our chemical space, spanning radiochemistry, medicinal chemistry, natural product synthesis, synthetic method development, polymer synthesis, and pharmaceutical process development where collections of diverse and ever-increasingly complex molecules are created daily.

It is ironic that this neglected scale regime is precisely where synthetic organic electrochemistry originally flourished.^[3,4] In fact, explorations had begun in the early 19th century when Michael Faraday performed the electrolysis of acetic acid (Figure 1B).^[5] The rich history of the field is replete with intriguing and enabling discoveries. The venerable Kolbe electrolysis (1847) represents one of the earliest C–C bond forming reactions;^[6] the Tafel rearrangement offers a powerful means to access various hydrocarbons.^[7] Between the 1940s and the 1960s, the Simons fluorination reaction^[8] and the Monsanto adiponitrile process^[9] highlight the innate ability of electrolysis to accomplish challenging chemical transformations in scalable fashions. The applications of electrogenerated acids/bases^[10,11] and chiral electrodes^[12] in the 1970s and 80s represent new vistas in organic chemistry that are worth revisiting. The invention of mediators ameliorated problems associated with heterogeneous electron transfer at electrode surfaces, including kinetic barriers and electrode passivation.^[13] The use of chromium complexes to facilitate the electrosynthesis of quinones was explored in as early as the 1900s.^[14] Efforts between the 1960s and 1980s led to the popularization of versatile triarylamine^[15] and nitroxyl mediators.^[16] The concept of

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The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/anie.201707584>.

Conflict of interest

The authors declare no conflict of interest.

electrochemical mediators offers a myriad of future opportunities as numerous chemical species can conceivably be oxidized or reduced in electrode processes to serve as redox catalysts.^[4d] The invention of the Shono oxidation (1975) allows the expeditious modification of ubiquitous amide functionalities;^[17] Yoshida's use of electroauxiliaries allowed access to various carbocation intermediates through electrolysis in a chemoselective fashion (1986).^[18]

Toward the end of the 20th century, cyclization reactions devised by Little,^[19] Schaefer,^[20] and Moeller^[21] epitomize the ability of electrochemistry to forge complex molecular architectures. Yoshida's cation pool technology circumvented the long-standing issue of nucleophile compatibility in anodic oxidation reactions.^[22] The beginning of the new century witnessed continued development in this area—some notable accomplishments include Waldvogel's selective biaryl crosscoupling reactions^[23] and Yoshida's C–H amination methods with stabilized cation pools.^[24]

Many have attributed the under-utilization of electroorganic chemistry to the existence of analogous non-electrochemical technologies. However, the distinct advantages of electrochemistry are evident through the few instances of its application in complex molecule synthesis (Figure 1C). Electrochemistry enables the generation of reactive intermediates from simple and ubiquitous functional groups. An illustrative example is Corey's synthesis of β -onoceradiene, featuring a late-stage Kolbe electrolysis as the key step.^[25] This electrochemical transformation allowed the use of a readily available carboxylic acid (3 steps from sclareolide) as alkyl radical precursors; such mode of alkyl–alkyl bond formation through chemical means is still a subject of ongoing interest for many academic groups.^[26] Little's synthesis of quadrone,^[27] Moeller's synthesis of alliacol,^[28] and Trauner's synthesis of guanacastepene E^[29] highlight the ability of electrochemistry to expediently invert the intrinsic polarity of common structural motifs—the corresponding chemical umpolung processes would conceivably require multiple functional group manipulations or the use of costly and air/ moisture sensitive metal reagents. Nicolaou's synthesis of alkanin and shikonin is a forceful reminder of the exceptional mildness and selectivity of electrochemical reactions—the sensitive naphthoquinone core was furnished directly from a methyleneacetal-protected system.^[30] Harran's synthesis of DZ-2384 employed an electrochemical macrocyclization on decagram scales (> 60 g), underscoring the scalability and robustness of electrochemistry.^[31] The analogous chemical conditions employing hypervalent iodine were deemed impractical on large scales due to the scale-dependence of reaction yields and byproduct formation. The scalability of electrochemical processes is also evident from Waldvogel's debromination methodology which has found applications in the syntheses of cyclosporine A analogs and HCV drug candidates in collaboration with Novartis.^[32] In these examples, the compatibility of various functional groups under electrolytic conditions testifies to the potential utility of electrochemical technologies. Electrochemistry also allows the exquisite control of chemoselectivity by “dialing in” reaction potentials. This can be illustrated through our own synthesis of dixiamycin wherein controlling the anode potential enabled the selective *N,N*-dimerization of the carbazole motif in the presence of a carboxylic acid and an alcohol.^[33] Extensive efforts to accomplish this transformation using chemical oxidants were unsuccessful.

