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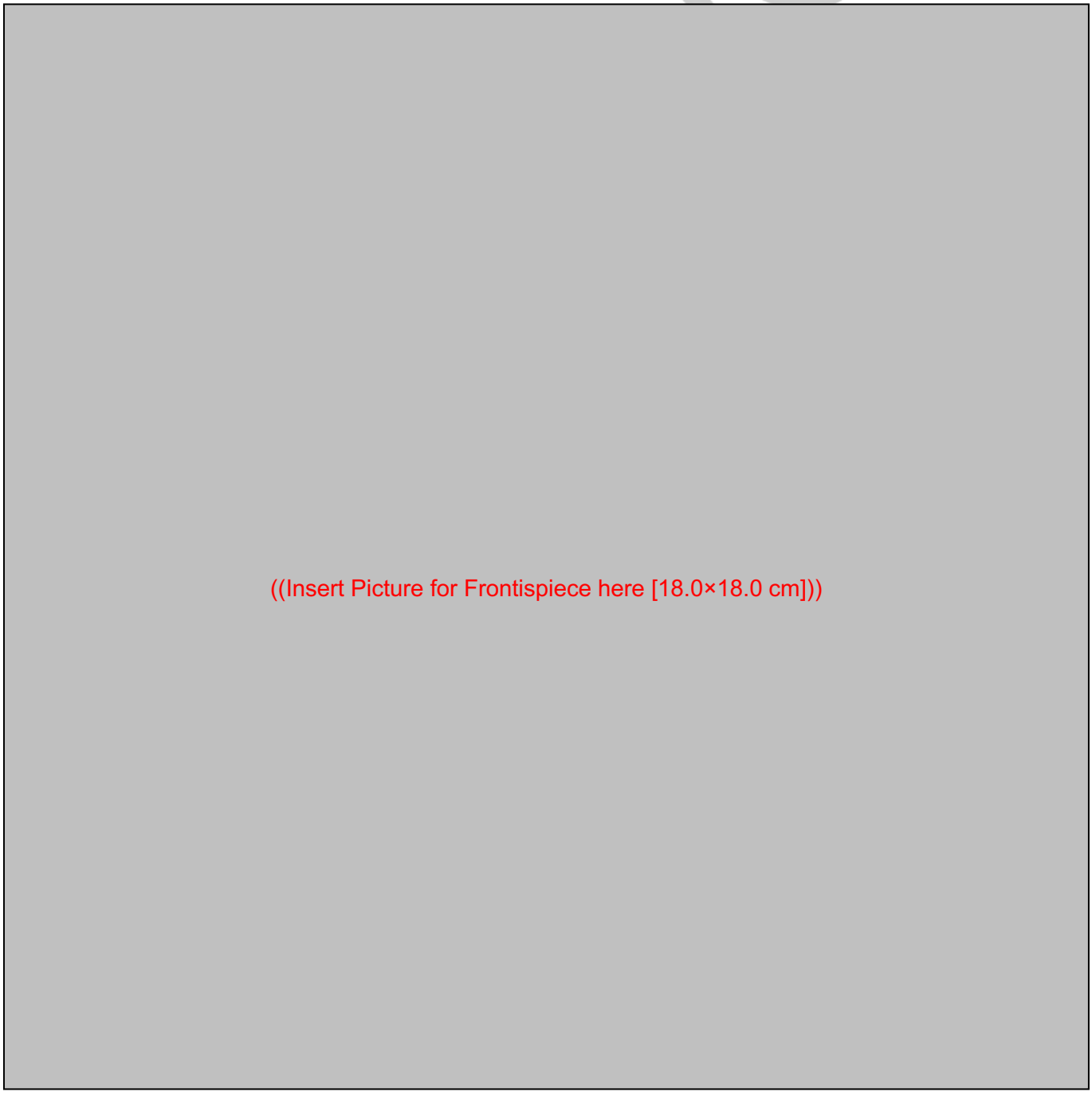
PERSONAL ACCOUNT

The longer route can be better: Electrosynthesis in extended path flow cells

Richard C. D. Brown*[a]

Dedicated to Professor Derek Pletcher for his many contributions to electrosynthesis and electrolysis cell development



Abstract: This personal account provides an overview of work conducted in my research group, and through collaborations with other chemists and engineers, to develop flow electrolysis cells and apply these cells in organic electrosynthesis. First, a brief summary of my training and background in organic synthesis is provided, leading in to the start of flow electrosynthesis in my lab in collaboration with Derek Pletcher. Our work on the development of extended path electrolysis flow reactors is described from a synthetic organic chemist's perspective, including laboratory scale-up to give several moles of an anodic methoxylation product in one day. The importance of cell design is emphasised with regards to achieving good performance in laboratory electrosynthesis with productivities from hundreds of mg h^{-1} to many g h^{-1}, at high conversion in a selective fashion. A simple design of recycle flow cell that can be readily constructed in a small University workshop is also discussed, and simple modifications to improve cell performance. Some examples of flow electrosyntheses are provided, including Shono-type oxidation, anodic cleavage of protecting groups, Hofer–Moest reaction of cubane carboxylic acids, oxidative esterification and amidation of aldehydes, and reduction of aryl halides.

1. Introduction

Organic electrosynthesis has experienced a remarkable boom during the last decade, with recent and past developments captured very well within a large number of books and review articles.[1] The basic principles and methods of electrosynthesis are well-described in these works, and it is not the aim of this personal account to attempt to duplicate them here. The intent is to describe my own experience of organic electrosynthesis and cell development, which has almost exclusively involved flow systems for reasons that will be outlined in the sections below. This account is written very much from the perspective of a synthetic organic chemist, starting from a point where there was no practical experience of electrosynthesis or flow chemistry in my lab. The intention is for the general ideas and approaches to be accessible to organic chemists, rather than to provide a more detailed theoretical description, which can be found elsewhere.[2]

1.1. An "Extended Path" towards Electrosynthesis in Flow

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As an undergraduate in the late 1980's at the University of Southampton I became fascinated by organic synthesis, and in particular, excellent undergraduate lectures by Philip Parsons and Philip Kocienski drew me towards natural product total synthesis. I was lucky enough to get a PhD studentship to join Professor Philip Kocienski's group in 1990, working on the total synthesis of the polyether ionophore antibiotic salinomycin (Figure 1(a)). He was an excellent supervisor and mentor, who possessed a great skill for extracting the latest results from us during regular rounds of the labs, thwarting any efforts to keep something back for the next visit, which could be only a few hours later! The work on salinomycin went well, and we completed a total synthesis using an Achmatowicz-type rearrangement to perform oxidative dispiroacetalisation of a 2,5-disubstituted furan intermediate.[3] My PhD certainly reinforced my enthusiasm for stereocontrolled synthesis and total synthesis, and I think that a seed of interest in electrochemical synthesis was sown during this period. However, it would be many years before any practical application.

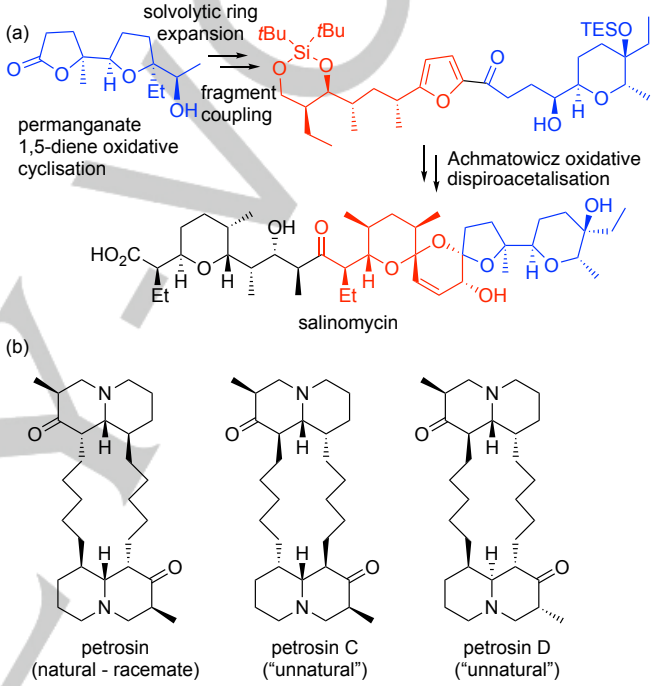


Figure 1. PhD and postdoctoral research. (a) Total synthesis of salinomycin using furan and diene oxidations as key steps. (b) Total synthesis of unnatural petrosin diastereoisomers C and D.

