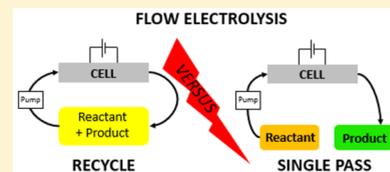


## Flow Electrolysis Cells for the Synthetic Organic Chemistry Laboratory

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**ABSTRACT:** Electrosynthesis has much to offer to the synthetic organic chemist. But in order to be widely accepted as a routine procedure in an organic synthesis laboratory, electrosynthesis needs to be presented in a much more user-friendly way. The literature is largely based on electrolysis in a glass beaker or H-cells that often give poor performance for synthesis with a very slow rate of conversion and, often, low selectivity and reproducibility. Flow cells can lead to much improved performance. Electrolysis is participating in the trend toward continuous flow synthesis, and this has led to a number of innovations in flow cell design that make possible selective syntheses with high conversion of reactant to product with a single passage of the reactant solution through the cell. In addition, the needs of the synthetic organic chemist can often be met by flow cells operating with recycle of the reactant solution. These cells give a high rate of product formation while the reactant concentration is high, but they perform best at low conversion. Both approaches are considered in this review and the important features of each cell design are discussed. Throughout, the application of the cell designs is illustrated with syntheses that have been reported.



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electrode reactions. Many interesting conversions have been reported in books<sup>1-4</sup> and reviews<sup>5-11</sup> and there are examples where electrolysis has been scaled up for the commercial manufacture of an organic product.<sup>12,13</sup> In reality, however, organic electrosynthesis has largely been carried out in laboratories specializing in the technique and it has never become part of the routine armory of the synthetic organic chemist. Why has electrolysis largely been ignored by synthetic organic chemists? One reason is certainly the absence of equipment and support designed specifically for convenient laboratory synthesis by non-electrochemists. In the academic literature on organic electrosynthesis, glass cells (beaker cells, “pot” cells, and H-cells) predominate. While easily assembled from laboratory glassware, such cells only allow slow chemical change under poorly defined and often irreproducible conditions. Yields and conversions can be well below what could be achieved, and attempts by others to repeat the synthesis can also lead to results below expectations. Hence, their use seldom leads to a “convenient synthesis” attractive to other chemists. In addition, papers often stress the advantages of “controlled potential” and advocate the use of a potentiostat. Potentiostats are convenient for very small scale electrolysis, but their use limits the cell current that can be used and hence the cell productivity. In any case, a much cheaper power supply to give a constant current generally suffices for electrosynthesis, provided that an appropriate cell current for the reactant concentration and mass transfer conditions are selected. There is also substantial literature on flow electrolysis cells,<sup>12,14</sup> and

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they are the “workhorses” of electrochemical technology in applications such as the modern chlor-alkali industry.<sup>12,15,16</sup> In organic electrosynthesis, flow cells with solution recycle can support selective syntheses and certainly allow the fast formation of product while the reactant concentration is high, but the rate drops with the reactant concentration. Hence, many electrosyntheses are reported with only a low conversion, inconvenient for laboratory synthesis. Moreover, in the literature, the emphasis is on the engineering aspects of cell operation, and the experiments with the laboratory flow cells are viewed as a stage in the scaleup of cells to the several square meter dimensions necessary for commercial production. In contrast, the need for flow cells designed for laboratory organic synthesis has seldom been recognized.

Recently, there has been much interest in organic synthesis carried out in microflow systems.<sup>17–20</sup> A large number of convenient syntheses with high conversions and selectivities have been reported. A consequence has been the growth of interest in flow electrolysis cells specifically designed for the synthetic organic laboratory.<sup>21–23</sup> This, therefore, seems an appropriate time to reassess the literature on flow cells in general in order to demonstrate that flow cells are a viable, more attractive approach to organic electrosynthesis for laboratory synthetic organic chemists.

## 2. GENERAL BACKGROUND

### 2.1. A Definition

For the purposes of this review it is important to define what is meant by a ‘convenient laboratory synthesis’. It is intended to include the chemical transformations routinely carried out in the laboratory where (1) the intention is to prepare 10 mg–100 g of product; (2) there is a requirement for high selectivity; (3) straightforward isolation of pure product is desirable, so full conversion of reactant to product and the absence of electrolyte are advantageous; and (4) the reaction goes to completion with an electrolysis time preferably of minutes, but certainly no more than a few hours.

