

Selective organic electrosynthesis: general discussion

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Shahid Rasul opened the discussion of the introductory Spiers Memorial Lecture by Toshio Fuchigami: From your overview (<https://doi.org/10.1039/d3fd00129f>), which top three electrochemical reactions for electrosynthesis are most suitable for commercialization, considering the significant challenge of scaling in electrochemistry?

Toshio Fuchigami answered: In consideration of the significant challenge of scaling in electrochemistry, (1) anodic homo- and cross-coupling of arenes (Scheme 13 in my Lecture article (<https://doi.org/10.1039/d3fd00129f>)), (2) micro-flow cell, thin-layer flow cell, and a parallel laminar flow cell (Fig. 4 in my Lecture article), as well as (3) PTFE-fiber-coated electrodes, are most suitable for commercialization.

Mickaël Avanthay opened the discussion of the paper by Alexander Kuhn: Does the magnetic fields contribute to the chemistry in any way other than moving the swimmer (*i.e.* heating, *etc.*)?

Alexander Kuhn answered: There is no heating because local currents are too low to generate Joule heating. We have performed control experiments to check whether more exotic effects like chiral induced spin selectivity (CISS) effects might contribute to the enantioselectivity, but inverting the direction of the magnetic field leads to the same %ee, and we think that the enhanced efficiency is solely due to the magnetohydrodynamic (MHD) effect which provides a more efficient flux of prochiral starting compounds to the swimmer surface. The magnetic field doesn't change the electron transfer kinetics but impacts only the mass transfer.

Mickaël Avanthay asked: Have you ever tried to tether the microswimmers?

Alexander Kuhn answered: We have performed experiments, also described in our paper, where we have used a rather macroscopic version of such a core-shell wire (<https://doi.org/10.1039/d3fd00041a>). We have fixed it at the bottom of the beaker and have added tracer particles in order to visualize the local MHD effect. From the supplementary file videos one can clearly see clockwise and anti-clockwise motion of the tracer particles at the two extremities of the wire.

Pim Broersen asked: When you are not applying the magnetic field during the reaction, is there more hydrogen production due to substrate mass transfer being limited?

Alexander Kuhn responded: We did not quantify how much the ratio of electrons that are used for the enantioselective reduction *versus* the electrons that are used for hydrogen evolution, is changing when applying the magnetic field or not. On the one hand, a first guess might be that in the absence of a magnetic field, more electrons are used for hydrogen evolution because there is not enough prochiral educt present at the oligomer surface due to mass transport limitations. However, on the other hand, in the absence of the MHD effect the produced hydrogen bubbles also have a tendency to stick for a longer time at the swimmer surface, due to the absence of hydrodynamic motion, thus partially blocking the interface and therefore also slowing down the arrival of protons. Thus, it is difficult to predict the final impact of the magnetic field on the ratio between these two competing processes. However, it is obvious from our measurements, that the presence of the magnetic field greatly enhances the production rate of the chiral molecule.

Pim Broersen continued: When comparing the performance of the swimmers with and without the magnetic field, did you observe a different rate of the reaction, and does this lead to a different rate at which the zinc 'fuel' is consumed.

Alexander Kuhn answered: Indeed, when applying the magnetic field the global reaction rate increases significantly due to enhanced mass transport. This means intrinsically that zinc has to dissolve faster in order to provide the electrons necessary for the reduction of the prochiral starting compound.

Christoph Bondue asked: You mentioned that enantiomeric excess does not change when applying magnetic field – do you think this is because the magnets are weak?

Alexander Kuhn answered: Right now the magnets we are using have a strength of around 200 mT. We could try to use stronger magnets, but I think that this won't affect the %ee, because it will just change the speed of the swimmers as the Lorentz force will be stronger and thus increase the hydrodynamic motion helping to provide fresh prochiral starting molecules to the surface of the swimmers. Therefore the global yield for a given reaction time, or in other words the production rate, will increase but not the ratio between the two enantiomers. There could be one reason to see a change in %ee: if some kind of spin selectivity were involved in the reaction mechanism, but we have no indication for such an additional effect so far.

Kevin Moeller queried: Can you change the potential the swimmer reduces at by altering the oligomer?

Alexander Kuhn responded: The potential at which the enantioselective reduction reaction is carried out can be controlled by changing the chemical nature of the oligomer layer. Our Italian collaborators have a series of different monomers that can be used to deposit oligomer films having chiral features. Depending on their chemical structure, they will be redox active at different potentials.