It was not uncommon at the time to look for postdoctoral opportunities in the USA, and letters went off in the mail to prospective supervisors. A second piece of good fortune was a positive response from Clayton Heathcock, probably many weeks later, with the offer of a place. Ultimately, I applied for and obtained a NATO postdoctoral fellowship to work in his lab at UC Berkeley between 1994 and 1996. The time in Clayton's group was another fantastic experience, and also an introduction to alkaloid chemistry, and molecules that were less user-friendly than the better-behaved polyethers that I had become accustomed to in Southampton. Two diastereoisomers (named petrosins C and D) of a small group of diastereomeric macrocyclic bisquinolizidinone natural products called petrosins were synthesised (Figure 1(b)). [4] The availability of these "unnatural" [5] synthetic diastereoisomers supported an investigation to rationalise why petrosin was isolated as a racemate, while another diastereoisomer, petrosin B, was enantioenriched.

Beautiful work by a very talented graduate student in Clayton's group, Bob Scott, demonstrated that racemic petrosin was the predominant "kinetic" diastereoisomer obtained from a "stereo-uncontrolled" synthesis, and petrosin was also the major "thermodynamic" product obtained from isomerisation of a mixture of synthetic diastereoisomers by a retro-Mannich–Mannich process. [6]

During the latter stages of my postdoc I submitted an application for a Royal Society University Research Fellowship, which was ultimately successful, allowing me to begin an independent career in 1996 in the Department of Chemistry in Southampton. Immediately prior to taking this up, I had an unusual opportunity to spend 6 months at Pfizer Central Research in Sandwich in the combinatorial chemistry group led by Nick Terrett. This was during a rather exciting post-Viagra period where the site was in the midst of significant expansion. At that time there was great interest in technology and automation (which I shared) and how to make and (ideally) purify the large compound libraries that had come into favour. Aside from exposure to the latest reactors and technology for chemical synthesis, Sandwich was a great place to learn techniques of solid-phase synthesis, which was to become one of the research themes in my lab over the coming few years. Early research plans also included electrosynthesis, and some ideas involving modified electrodes; unfortunately, I remember some unproductive hours spent in the lab trying to functionalise carbon fibres with little in the way of understanding of relevant materials chemistry or characterisation methods. I also recall one of the medicinal chemists telling me that they had some carbon electrodes in the back of a cupboard somewhere, although I don't think that we ever found them! Sadly, the impetus was lost and even after moving to Southampton in September 1996, and preliminary discussions with experts in our internationally-renowned electrochemistry group, I failed to get the electrochemistry up and running. Looking back, this was a missed opportunity, although the years between 1996 and 2008 did allow me to follow other research interests in diene oxidative cyclisation, [7] total synthesis, [8] and a variety of excellent collaborations. [9]

I already mentioned the excellent electrochemistry group that we have in Southampton (I am not in the electrochemistry group!), and in 2008, one of them (Derek Pletcher) proposed that we apply to a flow chemistry call from the Engineering and Physical Sciences Research Council (EPSRC), to develop laboratory electrosynthesis in flow reactors with extended channels. The grant was in association with Pfizer and a flow equipment company, Syrris, and marked the start of a collaboration between Derek and myself which continues to this day. Collaborating with Derek has been extremely rewarding and educational, and he has been instrumental in all of the electrosynthesis and reactor development described in this personal account.

The original grant application sought to develop a design of flow electrolysis cell that would allow high fractional conversion to be achieved selectively on scales commensurate with typical research laboratory applications (e.g., 100 mg to a few grammes). Of course, scale is an ambiguous term here because the amount of material processed is dependent on a number of factors including concentration, flow rate and how long the flow experiment is run for, assuming that the electrolysis is stable and enough starting material is available. Suffice to say that we wanted to be able to produce practically useful amounts of products, selectively and in a reasonable time. The electrolysis channel design was also to be included in a flow electrosynthesis system being developed by Syrris (Figure 2), and a modified version subsequently became available commercially within their Asia Flux Electrochemistry module.[10] The performance of the reactor was to be demonstrated using robust anodic electrosyntheses in the first instance, before moving on to other electrochemical conversions of interest. Further description of this electrolysis channel and other flow cells are provided below, but first, some attention is given to the considerations that have guided our cell designs.

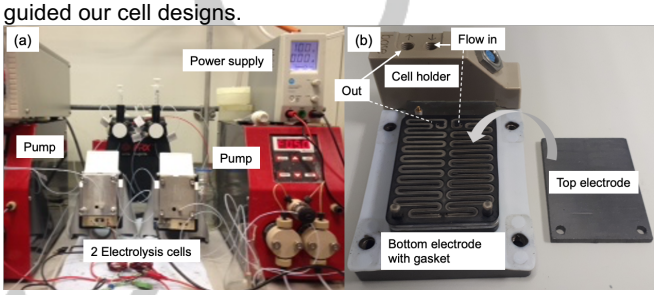


Figure 2. (a) Photograph of two flow electrolysis reactors with associated pumps and power supplies. (b) Example of prototype Syrris extended path electrolysis flow electrochemical cell with a serpentine channel design, created between two plate electrodes using an elastomer spacer that locates into a machined recess in bottom electrode.

Richard C. D. Brown was born in Canterbury, England, in 1968. He graduated with B.Sc. (1990) and Ph.D. (1994, with Prof. Philip Kocienski) degrees from the University of Southampton. After a NATO postdoctoral fellowship (1994–1996) with Prof. Clayton Heathcock at the University of California–Berkeley and six-months at Pfizer Central Research in Sandwich, UK, he joined the chemistry staff at the University of Southampton. From 1996 to 2004 Richard held a Royal Society University Research Fellowship in Southampton and was promoted to professor in 2010. His research interests include natural product total synthesis, synthetic methodology, and electrosynthesis in flow reactors. He is author and coauthor of more than 100 journal and book articles.

2. Electrosynthesis in Flow Reactors

2.1. Why use flow reactors for electrosynthesis?

So, why carry out electrosynthesis in flow? This is an important question, as around 2008 when our own work began, flow chemistry was far from a routine technique in synthetic chemistry labs and electrosynthesis was probably even less familiar to the majority of organic chemists. Therefore, simultaneously moving away from chemical reagents and beakers/flasks by combining electrosynthesis and flow might have seemed to be a step too far for many. Organic electrochemistry has been carried out in batch since the earliest pioneering studies, and beaker-type cells have been widely adopted due to their simple construction from readily available laboratory glassware such as beakers or flasks. Beaker cells, in their simplest form, consist of two electrodes immersed in a vessel containing the bathing electrolyte solution, and a current is passed through the cell, controlled by a power supply or potentiostat, to achieve the desired electrochemical conversion. Further "standard" features may include a reference electrode and/or a separator between the anode and cathode chambers, the latter becoming important when the chemistries at the two electrodes are not compatible. While batch reactor designs have been refined, it has long been recognised that their performance can be limited by electrode area to solution volume ratios, and by inefficient mass transfer regimes, which are also poorly defined. These features reduce rates of conversion and extend the electrosynthesis reaction time. One approach to improve performance is by rotating the working electrode, which reduces the thickness of the diffusion layer and improves mass transport. However, this introduces additional complexity into the design and operation of the electrolysis cell.

Electrosynthesis in flow can offer some important advantages compared to batch, and a variety of cell designs have been described for laboratory and scale-up applications.[2c,2d],[11-14] Flow systems in general offer certain advantages over traditional batch reactors for chemical synthesis and these have been nicely reviewed.[15] Flow reactors possessing high surface area to volume ratios benefit from efficient heat and mass transfer, effective mixing of flow streams, and allow for controlled manipulation of reactive intermediates. Improved process safety, in-line analysis and the ability to turn a flow process on and off provide additional opportunities.

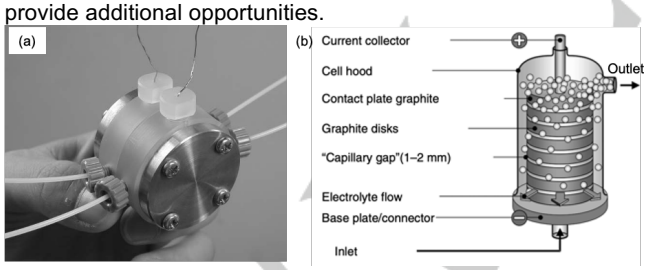


Figure 3. Flow electrosynthesis at both ends of the scale: from milligrammes to multi-kilos. (a) Microfluidic electrolysis cell used in Yoshida's pioneering studies in microflow electrosynthesis.[17a] Reproduced from ref [17a] with permission from The Royal Society of Chemistry. (b) Diagram of a bipolar stack capillary gap electrolysis flow cell used by BASF at manufacturing scale.[17d] Reproduced with permission from ref [17d]. Copyright 2007 John Wiley and Sons.