Current (charge) efficiency is not always important in laboratory synthesis. It is only important when competing reactions (oxidation/reduction of the reactant to alternative products or of solvent/electrolyte) lead to loss of reaction selectivity or complicates the isolation of pure product. Certainly, energy efficiency only becomes a factor on the much larger scale essential for commercial manufacturing of high-tonnage, low-value products.

### 2.2. The Rules

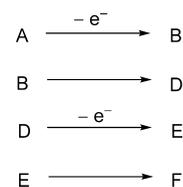
In general, in organic electrosynthesis, the role of the electrode reaction is to convert the reactant molecule into a reactive intermediate that then decays to the product in a sequence of reactions in the solution close to the electrode. This coupled chemistry commonly involves further electron transfer. For a  $2e^-$  transformation of reactant (A) into product (F), a common mechanism (written for an oxidation) is shown in Scheme 1.

Clearly, a high-yield transformation requires both control of the electron transfer reactions and choice of the solution conditions (solvent, pH, electrolyte, temperature, etc.) so that the reactive intermediates decay by a single pathway.

The design of convenient electrosyntheses, as defined above, is only possible with the recognition of a number of fundamental rules of electrochemistry.<sup>2,3,24,25</sup>

(i) Electrodes carry out oxidation or reduction, and for chemical change to occur, charge must be passed through the

### Scheme 1. Typical Electrochemical Oxidation Mechanism



cell. The amount of charge,  $Q$ , required may be calculated using Faraday’s law.

$$Q = mnF \quad (1)$$

where  $m$  is the number of moles of reactant to be converted,  $n$  is the number of electrons/reactant molecule involved in the transformation, and  $F$  is the Faraday constant (the charge on a mole of electrons).

Table 1 reports the cell current and a possible electrode area for four rates of product formation and it emphasizes that

**Table 1. Cell Current and Electrode Areas for a Monopolar Electrolysis Cell Required for the Desired Product Formation Rates**

| product formation rate <sup>a</sup> (g h <sup>-1</sup> ) | cell current (A) | electrode area <sup>b</sup> (cm <sup>2</sup> ) |
|----------------------------------------------------------|------------------|------------------------------------------------|
| 0.1                                                      | 0.06             | 0.6                                            |
| 1                                                        | 0.55             | 5.5                                            |
| 10                                                       | 5.5              | 55                                             |
| 100                                                      | 55               | 550                                            |

<sup>a</sup>Product from a  $2e^-$  transformation, with molecular weight 100 Da and a fractional current efficiency of 1.0. <sup>b</sup>Assuming a current density of 100 mA cm<sup>-2</sup>.

convenient synthesis requires a significant cell current and a cell of some size, even with a relatively high current density (requiring a high reactant concentration and efficient mass transfer). For lower current densities, the cell dimensions increase significantly (the required electrode area is inversely proportional to the current density).

(ii) All electrolysis cells have both an anode and cathode, and in terms of electrons, the same amount of chemistry occurs at each electrode. Hence, for clean synthesis, the counter electrode chemistry must be considered. While a separator may be used, it must be recognized that transport of all solution-soluble species through the separator can occur, and indeed, transport of ions is essential to the passage of charge through the cell (see below).

(iii) Chemical change cannot take place faster than the reactant reaches the electrode surface, as the electron transfer can only occur within molecular dimensions from the surface. Therefore, the fastest chemical change is determined by the mass transfer regime (i.e., how fast reactant travels to the electrode, which is quantified by the mass transfer coefficient,  $k_m$ ). The rate of conversion is determined by the cell current,  $I_{\text{cell}}$ . Assuming that the fractional current efficiency for the desired reaction is 1.0 and that the reaction is mass transfer controlled, the cell current is given by

$$I_{\text{cell}} = nFAk_m c \quad (2)$$

where  $A$  is the electrode area and  $c$  the concentration of reactant. Always the cell current can be increased by increasing the concentration of reactant, the electrode area, or the mass transfer coefficient. Alternatively, in a cell with uniform current

density over the working electrode surface, the cell current can be written as a function of the current density,  $j_L$ .

$$I_{\text{cell}} = j_L A \quad (3)$$

(iv) For a mass transfer controlled reaction, the fractional conversion ( $X$ ) as a function of time ( $t$ ) of a volume of reactant solution ( $V$ ) using an electrode of area  $A$  is given by

$$X = 1 - \exp \frac{-k_m A t}{V} \quad (4)$$

stressing the importance of efficient mass transport and a high electrode area/solution volume ( $A/V$ ) ratio in a cell design for faster conversion. For reactions that are not mass transfer controlled, the conversion will be slower. To illustrate the difficulty in achieving high conversions, Table 2 estimates the