Eniola Sokalu commented: You have shown that the magnet can generate an electric field in the solution and thus, influencing bubble removal, meaning you can expose active sites for further reactions. Have you had any thoughts on potentially optimising the shape of the magnet or finding a way to generate magnetic 'local hotspots'?

Alexander Kuhn responded: We don't generate an electric field in solution with the magnet, but the redox reactions at the swimmer generate an electron and ion flux, which under the influence of the magnetic field induces the Lorentz force. The latter triggers a boost of motion of the swimmer which in turn helps in removing the bubbles from the surface for more efficient delivery of the prochiral starting compound to the swimmer surface for the catalytic transformation. Replacing a homogeneous magnetic field by inhomogeneous magnetic fields can have some beneficial effects, especially if the magnetic pattern is changing as a function of time because the swimmers will always try to move towards positions with the highest magnetic field strength, a phenomenon that we already observed. This would allow to further control their trajectory and eventually further enhance their speed.

Shelley D. Minter asked: Considering that in the modern day we are focusing on sustainability, can you replace the sacrificial anode with something that will be greener?

Alexander Kuhn answered: This is a very important comment. Indeed the current system is based on the gradual consumption of the zinc wire which acts as a fuel, simultaneously for the electroreduction of the prochiral starting compound, but also to trigger motion *via* the hydrogen bubble evolution. This type of energy source can be easily replaced by other reactions which are more sustainable/greener. An interesting option is to use for example an enzymatically driven oxidation reaction (*e.g.* of abundant fuel molecules such as glucose). In this case the swimmers don't get consumed like in the present case, but can in principle work for a long time if the enzyme is stable and substrate is available. We've already explored this kind of concept by combining an enzymatic reaction with the inherently chiral oligomers (see ref. 1) in order to design an autonomous swimmer. However in this case reactions went the other way round: a target molecule was oxidized on the chiral oligomer surface and the electrons were delivered to bilirubin oxidase for reducing oxygen. The ion flux that accompanies this electron transfer leads then to self-electrophoretic motion, which in addition

shows a directionality that depends on the chirality of the target molecule. We are currently further exploring such combinations.

1 S. Arnaboldi, G. Salinas, A. Karajić, P. Garrigue, T. Benincori, G. Bonetti, R. Cirilli, S. Bichon, S. Gounel, N. Mano and A. Kuhn, *Nat. Chem.*, 2021, 13, 1241–1247, DOI: [10.1038/s41557-021-00798-9](https://doi.org/10.1038/s41557-021-00798-9).

Dylan G. Boucher said: As the inspiration for this system is more efficient mass-transfer, it seems the long-term vision is a reactor with many micro-swimmers operating simultaneously. What happens when they hit each other? Do they short circuit? What are the design principles for preventing collisions in reactors with large concentrations of swimmers?

Alexander Kuhn answered: This is an interesting point. For the moment we perform our experiments only with a small amount of swimmers present simultaneously, so the probability of them running into each other is very small. Also they have more of a tendency to avoid each other, most likely due to a small meniscus present around every swimmer. Actually, we are actively investigating this type of interaction because we would like to understand the swarming behavior of these objects, that means how they self-organize when there are (too) many of them. The interesting point is that if you think about these systems in more detail, actually every swimmer is an individual tiny magnet because of the local electric current, which obviously generates, according to the corkscrew rule, a tiny magnetic field around every swimmer. So if there are no other perturbations (like the bubble generation in our present system) it should be possible to see the effect of these small local magnetic fields on the self-organization of the swimmers. One possibility to reach this situation, is to replace the present dissolution of zinc (or magnesium) with another type of oxidation reaction, for example based on enzymatic reactions which won't produce bubbles.

T. Leo Liu queried: Can mechanic stirring work instead of a magnetic field? What is the effect of magnetic field strength? Can the magnetic field be used for a flow cell?