Toward this end, electrochemistry proffers reactivities and selectivities not within the purview of most chemical reagents.

Notwithstanding these advantages, it remains an unassailable truth that, for most organic chemists, electrochemistry represents a technique employed as a “last resort” rather than a routinely surveyed method. Admittedly, our own explorations in the area, beginning with the synthesis of dixiamycin, were born out of sheer desperation. Given the aforementioned rich history and useful reactivity enabled by electrochemistry, why is it rarely employed by modern day chemists? We hypothesize that the answer is due to a lack of engineering savvy directed in this area rather than a lack of potential interest.

For example, NMR spectroscopy would be nothing more than a fringe technique used by only a handful of physicists if not for engineering advances in equipment technology. Consider the fate of computer sciences if each user were required to construct a “Turing machine” from scratch. In a similar vein, aspiring electroorganic chemists face such a quandary. To be sure, all the enabling technologies behind electrosynthesis had matured by the second half of the 20th century (Figure 1B). The first battery (Volta pile) was invented in 1800,^[34] enabling simple electrolysis experiments; the first potentiostat was developed in 1942 where the potential of an electrochemical cell could be precisely controlled (shown in Figure 1B is a device from Janke & Kunkel that was manufactured in the same era).^[35] Prototypes of divided cells were devised in 1898 which circumvented the problem of interfering anodic and cathodic reactions.^[36] The first polarography and cyclic voltammetry experiments were conceived in 1922^[37] and 1952^[38] respectively, allowing the accurate determination of redox potentials of various functionalities. However, these technologies have yet to be integrated into a tailor-made device for laboratory electrosynthesis. As a result, chemists are required to engineer their own setups prior to attempting any electrochemical experiments. One of us (P.S.B.) still vividly recalls the painstaking experience motivating students to pick up a soldering gun and work out the (relatively) complex engineering problems. Inconveniences aside, the non-standardized setup introduce numerous variabilities, severely undermining the reproducibility of experiments. This creates one of the biggest challenges in electroorganic chemistry, perhaps its greatest barrier to widespread adoption. During our own practice, seemingly menial factors stemming from the lack of standardization have frustrated our efforts repeatedly (see below). Such unpredictability has precluded much synergy between electrochemistry and organic synthesis (Figure 2). We earnestly believe that the huge potential of electrochemistry can only be realized with the invention of standardized devices that cater to the specific needs of the synthetic community.

What constitutes an “ideal instrument” in synthetic organic electrochemistry? Our forays in this area and discussions with those in the community lead us to believe it must have all of the following features (Figure 3).

1) Standardization

Reproducibility is the pillar of experimental chemistry; it requires the standardization of each reaction parameter. In our own experience with electrochemical C–H oxidation

reactions,^[39,40] this process is prohibitively challenging with added factors such as electrode, electrolyte, current, potential, and resistance all playing crucial roles in the reaction. We have exercised extra caution to ensure the uniformity of all conceivable variables, including the size of electrodes while crafting our “home-made” cells; detailed experimental protocols were furnished in the supporting information. However, we were baffled by feedback from industrial collaborators that, despite having adhered closely to our instructions, they were unable to obtain products in similar yields. After several rigorous troubleshooting sessions, we realized that it was the distance between electrodes that triggered the vexing problems. While reproducibility issues were smoothly resolved in our case, it is highly probable that similar problems will arise where seemingly trivial parameters exert a substantial impact on the reaction outcome. The lack of reproducibility will undoubtedly slow down the progress of electroorganic chemistry; it may deter potential practitioners from entering the field altogether. Therefore, the ideal electrochemical device must offer standardized setups, including reaction vessels, electrodes, potentiostat, and supporting parts conjoining these components.