**Table 2. Influence of Mass Transport Conditions and Electrode Dimensions on the Time Taken for 95% Conversion of Reactant in 1 L of Solution: (a) Poor Mass Transfer,  $k_m = 10^{-4} \text{ cm s}^{-1}$ ; (b) Moderate Mass Transfer,  $k_m = 10^{-3} \text{ cm s}^{-1}$ ; and (c) Efficient Mass Transfer,  $k_m = 10^{-2} \text{ cm s}^{-1}$**

time to 95% conversion

| electrode plate dimensions<br>(cm × cm) | $A/V$<br>( $\text{cm}^{-1}$ ) | time to 95% conversion |         |          |
|-----------------------------------------|-------------------------------|------------------------|---------|----------|
|                                         |                               | case a                 | case b  | case c   |
| 1 × 1                                   | $10^{-3}$                     | 350 days               | 35 days | 3.5 days |
| 10 × 10                                 | 0.1                           | 3.5 days               | 8.4 h   | 50 min   |
| 30 × 30                                 | 0.9                           | 9.3 h                  | 56 min  | 5.6 min  |
| 100 × 100                               | 10                            | 50 min                 | 5 min   | 30 s     |

times required to obtain a 95% conversion for a reactant in a 1 L volume of solution in cells with different electrode areas and efficiencies of mass transfer. In a 1 L beaker cell, typical designs in the literature would have an electrode area of  $<100 \text{ cm}^2$  (giving an  $A/V$  ratio  $<0.1$ ) and an unstirred or slowly stirred electrolyte equivalent to a mass transfer coefficient of  $10^{-4} \text{ cm s}^{-1}$  (case a); this leads to a very long electrolysis time for high conversion. Increasing the  $A/V$  ratio and introducing efficient stirring (case b) leads to more rapid product formation. The highest  $A/V$  ratio and most efficient mass transport regime (case c) are probably only achievable with a large industrial unit.

(v) In many cell designs, the objective is to achieve the same chemical transformation and the same rate of reaction over the whole surface of the working electrode. This requires that the working electrode has a uniform potential over its surface and a uniform flux of reactant to the whole surface, hence, uniform current density. An equal potential over the surface is only possible if all points on the surface of the working electrode are equivalent in position with respect to the counter electrode so that the potential drop through the interelectrode solution is constant. A uniform flux of reactant necessitates a uniform mass transfer regime and implies an even concentration of reactant close to the surface. In contrast, when using a flow cell and the objective is to achieve a high conversion of reactant to product in a single pass of the reactant solution through the electrolysis cell, it is still advantageous to have an equipotential surface, but clearly, the flux of reactant must drop from entry to exit of the cell. Hence, the local current density will drop along the channel from inlet to outlet.

### 2.3. Divided vs Undivided Cells

In some cells, a separator (a glass frit, a porous ceramic, a porous polymer sheet, or an ion-selective membrane) is placed between the anode and cathode, in order to “separate” the chemistries at the two electrodes. This is necessary when the reactant or product of the desired reaction at the working electrode has chemistry at the counter electrode or products from the counter electrode reaction interfere with the synthesis at the working electrode.

It is, however, important to understand the term “separator” as used in the description of electrolysis cells. As noted above, the passage of charge through all cells is essential to chemical change at the electrodes and this requires the movement of ions between the electrodes (cations from anode to cathode and/or anions from cathode to anode); the passage of 1 mol of electrons at the electrode surfaces necessitates the movement of 1 mol of ionic charge through the separator. In addition, these ions will be accompanied by solvent. With ion permeable membranes, the ion movement will largely be selective (cation vs anion)<sup>26–28</sup> and determined by the charge on the membrane polymer. With porous materials, both anions and cations will be transported, with the ratio determined by the transport number of the ions in the electrolyte solutions. Furthermore, porous separators only slow down the mixing of anolyte and catholyte and diffusion of all species (including reactants and products of the electrode reactions) will occur through the separator whenever there is a concentration gradient across the separator. The extent of mixing will depend on pore dimensions and will increase with electrolysis time. Even with ion-permeable membranes, some leakage of organics is inevitable, but it will be slow compared to diffusion through a porous separator.

