Flow cells and reactor design: general discussion

Anas Alkayal, Mickael Avanthay, Belen Batanero, Pim Broersen, Richard C. D. Brown, Luke Chen, Ping-Chang Chuang, Toshio Fuchigami, Shinsuke Inagi, Dipannita Kalyani, Kevin Lam, Maya Landis, T. Leo Liu, Matthew J. Milner, Robert Price, Naoki Shida and Thomas Wirth

Anas Alkayal opened discussion of the paper by Thomas Wirth: Have you tried to run a control reaction in the absence of oxygen? Did this lead to undesired compounds such as dimers? I would like to take this occasion to mention that I am always interested in Professor Wirth's research. I am keen to attend his lectures at conferences. Furthermore, I usually share his latest papers with my colleagues in our group meetings/literature review weeks.

Thomas Wirth answered: There is no reaction in the absence of oxygen, no superoxide radical anion can be generated. The substrate might decompose in an uncontrolled way, depending on its oxidation potential.

Anas Alkayal asked: Since you have not realised a big yield of by-products, does that mean the flow chemistry makes the procedure more productive?

Thomas Wirth replied: Often flow chemistry does produce cleaner products due to better de ned reaction conditions. Typically shorter reaction times compared to batch also can suppress the formation of side products.

Anas Alkayal questioned: When you start the reaction there are 3 phenyl rings around the double bond, but the corresponding carbonyl product has just 2 phenyl rings; why was one of the rings released?

Thomas Wirth answered: In the reaction the double bond is cleaved similar to an ozonisation. Therefore, two different carbonyl-containing products are being obtained. Any aldehyde obtained in the reaction is further oxidised and cannot be isolated.

Ping-Chang Chuang asked: In the paper (https://doi.org/10.1039/d3fd00050h), higher product yields are achieved when applying back-pressure in your ow system. What is the reason for this kind of set-up?

Thomas Wirth replied: A pressurised system probably allows a better mixing in the biphasic system. Back-pressure regulation has been applied to have a careful control over the residence time. Results without a back-pressure regulator indicate less de ned reaction conditions.

Luke Chen requested: Please can you comment on the mass balance given the sub-optimal yields. Is this the result of poor conversion of starting material or are there other impurities being formed? If there is high starting material recovery, can the process be recycled to achieve full conversion?

Thomas Wirth responded: Usually there is no starting material le and only product is formed. We are currently investigating the stability of the product(s) towards the reaction conditions and if decomposition could be a reason for lower yields. Other side products have not been observed or identified.

Toshio Fuchigami asked: In order to generate super oxide ions efficiently, gas diffusion electrodes seem be more suitable than ordinary cathodes. Have you tried?

Thomas Wirth replied: This is an excellent suggestion. We have not tried this, but will certainly find out if the use of gas diffusion electrodes can enhance such reactions.

Shinsuke Inagi enquired: Where does the oxygen reduction occur, in the liquid or gas phase? Although the following reaction takes place in solution, superoxide ions can also be generated in the gas phase and dissolve readily in solution due to their improved solubility. If this works, the segmented ow approach would be very significant.

Thomas Wirth answered: In the batch reaction, the oxygen reduction will take place in the liquid phase. We assume the same happens in the ow reaction, but here also the gas is in direct contact with the electrode for a potential reduction. One would need to carefully think of a possible experimental setup for distinguishing between these reactions.

Richard C. D. Brown said: With reference to the mechanism proposed in Fig. 3 of your paper (https://doi.org/10.1039/d3fd00050h), radical cation and superoxide intermediates are generated at opposing electrodes. These species are then required to reach each other through mass transport in order for them to react to give intermediate A. Have you investigated the influence of the interelectrode gap on the reaction?

Thomas Wirth responded: In this reaction, we have not yet investigated the influence of the interelectrode gap. In other reactions with oxygen gas we have done this and did not find a meaningful relation between the outcome of the reaction and the interelectrode gap.

Micka¨el Avanthay asked: Is it possible to saturate the solution for the ow reactor with oxygen (or to run a “batch solution” through the ow reactor), to avoid the need of a gas inlet and a back-pressure regulator?

