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Electroorganic Synthesis Under Flow Conditions

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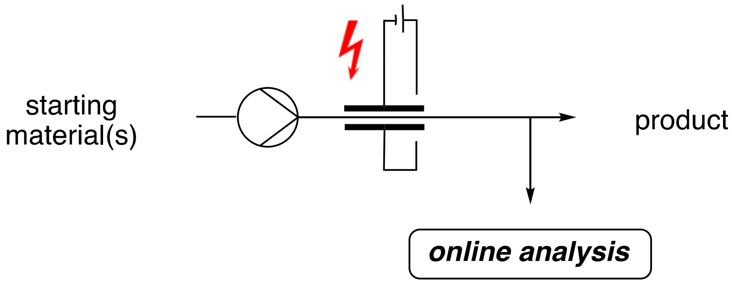
CONSPECTUS

Despite the long history of electroorganic synthesis, it did not participate in the mainstream of chemical research for long time. This is probably due to the lack of equipment and standardized protocols. However nowadays organic electrochemistry is witnessing a renaissance and a wide range of interesting electrochemical transformations and methodologies has been developed, not only for academic purposes but also for large scale industrial production. Depending on the source of electricity, electrochemical methods can be inherently green, environmentally benign and can be easily controlled to achieve high levels of selectivity. In addition, the generation and consumption of reactive or unstable intermediates and hazardous reagents can be achieved in a safe way. Limitations of traditional batch-type electrochemical methods such as the restricted electrode surface, the necessity of supporting electrolytes and difficulties in scaling up can be alleviated using electrochemical flow cells. Microreactors offer high surface-to-volume ratios and enable precise control over temperature, residence time, flow rate and pressure. In addition, efficient mixing, enhanced mass and heat transfer and handling of small volumes leads to simpler scaling-up protocols and minimize safety concerns. Electrolysis under flow conditions reduces the possibility of overoxidation as the reaction mixture is flown continuously out of the reactor in contrast to traditional batch-type electrolysis cells.



In this account, we highlight our contributions in the area of electroorganic synthesis under flow conditions over the past decade. We have designed and manufactured different generations of electrochemical flow cells. The first-generation reactor was effectively used in developing a simple one-step synthesis of diaryliodonium salts and used in proof-of-concept reactions such as the trifluoromethylation of electron-deficient alkenes *via* Kolbe electrolysis of trifluoroacetic acid in addition to the selective deprotection of isonicotinyloxycarbonyl (*i*Noc) group from carbonates and thiocarbonates. The improved second-generation flow cell enabled the development of efficient synthesis of isoindolinones, benzothiazoles and thiazolopyridines, achieving gram-scale of some of the products easily without changing the reactor design or re-optimizing the reaction parameters. In addition, the same reactor was used in the development of an efficient continuous flow electrochemical synthesis of hypervalent iodine reagents. The generated unstable hypervalent iodine reagents were easily used without isolation in various oxidative transformations in a coupled flow/flow manner and could be easily transformed into bench-stable reagents *via* quantitative ligand exchange with the appropriate acids. Our second-generation reactor was further improved and commercialized by Vapourtec Ltd. We have demonstrated the power of online analysis in accelerating optimizations and methodology development. Online mass spectrometry enabled fast screening of the charge needed for the cyclization of amides to isoindolinones. The power of online 2D-HPLC combined with a DoE approach empowered the rapid optimization of stereoselective electrochemical alkoxylations of amino acid derivatives.

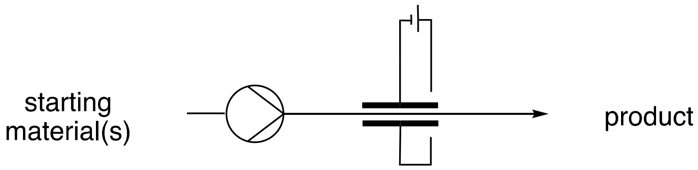
1. INTRODUCTION

Electroorganic synthesis has a long history that can be dated back to first experiments carried out by Faraday in the eighteenth century. Nowadays, it has been rediscovered as a very powerful method and a wide range of interesting electrochemical transformations have been developed on the laboratory scale as well as on industrial scale.[1–4] Electrochemical methods are inherently green and environmentally benign as toxic and dangerous chemical oxidizing and reducing agents are replaced by electricity, which, when generated from renewable sources, will improve the overall ecological footprint of the chemical transformations.[5] Careful selection of the electrode material, control of the electrode potential and the composition of the double layer are powerful tools to direct the outcome of electrochemical transformations. This enables to achieve high degrees of selectivity and facilitates the controlled generation and consumption of reactive intermediates and hazardous reagents.[1a] Despite the clear advantages of applying electricity in organic synthesis, it stayed out of the mainstream for a long time.[6] This could be due to the lack of standardized equipment and protocols,[7] which makes the reproduction of results difficult. Due to the poor conductivity of organic solvents, supporting electrolytes are required to reduce the ohmic resistance which also poses difficulties in scaling up.[8]

The intrinsic advantages of microreactor technology and flow chemistry techniques[9] can offer practical solutions for the typical limitations of batch-type electrolysis. Microreactors have high surface-to-volume ratios and allow a very precise control over reaction parameters such as temperature, residence time, flow rate and pressure. Efficient mixing, enhanced mass and heat transfer and handling of small volumes are additional factors that increase the safety of flow methods and simplify scaling-up protocols.[10,11] Therefore, combining the advantages of electroorganic synthesis and flow chemistry is highly desirable as it will lead to safer, more selective, controllable, more efficient, economic and eco-friendly chemical processes.

2. ELECTROCHEMICAL FLOW CELLS

Electrolysis under flow conditions is as simple as pumping the reactant solution into an arrangement of two electrodes with a typically small interelectrode gap. The short distance between the two electrodes reduces the ohmic resistance, therefore the electrolysis can be done with low concentrations of supporting electrolyte or even without supporting electrolyte at all. In addition, removing the reaction mixture continuously under flow conditions, minimises the opportunity of overoxidation, which is one of the main problems of electrolysis under batch conditions. A schematic representation of such a reaction setup is shown in Scheme 1.



Scheme 1. Schematic representation of electrolysis under flow conditions.

Several research groups have developed their own implementation of the above electrode arrangement and many electrochemical flow cells have been designed, produced and utilized in a wide range of chemical transformations.[12–14] Some electrochemical flow cells have also been commercialized[15–17] which has encouraged more research groups to consider flow electrochemistry as a viable alternative in synthesis.

