Unlocking the Potential of High-Throughput Experimentation for Electrochemistry with a Standardized Microscale Reactor

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Organic electrochemistry has emerged as an enabling and sustainable technology in modern organic synthesis. Despite the recent renaissance of electrosynthesis, the broad adoption of electrochemistry in the synthetic community and, especially in industrial settings, has been hindered by the dearth of general, standardized platforms for high-throughput experimentation (HTE). Herein, we disclose the design of the HTe-Chem, a high-throughput microscale electrochemical reactor that is compatible with existing HTE infrastructure, and enables rapid evaluation of a broad array of electrochemical reaction parameters. Utilizing the HTe-Chem to accelerate reaction optimization, reaction discovery, and chemical library synthesis is illustrated using a suite of oxidative and reductive transformations under constant current, constant voltage, and electrophotochemical conditions.
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ABSTRACT: Organic electrochemistry has emerged as an enabling and sustainable technology in modern organic synthesis. Despite the recent renaissance of electrosynthesis, the broad adoption of electrochemistry in the synthetic community and, especially in industrial settings, has been hindered by the dearth of general, standardized platforms for high-throughput experimentation (HTE). Herein, we disclose the design of the HTChem, a high-throughput microscale electrochemical reactor that is compatible with existing HTE infrastructure, and enables rapid evaluation of a broad array of electrochemical reaction parameters. Utilizing the HTChem to accelerate reaction optimization, reaction discovery, and chemical library synthesis is illustrated using a suite of oxidative and reductive transformations under constant current, constant voltage, and electrophotochemical conditions.

Introduction

Over the past decade, synthetic electrochemistry has garnered significant interest in the organic chemistry community. In an electrochemical reaction, electrons flowing between an anode and a cathode provide the redox equivalents to drive chemical transformations in lieu of traditional chemical oxidants or reductants. Under a sufficient current or potential, substrates can be oxidized or reduced at the electrode to generate reactive intermediates such as radicals and radical ions. The broad potential range of an electrochemical system allows for the activation of inert chemical bonds, thus driving highly endergonic reactions that are otherwise challenging or, sometimes, impossible. Meanwhile, by precisely dialing in a current or potential, chemists can select for a specific electron transfer reaction to occur in the presence of various reactive functional groups and do so with control over the reaction rate. These features make electrochemistry an attractive strategy for discovering fundamentally new chemical transformations and promoting green and efficient synthesis.

A myriad of powerful electrochemical reactions developed in the past decade have shown the promise of electrochemistry as an enabling technology in both academic and industrial research. Despite the established advantages, electrochemical methods have seen only limited adoption in the pharmaceutical industry, primarily due to a lack of standardization and experimental flexibility. A lack of standardized electrolysis setups can render reaction reproduction challenging. To address this issue, standardized reactors for electrosynthesis have been designed and deployed, including an early-generation spatially addressable electrolysis platform (SAEP) and the recently commercialized ElectraSyn 2.0, e-Hive, and IKA Screening System. These critical technology advancements have substantially accelerated the development and adoption of new electrosynthetic methods in the broader organic chemistry community. Despite the success achieved with each of these systems, the ability to easily explore a broad array of electrochemical reaction parameters in a high-throughput fashion remains elusive and highly desirable. In this regard, an ideal standardized reactor platform should allow for convenient and modular programming of various experimental parameters. Although the multitude of reaction parameters present in electrochemical systems open opportunities for reaction discovery, they also pose unique challenges. For example, electrochemical parameters such as cell geometry, mode of operation (constant current or constant voltage), applied current or potential, electrode material, and electrolyte can be leveraged to improve reactivity. Nevertheless, this additional complexity introduces a barrier to begin investigating electrochemical reactions and also increases the number of conditions that must be evaluated. Thus, the full optimization can require significantly more screening experiments than traditional organic transformations.