Thomas Wirth replied: Using an oxygen saturated solution is possible, but will yield only trace amounts of product. Additional oxygen is necessary (also in the batch reaction, which is performed under an oxygen atmosphere).

Belen Batanero enquired: Have you tested another electrolyte or solvent, for instance lithium perchlorate or DMF? Flow is not high; have you tried reactions with faster ow? What should happen?

Thomas Wirth responded: We have not yet investigated other solvents or electrolytes as we used mainly the reported (batch) reaction conditions. Higher ow rates lead to lower conversions.

Belen Batanero commented: In this reaction the low yield can be justified by a further reaction of the obtained product (ketone) with superoxide anion.

Thomas Wirth replied: We are currently investigating the ketone stability under the reaction conditions.

Matthew J. Milner asked: Dioxetanes such as the proposed intermediate are in special cases stable enough for isolation, suggesting that the decomposition of B to form the product ketone may be slow enough for the dioxetane to persist in solution at least long enough to reach an electrode. What is the lifetime of such di- and tri-substituted dioxetanes? Is it possible that the dioxetane is being further oxidized or reduced at one of the electrodes, especially given the constant current conditions and the relatively high potential required to oxidize an alkene?

Thomas Wirth responded: We have never attempted to isolate the proposed dioxetane intermediates. They probably can be oxidised further if they have a sufficiently long lifetime under the reaction conditions.

Micka¨el Avanthay opened discussion of the paper by Richard C. D. Brown: The selectivity increases as more mediator is used with very good selectivity at 1 equivalent. Would one observe an erosion of that selectivity with an excess of mediator due to reduction of the intermediate radicals by the mediator?

Richard C. D. Brown replied: We did not originally perform simulations using an excess of the mediator (phenanthrene) as it is desirable to use as little mediator as possible for practical reasons. However, the point raised is highly relevant as the concentration of the mediator is expected to affect the flux of mediator towards the electrode and, consequently, the flux of mediator radical anion away from the electrode. To address the question more fully we have performed additional simulations with 2.0 and 10 equivalents of mediator (Fig. 1 here). For the present reaction system, the effects are rather subtle, and can be summarised as follows:

Both show almost identical selectivity pro les to the simulation using 1 equivalent of phenanthrene. Formation of the cyclised product is favoured (reaction layer detachment is achieved very rapidly).

The mechanism switches from direct to mediated a er a shorter time interval as the amount of mediator is increased.

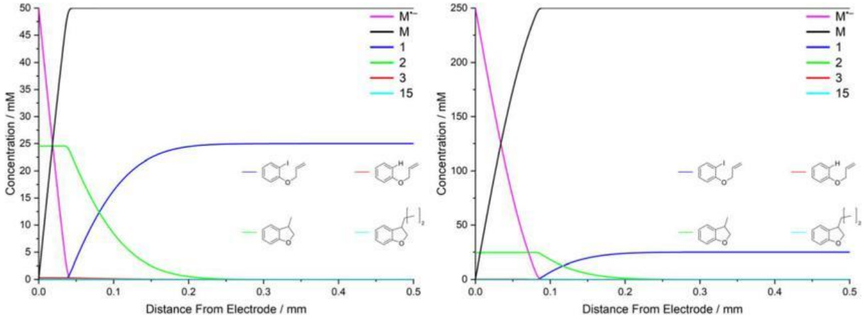

Fig. 1 Concentration profiles for species 1, 2, 3, 15, M and Mc¯ for simulated electrolysis under constant potential of −2.8 V vs. SCE at t = 1 s. Left: mediator loading of 2.0 equivalents. Right: mediator loading of 10 equivalents.

Increased flux of the mediator radical anion pushes the homogeneous reaction layer outwards from the electrode, and “detachment” from the electrode occurs sooner with higher concentrations of mediator.

Toshio Fuchigami commented: Cathodic reduction of halides usually generates radical and/or anionic species. Therefore, mediators are usually used in order to generate radicals selectively.

Richard C. D. Brown responded: Yes, that is correct. The purpose of our simulations is to better understand where the homogeneous coupled chemistry takes place relative to the electrode, and the factors controlling this. We also highlight that it is not necessary for the mediator to be more easily reduced than the substrate (with respect to reduction potentials), as is frequently stated in the literature.