Our laboratory has also contributed to the design, production and application of electrochemical flow cells. In 2011, our first-generation of electrochemical flow reactors has been published.[18] This reactor consists of two circular platinum electrodes (0.1 mm thick) mounted on two PTFE disks (35 mm diameter, 4 mm height). The two electrodes are separated by a fluorinated ethylene propylene (FEP) foil of different thicknesses, into which a rectangular reaction channel is cut (3 × 30 mm) giving an overall reaction volume of 23 μL (FEP foil 254 μm thick). The housing for the two electrodes and the FEP gasket comprised of two circular aluminium bodies (50 mm diameter, 25 mm height). The whole device is sandwiched together by steel screws and wing nuts (Figure 1). This reactor allowed the performance of simple electrochemical flow protocols such as the synthesis of diaryliodonium salts,[18] the difluoro- and trifluoromethylation of alkenes[19] and the deprotection of the isonicotinyloxycarbonyl (*i*Noc) protecting group from carbonates and thiocarbonates[20] (*vide infra*).

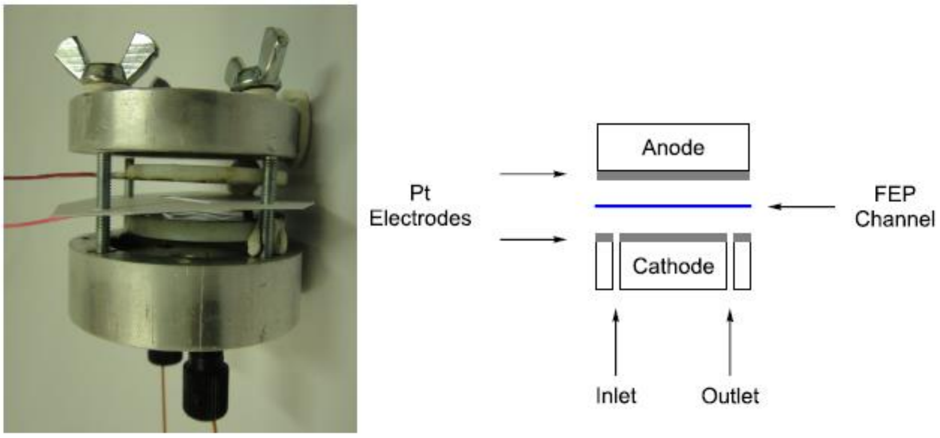


Figure 1. First-generation electrochemical flow cell developed by Wirth *et al*.

Although the above reactor was used successfully in several promising transformations, it suffered from some limitations. Only platinum electrodes could be used and, in addition, removing the glued thin platinum foils for replacement or repair was a tedious process. Loss of expensive electrode cut off material as a result of the circular reactor design and too fragile electrical connections to the electrode were additional major limitations. An improved reactor (second-generation) was designed and manufactured.[21] The second-generation reactor (Figure 2) comprises of two square aluminium bodies (75 x 75 x 25 mm) containing a square space in the centre (50 x 50 mm^2, variable deepness), where the electrodes are placed. The electrodes are connected by copper plates or stainless steel sheets welded to copper wires, and connected to the power supply. The two electrodes are again separated by a fluorinated ethylene propylene (FEP) spacer and the reaction takes place in a channel cut into the FEP spacer. The robustness and flexibility of the new design allowed the use of any electrode material which can be easily changed or replaced. This led to a much more facile and efficient screening of reaction conditions and longer operation times with minimum maintenance and easy cleaning. In addition, the material of the reactor body could be changed from aluminium to polymeric material that allowed its fast manufacture using low cost additive manufacturing (3D printing) with the possibility of facile modification / customization.

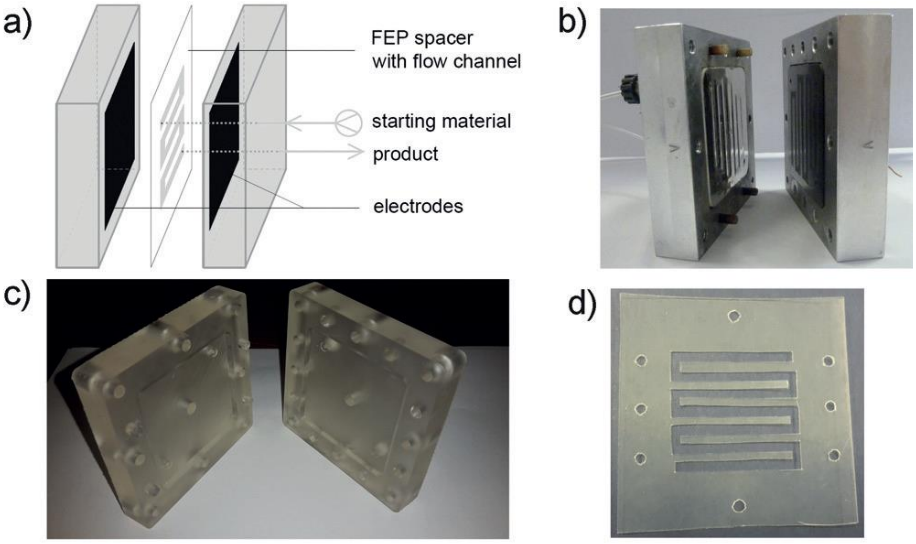


Figure 2. Second-generation electrochemical flow cell developed by Wirth *et al.* a) Schematic representation; b) Aluminium reactor; c) Reactor made by additive manufacturing (3D printing) using resins consisting of methacrylic acid esters; d) FEP spacer with flow channel. Reproduced with permission from ref. 21. Copyright 2017 Wiley.

The reliability and efficiency of the second-generation reactor and its successful application in the synthesis of isoindolinones[21] and benzothiazoles[22] as shown below encouraged the leading flow technology company Vapourtec Ltd[23] to adopt the design as a base for their commercial electrochemical flow reactor, the Ion reactor. The Ion reactor[24] (Figure 3) features several additional advantages including the ability to heat and cool the reactor in the temperature range between –10 °C to +100 °C, to operate at pressures up to 5 bar, a large flexibility in electrode distances through different spacers, also modified electrode area / reactor volumes and the option to add a second flow stream during the electrolysis into the reactor.