High-throughput experimentation (HTE) using standardized 24- or 96-well plates is routinely used for reaction discovery, optimization, and library synthesis in the pharmaceutical industry and beyond. The parallelization involved allows chemists to rapidly explore a large number of reaction parameters, generate a complete dataset, and optimize toward global maxima rather than local maxima, the latter of which are often encountered in traditional one-factor-at-a-time (OFAT) optimization. The adoption of standardized HTE systems, including parallel plate reactors, multichannel pipettors, liquid and solid handling robots, and stirring systems, has streamlined workflows by ensuring the compatibility of all equipment. This standardization also enables the use of pre-plated reagent libraries, which is particularly useful for the screening of catalysts, ligands, and reagents. Consequently, plate-based HTE, first introduced by the biology community in the 1950s, has today been expanded to virtually all research space in organic synthesis.

The integration of HTE capabilities with organic electrosynthesis is needed to dramatically improve the
adoption of electrochemistry in organic chemistry research.\textsuperscript{27} To this end, we aim to design an HTE platform that is compatible with the current HTE infrastructure and allows for the screening of all common electrochemical reaction parameters. An ideal HTE reactor for electrosynthesis will enable rapid screening of features unique to electrochemistry such as mode of operation (constant current or constant voltage), applied current or potential, applied charge, and electrode material. In addition, the reactor should be amenable to reactions at different temperatures and under air- and water-free conditions. Furthermore, the reactor will accommodate micro-scale reactions (< 400 μL total reaction volume) to reduce material consumption, minimize cost, and improve safety. Finally, the screening platform should accommodate recent advancements such as electrophotochemistry\textsuperscript{2,28} and alternating current electrolysis.\textsuperscript{29,30} Notably, despite significant recent advances, a general, standardized HTE reactor that satisfies these desirable criteria remains elusive.\textsuperscript{31}

Herein, we report the design of a 24-well plate high-throughput electrosynthesis reactor, namely HT\textsuperscript{e}-Chem, that presents all the aforementioned features and capabilities. By showcasing a selection of electrosynthetic transformations, we demonstrate the versatility of this new reactor for reaction discovery, optimization, and library synthesis in a variety of electrochemical applications.

**Design of HT\textsuperscript{e}-Chem**

An important design principle for the HT\textsuperscript{e}-Chem reactor is that it needs to be based on a standardized commercial platform and should be operationally simple, modular, and chemically resistant. Our investigation commenced with a 24-well microscale HTE photochemistry reactor (Fig. 1A), which features a 4 row by 6 column plate with 8 x 30 mm glass vial inserts. This parent reactor has been extensively used in both academic and industrial settings for high-throughput screening experiments and is compatible with standardized equipment and existing infrastructure such as automated reagent addition systems and pre-plated reagent libraries.\textsuperscript{20,32} The reactor block has an insert for a temperature probe and can be heated or cooled using common laboratory temperature-control systems; it is also compatible with both magnetic rotary and tumble stirring. Finally, the base allows for efficient illumination of the vials with commercial HTE photochemistry equipment through the bottom of the reactor. Thus, this parent system provides an ideal platform for our design of a standardized and modular electrochemical HTE reactor.

The HT\textsuperscript{e}-Chem (Fig. 1) employs two parallel cylindrical rods with a diameter of 1.6 mm as the electrodes (E). Numerous conducting materials are commercially available in these dimensions in high purity, including graphite, nickel, stainless steel, copper, titanium, magnesium, zinc, platinum, tin, and aluminum. The electrodes are held closely apart at 1.54 mm distance (from surface to surface) and can perfectly fit in the microscale cells of the baseplate, resulting in a reaction volume (200–600 μL) of up to 25 times lower than a typical electrochemical batch reactor. This compact arrangement reduces reagent usage and ensures sufficient conductivity at a low electrolyte concentration, while the cell geometry resembles that of a traditional batch cell and provides good scaling behavior. To keep the electrodes parallel, we designed an alignment plate (D) made from a chemically resistant and...
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The modular design of the HTeChem reactor allows for flexibility of reaction setup because the replacement of a single component is possible. For example, alternating current electrolysis can be easily implemented by substituting the power controllers for a waveform generator. In addition, electrophotochemical reactions can be readily carried out using an external, commercially available LED array (vide infra). Further, the design could, in principle, be extended to a 96-well plate format without major modifications. In the following section, we present the application of the HTeChem for a variety of known and new electrosynthetic transformations and demonstrate its exciting potential to accelerate the broader implementation of electrochemistry in the pharmaceutical industry.