Toshio Fuchigami remarked: Cathodically generated radical species are further reduced to generate anionic species. Sonication should be effective for avoiding the further reduction of radical species since the resulting radical species move away from the cathode. Furthermore, sonication causes local heating, which promotes radical cyclization.[1]

1 Y. Shen, M. Atobe and T. Fuchigami, Org. Lett., 2004, 6, 2441, DOI: 10.1021/ol049152f.

Richard C. D. Brown responded: This is an interesting point, and increasing temperature and sonication would indeed be anticipated to have a bene cial effect on mass transport and rates of cyclisation as is highlighted in Professor Fuchigami’s elegant studies of oxidative cyclisation reactions using sonoelectrosynthesis. It would be interesting to examine the influence of sonication using our ow reactors, although there are some technical challenges that we need to overcome.

Pim Broersen asked: What happens to the system once you introduce turbulence to it, would the selectivity go down since more substrate would reach the electrode? Also, would you say that this is one of the few ow systems where laminar ow would be preferred over turbulent ow to increase selectivity?

Richard C. D. Brown answered: This is an important point, and any increase in mass transport will compress the diffusion layer towards the electrode. Turbulent ow would be expected to increase the flux of the substrate to the electrode, pushing the homogeneous reaction layer closer to the electrode. There would be conditions where turbulent ow would lead to decreased selectivity – as implied in the question – depending on the opposing fluxes of the mediator (M) radical anion and substrate. Therefore, in some situations laminar ow may be advantageous. Our feeling is, though, that even with turbulent ow, detachment of the reaction layer (albeit much closer to the electrode) may be achieved with sufficient flux of mediator radical anion and very fast electron transfer (ET) and coupled chemistry. We have yet to simulate turbulent ow conditions, although preliminary simulation using a rotating disc electrode did show the effect of compressing the diffusion layer so that it was closer to the electrode.

Naoki Shida enquired: The model study of ow electrolysis with the molecular mediator by COMSOL seems highly useful. Is it possible to use this type of simulation to predict the concentration of mediator for the bulk conversion of the substrate under ow electrochemical conditions?

Richard C. D. Brown responded: The simulations will prove useful in deter-mining optimum conditions such as the concentration of the mediator required in preparative ow reactions. In the present case, the key criterium is to achieve detachment of the homogeneous ET from the cathode. We are currently devel-oping models to identify the key parameters or groups of conditions where this can be achieved. It does, however, require some knowledge of kinetic and physical parameters for the speci c process to input into the simulations.

Luke Chen opened discussion of the paper by Dipannita Kalyani: Do you see reproducibility in each of the wells across the plate and are duplicate wells required? How well can the reactions from the small, plate scale be transferred to more synthetically useful scales and have you been able to isolate products?

Dipannita Kalyani replied: We have done validation studies to show the reproducibility across wells. We have been able to scale up the reactions from HTe¯Chem scale to 0.3 mmol scale with a minor change in reaction conditions.

Kevin Lam asked: Is there a specific reason for choosing a cobalt electrode?

Dipannita Kalyani answered: Use of the cobalt electrode was important to suppress the background reaction in the absence of electricity.

T. Leo Liu requested: Kalyani, thanks for sharing the interesting cross-electrophile results. Can you comment on the difference with pyridinium vs. alkyl halide regarding reaction selectivity and scope?

Dipannita Kalyani responded: We have not done the systematic comparison yet.

Kevin Lam asked: Are pyridinium compounds of choice for the industry? They seem to lead to a lot of waste and not to be the most atom-economical options.

Dipannita Kalyani answered: Pyridinium chemistry is ne for medicinal chemistry.

Belen Batanero enquired: Have you used a ow cell or a batch conventional cell? Is your reaction performed under constant current conditions?

Dipannita Kalyani replied: Have not used a ow cell yet. We have used IKA ElectraSyn for scale ups. Constant current or constant voltage conditions work for our reactions.

Kevin Lam asked: What is the best way to start collaborating with Merck & Co., Inc. Rahway, NJ, USA?