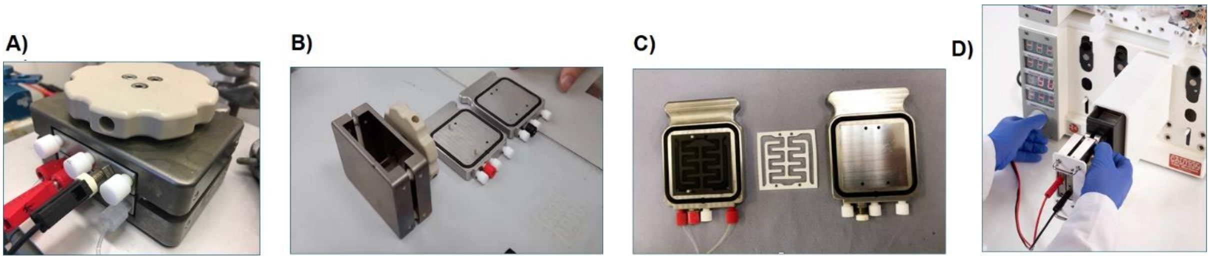
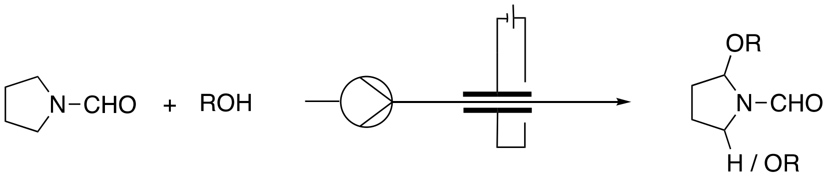


Figure 3. Vapourtec Ion electrochemical reactor. A) Standalone reactor; B) Reactor-housing and electrode holders; C) Electrodes on holders and spacer; D) Reactor integrated with Vapourtec cooling and heating module.

The performance of the Vapourtec electrochemical Ion reactor was assessed in our laboratory using the Shono oxidation[25] as a model reaction. The Ion reactor proved to be very efficient where the model substrate pyrrolidine-1-carbaldehyde **1** was converted to the corresponding methoxylated product **2** (R = Me) in 94% yield at a relatively high flow rate (2 mL/min) in a single pass, allowing the reaction to benefit from the cooling capabilities of the system. Alcohols rather than methanol such as ethanol, *n*-propanol, *n*-butanol, and *n*-pentanol were also successfully used as nucleophiles in this reaction. In addition, using two serial connected reactors led to the formation of the dialkoxylated products in reasonable to high yields (Scheme 2).[26]



1

2

11 examples
monoalkoxy products up to 94%
dialkoxy products up to 83%

Scheme 2. Assessment of the productivity of the Ion electrochemical reactor using Shono oxidation as a model reaction.

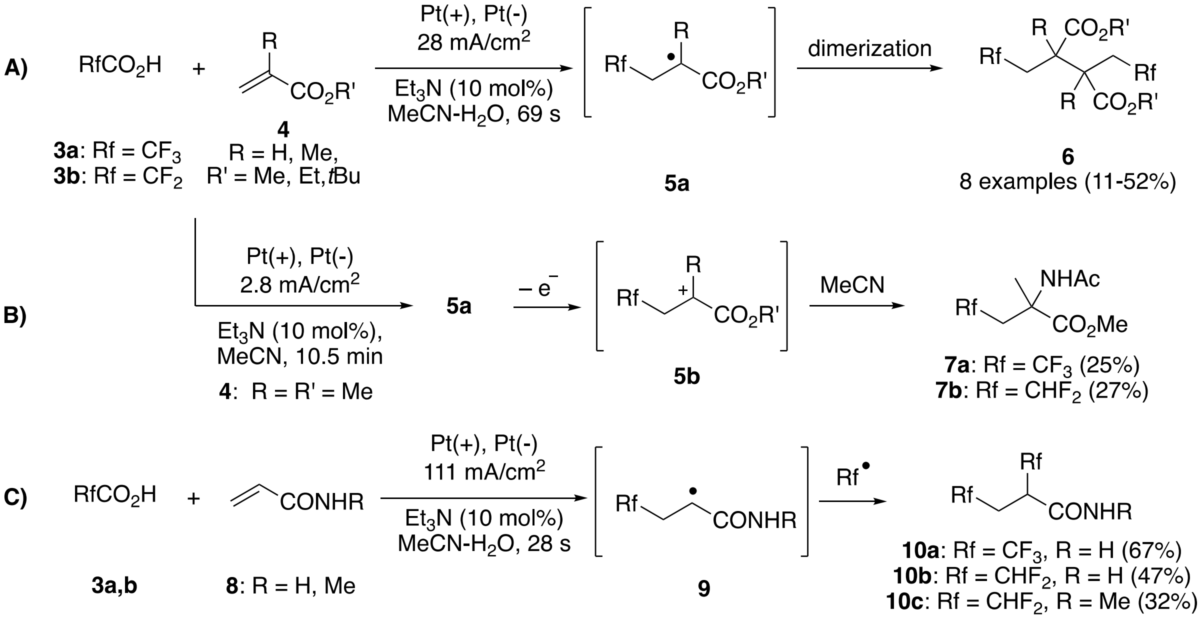
3. SYNTHETIC APPLICATIONS

Over the last decade we have contributed to the development and the advancement of electroorganic synthesis under flow conditions. Using initially our in-house manufactured electrochemical flow cells of the first and second generation and now the commercially available Vapourtec electrochemical Ion reactor, many interesting chemical transformations have been developed in our laboratory that will be highlighted in the following sections.

3.1. DIFLUORO- AND TRIFLUOROMETHYLATION OF ELECTRON-DEFICIENT ALKENES

Nowadays, many drugs, drug candidates and agrochemicals incorporate fluorine. The introduction of fluorine into drug molecules is known to increase its lipophilicity and improve its metabolic stability and several pharmacokinetic properties.[27] The importance of the trifluoromethyl group (CF_3) as a structural motif in many chemicals of pharmaceutical interest is notable and led to a burst in the development of reagents and methodologies of its incorporation into organic molecules.[28] Despite the development of a wide range of highly effective trifluoromethylation agents,[28,29] trifluoroacetic acid remains a highly appealing source of the CF_3 group in terms of availability and cost, especially on large scale.[30]

We investigated the flow electrochemical generation of trifluoromethyl and difluoromethyl radicals (Rf radicals) *via* Kolbe electrolysis[31,32] of trifluoro acetic acid (TFA) and difluoro acetic acid (DFA), respectively, using the first-generation electrochemical flow cell (Figure 1).[19] Both carboxylic acids underwent facile electrochemical decarboxylation in the presence of 10 mol% of Et_3N in MeCN-H_2O mixture and the generated radicals were trapped using electron-deficient alkenes. The reaction outcome could easily be controlled by adjusting the current density and flow rate (Scheme 3). Performing the reaction by applying a current density of 28 mA/cm^2 and a flow rate of 20 μL/min using a 23 μL channel (calculated residence time of 69 s) led to the dimerization of the radical **5a** resulting from the addition of the initially formed Rf radicals to the double bond of the olefinic substrates (Scheme 3A). Changing the solvent to acetonitrile and lowering the current density to 2.4 mA/cm^2 and the flow rate to 5 μL/min, using a larger channel (53 μL, RT = 10.5 min) led to further oxidation of radical **5a** to the corresponding carbocation **5b** that is reaction in a Ritter reaction with the solvent giving the acetamidation product **7** (Scheme 3B). Using acrylamide (**8**) as the olefinic substrate at a higher current density (111 mA/cm^2) and a short residence time (28 s) led to an 1,2-addition of Rf radicals across the double bond (Scheme 3C). This behaviour could be attributed to the high current density that can concentrate the Rf radicals on the electrode surface and the presence of nitrogen in the substrate which led to a stronger adsorption of the acrylamide on the electrode surface slowing down the diffusion of the initially formed radical to the bulk solution allowing more time to react with a second Rf radical. The isolated yields in all cases were either similar or better than the yields of the corresponding experiments in batch.[33]