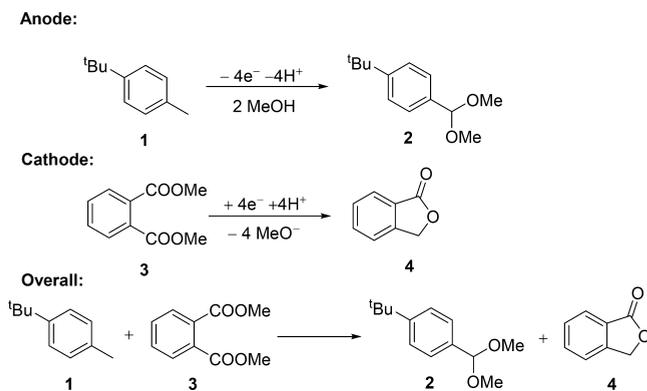
Recognizing that incorporating a separator into an electrolysis cell increases the complexity of its design and fabrication and, anyway, they are imperfect in stopping mixing between anolyte and catholyte, can a separator be avoided? Clearly, the answer is yes if the chemistries at the two electrodes do not interfere with one another. This can be achieved in several ways.<sup>29</sup> In one approach, the cell is set up with a desired oxidation reaction at the anode and a desired reduction at the cathode, allowing two syntheses to be carried out simultaneously in the cell. Clearly, such “paired electro-syntheses” require that the cathode reactant and product are inactive at the anode and the anode reactant and product inactive at the cathode. One example shown in Scheme 2, is the simultaneous oxidation of 1 to 2 and reduction of 3 to 4, which has been exploited on a commercial scale, by BASF in Germany.<sup>30</sup>

Another strategy involves the synthesis of the same product at both electrodes. Here, an example is the electrosynthesis of peracetic acid from acetic acid using hydrogen peroxide intermediate produced both at a boron-doped diamond anode by water oxidation and by oxygen reduction at a carbon felt gas diffusion electrode.<sup>31</sup>

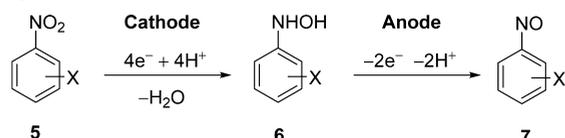
A third approach is to use both cathode and anode reactions in the chemical sequence leading from feedstock to product. An example is the conversion of nitrobenzenes 5, via 6, to give nitrosobenzenes 7<sup>32,33</sup> using a buffer of pH 4–6 and a cell with two flow-through carbon felt electrodes. The solution flow is first through the cathode and then through the anode (Scheme 3).

Counter electrode chemistry can be particularly invasive if the electrolysis employs an aprotic solvent (the anode and cathode reactions of aprotic solvents are seldom clean). Hence,

### Scheme 2. Example of a Commercial Paired Electrosynthesis Process

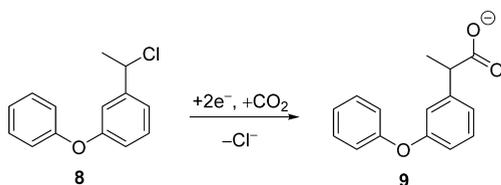


### Scheme 3. Conversion of Nitrobenzenes to Nitrosobenzenes Using Both Cathode and Anode in the Cell



for syntheses at cathodes in aprotic solvent, a common selection of anode reaction is the use of a soluble metal anode.<sup>34,35</sup> The most common metals are magnesium, aluminum, zinc, and tin, although any metal that readily dissolves anodically to give a soluble metal ion can be used. The multicharged cations formed can have the additional role of stabilizing or precipitating anionic products formed at the cathode. This approach was used in a pilot plant for the electrocarboxylation of the benzyl halide **8** in an aprotic medium to give the anti-inflammatory drug fenoprofen (**9**), using Mg electrodes (Scheme 4).<sup>36,37</sup>

### Scheme 4. Synthesis of the Anti-Inflammatory Drug **9**, Using a Dissolving Mg Electrode

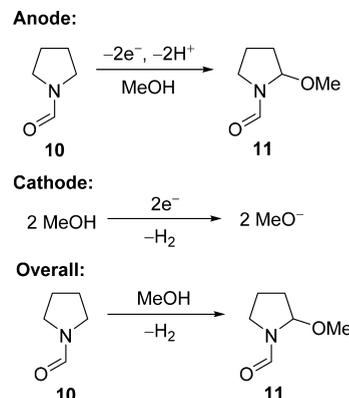


The process required the development of a novel cell design, the “pencil sharpener cell”. This innovative design allowed the maintenance of a constant, narrow interelectrode gap as the magnesium anode was consumed by the electrolysis. The pilot plant operated with 60 kg batches of reactant converted to product with a batch time of 28 h.