Electron transfer in the context of direct electrolysis is a heterogeneous phenomenon, occurring at, or very close to, the interface of an electron conductor (electrode) and an ion conductor (electrolyte). This imposes limitations on the performance of electrochemical cells due to mass transport and available electrode area, which can restrict rates of conversion.[16] An efficient mass transfer regime continuously provides substrate to the electrode surface, increasing conversion rates for electrochemical reactions proceeding under mass transfer control. Flow reactors with small interelectrode gaps and high electrode surface area to volume ratio are particularly attractive in this regard, providing improved mass transfer and rates of conversion compared to traditional beaker cells. The value of flow reactors in electrosynthesis has certainly been appreciated for some time, with elegant studies on the microreactor-scale to impressive industrial syntheses of organic products (Figure 3).[2d],[12,13],[17]

2.2 General approaches to electrosynthesis in flow

When considering equipment to perform laboratory electrosynthesis in flow, a number of basic criteria need to be established including scale (or rate of conversion), how conversion is to be achieved (single pass or multiple passes), requirement for a separator to minimise interaction of the cathode and anode chambers.[2],[11] There is a growing number of commercial flow cells available for electrosynthesis,[10],[18] but it is important that potential users are familiar with the way cells work and their limitations, and how that matches with intended applications and future needs.[2c-e],[11] Careful consideration is needed to avoid disappointing user experience and, sometimes costly, equipment being relegated to the back of a cupboard. Alternatively, there are also flow cell designs that can be fabricated economically in a small workshop,[19] or by 3D printing.[2c,e],[20]

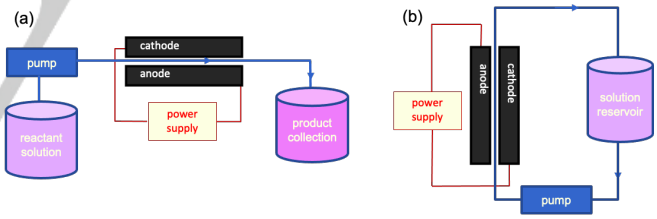


Figure 4. Simplified representation of approaches to electrosynthesis in flow. (a) Single pass approach, where a desired conversion is achieved in one pass through the cell. (b) Multiple pass approach where electrolyte is passed through the cell, often many times, to achieve a desired conversion of starting material to product.

Two broad approaches to electrosynthesis in flow can be considered (Figure 4); one where conversion is achieved by passing the electrolyte through the electrolysis cell multiple times, or another where a single pass is employed to achieve the desired conversion.[2b,d],[11],[21,22] Undivided arrangements simplify cell design, and are preferred where the anode and cathode reactions don't interfere. Introducing ion-permeable separators to segregate the anode and cathode chemistries might appear to be attractive, but they do introduce complications such as a more complex cell design, acidification of the anolyte and increased cell resistance. Constant, or controlled, current approaches are

convenient for organic electrosynthesis, and the amount of charge per unit time is directly related to the rate of electrolysis, assuming that the process is a selective one and operating within limitations of mass transfer control. For operation under constant current, supply of the substrate (or mediator) to the electrode should match or exceed the desired current; in other words, if the current is set too high, there will not be sufficient substrate available at the electrode and other species will be oxidised or reduced. Thus, efficient mass transport will allow selective conversion at increased currents leading to higher rates of production. In all electrolysis cells, improved performance may be achieved by appropriate design, which should be tensioned against practical factors such as complexity, cost, ease of assembly/disassembly, efficient use of electrode materials, ability to machine or 3D print with appropriate materials and so on.[2c,e] In our work, together with engineering collaborators, we have designed and fabricated reactors based on single and multiple-pass approaches. Our main focus to date, however, has concerned a single pass approach, where an extended flow channel is formed between two electrodes with relatively narrow interelectrode separation (Figure 5). The rationale for this is provided in the ensuing sections.

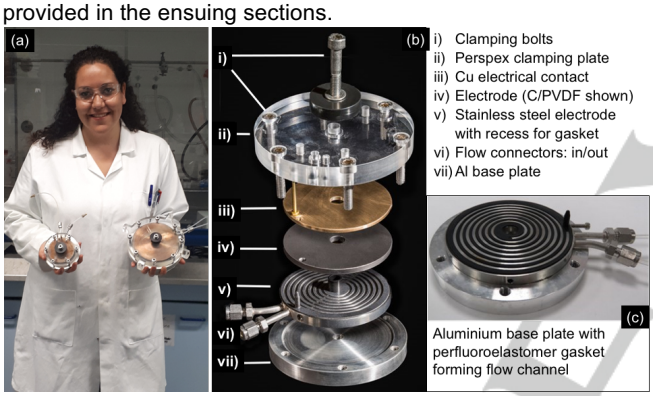


Figure 5. Examples of electrolysis flow cells with extended paths. (a) Dr Ana Folgueiras holding Ammonite 8 and Ammonite 15 reactors. (b) Expanded view of Ammonite. (c) Ammonite with flow channel exposed.

2.3 Channel design in single pass flow electrolysis cells

Table 1. The effect of mass transfer and electrode area on the time taken to achieve 95% conversion (X = 0.95) of a reactant in 1 L of solution.[a]

A —electrolysis under mass transport control in 1 L of solution→ **B**

$$X = 1 - \exp\frac{-k_m A t}{V}$$

X is fractional conversion; k_m is the mass transfer coefficient; A is the electrode plate area; V is reaction volume; t is time.

Electrode plate dimensions and (A/V)[a]	Time (t) taken to reach 95% conversion (fractional conversion, X = 0.95) for different mass transfer coefficients (k_m)		
	k_m = 10^{-4} cm s^{-1}[b]	k_m = 10^{-3} cm s^{-1}[c]	k_m = 10^{-2} cm s^{-1}[d]
1 cm^2 (10^{-3} cm^{-1})	350 days	35 days	3.5 days
100 cm^2 (0.1 cm^{-1})	3.5 days	8.4 h	50 min

[a] Adapted from ref [2d]. [b] Inefficient mass transfer. [c] Moderate mass transfer. [d] Efficient mass transfer.

In the context of a single pass flow electrolysis approach, the significance of an extended electrolysis path is picked up below, but first other design criteria are discussed. Benefits of minimising the interelectrode gap by bringing the anode and cathode closer together are well known.[22,23] Decreased electrical resistance owing to proximity of the electrodes can permit the use of low concentrations of supporting electrolyte, or obviate the need for it altogether. In extended path cells used in our work the interelectrode gaps are between 0.2 and 0.75 mm;[19b],[24] in our experience, smaller distances between the electrodes were found to be problematic in practical application with increased cell currents (e.g. >5 amps in the Ammonite 15 reactor, see below). Mass transfer distances to the electrodes is reduced in narrow gap cells. An increased electrode surface area to cell volume ratio also goes hand in hand with narrow gap designs. The impact of mass transfer and electrode area/reaction volume upon cell performance is nicely illustrated by considering the time taken to reach 95% conversion for a selective mass-transfer controlled electrochemical conversion of hypothetical species **A** to **B** in 1 L of solution (Table 1).[2d] In a cell with poor mass transfer properties and a small electrode area (1 cm^2) it requires about 1 year to reach 95% conversion. By contrast, efficient mass transfer and a 100 cm^2 electrode enables the same conversion in less than 1 h.

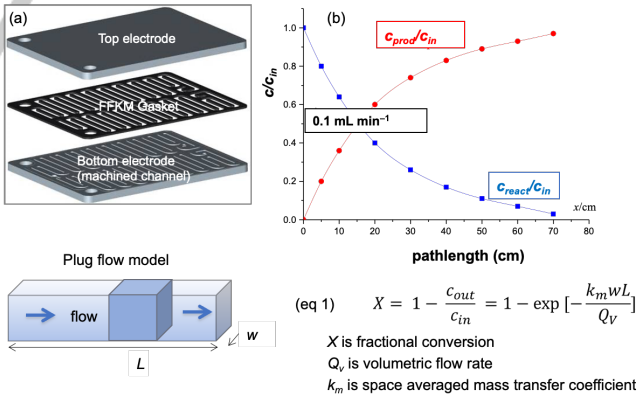


Figure 6. (a) Example of an extended path serpentine channel design, created between two plate electrodes using an elastomer spacer that locates into a machined recess in one of the electrodes. Gasket creates flow channel width: 0.15 cm; depth: 200 µm; length: 70 cm; volume: ~0.21 cm^3 with electrode area of 10.5 cm^2. (b) Using a simple plug-flow model (eq 1) to predict conversion for an electrochemical reaction operating under conditions of mass transfer control for different pathlengths.