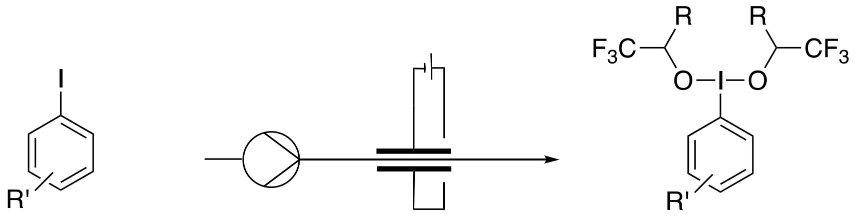


Scheme 3. Electrochemical generation of CF_3 and CHF_2 radicals and reactions with electron-deficient alkenes.

3.2. CONTINUOS FLOW SYNTHESIS OF HYPERVALENT IODINE REAGENTS

Hypervalent iodine reagents are versatile, mild, selective oxidants that found tremendous applications in organic synthesis.[34,35] They are environmentally benign alternatives to heavy metal oxidants, but their preparation requires the use of chemical oxidants usually in excess generating a lot of waste,[36] which is not atom efficient and renders the use of hypervalent iodine reagents less green. On the other hand, synthesis of hypervalent iodine reagents *via* anodic oxidation of iodoarenes eliminates the necessity of hazardous and sometimes expensive chemical oxidants and improves the ecological impact of the whole process.[37–39]

Recently, we reported the first general approach for the synthesis of iodine(III) reagents *via* anodic oxidation under flow conditions.[40] Using our second-generation flow cell (Figure 2) and the Vapourtec electrochemical Ion reactor (Figure 3), the anodic oxidation of iodoarenes was optimized and a reliable continuous flow generator of hypervalent iodine reagents developed. Initial trials to directly obtain common bench stable hypervalent iodine reagents such as (diacetoxyiodo)benzene or Koser's reagent by oxidation of iodobenzene were not successful as some experiments couldn't be completed due to a fast blockage of the reactor channels. However, using fluorinated alcohols such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 2,2,2-trifluoroethanol (TFE) and glassy carbon (GC) as anode material allowed the successful anodic oxidation of iodobenzene to the corresponding iodine(III) reagents **12a** and **12b** in quantitative and 80% yield, respectively, while the reported yields of similar transformations in batch[41] never exceeded 67% yield. Under the optimized reaction conditions several iodoarenes were oxidized to the corresponding hypervalent iodine reagents in good to high yields as shown in Scheme 4.



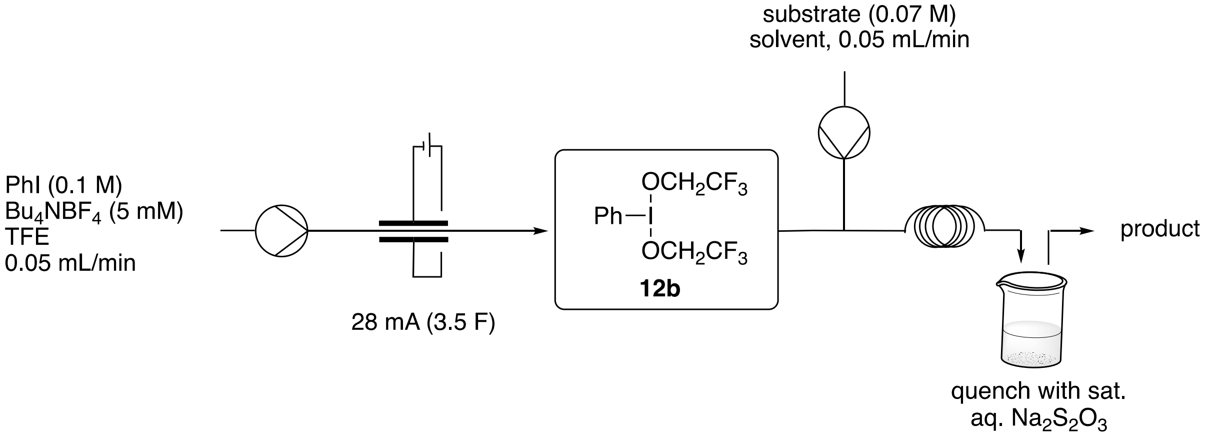
11
in $F_3CCH(R)$-OH

12

R = CF_3	R = H
12a R' = H: quant.	**12b** R' = H: 80%
12c R' = 4-Me: 85%	**12d** R' = 4-Me: 85%
12e R' = 4-OMe: decomp.	**12f** R' = 4-OMe: decomp.
12g R' = 4-CF_3: 67%.	**12h** R' = 4-CF_3: 54%
12i R' = 3-Me: 42%.	**12j** R' = 3-Me: 43%
12k R' = 3-CF3: 65%.	**12l** R' = 3-CF_3: NR

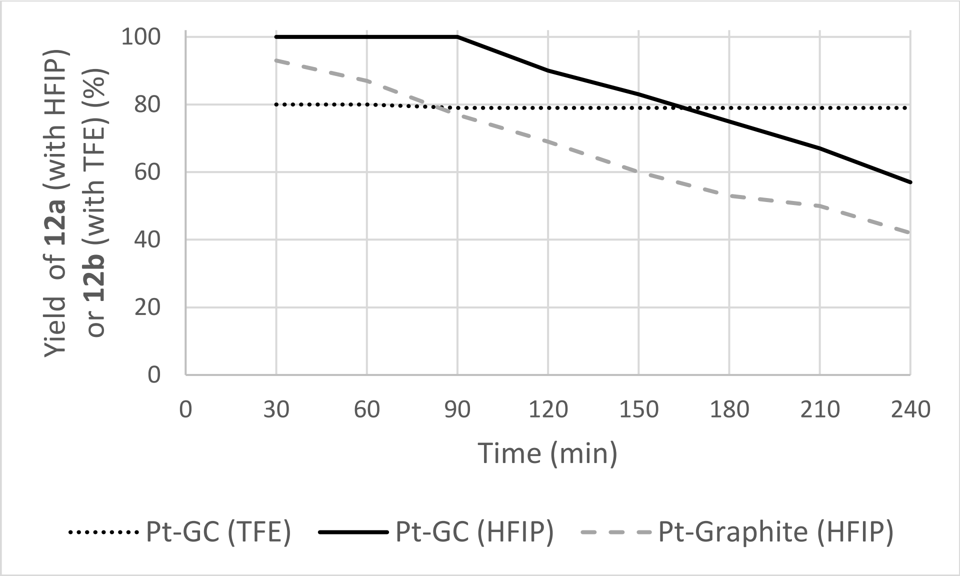
Scheme 4. Continuous flow electrochemical generation of hypervalent iodine reagents.