Alexander Kuhn replied: Mechanic stirring can for sure also increase the production rate, but it is not as efficient as magnetic field-induced stirring (*i.e.*, MHD). We compared in previous work,¹ the efficiency of both and found that even when mechanically stirring the solution around a static wire, the production rate of chiral molecules is lower than with the swimmers of an equivalent length. The reason for this resides most likely in the fact that mechanical stirring is a top-down approach and the solution will not be stirred right at the interface because of the hydrodynamic boundary layer. In contrast, MHD induces liquid motion right at the interface as this is the place where the driving force (Lorentz force) is generated, so it is a bottom-up phenomenon. Obviously in this latter case, the stronger the magnetic field, the stronger the Lorentz force (as it is the cross product between the local current and the magnetic field), and thus the stronger the generated hydrodynamics. In the present work, we use moderate magnetic fields of around 200 mT, so there is still the possibility to enhance the effect using stronger magnets.

I don't see any reason why this phenomenon can't be used in a flow cell.

1 S. Arnaboldi, G. Salinas, G. Bonetti, P. Garrigue, R. Cirilli, T. Benincori and A. Kuhn, *Angew. Chem.*, 2022, **134**, e202209098, DOI: [10.1002/ange.202209098](https://doi.org/10.1002/ange.202209098).

Chia-Yu Lin commented: The magnetic field could induce the induction heating to modify the kinetics of the electrochemical reactions. Did you examine this effect?

Alexander Kuhn replied: We didn't investigate more precisely whether local heating might contribute to the enhanced reaction kinetics. However we estimated the local currents typically flowing through the swimmers and these values are very small, so I don't think that a related Joule effect would lead to a significant increase in temperature of the swimmer or around the swimmer.

Shahid Rasul asked: Do these factors – process intensification, applied magnetic field, and improved mass transfer – have any observable impact on overpotential in electrochemical reactions?

Alexander Kuhn replied: In our specific case the magnetic field does not change the overpotential of the electron transfer. It helps to improve the mass transport of electroactive species towards the catalytically active interface of the swimmers.

Shahid Rasul added: Do different interfaces such as platinum and zinc significantly influence selectivity in electrochemical reactions?

Alexander Kuhn answered: The selectivity can be influenced by the overall driving force which is directly related to the composition of the swimmers. If a very reactive metal, such as magnesium, is used as the core material of the swimmers, the driving force is very high and this can have a negative impact on the enantioselectivity. Therefore in general a metal core with a modest reactivity leads to a better selectivity.

T. Leo Liu queried: Is the magnetic stirring approach scalable? Can it be used in a flow cell?

Alexander Kuhn answered: Yes I think it is scalable. For the moment we've only worked with a small number of swimmers in the context of these proof-of-principle experiments, but obviously the number of swimmers can be increased. However, above a certain threshold concentration they might interact with each other and efficiency won't scale anymore with the number of swimmers. I don't see how and why they should be integrated in a flow cell because first of all they might be washed out with the flow, and second, their effect might be limited as there is already hydrodynamics in the cell.

Belen Batanero further questioned: How possible is it to scale up the process?

Alexander Kuhn replied: The process might be scaled up using many swimmers simultaneously, ideally as a kind of powder of active particles that is added

to the solution containing the prochiral starting compound and then exposed to the external magnetic field.

Belen Batanero asked: In these magnetic swimmer processes what time scale order is handled? Can they continue overnight?

How general is the oligomer with respect to other asymmetric reductions? Can enantioselectivity can be improved? Do you know the detailed induction mechanism?

Alexander Kuhn replied: The swimmers can stay active as long as there is “fuel” available, that means as long as the zinc wire is not completely dissolved they will swim. However enantioselectivity slowly decays as a function of time. The BT_2T_4 oligomer that we use right now can be employed not only for this stereospecific reaction transforming acetophenone into phenylethanol, but also for other enantioselective reactions as has been shown by our Italian collaborators in a long series of publications. We have tested our swimmer concept for example, for the reduction of phenylglyoxylic acid into mandelic acid.¹ In addition, other oligomers with similar stereoselective features are available, which further opens up the spectrum of possible asymmetric reactions. We don't know for the moment the detailed molecular mechanism that leads to this outstanding stereoselectivity (hydrogen bonding, π - π interactions *etc.*), but we are actively working on its elucidation.

1 S. Arnaboldi, G. Salinas, G. Bonetti, P. Garrigue, R. Cirilli, T. Benincori and A. Kuhn, *Angew. Chem.*, 2022, **134**, e202209098, DOI: [10.1002/ange.202209098](https://doi.org/10.1002/ange.202209098).