The influence of electrode pathlength on conversion is another parameter to be considered when targeting high conversions in a single pass.[2a] The example shown relates to the prototype Syrris flow cell (Figure 6(a)), but the approach has also been applied to other flow cells we have worked on. The theoretical relationship of reactant/product concentration and pathlength is presented for a selective electrochemical conversion that is under mass transfer control, where conditions of simple plug flow are assumed (Figure 6(b)).[2a] We established the space averaged mass coefficient k_m at different flow rates experimentally from slow scan voltammetry of the $Fe(CN)_6^{3-}/Fe(CN)_6^{4-}$ couple in the electrolysis cell.[19b] As the channel dimensions are known, (eq 1) can be applied to predict conversion. Some important features are illustrated; firstly, the concentration of product increases along the channel asymptotically, and at a flow rate of 0.1 mL/min high fractional conversion is achieved when the channel is 70 cm in length. A shorter channel would give lower fractional conversion at the same flow rate. The rate of conversion is proportional to current, so current distribution is not uniform along the channel, and will be highest close to the inlet and reduce exponentially towards the end as full conversion is approached. Fractional conversion is related to flow rate, and when increased to 3 mL/min the theoretical conversion is predicted to fall to 50% for a path length of 70 cm (not shown). Therefore, high conversion at higher flow rates requires either a different cell design with improved mass transfer (and/or longer pathlength),[24a] or multiple passes through the reactor, or a combination thereof.

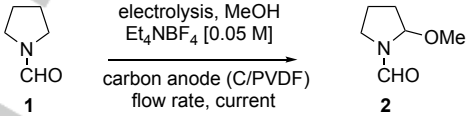
It should be emphasised that the simple model above, based on plug flow, neglects the mixing effect of any gas bubbles often produced during electrolysis (e.g. cathodic hydrogen evolution) or increased flow rate and mass transfer caused by the gas formation in the flow channel, both of which will certainly affect conversion (see below). None the less, this simple model has proved to be a useful tool to guide current and flow rate selection from a practical perspective.[2a] On the other hand, slowing down the flow rate might appear to offer a means to achieve high conversion in a single pass with shorter flow channels. However, the mass transfer regime, and hence limiting current, deteriorate at low linear flow rates resulting in slower rates of production.

Extended channel flow cells that we have worked on comprise of two electrodes, often a carbon-filled polymer anode and a stainless steel cathode, separated by a spacer to create a flow channel (e.g. Figures 2, 5 and 6).[2b],[19b],[24] The electrolyte solution is pumped along the channel between the two electrodes passing a current, which can be estimated using the plug flow model based on the mass transfer coefficient, concentration of the reactant, flow rate, cell dimensions and number of electrons involved in the transformation of interest.[2a] Examples of our flow cell designs include serpentine, star-shaped, and spiral channels. A chemically highly-resistant insulating fluoropolymer spacer between the electrodes also serves as the gasket to seal the cell when pressure is applied evenly with suitable bolts or cell holder. It was found that building a recess into one of the electrodes, most commonly the steel one, locates the gasket/spacer and prevents it moving around, ensuring a reliable seal is achieved.

2.4 Experimental evaluation of flow cell performance

To evaluate the performance of flow reactors experimentally we chose a reliable and well-established electrochemical reaction, which is anodic methoxylation of *N*-formylpyrrolidine in MeOH (Table 2).[25] Interestingly, for this test reaction our flow cells performed better than the theoretical model illustrated above. The influence of increased flow rate is evident from a lower conversion at 2 mL min^{-1} (86%) compared to 0.25 mL min^{-1} (100%) for a 0.1 M solution of *N*-formylpyrrolidine in MeOH. However, conversion was higher than expected, which we attributed bubbly flow from evolution of gas on the counter electrode during the electrolysis. Increased rate of production of **2**, while maintaining high fractional conversion, is seen by increasing concentration of **1** to 0.5 M at the lower flow rate. Of course, a corresponding increase in current is required to drive the increased productivity. It is perhaps surprising that larger amounts gas produced at the counter electrode at higher current does not degrade performance of the cell.

Table 2. The effect of flow rate and concentration on conversion and yield for the methoxylation of **1** in the Ammonite 8 electrochemical flow cell (see Figure 5).[a]



1 **2**

Conc. **1**	Flow rate (mL min^{-1})	Current (mA)	Conversion (Yield **2**)[b]	Rate of production of **2**
0.1 M	0.25	100	100% (88%)	0.17 g h^{-1}
0.1 M	2.0	800	86% (81%)	1.26 g h^{-1}
0.5 M	0.25	500	96% (85%)	0.82 g h^{-1}

[a] Path length = 100 cm, channel width = 0.2 cm, interelectrode gap = 0.5 mm (working electrode area = 20 cm^2). [b] Calibrated GC.

The gas bubbles arise from reduction of MeOH to give MeO^- and H_2 gas, and is clearly visible in the plastic tubing exiting the flow reactor (Figure 7 (a) and (c)). To put this in context, a current of 1 A will produce approximately 7 mL/min of H_2 gas due to the counter electrode reaction. An early concern of ours (shared by at least one funding application reviewer!) was the potential for gases formed in the flow channel to create resistance between the electrodes, resulting in poor performance. Furthermore, significant gas evolution pushes electrolyte out of the cell with increasing flow rate, shortening residence time (time between the electrodes!). Various engineering solutions were envisaged to deal with potential problems arising from gas evolution; fortunately, there has been no need to implement any of these to date. In fact, bubbles created in the flow channel can improve cell performance under certain conditions, and even relatively large volumes of gas appear to be tolerated. It is worth pointing out that

others have taken different approaches, for example, running cells under pressure to compress the gas.[22],[26]

The influence of the gas bubbles on mass transfer in the flow channel was initially picked up by colleagues Peter Birkin and Jekaterina Kuleshova, who showed experimentally that decreasing bubble size had some advantages in terms of mixing.[27] Formation of larger bubbles was seen to be suppressed in a test cell by addition of small quantities of surfactant, and subsequent CFD simulations by Engineering collaborators Steven Pickering and Medhat Sharbi at the University of Nottingham showed early detachment of smaller bubbles due to the effect of surfactant. In terms of flow electrosynthesis, the size of the bubbles in the effluent from the Ammonite 8 electrolysis cell was visibly reduced by addition of 0.02 equivalents of a polyether surfactant to the electrolyte solution (Figure 7 (c)). Perhaps more importantly, improved current efficiency was achieved with surfactant present for the anodic methoxylation (Figure 7 (b)). We believe that this is due to increased mass transfer caused by smaller bubbles in the flow channel, highlighting additional opportunities to enhance electrolysis flow cell performance.[28]

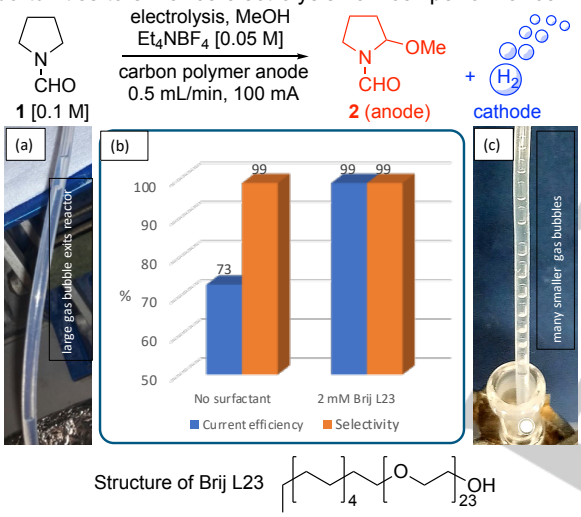


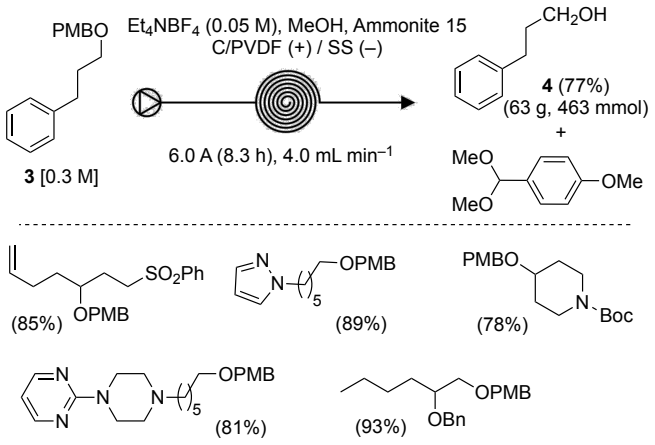
Figure 7. Influence of surfactant on the size of bubbles produced by cathodic reduction of MeOH in the Ammonite 8 flow reactor during the anodic methoxylation of *N*-formylpyrrolidine. (a) Large bubbles in the effluent without added surfactant. (b) Current efficiency and selectivity with and without surfactant. (c) The size of bubbles remains smaller when a low concentration (0.002 M) of a surfactant, Brij L23, is present in the electrolysis solution.