However, the above iodine(III) reagents **12** are not bench stable and decompose rapidly upon removal of the solvent. But they can be used directly in various hypervalent iodine mediated oxidative transformations such as oxidation of sulfides, phenol dearomatization, oxidative heterocyclization and *α*-functionalization of carbonyl compounds. These reactions were all easily achieved in high yields by coupling the flow of the *in situ* electrochemically generated unstable hypervalent iodine reagents with a second flow of the substrate, illustrating the power of combining the benefits of electrochemistry, hypervalent iodine chemistry and flow chemistry using a very simple reaction setup (Scheme 5).



Scheme 5. Electrochemical generation and utilization of hypervalent iodine reagent **12b** in a coupled flow reaction system.

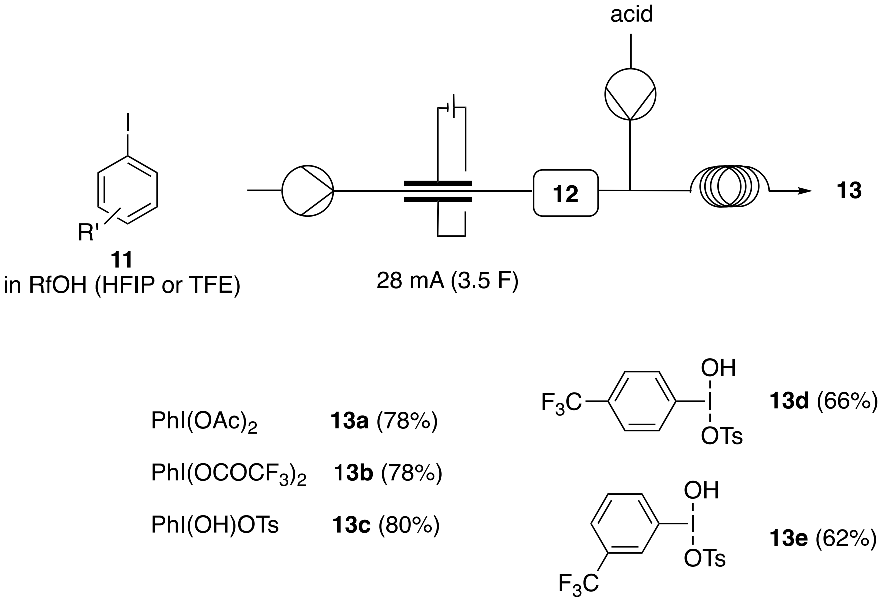
Although the anodic oxidation of iodobenzene in HFIP was more efficient (100% yield) than in TFE (80% yield), the above reactions (Scheme 5) were performed using TFE rather than HFIP because the product of the electrochemical step decreased over time due to the passivation of electrodes when using HFIP which was not observed when using a glassy carbon (GC) anode and TFE (Figure 4).



[PhI] = 0.1 M, [TBATFB] = 0.005 M, Flow rate = 0.05 mL/min. Yield calculated by ^{1}H NMR from crude solution using $PhNO_2$ as internal standard.

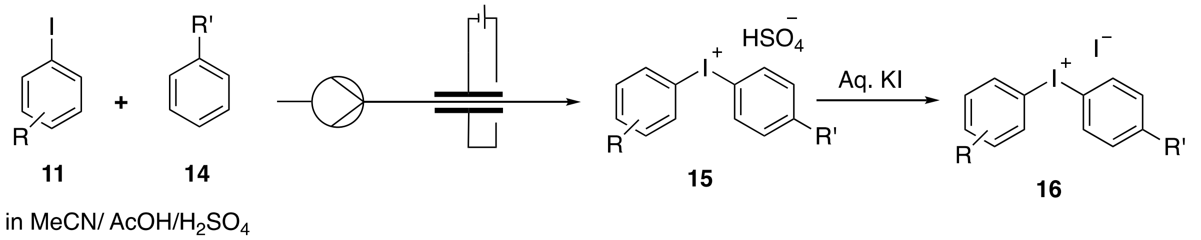
Figure 4. Time-dependent yield of the electrogenerated iodine(III) reagents **12a** and **12b** under different reaction conditions.

In addition, the unstable electrochemically generated hypervalent iodine reagents **12** were easily transformed into stable hypervalent iodine reagents *via* quantitative ligand exchange by treatment with acids in batch or flow (Scheme 6), leading to a very facile synthesis of the otherwise challenging electron-deficient hypervalent iodine reagents **13d** and **13e**.



Scheme 6. Electrochemical synthesis of bench stable hypervalent iodine reagents.

Eight years ago, we have developed a simple one-step protocol for the synthesis of diaryliodonium salts[18] using our first-generation electrochemical flow cell. Injecting the iodoarene and arene in an acetonitrile/acetic anhydride/sulfuric acid mixture into the reactor (80 µL/min) while applying a constant current (30 mA) led to the formation of diaryliodonium salts **15** that are precipitated in the form of iodides **16** upon treatment with aqueous potassium iodide. The products were collected by simple filtration (Scheme 7). The symmetrical and unsymmetrical diaryliodonium salts **16** were obtained in moderate to good yields (18–72%). The method is operationally simple and highlighted the feasibility of using electrolysis under flow conditions in iodine chemistry.