Moreover, the application of an undivided cell can be advantageous. Almost always, anode reactions lead to the formation of protons, and cathode reactions to the formation of base. Hence, during electrolyses, solutions in a divided cell can show strong changes in pH with conversion, possibly leading to undesirable side reactions (e.g., hydrolysis of reactant and/or product). In an undivided cell, the counter electrode chemistry is readily used to counterbalance the pH swing at the working electrode and hence to avoid the competing chemistry. Examples of creating pH balance using the cathodic generation

of base in anodic syntheses would include the paired synthesis described in Scheme 2 and the methoxylation of *N*-formyl-heterocycles **10** to give **11** (Scheme 5).<sup>38–42</sup>

### Scheme 5. Example of Using the Counter Electrode Chemistry to Balance the pH



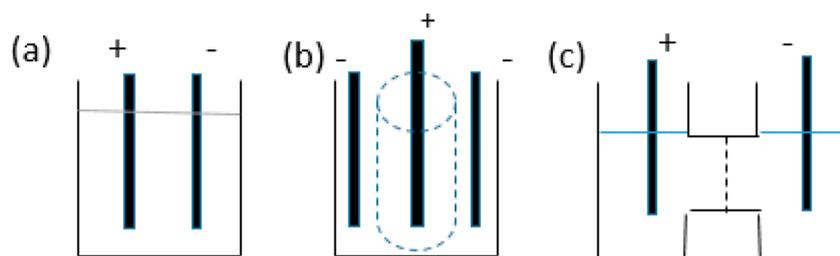
## 3. BEAKER CELLS AND H-CELLS

Figure 1 illustrates typical designs of (a) a beaker cell, (b) a pot cell, and (c) an H-cell. Such cells are usually constructed from glass and easily put together in the laboratory. Moreover, they are easily adapted for oxygen- and water-free operation and electrolysis at slightly elevated temperatures.

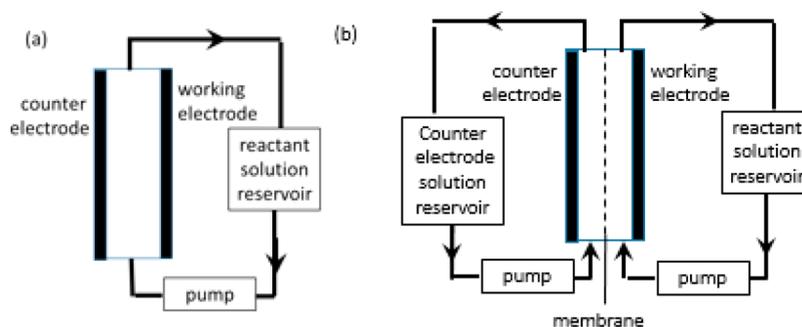
Why then are such cells not recommended? The main reason is the slow rate of chemical change leading to very extended electrolysis times to obtain grams of product and/or high conversions as well as selectivities below those that can be achieved. As noted in the discussion of Table 2, with these cells, the time for 95% conversion is often many hours and can be several days. The slow rate of conversion is a consequence of the following: (a) the mass transfer regime (characterized by a mass transfer coefficient,  $k_m$ ) and (b) the ratio of electrode area to electrolyte volume ( $A/V$ ).

With regard to the mass transfer regime, operating with a still solution or slowly rotating magnetic stirrer in a beaker cell leads only to inefficient mass transport and corresponds to case a in Table 2. Using fast rotation of the magnetic stirrer or a fast stream of targeted gas bubbles improves the mass transport regime, approaching case b. Using an efficient paddle stirrer or rapid rotation of the electrode will improve the performance further, but case c is very difficult to achieve in beaker cells. With pot cells and H-cells, it is even more difficult to increase the movement of the solution and hence to improve the mass transport regime.

With regard to the ratio of electrode area to electrolyte volume ( $A/V$ ), Table 2 illustrates that the electrolysis time is very sensitive to the ratio  $A/V$ . In many cells used in the laboratory,  $A/V \ll 1$ . It is maximized in a beaker cell by using two concentric, cylindrical electrodes with the working electrode close to the edge of the beaker. In principle, the  $A/V$  ratio can reach 0.25. Another possible way to enhance the  $A/V$  ratio in beaker cells is to use a block of reticulated vitreous carbon as the working electrode; with 3D electrodes, however, the IR drop through the solution within the electrode structure may limit the surface area that is active; see the discussion below.