2.5 Laboratory scale-up

Despite the fact that electrolysis, including organic electrosynthesis, has been conducted on very large scales in batch and flow systems for many years,[1b],[2c,e],[12],[29] we encountered concerns from some organic chemists relating to the ease of scaling-up electrochemistry. The pathway to laboratory scale-up of electrosynthesis often begins in batch reactors, then possibly larger batch reactors, before moving to flow. The transition from 100s mg to multi-gramme (e.g. 1–10 g) quantities may be accomplished using the same extended path cell by simply running for longer, and/or increasing concentration. However, it was recognised that larger amounts of material (100–1000 g), which might be needed to progress a development project in pharma for example, would not be conveniently addressed using a small lab reactor such as the Ammonite 8. Numbering up was unappealing to us as it requires complex manifold systems to split flow or multiple pumps and power supplies. Therefore, together with Bashir Harji at Cambridge Reactor Design (CRD), as part of an EPSRC-funded Factory in a Fumehood project, the larger Ammonite 15 reactor was developed.[24a] The extended flow path of 200 cm with a channel width of 0.5 cm provides an electrode surface area of 100 cm^2, which is 5 x larger than the Ammonite 8. Direct cooling or heating of the reactor is effected through is its base by placing it on a temperature control plate (CRD Polar Bear Cub), with no need for recirculating coolant.

Figure 8. Example of large-scale/high productivity anodic methoxylation in the Ammonite 15 performed by Dr Rob Green.

Using the Ammonite 15 equipped with a carbon-filled polymer anode and stainless steel cathode methoxylation of *N*-formylpyrrolidine (**1**) was achieved selectively with high conversion and productivity (Figure 8). For the increased currents that go hand in hand with higher rates of production, Joule heating becomes more of an issue, but at a current of 9 A the reactor temperature was stable using Polar Bear cooling alone, and more than 3 moles (427 g) of isolated methoxylated product was obtained over a 24 h period. The set-up, including substrate and product vessels, Ammonite 15 reactor, peristaltic pump, Polar Bear and power supply has a footprint that takes up about half of a 2 m fumehood. A higher rate of production of >20 g h^{-1} was obtained by increasing the flow rate to 16 mL min^{-1} with a substrate concentration of 0.2 M. However, at the higher current of 12 A it was not possible to maintain ambient temperature of the reactor by removing heat from the base alone. None the less, good performance was still realised.[30]

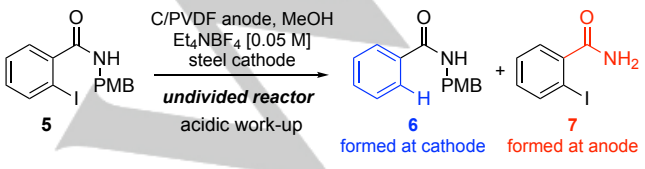


Scheme 1. Top: multi-gramme scale PMB ether deprotection using the Ammonite 15 cell. Below: additional examples of PMB ether substrates that underwent anodic deprotection in the Ammonite 8.

The Ammonite 15 reactor was also applied to the anodic cleavage of *para*-methoxybenzyl (PMB) protection from a test PMB ether substrate **3** giving multi-gramme quantities of the isolated deprotected alcohol **4** (Scheme 1).[31] At a substrate concentration of 0.30 M, flow rate to 4.0 mL min^{-1} and 6.0 A current, 63 g of the alcohol **4** was obtained over 8.3 h (55.5 mmol h^{-1}) without additional optimization of conditions developed in the smaller Ammonite 8 reactor. The anodic deprotection conditions were demonstrated for a variety of PMB-protected alcohols in the smaller Ammonite 8 electrochemical reactor (Scheme 1, bottom).[31]

Protecting groups are often unavoidable in synthesis, and in a research laboratory setting hazardous or highly energetic reagents are frequently applied in their removal. Typical deprotection protocols for PMB ethers involve oxidants such as DDQ and CAN, or strong acids,[32] all of which become less desirable as scales increase. Anodic oxidation offers a more attractive "reagentless" approach,[33] leading to the desired alcohol and the oxidised protecting group in the form of its dimethyl acetal, with hydrogen gas evolution at the cathode. But is it really more sustainable? The supporting electrolyte Et_4NBF_4 can be recovered by precipitation and reused after recrystallisation, and the PMB containing co-product is removed as its bisulfite adduct, avoiding chromatographic separation. Sustainability metrics applied to the flow electrochemistry process compared favourably with chemical methods. We should acknowledge, however, that none of the processes, including ours, were optimised in this regard.

2.6 Flow electrosynthesis in recycle mode



Scheme 2. Unselective electrolysis of **5** in an undivided flow reactor giving rise to cathodic and anodic products **6** and **7**, respectively.

More recently, we investigated anodic cleavage of PMB protecting groups from amides in a Shono-type process.[25a],[34-36] Electrolysis of *N*-PMB 2-iodobenzamide **5** in undivided cells gave mixtures of the anodic methoxylated product (hydrolysed to **7** upon acid w/u) and the formal hydrogenolysis product **6** produced at the cathode (Scheme 2). The latter arises by a two-electron ECE pathway with protonation by a component of the electrolyte solution, most likely MeOH.[37,38] Although, for reasons mentioned above, separators are avoided where possible in electrosynthesis, we wanted to add a simple divided flow cell to our available equipment. An additional motivation was to show that a simple flow cell could be fabricated in a university workshop, and its performance for application to organic electrosynthesis could be enhanced in a systematic and predictable way. By contrast to the narrow-gap single pass approach we had pursued almost exclusively up to that point, the electrolysis cell would operate in recycle mode with a comparatively low fractional conversion in each pass.

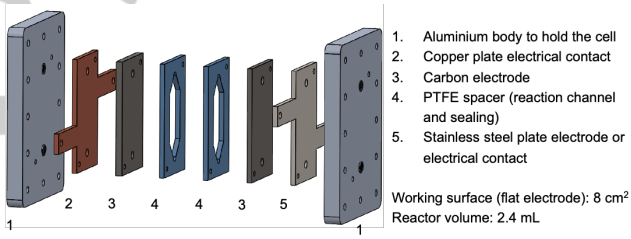


Figure 9. A parallel plate electrolysis cell intended to operate in recycle mode. A separator can be inserted between the PTFE spacers, and turbulence promoters or porous electrodes can be housed within the reaction channel.

The design, which was implemented by Dr Ana Folgueiras,[19a] is related to other parallel plate reactors,[2c-e],[12] and offers considerable flexibility in terms of scale, and electrode materials, which can be introduced as plates, foils or porous materials (Figure 9). The electrolyte chamber is created using a pair of PTFE spacers, which may also accommodate a separator allowing operation in divided mode. The mass transfer properties and performance of the cell were evaluated using the ferricyanide-ferrocyanide redox couple under different conditions (Table 3),[39] with and without turbulence promoters and 3D electrodes. Firstly, the flow rate was increased between 18 and 72 mL/min showing an anticipated increase in limiting current and mass transfer coefficient (an increased limiting current reflects increased mass transfer in the cell). Further improvement in the mass transfer properties was achieved by introducing a stack of polypropylene mesh into the electrolysis cell body. A final increase in limiting current was achieved by placing a reticulated vitreous carbon (RVC) block into the anolyte chamber in contact with the anode,[40] holding it in place using the pressure of the mesh against the counter electrode.

Table 3. The effect of flow rate, turbulence promoters (TP) and RVC electrode on mass transfer[a] in a parallel plate electrolysis cell.