**Applications**

We investigated the use of the HTeeChem in a suite of oxidative and reductive transformations under constant current and constant voltage conditions, as well as in electrophotocatalytic systems. Potential use cases for reaction discovery, screening, and library synthesis were surveyed.

**Oxidative Azidooxygenation Under Constant Current Conditions.** We set out to demonstrate the reliability and reproducibility of the HTeChem by quantifying the well-to-well variability in a TEMPO-mediated azidooxygenation reaction previously reported by the Lin group. This model reaction was carried out in all 24 wells of the reactor under identical conditions using constant current electrolysis. Scaling down the reaction to the microscale (17.5 μmol, 380 μL) with the HTeChem furnished the difunctionalized styrene (2) with an average yield of 89.1%, comparable to the 89% yield obtained in the original report under constant voltage conditions on a 0.2 mmol scale (Scheme 1). The percent standard deviation was only 2.2% and there was no impact on the vial position even using a commonplace rotary stir plate. The reliability of the HTeChem reactor was further validated by researchers in three independent laboratories at Cornell University and Merck & Co., Inc., Kenilworth, NJ, USA (see SI for details).

**Scheme 1. Azidooxygenation of 4-methoxystyrene (1) adapted from constant voltage to constant current conditions on the HTeChem. The yields are determined by HPLC using dimethyl terephthalate as the internal standard.**

Lin (2018):

![Scheme 1](image-url)
Reductive Silylation Using A Sacrificial Anode. In many non-mediated electrochemical reactions, identifying the correct electrode material is key to rendering a reaction efficient and selective. As the unique surface chemistry influences the optimal electrochemical parameters, an ideal experimental design would evaluate various electrode materials with a range of current densities or applied voltages. The HTChem presents precisely such capabilities, which we demonstrate in the further optimization of a reductive alylic silylation reaction recently developed in the Lin lab. By screening four currents with six cathode materials, we obtained the desired allylsilane (4) in a highest yield of 98% using platinum cathodes, representing a 23% increase over the original optimal 75% yield obtained on 1 mmol scale with a graphite cathode (Figure 2). Intriguingly, use of stainless steel and platinum cathodes furnished the highest yields at 1.5–2.0 mA, whereas employment of graphite cathodes provided high yields at 0.5–1.0 mA. These data highlight that factorial parallel screening allows the optimization toward a global maximum, while the traditional OPAT approach is prone to converging to local maxima (e.g. optimizing the current with a graphite cathode would result in the highest yield of 89%). Furthermore, the successful demonstration of this reaction showcases the HTChem’s compatibility with moisture sensitive, highly reducing conditions (–3.1 V vs. SCE or lower associated with the reduction of trimethylsilyl chloride). This implies the HTChem reactor has potential for use in other reactions that are mediated electrochemically.

Electrophotocatalysis Under Constant Voltage Conditions. By screening four currents with a graphite cathode, we aimed to leverage the HTChem to optimize this electrophotocatalytic transformation. Thus, three cell voltages, three supporting electrolytes, and two different reaction times were surveyed. Furthermore, the capability of 24-well parallel screening allows crucial control experiments to be carried out simultaneously with reaction optimization under identical conditions. Accordingly, we included no electrolysis, no light, no electrolysis with no light, and no catalyst control reactions within the same plate (Figure 3). Using the HTChem provided results resulting in a three-fold rate increase and furnished the desired product (7) in 78% yield after 24 h, as compared to the originally reported 71% yield after 72 h on 0.4 mmol scale, likely as a result of the improved light penetration and LED optical power. Notably, these reactions are also carried out under constant voltage electrolysis conditions, which is another important capability of the HTChem reactor. As HTChem is the first standardized platform for electrophotochemistry, we further established the reproducibility of the protocol. Setting up identical reactions in all 24 wells of the HTChem gave an average yield of 75.0% with a percent standard deviation of 5.2% (see SI).