Christoph Bondue opened the discussion of the paper by Long Luo: The AC method helps prevent overoxidation, keeping a radical, how does it help achieve site selectivity?

Long Luo answered: Yes, it does help. Check out our recent paper¹ and our review paper.² We have another paper discussing this topic coming out soon as well. Stay tuned!

1 D. Gunasekera, J. P. Mahajan, Y. Wanzi, S. Rodrigo, W. Liu, T. Tan and L. Luo, *J. Am. Chem. Soc.*, 2022, **144**, 9874–9882, DOI: [10.1021/jacs.2c02605](https://doi.org/10.1021/jacs.2c02605).

2 S. Rodrigo, C. Um, J. C. Mixdorf, D. Gunasekera, H. M. Nguyen and L. Luo, *Org. Lett.*, 2020, **22**, 6719–6723, DOI: [10.1021/acs.orglett.0c01906](https://doi.org/10.1021/acs.orglett.0c01906).

Pim Broersen asked: In your paper, when selecting the potential range between which you oscillate the AC, you base the reductive potential on the potential required to reduce the thiol (<https://doi.org/10.1039/d3fd00044c>). However, the species you need to reduce for catalytic turnover is a thiyl radical. Do you not expect the reduction potential of the radical to be different than of the thiol itself?

Long Luo answered: Great question. I am sure the reduction potentials for thiyl radical and thiol are different. However, we still maintain at a voltage bias that can reduce thiol because there is no thiyl radical at the very beginning of the reaction. Without applying such voltage bias, the reaction cannot be initiated.

Robert Price said: As your work employs AC frequencies, have you performed any AC impedance spectroscopy in order to evaluate your process?

Long Luo replied: No, we haven't but it is something interesting to explore. In principle, the impedance value should reflect the electrochemical processes in our system.

Richard C. D. Brown commented: The work described in your paper involves a complex interplay between electrochemical and chemical steps as well as mass transport with species diffusing towards and away from, the electrode as its potential is switched. Have you considered, or are you using simulations, to help understand the experimental outcomes or even guide optimisation of the conditions?

Long Luo responded: Yes, computational simulations will definitely help.

Kevin Moeller said: My thoughts are to do with the rate of the processes and whether the radical can be reduced to an anion by the back electron transfer? This would allow the trapping of electrophiles.

Long Luo responded: It will be interesting to investigate this question. In our system, we fixed the applied voltage between the two electrodes but not the electrode potentials. We will need to find out the electrode potential to test if the potential is negative enough to reduce radical to anion. There are a few species that can be reduced, including the oxidized amine, thiol, and possibly the α -amino radical.

Mickaël Avanthay asked: How does the speed of synthesis of polysaccharide on the e-synthesiser compare to the conventional, commercial synthesiser?

Toshiki Nokami replied: The synthesiser developed by Professor Ye and co-workers¹ is based on a conventional chemical method in solution phase and the reaction is extremely fast. But the reaction rate depends on the current value and the reaction scale. So, the e-synthesiser is also fast when we compare with other methods based-on solid-phase synthesis.

1 X.-S. Ye, *et al.*, *Nat. Synth.*, 2022, **1**, 854–863, DOI: [10.1038/s44160-022-00171-9](https://doi.org/10.1038/s44160-022-00171-9).

T. Leo Liu opened a general discussion of the paper by Toshiki Nokami: Does the coupling chemical step take place in the electrochemical cell (<https://doi.org/10.1039/d3fd00045a>)? What is the yield of each oxidation-coupling step?

Toshiki Nokami replied: Both oxidation (activation) and coupling occur in the anodic chamber of the electrochemical cell. Conversion of the starting material by anodic oxidation is almost quantitative in most cases; however, accumulation of the glycosylation intermediate is not 100%. Moreover, the yield of the coupling step between the accumulated intermediate and the building block, which is a thioglycoside with a protecting-group-free hydroxyl group, depends on the combination.

T. Leo Liu asked: What are side products in terms of 3% overall yield of your reaction?

Toshiki Nokami replied: The corresponding molecular ion peak of the cyclic hexasaccharide was observed as a major peak; however, the yield was less than 10%. I think that the major by-products may be hydroxy sugars which are reaction products between glycosyl triflate intermediates and water.

Belen Batanero said: You use an extremely low temperature, does it not function at room temperature, and what is the problem with working at 25 °C?