2) Modularity

Development of synthetic methodologies entails the systematic examination of each reaction parameter, including reagent choice, stoichiometry, solvent, reaction temperature, etc. Electrochemical reactions involve even more variables such as potential, current, electrode, electrolyte, and cell type. Thus, it is critical to be able to conduct multiple reactions in a timely fashion. While potentiostats with multiple channels have been developed to enable parallel electrolysis, such instruments are usually costly and will unlikely be available to most of practicing organic chemists. Serial setups wherein multiple reactions are connected in a serial circuit would supposedly offer an inexpensive alternative as most of the electrochemical reactions can proceed under simple galvanostatic (constant current) conditions. Nevertheless, in practice, we find it a cumbersome undertaking to set up serial experiments—the intertwining wires resemble a “Rube Goldberg” machine. Moreover, should the resistance of a single reaction rise abruptly (possibly due to substrate decomposition or electrode passivation), all other reactions are affected adversely. Consequently, we often resort to the inefficient “one reaction per potentiostat” approach. Thus, we covet a modular, “plug and play” device that is amenable for multiple concurrent reactions.^[41] Synthetic chemists are routinely required to procure materials on a variety of scales in a laboratory. In our opinion, an in-house made electrochemical apparatus does not accommodate such needs. For example, the lack of instrumentation has repeatedly forestalled our attempts to utilize electrochemical conditions at late stages during our total synthesis campaigns. In one case, the limited availability of advanced intermediates required electrolytic experiments to be conducted on ≈ 1 mg scales in a small volume of solvent. However, crafting a small cell with matching electrodes was challenging with tools at our disposal. Scaling up reactions has not been a straightforward endeavor, either. In our latest study on methylene C–H oxidation, we pursued a 50-gram scale oxidation of sclareolide. While the yield and selectivity of the reaction attest to the scalability and robustness of the technology, the limited current/potential range of our instrument necessitated long reaction times of nearly 5 days. Toward this end, an ideal instrument should permit the modular setup

of reactions in different sizes—specifically, it should possess a broad potential/current range and be equipped with cells or electrodes of different sizes. Moreover, it should allow the variation of electrodes and cell type (divided vs. undivided) with ease.

3) Analytical capability

Cyclic voltammetry has played a pivotal role in our explorations of electrochemistry. In the total synthesis of dioxamycin, a series of CV experiments has helped us determine the oxidation potential of the complex monomer, thereby allowing a chemoselective dimerization under potentiostatic conditions. During our forays toward allylic and methylene C–H oxidations, we have relied heavily on voltammograms to identify viable mediators. Conducting electrochemical experiments without such analytical capabilities can be likened to searching for a key in the darkness. As CV experiments require finely controlled variation of potential, many potentiostats utilized for preparative purposes do not possess sufficient levels of precision or the requisite sweeping function. As a result, in our own laboratory, CV measurements are taken on a separate instrument. An ideal device, in contrast, should combine preparative and analytical capabilities—in doing so, a practitioner could expeditiously locate his/her “key” to unlock the potential of electrochemical reactions.

4) Versatility and industrial design

For electronic devices, miniaturization is oftentimes a key criterion for mass adoption. The ability to do more with less confers accessibility, portability, and versatility. To the best of our knowledge, there are no all-inclusive electrochemical instruments which are dedicated to synthetic organic chemists. Consequently, to set up an electrochemical experiment, one needs to obtain a potentiostat, electrode materials, a reaction vessel, a stirrer plate, and so on. While there are some commercially available electrode sets and cells, they have generally failed to meet our synthetic needs. Instead, we often resort to make our own devices from lab equipment—cutting test tubes, carving out electrodes, soldering wires, and tuning potentiostats are routine exercises for students working in electrochemistry. Barring the labor-intensive assembly process, the final setup usually takes up lots of space—it is extremely unlikely for a synthetic chemist to keep a unit in his/her fume hood. Thus, we believe an ideal electrochemical instrument would be an all-inclusive apparatus with condensed preparative, analytical, and stirring capabilities all in the size of an average stirring plate.

5) An educational and user-friendly interface

While organic chemists are steeped in stoichiometry or molarity calculations, computing electrochemical variables such as charge, current density, and potential hardly seem intuitive—chemists would thus naturally eschew electrolytic reactions. This situation is reminiscent of the development of personal computers—prior to the introduction of Macintosh or Windows, operating systems comprising abstract command lines often appeared esoteric or even incomprehensible to a lay user. The entry barrier would only diminish when an educational interface transforms mathematical formulae into intuitive or graphical representations. In the context of electrochemistry, we desire an operating

interface that bridges the gap between chemical synthesis and electrochemistry—one that would demystify electricity as simply another reagent in a reaction. This involves the correlation between charge and stoichiometry, between current and the rate of addition; this interface should also provide guidance regarding electrode choice, recommended electrolytes, and cell type.