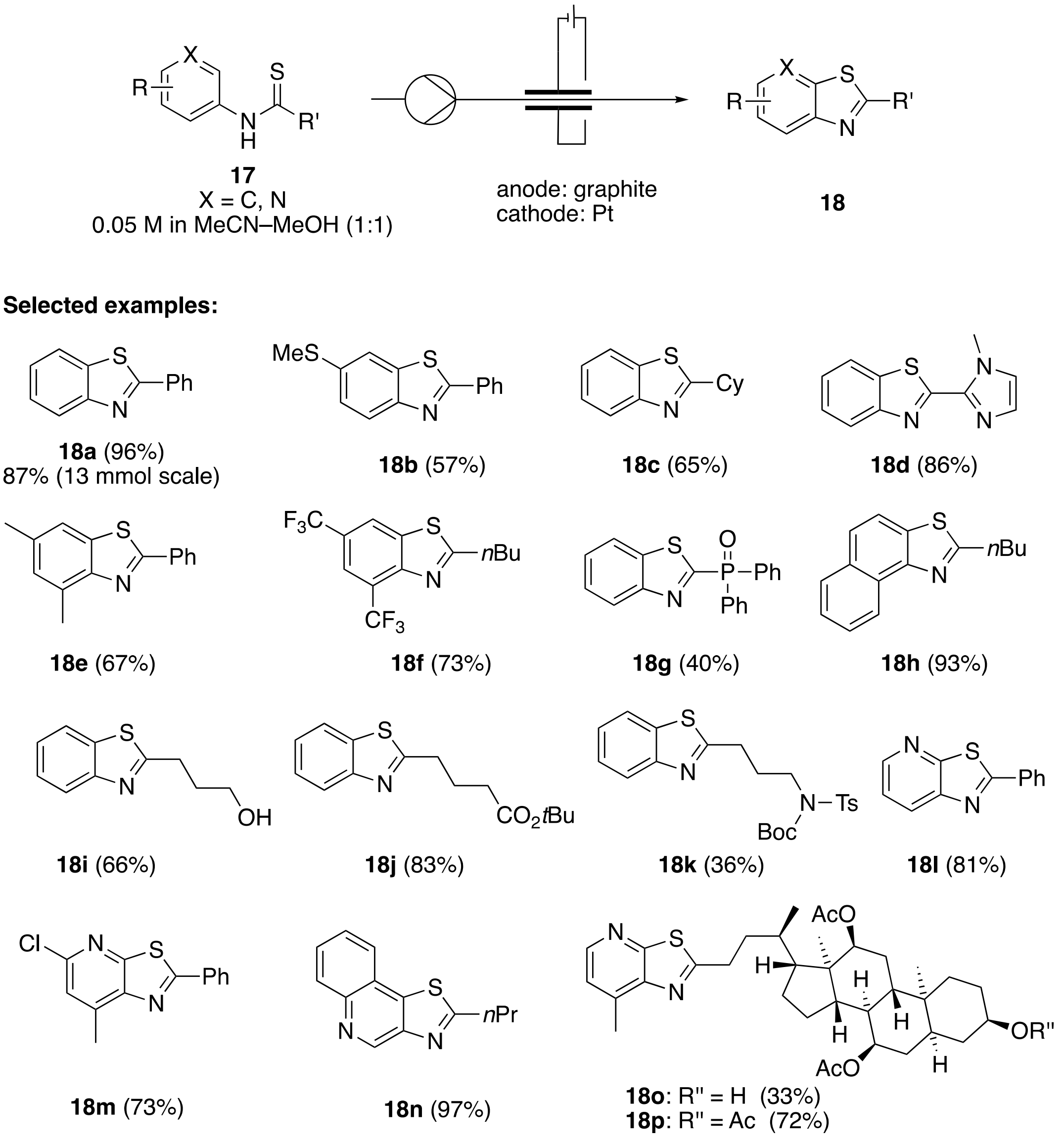


16a R = 4-Me, R' = Me: 72%
16b R = 4-Me, R' = Et: 51%
16c R = 4-Me, R' = *i*Pr: 60%
16d R = H, R' = Me: 44%
16e R = H, R' = Et: 39%
16f R = H, R' = *i*Pr: 19%
16g R = H, R' = *t*Bu: 64%
16h R = 3-Me, R' = Me: 36%
16i R = 3-Me, R' = Et: 25%
16j R = 3-Me,R' = *i*Pr: 18%

Scheme 7. One step electrochemical synthesis of iodonium salts.

3.3. DEHYDROGENATIVE C-S BOND FORMATION: SYNTHESIS OF BENZOTHIAZOLES AND THIAZOLOPYRIDINES

Benzothiazole is a notable structural motif in biologically active compounds.[42] The oxidative cyclization of *N*-arylthioamides is one of the major routes for constructing benzothiazoles. The process is extensively studied and can be achieved using metal catalysts,[43,44] hypervalent iodine reagents[45] and photoredox catalysis.[46] Also the electrochemical synthesis of benzothiazoles from *N*-arylthioamides was reported since 1979.[47,48] Recently, Xu *et al.*[49] developed an efficient electrochemical synthesis of benzothiazoles and thiazolopyridines in batch. Despite the wide substrate scope (49 examples) and the good efficiency (48-95% yield), the use of supporting electrolytes, the requirement of inert atmosphere and the use of TEMPO as a mediator in addition to difficulties in scale-up were considered to be limitations. In collaboration with Prof. Xu, we developed an efficient and reliable electrochemical method under flow conditions using our second-generation electrochemical flow cell.[22] Under flow conditions, laboratory grade solvents were used and there was no need for inert atmosphere, supporting electrolyte or catalyst. In addition, scaling up to gram scale allowed the easy synthesis of 2.4 g of **18a** in high yield (87%) using the same reactor for a longer time. The reaction showed a wide substrate scope (28 substrates) giving benzothiazoles and thiazolopyridines with a variety of functional groups in high average yield (Scheme 8). The current efficiency under flow conditions was improved in most cases compared to the corresponding reactions under batch conditions. The flow protocol improved the reported methods of the synthesis of benzothiazoles and clearly highlights the power and benefits of the electrochemical synthesis under flow conditions.[50]



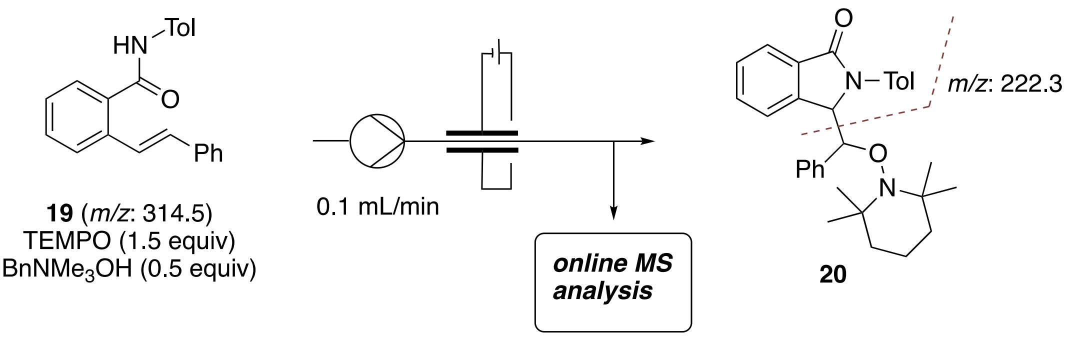
Scheme 8. Electrochemical synthesis of benzothiazoles and thiazolopyridines *via* dehydrogenative C-S bond formation.