Flow rate (mL min^{-1})	18	36	72
No TP[b] k_m (cm s^{-1})	7.77 x 10^{-4}	9.85 x 10^{-4}	1.35 x 10^{-3}
Using TP[b] k_m (cm s^{-1})	1.30 x 10^{-3}	1.74 x 10^{-3}	2.25 x 10^{-3}
Using 3D RVC electrode $k_m A_e$ (s^{-1})	2.02 x 10^{-2}	2.18 x 10^{-2}	2.38 x 10^{-2}

[a] Efficient mass transfer (10^{-2} cm s^{-1}); moderate mass transfer (10^{-3} cm s^{-1}); inefficient mass transfer (10^{-4} cm s^{-1}). [b] Stack of polypropylene mesh used as turbulence promoter (TP).

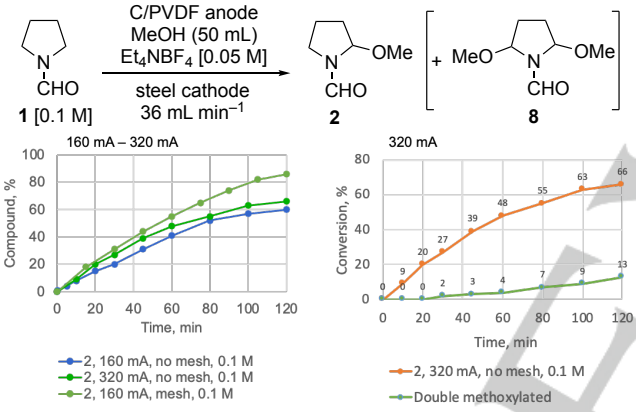


Figure 10. Conversion and selectivity for the methoxylation of **1** at different currents, and with and without turbulence promoter mesh.

The study showed that a relatively uncomplicated reactor design with mediocre performance can be significantly improved by implementing some simple modifications. This was demonstrated in a synthetic context using our favoured test reaction, which was carried out by continuously pumping the electrolyte through the flow cell at 36 mL/min for 120 min (1800 passes!). Using a cell current of 160 mA, an increase in conversion from 60% to 86% was realised by introducing the turbulence promoter mesh. Application of the RVC anode allowed full conversion at around 90 min using the same cell current (Figure 11, left), with selective formation of the methoxylated product.

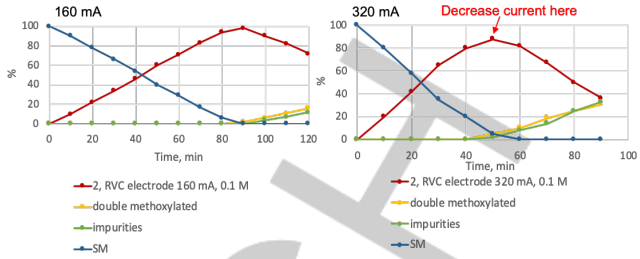
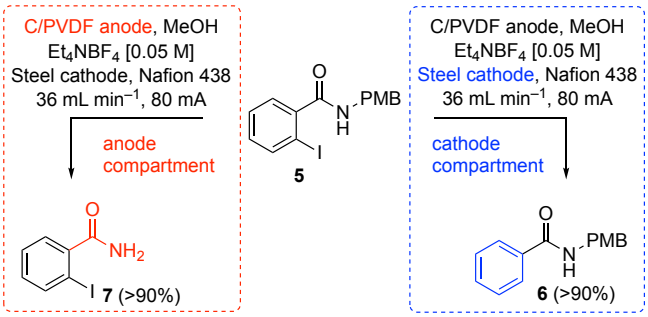


Figure 11. Influence of porous RVC anode on rate of conversion and selectivity for the anodic methoxylation of **1**.

This simple study nicely highlights the importance of knowing the mass transfer properties of the electrolysis cell and working within them. For example, if the mass transfer limited current is exceeded (e.g. 320 mA without turbulence promoter), an unselective electrolysis occurs with formation of over-oxidised product **8** (Figure 10, right); *N*-formyl pyrrolidine is not supplied to the electrode at a sufficient rate, and some mono-methoxylated product **2** is oxidised even at relatively low conversions. On the other hand, improving the mass transfer characteristics by introducing the mesh and increasing the electrode surface area with the RVC anode allows a higher current of 320 mA to be applied to reach 80% conversion in shorter time while maintaining high selectivity. At this point, reducing the current completed the conversion while maintaining high selectively (not shown).

Returning to the electrolysis of *N*-PMB 2-iodobenzamide **5**, the reaction was repeated in the parallel plate reactor in divided mode by inserting a Nafion® 438 membrane between the PTFE spacers that formed the electrolyte chamber. Selective oxidative cleavage of the PMB group could now be realised by recycling the substrate solution through the anode chamber giving **7**. Alternatively, reduction of the aryl iodide could be carried out selectively in the cathode chamber, highlighting the flexibility of such a simple cell.[19a]

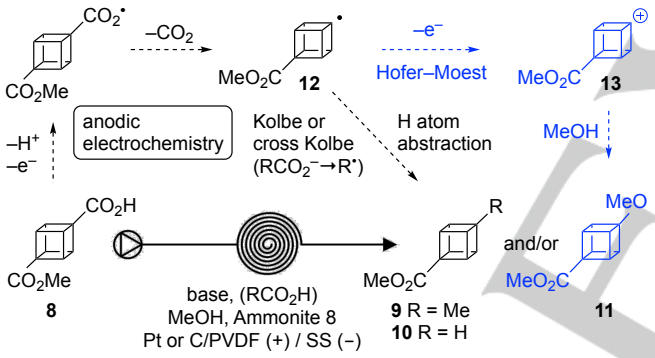


Scheme 3. Selective oxidation or reduction of iodobenzamide **5** in a divided parallel plate electrolysis cell.

3. Organic Transformations in Extended Path Electrochemical Flow Cells

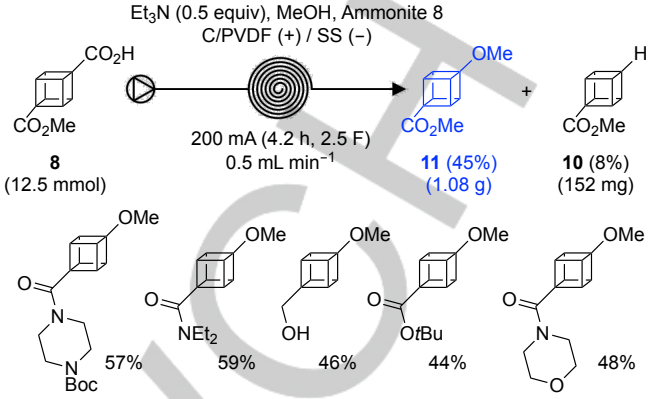
3.1 Hofer–Moest reactions of cubane carboxylic acids in flow

The ensuing sections provide an overview of some additional examples of electrosynthetic conversions performed in our lab using extended path electrochemical cells. A recent example is anodic methoxylation of cubane carboxylic acids in the Ammonite 8.[41] In addition to the inherent appeal and fundamental interest of a molecular cube comprised of carbon atoms,[42] applications of cubane extend from materials science to medicinal chemistry, where it has be introduced as a non-classical phenyl bioisostere.[43,44] In the latter context, cubyl-containing analogues of known drugs and molecules of pharmaceutical interest have shown improved physical and biological properties compared to parent systems.[45] A few years ago, during PhD student presentations as part of a collaborative programme, Diego Collin described some interesting cubane chemistry that he had been undertaking with Bruno Linclau, which required a practical large-scale synthesis of 1,4-cubanedicarboxylic acid.[46] This triggered our interest with respect to the reactivity of cubane carboxylates under anodic conditions, and whether they might participate in useful decarboxylative functionalisation by radical (Kolbe) or carbocation (Hofer–Moest) pathways (Scheme 4).[47] The potential for anodic functionalisation to provide a direct entry to useful cubane derivatives from a convenient starting material was also recognised.



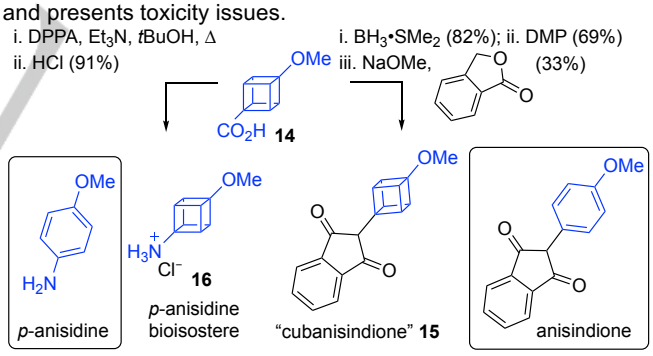
Scheme 4. Possible reaction pathways of cubane carboxylic acids under anodic oxidation conditions.