Figure 2. (A) Reaction conditions for the optimization of the reductive synthesis of allyl silanes. The reaction conditions that are varied on the plate are shown in bold. (B) Plate map and data for the optimization of the reductive synthesis of allyl silanes. The yields are determined by HPLC using 1,3,5-trimethoxy benzene as the internal standard.

Figure 3. (A) Reaction conditions for the optimization of the oxidative C–H amination of mesitylene (5) with pyrazol (6). The reaction conditions that are varied on the plate are shown in bold. (B) Trisaminocyclopropenium (TAC)(9) organocatalyst. (C) HTChem while running the electrophotocatalytic reaction. The reactor is irradiated by the Lumidox II® Gen II 24-position LED array at 445 nm with an optical power of 60 mW per vial. (D) 24-well plate data and experimental design. The yields are determined by HPLC using dimethyl terephthalate as the internal standard.
Discovery and Optimization of the Chlorination of Arylboronic Acids. Building on the successful adaptation of a variety of electrochemical reactions to the HT\textsuperscript{e}Chem, we set out to optimize a previously unknown transformation, namely the electrochemical chlorination of boronic acids. We envisioned that the anodic oxidation of an arylboronic acid would give rise to an aryI radical,\textsuperscript{39} which could then be intercepted by an persistent chlorine atom source such as [Mn\textsuperscript{III}]-Cl. This Mn\textsuperscript{III} species has been employed in our previous work as an effective Cl-atom transfer catalyst and can also be generated electrochemically from a Mn\textsuperscript{II} salt.\textsuperscript{40} This methodology would be complementary to reports of electrochemical bromination and iodonation\textsuperscript{41} of boronic acids and provide a sustainable alternative to known methods using stoichiometric electrophilic chlorination reagents.\textsuperscript{42,43}

The reaction was initially developed on a 0.2 mmol scale using home-made electrolysis cells by subjecting 4-tert-butylphenyl boronic acid (12) to our previously reported electrochemical alkene dichlorination conditions (see SI for details).\textsuperscript{44} When the electrolysis was conducted at 65°C, we detected a moderate yield (~30%) of the desired 4-chloro-tertbutylbenzene (10) in a procedure with manganese and a comparable 64% yield of 10 in metal-free conditions. Subsequently, we employed the HT\textsuperscript{e}Chem to identify the design parameters that were important for observed reactivities with the goal of optimizing the chlorination reaction while minimizing the detrimental side reaction (Figure 4). In a single plate, the substrate and activating agent, chloride source, proton source, catalyst, and necessity of electrolysis were investigated. These data revealed several key insights into the reaction: (1) 11 is not an intermediate en route to product 10 (via electrophilic arene chlorination), (2) electricity is required to furnish the desired product, and (3) protodeborylation of the boronic acid occurs spontaneously with AcOH but not with the more weakly acidic pyridine-HCl. Notably, by using 4-tert-butylphenyl boronic acid (as opposed to Ar–BF\textsubscript{3}K) as the substrate and pyridine hydrochloride as the acid and chloride source, protodeborylation was fully suppressed, giving 71% of the desired product (10) in a procedure with manganese and a comparable 64% yield of 10 in metal-free conditions.