4. COMBINING THE POWER OF FLOW ELECTROORGANIC SYNTHESIS AND ONLINE ANALYSIS

Developing a new reaction or methodology requires often a detailed investigation of reaction parameters and conditions as well as the execution of control experiments during the optimization phase, which is a lengthy and sometimes tedious and cumbersome process. The optimization process could be accelerated and simplified using appropriate online or inline analysis, where the reaction mixture is automatically sampled in intervals. Otherwise the analyser sensor or probe can be placed the inside the reaction vessel or solvent stream.[51]

4.1 ONLINE MASS SPECTROMETRY

Using the second-generation electrochemical flow cell, an efficient TEMPO-mediated electrochemical synthesis of isoindolinones was achieved *via* intramolecular trapping of the electrochemically generated radicals of double bond containing amide substrates.[21] The intramolecular cyclization of substrates **19** to isoindolinones **20** was studied in detail (Scheme 9). The outlet of the electrochemical reactor was connected to an online mass spectrometer *via* an automatic sampling valve. Monitoring the intensity of the base peak of the starting material **19** (*m/z* = 314.5 $[M+H]^+$) and the fragment of *m/z* = 222.3 of the cyclized product **20** (base peak), as shown in Figure 5, allowed a fast optimization of the required charge. It showed that at least 3 F/mol is necessary to achieve full conversion of the starting material.



Scheme 9. Monitoring the electrochemical cyclization of amide **19** to isoindolinone **20** with online mass spectrometric analysis. Reproduced with permission from ref. 21. Copyright 2017 Wiley.

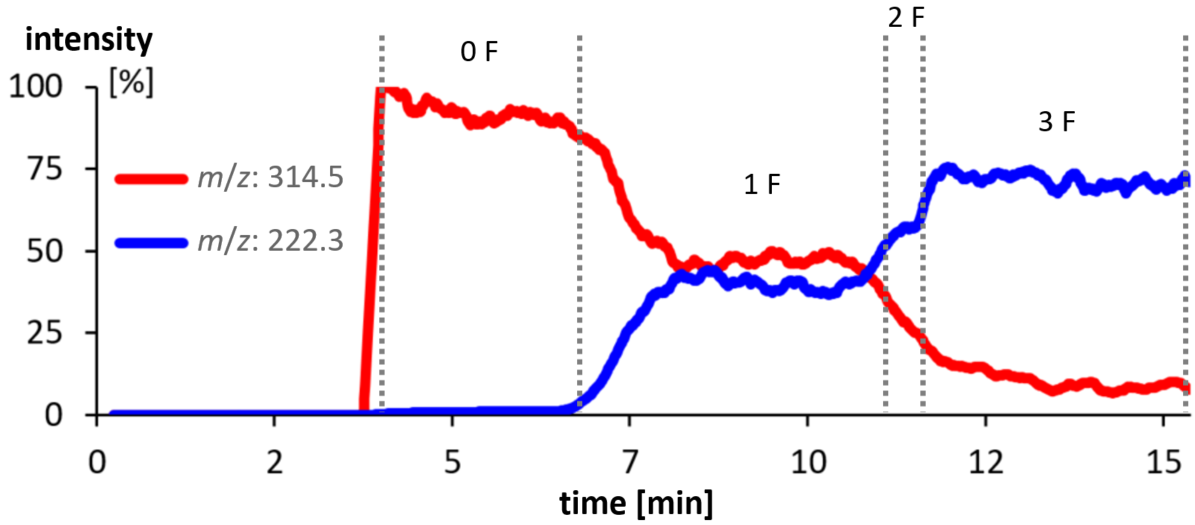
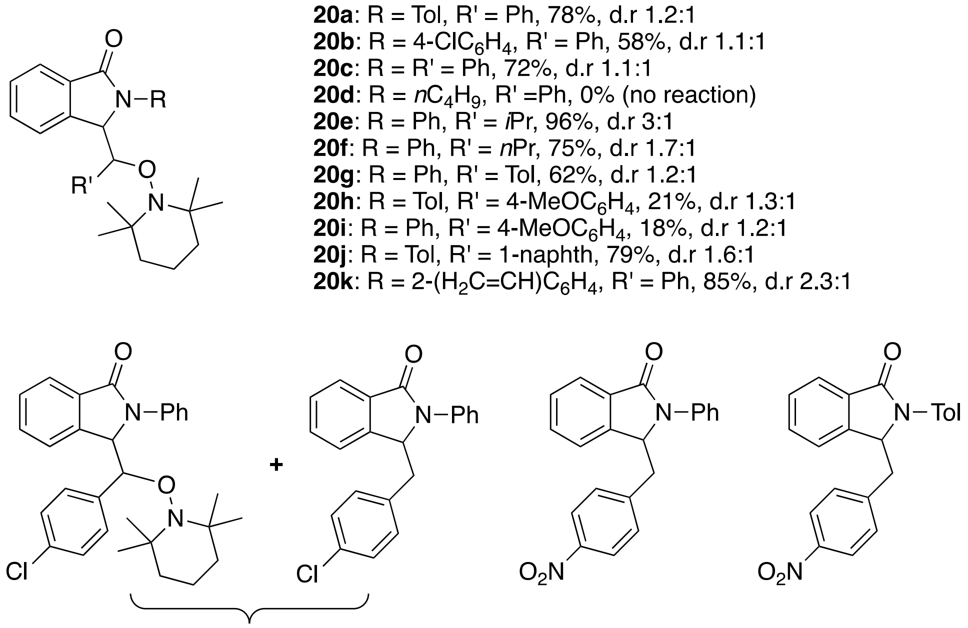


Figure 5. The output of the online MS analysis of the electrochemical conversion of **19** to **20**. Reproduced with permission from ref. 21. Copyright 2017 Wiley.

Under the optimized reaction conditions, different substrates were converted to the corresponding isoindolinones in 18–96% yield (Figure 6). The products arise from the addition of the anodically generated amidoyl radical to the double bond and trapping of the generated carbon radical by TEMPO. The presence of aromatic substituents on the amide nitrogen is crucial to stabilize the initially formed amidoyl radical and achieve the cyclization. With aliphatic substituents on the amidic nitrogen (R = *n*Bu), no reaction was observed. With electron-deficient alkenes, the TEMPO addition was not observed and the reduced products **23** and **24** were obtained in excellent yields, which was attributed to the higher stability of the generated carbon radicals that leads to their facile reduction at the cathode rather than trapping with TEMPO.