Toshiki Nokami responded: Some glycosylation intermediates can be treated at 0 °C; however, most glycosyl triflate intermediates are unstable at elevated temperature. Side reactions such as elimination of HOTf must occur at room temperature.

Belen Batanero asked: Do you need a previous activation of the electrode? How is the solution conductivity at low temperature? You have many protecting groups and they are so large that I wonder if the electrode surface was passivated.

Toshiki Nokami responded: We use the carbon fiber electrode after drying at 120 °C for several hours; however, pre-activation of the surface of the electrode is not needed. Conductivity of the solution at low temperature must be very low. So, we added more than 0.1 M of electrolyte Bu₄NOTf in dichloromethane (DCM). Of course, using DCM as a solvent is not ideal. But DCM is the only solvent which can dissolve the electrolyte at low temperature.

Kevin Lam suggested: Have you tried a weakly coordinating anion such as B(C₆F₅)₄⁻ in your supporting electrolyte? Would that allow the generation of the cation pool at room temperature?

Toshiki Nokami replied: Cation pools can be generated with B(C₆F₅)₄⁻. Professor Yoshida also reported generation of a glycosylation intermediate with B(C₆F₅)₄⁻; however, there is a catch. TfOH is added to the cathodic chamber and the triflate anion can move to the anodic chamber during electrolysis. So, I think that the accumulated species must be a glycosyl triflate, not glycosyl cations. Of course, we can generate cations at room temperature, but accumulation is difficult at that temperature. It depends on the stability of cations whether we can accumulate generated species or not. Some glycosylation intermediates which have neighboring groups at 2-OH can be accumulated at 0 °C because they form stable glycosyl dioxalenium ions.

Kevin Lam added: What happens when you try to generate a cation pool in the presence of a weakly coordinating anion? Does it decompose?

Toshiki Nokami answered: In many cases of cation pools a weakly coordinating anion is necessary to accumulate cations. Glycosylation intermediates are quite different from carbocations. Although glycosyl triflates are also unstable, there are covalent species and detectable by NMR at low temperature. The major decomposition pathways of glycosyl cations might be hydrolysis, elimination, intramolecular reaction with a protected hydroxyl group, and intermolecular reaction with anions of electrolytes. All our attempts to generate and accumulate

glycosyl cations using weakly coordinating anions failed. Although we did not check by-products carefully, glycosyl fluorides were produced exclusively in the presence of BF_4 anions. This means glycosyl cations are very reactive and I have never read any reports about detection of glycosyl cations. There are some modified ones, but they are stabilized.

Robert Francke said: Your comparison between different supporting electrolytes (triflate salts) showed a strong impact of the cation on cell voltage and product yield (Table 1 in your paper). What is the explanation for this?

Toshiki Nokami replied: It is still difficult to explain at this stage. We should investigate the effects of electrolytes on electrolysis (first step) and glycosylation (second step) separately. I think that electrolytes may influence the stability and reactivity of glycosyl triflate intermediates. We will investigate the stability of glycosyl triflate intermediates using several electrolytes.

Robert Francke added: The electrolyte effects shown in Table 1 are very interesting and may be worth investigating more closely. In addition to electrochemical double layer effects, differences in ion pair dissociation should be taken into account as a possible explanation. Conductivity measurements are suggested. It may also be worth analyzing electrolysis and chemical follow-up reactions separately to figure out in which of the two processes the salt effect comes into play.

Toshiki Nokami responded: These are very important comments. We will measure conductivity and viscosity as well. It is also important to investigate the influence of the electrolyte on electrolysis and the following chemical reaction separately.

Shelley D. Minter addressed all: Since many electrosynthesis systems are actually a cascade of reactions, is it possible to use time dependent control of potential/current or magnetic fields to improve flux through a cascade of reactions?

Alexander Kuhn replied: In our specific case we have no control over the potential/current as a function of time. We could vary the magnetic field as a function of time, but I don't think that this alone will improve the flux through a cascade of reactions if the magnetic field is homogeneous. However, temporal variations of the spatial distribution of the magnetic field strength might have a positive effect on the efficiency of such reactions, as the swimmers always try to move along magnetic field gradients towards positions having the highest field.

Long Luo replied: It is possible. AC frequency can be used to control the mediator concentration. We will need to look at particular reactions to figure out how to do it exactly.

Conflicts of interest

There are no conflicts to declare.