Dipannita Kalyani answered: Best starting point is to connect with a scientist at Merck & Co., Inc. Rahway, NJ, USA.

Maya Landis communicated: Would it be possible to investigate the likelihood that a substrate would be suitable for your reactions using other electrochemical techniques, e.g., cyclic voltammetry (CV), and do these techniques play a large role in R&D at companies like Merck & Co., Inc. Rahway, NJ, USA?

Dipannita Kalyani communicated in reply: Yes CV is appropriate to use as necessary.

Luke Chen opened a general discussion: My colleagues in medicinal chemistry are reluctant to try electrochemistry, let alone make use of ow and other reactor types. What advice and suggestions do you have to help bridge the gap in accessibility for the average synthetic organic chemist to make it easier to adopt new, developing technologies?

Richard C. D. Brown replied: It is a great time to try electrosynthesis, either in ow or batch reactors. There is a rapidly expanding array of transformations available including many that are well aligned with medicinal chemistry targets. There is also a good range of commercial equipment – budget permitting – to help lower the barrier and to provide a greater degree of reproducibility. Some caution should be applied, however, and a bad initial experience is more likely to deter future efforts. It is important to make sure that electrochemistry is appropriate for the planned synthesis, and can meet the objectives in terms of rates of production. This is relevant to the specific electrosynthesis and the equipment being used. Batch electrolysis cells are more familiar to the synthetic chemist, but ow offers an easier pathway to scale up. Providing time and freedom to employees to explore emerging technologies is important. This may be supported by collabo-rations with academia, and there are a growing number of groups focussing on electrosynthesis that would welcome interactions with industry. Great value can also be gained from collaborating with electrochemists and electrochemical engineers to avoid pitfalls, and disappointment. Visits to academic laboratories, or sponsoring a PhD student who can also spend some time engaged in technology transfer at the company, can also contribute to increase uptake of new technologies.

Dipannita Kalyani responded: Having training materials is helpful. Also showing the value of EChem in projects to access targets that are otherwise difficult to access can help folks to appreciate and use EChem.

Thomas Wirth answered: Nowadays with commercially available equipment the threshold to use this technique should be lower, but advice from a specialist might still be needed in order to understand the many reaction parameters which can play a role in electrochemical reactions.

Robert Price asked: In a lot of the work presented at this discussion, single ow cell modules are employed and, in some cases, full conversion of reactants is not achieved. Do you see the progression of these ow cells as remaining as single modules that could be linked in series to achieve full conversion, or is it likely that stack platforms/modules (like those developed in the fuel cell/electrolyser elds) could be employed to reduce ow cell footprint and increase conversion? Could this technology be borrowed (with modi cations) from existing designs within the aforementioned communities?

Dipannita Kalyani answered: We have not used ow cells for the pyridinium chemistry.

Richard C. D. Brown responded: Achieving high conversions in a reasonable timeframe has been one of the challenges in preparative organic electrosynthesis. This can be addressed through increasing electrode surface area/volume ratios and by improving mass transport.[1] Both of these features are commonly designed into ow electrolysis cells to improve productivity. Turbulence promoters are commonly used to improve mass transport in simple parallel plate reactors.[2] We have developed narrow interelectrode gap ow cells with extended channels as one way to achieve high conversion in a single pass.[3] Linking two or more cells in series can be viewed as effectively extending the length of the ow channel, and the potential (current) can be optimised for each stage. Higher conversion may also be achieved by either slowing down the ow rate or by multiple passes through the reactor, which is commonly applied in industrial electrosynthesis. An excellent example is the stacked bipolar electrode cells used at BASF on a massive scale.[4] It is correct that cells used in other areas, such as fuel cells and water puri cation, can and have been adapted for organic electrosynthesis and knowledge from other areas should be taken advantage of. In some cases the materials will need to be adapted to allow for use with organic solvents.