6) Future-proofing

Since the advent of the 21st century, futuristic features of electronic devices have propelled the digital revolution to new heights—the internet teems with new ideas and new accessories that could be readily incorporated into our electronics. On the contrary, laboratory equipment has largely lingered behind in the 20th century. An “over-the-air” upgradable lab instrument is almost unheard of; meanwhile, lots of instruments in academic laboratories still rely on archaic operating systems and data transfer technologies. To this end, we desire an electrochemical device that is future-proof: new features can be introduced with ease through software development and through easy-to-add accessories. More importantly, it should offer an open platform to garner the collective wisdom of the community—for example, users should be able to freely share optimal protocols and set parameters for various reaction manifolds.

7) Cost efficient

Finally, the cost of the instrument cannot be overlooked. For the community to embrace electrochemistry, a standardized electrochemical device should be priced on par with staple laboratory equipment, such as stirrer plates, that are accessible to every practitioner.^[42] Currently, most potentiostats are priced above \$5000 each, creating another barrier for the popularization of the technology.

Conclusion

With the development of the “ideal instrument” embodying these seven features, we envision electrochemistry to become an integral and indispensable part of drug discovery efforts and organic chemistry curriculum.

For a long time, organic synthesis was an anecdotal art—reproducibility was first attainable after pioneering companies such as Merck KGaA provided the community with fine chemicals of standardized quality. Technologies undergirding smartphones have been available for decades, but it was only through Apple’s ingenious engineering that they were integrated to benefit everyone. Similarly, the first electric car was designed some 100 years ago, but such technologies only experienced a renaissance recently. These examples are stunning testaments to the enabling roles of engineering toward the advancement of science and technology. Organic chemistry today is under increasing pressures of shortened timelines, shrinking IP space, and regulatory hurdles. With its innate sustainability, scalability, and versatility, electrochemistry is a promising technology allowing chemists to do more with less. To this end, we encourage the involvement of engineers to galvanize the field and to unleash its huge potential.

Acknowledgments

Funding for this work is provided by NIH (GM-118176). We thank Dr. Evan Horn for helpful discussions. Special thanks go to IKA Inc. for taking on this challenge and developing a product that meets all of the stringent criteria laid out in this Essay. We are indebted to the IKA team: Dirk Waldmann, Henry Huang, Eddie Alvarez, Shobin Shaji, Sebastian Wiegert, Franco Luciani, Santiago Arconada, Norman Khoo, José Roman, Shrikrishna K, Erhard Eble, Pascal Stiegelmann, René Stiegelmann, Refika Bilgic.

Biographies

Ming Yan was born in China in 1989, and was educated in China, Singapore, Germany, and the US. He received his undergraduate education from Lafayette College (2009–2012), which included a research internship at TSRI under the tutelage of Professor Phil S. Baran. He then returned to the Baran laboratory for his doctoral studies, where he is investigating the total synthesis of alkaloids.

Yu Kawamata was born in Japan in 1988, and completed his undergraduate education in Kyoto University. He obtained his master degree and his Ph.D. in the same university under the supervision of Professor Keiji Maruoka, and undertook a short-term internship at TSRI working on natural product synthesis with Professor Phil S. Baran. Upon completion of his doctoral studies, he returned to the Baran laboratory as a research associate and is currently pursuing his postdoctoral studies on organic electrochemistry.

Phil S. Baran was born in New Jersey in 1977 and received his undergraduate education from New York University in 1997. After earning his Ph.D. at TSRI in 2001, he pursued postdoctoral studies at Harvard University until 2003, at which point he returned to TSRI to begin his independent career. He was promoted to the rank of Professor in 2008 and is currently the Darlene Shiley Professor of chemistry. The mission of his laboratory is to educate students at the intersection of fundamental organic chemistry and translational science.

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Figure 1.

Synthetic organic electrochemistry: state of the art. Image credits: A) the image of microelectrode arrays adapted with permission from K. D. Moeller, "Electrochemically Generated Organometallic Reagents and Site-Selective Synthesis on a Microelectrode Array". *Organometallics* **2014**, *33*, 4607, © 2014 American Chemical Society; the image of "a modern industrial chlor alkali plant" © Stephen Lower (Ref. [1]), adapted under CC-BY-NC 2.5; B) the image of "Volta Pile" © Wellcome Images, adapted under CC-BY 4.0; the image of "Heyrovsky's Polarograph" © Lukáš Mižoch, adapted under CC-BY-SA 3.0; the

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Figure 2.

The tremendous promise of synthetic organic electrochemistry cannot be realized without a standardized instrument for its implementation.

Figure 3.
An electrochemical device for synthesis: our wish list.