With electrochemistry input from Dr Ana Folgueiras, and enabled by a decent supply of suitable intermediates, Diego and Ana were able to establish operationally simple conditions for carboxylate oxidation in the Ammonite 8 reactor in the presence of a tertiary amine base in MeOH to afford cubyl ethers as the major "Hofer–Moest" products (Scheme 5).[41] Although loss of a second electron from the putative cubyl radical intermediates **12** is clearly a favourable process at the anode, small amounts of products arising from radical pathways were also observed. The formal carboxylate hydrogenolysis product **10** likely derives from the cubyl radical **12** by H atom abstraction from a component of the electrolysis medium. In the presence of acetic acid, a trace of cross-Kolbe product **9** was also obtained, although we were not able to optimise this to a synthetically useful level. On the other hand, formation of Hofer–Moest products in flow was demonstrated on a set of derivatives, and readily translated to gramme-scale quantities of methyl ether **11** simply by extending run time.



Scheme 5. Gramme-scale Hofer–Moest reaction of cubyl carboxylic acid **8** in flow, and examples of cubyl ether products.

The value of cubyl methyl ether **11** was illustrated through a short synthesis of an analogue of the synthetic anticoagulant drug anisindione, wherein a non-classical bioisosteric replacement of the electron-rich anisole was realised (Scheme 6). Hydrolysis of the methyl ester group in **11** gave acid **14**, then a two-step conversion to the cubanecarbaldehyde and ensuing basic condensation with isobenzofuranone secured "cubanisindione" **15**. A cubyl amine building block, isolated as its hydrochloride salt **16**, was also accessed from cubane carboxylic acid **14**. The primary amine **16** provides a convenient reagent for non-classical bioisosteric replacement for *p*-anisidine, which is oxidatively labile and presents toxicity issues.



Scheme 6. Synthesis of a non-classical *p*-anisidine bioisostere **16** and "cubanisindione" **15**, an analogue of the anticoagulant anisindione.

3.2 Oxidative esterification and amidation of aldehydes promoted by N-heterocyclic carbenes (NHC)

Esters and amides are ubiquitous in natural and synthetic compounds and materials, and are traditionally prepared from highly reactive species such as acid chlorides or from carboxylic acids using coupling agents.[49] A different synthetic approach involves oxidative esterification and amidation of aldehydes.[50] Since the early report by Corey, Gilman and Ganem in 1968,[51] cyanide has been known to promote oxidative esterification of

aldehydes using a large excess of MnO_2. Related oxidative amidations were described later.[52] However, "activated" allylic or benzylic aldehydes are a prerequisite for efficient oxidation of the cyanohydrin intermediates in all of these processes. The scope of this oxidative coupling approach to carboxylic acid derivatives was extended to "non-activated" aldehydes by using *N*-heterocyclic carbenes as reagents or catalysts.[53,54] None the less, a stoichiometric excess of chemical oxidant such as MnO_2 was typically employed.

A plausible mechanism proceeds via a Breslow intermediate **17**,[55] leading to an acylazolium **18** upon oxidation, which readily acylates alcohols (Figure 12). Prior to the upsurge of interest in this oxidative strategy, Diedrich and co-workers demonstrated the synthesis of methyl esters from aldehydes by an indirect electrochemical approach where thiazolium adducts could be oxidised using flavin mediators.[56] In 2011, Boydston and co-workers reported that Breslow intermediates were readily oxidised directly at the anode in a batch electrolysis cell, undergoing transformation to various esters *in situ*.[57] The same group subsequently showed that thioesters could also be prepared by combining electrolysis with NHC catalysis.[58] It is of interest that formation from NHCs from azolium ions is known as a cathodic transformation with evolution of H_2.[59]

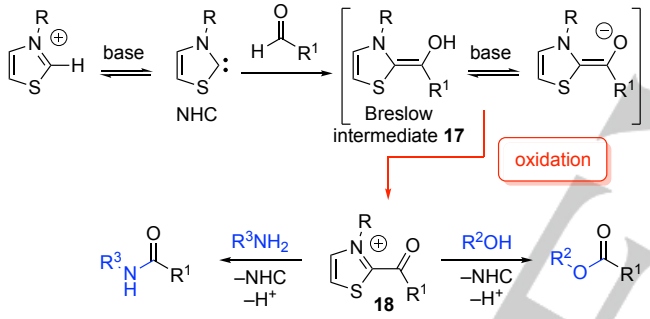


Figure 12. Proposed pathways for oxidative acylation mediated by N-heterocyclic carbenes

Flow electrosynthesis methodologies to perform "routine" laboratory interconversions such alcohol oxidation,[60] and oxidative acylations were viewed by us as attractive entry points to enable and encourage wider uptake of flow electrolysis by synthetic chemists. Robert Green joined our group as a PhD student to investigate anodic functional group transformations in flow, including NHC-promoted oxidative esterification and amidation of aldehydes. His initial optimisation applied a design of experiment (DOE) approach, and decent yields of esters and amides (see below) were obtained. The work was written up and submitted for publication, but unfortunately, our original manuscript describing the flow esterification and amidation reactions was rejected. Ultimately, this turned out to be both fortunate and a learning experience, leading us to reinvestigate both reactions (Figure 13).[61,62] A key realisation was that the window of flow rate / current we originally set in the original DOE had been too conservative, and increasing these parameters significantly improved experimental results, both in terms of yield and rate of conversion.

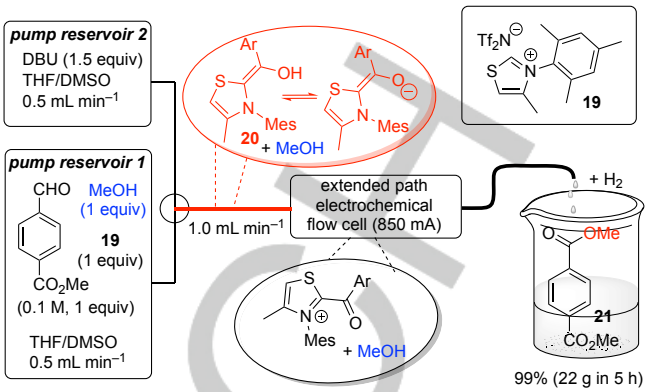


Figure 13. Diagram showing the flow mixing regime for oxidative amidation of aldehydes using NHC formed *in situ* from thiazolium salt **19**.

A diagram of the flow set-up shows how base (DBU) mixed with a solution containing equimolar amounts of aldehyde, alcohol and thiazolium salt to give a red solution, visible through the tubing, believed to be Breslow intermediate **20** (or its conjugate base). The mixture passed through the extended channel electrolysis cell, with a residence time of less than 12 seconds! (in reality the residence time was considerably less due to H_2 production at the counter electrode). The ester **21** was obtained in close to quantitative yield, highlighting both the ease with which the electrochemical oxidation occurs and favourable mass transfer achieved within the extended channel cell.

A further benefit of the flow approach, means that the ester **21** can be produced on a 20 g scale and in high yield by simply running the experiment for an extended time (5 h; ~4 g h^{-1} of **21**). Furthermore, no precautions other than using commercial dried solvents were needed. Using the thiazolium as bistriflimide salt **19** rather than its tetrafluoroborate did give greater reproducibility, which was ascribed to a lower tendency to absorb moisture. The improved yield at higher flow rates (commensurate increase in current) is believed to be due to the shorter time between formation of the Breslow intermediate (T-piece mixing) and its oxidation (entering the electrolysis cell).

Of course, it is desirable to perform such transformations using substoichiometric thiazolium, and although all reaction steps are rapid, it is a lot to expect multiple turnovers during a single pass of the reactor (residence time < 12 s). None the less, reducing the loading of the thiazolium salt to 0.5 equiv still afforded the ester in a respectable yield (76%), and at 0.2 equiv of **19**, 2 turnovers were achieved (40% yield) in one pass. We did not attempt to optimise the catalytic process, which would require a different flow regime (e.g. recycling). NHC-Promoted oxidative esterification was shown to proceed in good to excellent yields for a range of aldehydes, including aryl and aliphatic examples, with primary alcohols (Figure 14).