With these promising results, we carried out additional optimization of various other parameters including the catalyst (none, Mn(OTf)\textsubscript{2}, Ni(OTf)\textsubscript{2}, Fe(OTf)\textsubscript{3}), applied charges (2 F, 3 F, 4 F), and loading of pyridine-HCl (5, 20 equiv) on a single plate, which resulted in a further improved, metal-free protocol delivering quantitative yield (>99%) of 10 (see SI for details). Scaling this chlorination to 0.2 mmol scale furnished the same quantitative yield. These optimization data also showed that our initial mechanistic design employing a Mn catalyst is unnecessary, and that the electrochemical chlorinating agent can be generated directly via anodic oxidation. Finally, we note that the chlorination of boronic acids was rapidly developed through only two plates of screening experiments, thus significantly accelerating the optimization workflow vis-à-vis traditional screening strategies.

Electrochemical C–C Coupling Reactions. Various electrochemical C–C coupling reactions have been reported recently, and adopting such transformations using the HT\textsuperscript{e}Chem could enable rapid generation of diverse product libraries for medicinal chemistry studies. We successfully translated two such reactions, which were originally discovered using larger-scale commercial reactors, to the HT\textsuperscript{e}Chem conditions (Scheme 2). For example, Baran and Minteer disclosed a reductive ketone-olefin coupling for the synthesis of medicinally relevant scaffolds.\textsuperscript{46} To adapt this method to the HT\textsuperscript{e}Chem, we investigated a variety of cathode materials and applied currents and successfully replicated the reported results. Notably, the screening experiments allowed us to discovery a new optimal system using copper as the cathode, which was not examined in the original report and provided an improved 94% yield in the synthesis of 16 (see SI for details).

In another report by Waldvogel and co-workers, an oxidative C–H/C–H coupling was achieved to furnish valuable diarylmethanes 19 with hydrogen as the sole by-product. In an one-pot sequence, an electrochemically generated benzyl hexafluoroisopropyl ether 20 undergoes subsequent substitution with an electron-rich arene 18 in the presence of trifluoroacetic acid.\textsuperscript{47} This report showed that boron-doped diamond (BDD) electrodes promoted the optimal reactivity, generating product 19 in 93% yield on 1 mmol scale. Interestingly, the HT\textsuperscript{e}Chem screening led us to further improve this methodology at a 17.5 µmol scale and obtain the coupling product in quantitative yield with less expensive graphite electrodes (see SI for details).

**Figure 4.** (A) Reaction conditions for the optimization of the electrochemical chlorination of aryI boronic acid (9). The reaction conditions that are varied on the plate are shown in bold. (B) Plate map with reaction yields of the desired 4-chloro-tertbutylbenzene (10) (green) and of tert-butylbenzene (11) (red). The yields are determined by HPLC using dimethyl terephthalate as the internal standard.
procedure on 1 mmol scale to µmol scale, the applied current cyanopyridines. Conditions via the coupling of iminium chlorides with synthesis of 24 hindered primary amines under reductive industry for parallel library synthesis using electrochemical capability is of substantial interest to the pharmaceutical rapidly generate a 24-membered library of compounds. This optimization, use of the HTLibrary synthesis.

(See the SI for isolated yields and analytical details).

determined by HPLC range from good to moderate (83 yields

Figure 5. A reductive library synthesis of hindered amines. The yields shown in the plate map are LCAP. Calibrated yields determined by HPLC range from good to moderate (83–53%) (See the SI for isolated yields and analytical details).
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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

BDD, boron-doped diamond; CCE, constant current electrolysis; CVE, constant voltage electrolysis; HPLC, high performance liquid chromatography; HTE, high-throughput experimentation; LCAP, liquid chromatography area percent; LED, light-emitting diode; OFAT, one-factor-at-a-time; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

References


See SI for Harsh Chemical Conditions That Might Not Be Fully Compatible with Our System.


Preliminary Data Suggested That the Azide Loading Could Be Reduced to 1.5 Equivalents under Constant Current Conditions.


Ye, K. Y.; Pombar, G.; Fu, N.; Sauer, G. S.; Keresztes, I.; Lin, S. Anodically Coupled Electrosynthesis for the