1 D. Pletcher, R. A. Green and R. C. D. Brown, Chem. Rev., 2018, 118, 4573–4591, DOI: 10.1021/acs.chemrev.7b00360.
2 A. A. Folgueiras-Amador, A. E. Teuten, D. Pletcher and R. C. D. Brown, React. Chem. Eng., 2020, 5, 712–718, DOI: 10.1039/d0re00019a.
3 (a) R. A. Green, R. C. D. Brown and D. Pletcher, J. Flow Chem., 2015, 5, 31–36, DOI: 10.1556/ jfc-d-14-00027; (b) R. C. D. Brown, Chem. Rec., 2021, 21, 2472–2487, DOI: 10.1002/ tcr.202100163.

4 D. Hoormann, H. Pütter and J. Jörissen, Chem. Ing. Tech., 2005, 77, 1363–1376, DOI: 10.1002/cite.200500086.

Thomas Wirth replied: Stacked ow reactors are already reported and have been used to increase conversion and/or productivity. Industrial scale stacked reactors are also reported, often including cooling layers/liquids for thermal management.

Naoki Shida enquired: Automated electrosynthesis is highly desired to generate large amounts of data. Flow electrosynthesis and high-throughput electrosynthesis are critical enablers. Is there any idea or comment on implementing these technologies for automated electrosynthesis?

Richard C. D. Brown replied: Parallel batch electrosynthesis systems have been developed and some are commercially available. These formats are undoubtedly useful for reaction optimisation and high throughput synthesis. We don't have any direct experience of these, but technical points to consider would include ensuring that electrodes can be easily cleaned and electrolyte doesn't complicate the analysis or isolation. Flow systems with on-line real-time analysis seem attractive for optimisation as conditions such as ow rate, current density, concentrations etc. can all be varied using computer control. Complications include potential for electrodes fouling, and the need to change the cell to investigate different electrode materials. Together with experts in self-optimisation (Professor Mike George and co-workers), we explored optimisation of an alcohol oxidation in the Ammonite 8 ow electrolysis cell using a "self-optimisation" system developed by their team.[1]

1 J. Ke, C. Gao, A. A. Folgueiras-Amador, K. E. Jolley, O. de Frutos, C. Mateos, J. A. Rinc´on, R. C. D. Brown, M. Poliakoff and M. W. George, Appl. Spectrosc., 2022, 76, 38–50.

Thomas Wirth responded: We have already reported some results using automated electrochemistry, which are also taken on by several other groups working in this area as fully automated systems are now also commercially available. See ref. 1–3.

1 N. Amri and T. Wirth, Synlett, 2020, 31, 1894, DOI: 10.1055/s-0040-1707141.
2 N. Amri and T. Wirth, Synthesis, 2020, 52, 1751, DOI: 10.1055/s-0039-1690868.
3 N. Amri and T. Wirth, J. Org. Chem., 2021, 86, 15961, DOI: 10.1021/acs.joc.1c00860.

Pim Broersen asked: When you do some technoeconomic analysis on scaling electrocatalytic reactions such as large scale production of hydrogen, the material use quickly becomes prohibitive. A PEM electrolyzer is for example much more expensive to build than a nickel alkaline electrolysis system. When looking at the products made in your reactions, there is a bit more leeway as they are more expensive. Where do you think the limit is in material use for the electrodes for these more complex chemicals? Will it be possible to design these systems at scale when more expensive electrode materials such as gold or platinum need to be used, or is it similar to the electrocatalysis eld and are we limited to cheap materials such as stainless steel and carbon?

Richard C. D. Brown responded: Cheaper materials such as graphite and steel will always be attractive for large scale applications, and fortunately, they are applicable to many electrosyntheses. New electrode materials – or applications of known materials – is certainly an area of interest. A good example is leaded bronze for use in cathodic reductions in place of lead, the latter being undesirable for production of pharmaceutical intermediates. Personally, I have never performed a technoeconomic analysis, but I believe that this will ultimately have to be justified by the value of the product and the lifetime of the electrodes. Innovations such as depositing costly electrode materials on cheaper substrates may also contribute to providing workable solutions where cheaper electrode materials are not suitable.

Thomas Wirth answered: For large-scale production cheaper electrode mate-rials are certainly required, but depending on the process even noble metal electrodes can be a solution for processes adding a high value to a certain product.

Conflicts of interest

There are no conflicts to declare.