21 (56%, dr. 1.3:1) **22** (21%) **23** (91%) **24** (94%)

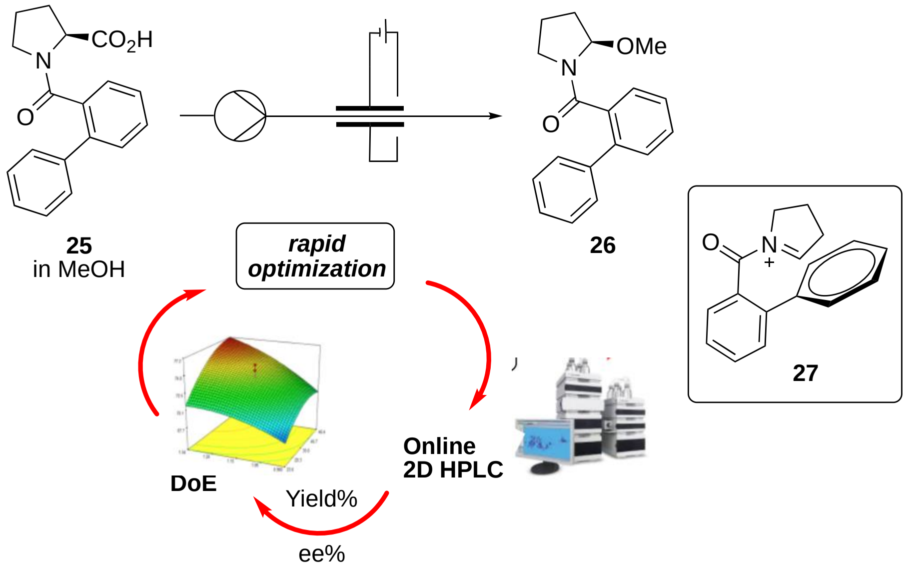
Figure 6. Substrate scope of the electrochemical synthesis of isoindolinones. Reproduced with permission from ref. 21. Copyright 2017 Wiley.

4.2 ONLINE 2D-HPLC

Optimization of stereoselective transformations requires information not only on the reaction yield but also on the stereoselectivity of each experiment, which can be quite time-consuming. Hence, developing analytical methods to obtain the desired information directly from the reaction mixture without isolation or purification are of great importance and have the potential to dramatically speed up the optimization process.

We developed a rapid, reliable and efficient analytical method to evaluate the outcome of the stereoselective electrochemical alkoxylation of amino acid derivatives.[52] The electrochemical transformation of the proline derivative **25** into the methoxylated product **26** was studied in detail (Scheme 10). The reaction proceeds *via* the electrochemical decarboxylation of **25** and oxidation of the resulting radical to the iminium ion **27** which is trapped by methanol. The presence of the bulky substituent at the nitrogen atom is responsible of the face selectivity of the nucleophilic addition of methanol to **27**, and the formation of product **26** that retains the chirality of the starting material, a phenomenon known as memory of chirality.[53,54]

Connecting the outlet of the Vapourtec Ion electrochemical rector with an 2D-HPLC system *via* an automatic sampling valve enabled to obtaining the percentage yield and the percentage enantiomeric excess of each experiment within only 15 minutes. With this rapid analytical method in hand, we were able to obtain a wealth of information about the reaction in a very short time. In only 24 hours we obtained enough information for statistical analysis using Design of Experiments (DoE) software. The DoE led to a fast identification of significant reaction parameters and demonstrated the high impact of charge and anode material on the reaction outcome and the low impact of temperature. With the help of DoE we were able to achieve high yields (up to 100%) and enantioselectivities up to 70% in a very short time, demonstrating the power of combining electrochemical flow synthesis, online analysis and DoE approach.



Scheme 10. Memory of chirality: Fast optimization with online 2D-HPLC and DoE approach.

5. CONCLUSIONS AND OUTLOOK

Application of electrochemical methods in organic synthesis is witnessing a renaissance and becoming a better recognized methodology in chemical research. Electroorganic synthesis under flow conditions offer practical solutions to some of the limitations of batch-type electrolysis such as the necessity of supporting electrolyte, limited reaction area and scaling up difficulties. In addition, lack of standardized equipment that retarded the development of electrochemical methods for long time is not a limitation anymore after the commercialization of several batch and flow electrochemical devices.

Over the past decade, we have contributed effectively to the development of electrochemical flow cells and to the establishment of reliable electrochemical methods for organic synthesis. In 2011 we published our first-generation flow cell, which was successfully applied in various transformations such as developing a one-step protocol for the synthesis of diaryliodonium salts and electrochemical generation of di- and trifluoromethyl radicals from readily available di- and trifluoroacetic acid, in addition to electrochemical deprotection isonicotinyloxycarbonyl (*i*Noc) group from carbonates and thiocarbamates.

In 2017 we reported our second-generation electrochemical flow cell. The new design is more efficient, more flexible, more robust and can operate for long time with minimal maintenance. In addition, it can be customised and manufactured quickly with low cost *via* 3D printing. This reactor was used to develop efficient and simple electrochemical protocols for the construction of heterocyclic systems such as Isoindolinones, and benzothiazoles and thiazolopyridines in addition to the development of a general continuous flow synthesis of hypervalent iodine reagent. Furthermore, this reactor was further improved and commercialized by the leading flow technology company Vapourtec Ltd under the name Ion reactor.

Electroorganic synthesis under flow conditions is still in its infancy and offers a lot of opportunities for developing elegant chemical transformations with high efficiency, low cost and minimum waste. We have demonstrated the power of combining electroorganic synthesis, flow chemistry, online analysis techniques and DoE approach in speeding up methodology development. Using DoE approach in combination with fast and efficient online analysis methods is a very interesting research area that needs more efforts to be established as routine practices in synthetic organic chemistry research.

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The authors declare no conflict of interests.

Biographies

Mohamed Elsherbini was born 1980 in Mansoura, north of Egypt. He completed his PhD in 2014 at Mansoura University under the supervision of Prof. H. H. Zoorob and Prof. W. S. Hamama. His doctoral studies were on the synthesis of biologically active selenium-containing heterocycles. After working as a chemistry lecturer at the Saudi Mining Polytechnic, he moved to Cardiff University in 2016 to join the group of Prof. T. Wirth, where he is currently doing research in the chemistry of hypervalent iodine reagents and organic electrochemistry.

Thomas Wirth is professor of organic chemistry at Cardiff University. After receiving his PhD from TU Berlin, he stayed at Kyoto University as a JSPS fellow. Then he worked independently at the University of Basel before taking up his current position at Cardiff University in 2000. He was awarded the Werner-Prize from the New Swiss Chemical Society, the Wolfson Research Merit Award from the Royal Society and the Bader-Award from the Royal Society of Chemistry. In 2016 he was elected as a fellow of The Learned Society of Wales. His main interests of research concern stereoselective electrophilic reactions, oxidative transformations with hypervalent iodine reagents and flow chemistry performed in microreactors.

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