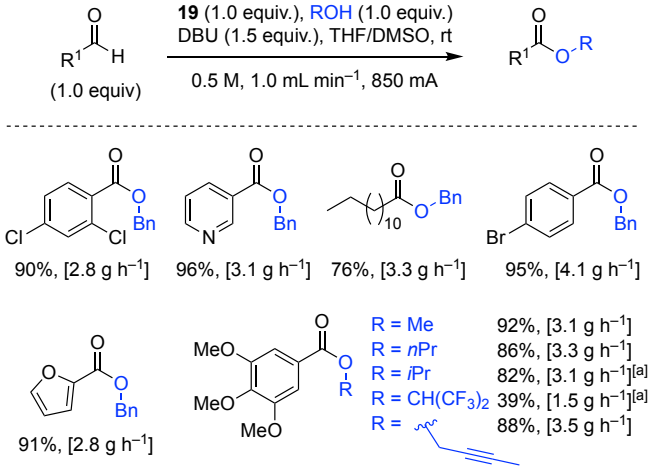


Figure 14. Oxidative esterification of aldehydes in an extended path electrolysis flow reactor showing isolated yields and rates of product formation. [a] 5 equiv of ROH.

Oxidative amidation of aldehydes proved to be a more challenging task due to competing reaction of the amine with the aldehyde, excluding direct transfer of the oxidative esterification conditions by simply exchanging the alcohol with amine. However, an advantage of flow is the ability to accurately control the order in which components mix. Thus, a modified flow regime ensured that Breslow intermediate formed prior to addition of the amine and then, anodic oxidation of the mixture in the electrolysis cell gave the acylating species (Figure 15). Initially, the amidation process was found to be somewhat capricious, due to the relatively slower reaction rate of amines with the acyl thiazolium intermediate **22**, compared to alcohols.[63] Our solution was to introduce a thermal reactor module after the electrolysis cell, driving the amide formation to completion.[62]

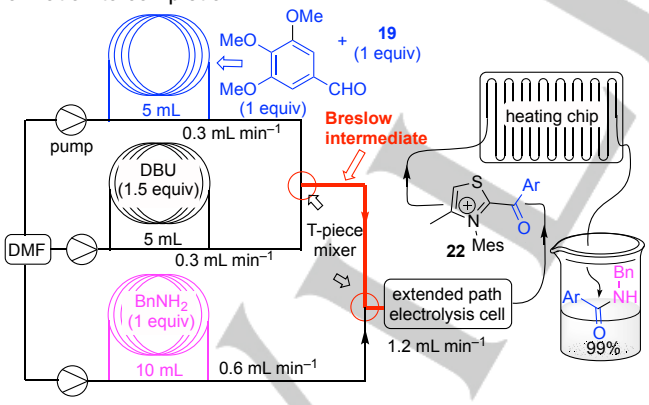


Figure 15. NHC-Promoted anodic formation of secondary amides from aldehydes in an extended path electrolysis flow reactor. Isolated yields and productivities.

The anodic NHC-promoted amidation process was exemplified by the synthesis of a range of secondary amides, achieved with good to excellent yields and productivities of >2 g h^{-1} in the same small laboratory electrolysis cell (Figure 16). We have yet to properly investigate the NHC-catalysed variant of this anodic amidation process, or indeed combing it with an initial alcohol oxidation, but these would be attractive future directions.

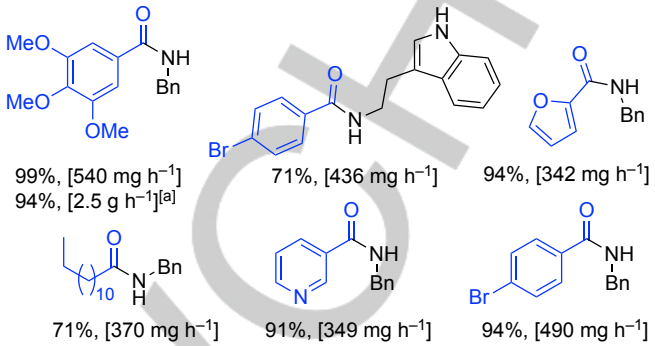


Figure 16. Oxidative amidation of aldehydes in an extended path electrolysis flow reactor showing isolated yields and productivities. [a] 2.5 mmol scale with increased concentration of aldehyde [0.125 M], 510 mA.

4. Conclusions

High conversion together with high selectivity is possible for a variety of organic electrosynthetic transformation using extended channel length microflow cells. Factors to be considered in design of electrolysis cells has been highlighted, and in particular, the impact of mass transfer, electrode area and channel dimensions on cell performance have been emphasised. Optimum performance with respect to rate of conversion and selectivity relies on the use of an appropriate cell current for the concentration of reactant and the flow rate through the electrolysis. Perhaps it is convenient for organic chemists to think of the amount of charge (number of electrons) required for an electrochemical conversion in the same way as we do for stoichiometry of chemical reagents. A good starting point for electrolysis is the amount of charge required for full conversion; too much can lead to other electrode processes including over oxidation of the product, and too little will clearly not allow full conversion of starting material to be achieved. A compatible counter electrode reaction should be available, and for the anodic syntheses discussed here it is hydrogen evolution which also serves to neutralise protons generated at the anode. An ideal solution is paired electrosynthesis, where both electrodes perform synthetically useful conversions.[64]

It should be recognised that a single pass approach is not optimum for all electrosyntheses (although good cell performance remains important). For example, in a process involving a substoichiometric mediator where relatively slow chemical steps are linked with fast electron-transfer in a catalytic cycle, then short residence times in the electrolysis cell may not be sufficient for turnover to occur. In these cases, operating the cell in recycle mode may be advantageous. Although the electrolyte can be recirculated through any flow electrochemical cell, we have described a simple parallel plate design that can be readily fabricated in a university workshop that is suitable for application in organic synthesis in multi-pass mode. The factors affecting the

performance of the cell have been discussed, with a view to guiding potential users towards simple steps to optimise it for application in organic electrosynthesis.

Recent advances in organic electrosynthesis stand upon foundations laid by pioneering electrochemists, organic electrochemists and chemical engineers, extending back over many decades. Some of the barriers that, in the past, inhibited wider translation of electrosynthesis into mainstream organic synthesis are being smoothed out. It is clear that, during the last decade, electrosynthesis has finally captured the attention of mainstream synthetic organic chemistry, and is no longer simply a curiosity. This remarkable turnaround is evident from the large, and growing, number of reported organic electrosyntheses, in batch and flow reactors. Drivers include the pursuit of greater sustainability, which is enabled by replacing chemical reagents, specifically toxic, scarce or hazardous ones, with (sustainable) electricity (ideally, not produced by burning chemicals!). On the other hand, it is great to see examples of new reactivity and fundamental interest in mechanisms of electrochemical reactions. Pleasingly, interest and excitement in organic electrosynthesis extend across academic and industrial groups, with active research laboratory and scale up applications evident. Present interest in continuous processing in general, and increasing reports of electrosyntheses flow indicate this area is likely to develop increasing momentum in the coming years, which I hope will be enabled by extended channel length electrolysis cells.

Acknowledgements

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Figure 17. Some of the important people. From bottom left to right: Alex Teuten, Dr Katie Jolley, Domenico Romano, Dr Ana Folgueiras, MateoSalam-Perez and Jack Hodgson (socially distanced!). Top centre: Prof Derek Pletcher. Top right: Dr Rob Green.

Keywords: electrosynthesis • flow chemistry • single-pass electrolysis cells • anodic oxidation • flow reactors

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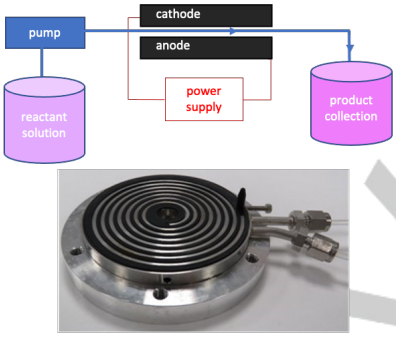
Layout 1:

PERSONAL ACCOUNT

In this personal account I provide an overview of collaborative research to develop flow electrolysis cells, and highlight some applications of these cells in organic electrosyntheses. The main focus is on cells possessing extended path-lengths, and how they can facilitate high conversions, selectively, in a single pass on scales suitable for laboratory applications. Factors affecting cell performance and optimisation are discussed, from an organic chemist's perspective.



Extended path flow electrolysis reactors targeting high, selective conversion in one pass

*Richard C. D. Brown**

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The longer route can be better: Electrosynthesis in extended path flow cells

Layout 2:

PERSONAL ACCOUNT

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