**Figure 1.** Typical glass cells used for electrosynthesis in the literature: (a) undivided beaker cell, (b) beaker cell with a porous pot separator, and (c) H-cell with porous separator.



**Figure 2.** Laboratory arrangement for electrosynthesis using a flow cell with recycle of reactant solution: (a) undivided cell and (b) divided cell.

Higher and more uniform mass transfer as well as a higher  $A/V$  ratio are much easier to achieve in flow cells. With beaker and other glass cells, differences in stirring procedures,  $A/V$  ratio, and electrode placement between cells in different laboratories can easily lead to different selectivities and conversion rates; this apparent lack of reproducibility damages the reputation of electrosynthesis among synthetic chemists.

In all cells, the reaction selectivity depends on controlling the electrode potential (usually via control of the cell current, reactant concentration, and mass transfer regime) to ensure that the same reactive intermediate is produced with a relatively uniform concentration over the whole electrode surface. This requires that all points on the working electrode surface are equivalent geometrically with respect to the counter electrode (so that the  $IR$  drop (voltage drop) through the solution between the electrodes is the same over the whole surface) and there is also a uniform mass transport regime over all the working electrode. Few designs of beaker cells can achieve these goals. Hence, for example, if two plate electrodes are used, then the backs should be covered with insulating material; otherwise, the front and back of the working electrode will carry quite different current densities, the back doing little chemistry. Uniform current distribution and absence of edge effects are much more easily achieved in other cell designs, e.g., parallel plate flow reactors; see the following section. Also a good selectivity depends on selecting solution conditions so that the reactive intermediates decay by a single pathway. It is also helped by rapid electrolysis, since competing homogeneous chemical reaction (e.g., reactions catalyzed by  $H^+$  and  $OH^-$ , hydrolysis by trace water) become more important with time.

Overall, glass cells are a poor choice for convenient electrosynthesis. The only advantage is their similarity to other laboratory apparatus. It also has to be said that the designs shown in textbooks are too often even poor designs of beaker and H-cells, failing to achieve a high  $A/V$  ratio, good mass transfer, or uniformity of electrode potential.

#### 4. PARALLEL PLATE CELLS WITH FLOW AND SOLUTION RECYCLE

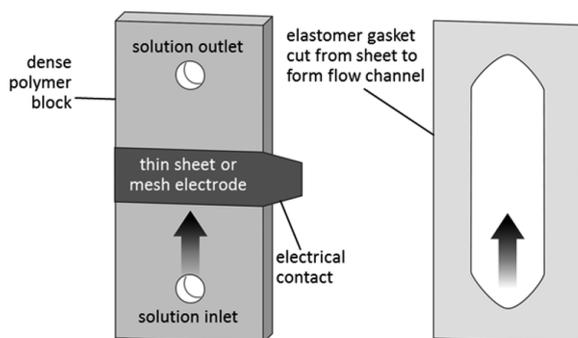
In the manufacture of chemicals by electrolysis on a commercial scale, parallel plate cells in a stack within a filter press are a frequent choice of technology.<sup>12,13</sup> On this larger scale, both divided and undivided cells have been operated. The linear flow rate through the gap between the electrodes is usually as rapid as possible, so as to enhance the mass transfer of reactant to the electrode. This maximizes the cell current and rate of conversion (in terms of grams/second), but in consequence, the residence time of reactant within the cell is short so that the conversion per pass is low. To achieve an acceptable conversion, the reactant solution is recycled between a reservoir and the cells. A high overall conversion requires a long electrolysis time, as the current will drop (exponentially with time) as the reactant concentration decays with conversion to product. If a low conversion is acceptable, the highest cell productivity is achieved by adding reactant continuously so that its concentration remains high.

Parallel plate cells have a number of advantages: (1) all points on the working electrode surface are equivalent with respect to the other electrode; (2) using simple polymer spacers, a constant narrow interelectrode gap is easily achieved; (3) uniform flow in the gap between the two electrodes can be realized; (4) a separator can be introduced without major changes to the cell design; and (5) scaling can readily be achieved by changing the area of the plate electrodes or using multiple cells in parallel.

Laboratory parallel plate reactors maintain these advantages. Usually a single pair of electrodes is sufficient for the desired rate of conversion, and the cell may be divided or undivided. Figure 2 shows laboratory setups featuring cells, reservoirs, and pumps.

The overall conversion can still be estimated using eq 4 provided  $V$  is now the volume of reactant solution in the reservoir. The simplest cell is based on two electrode plates separated by a spacer/gasket fabricated from an elastomer

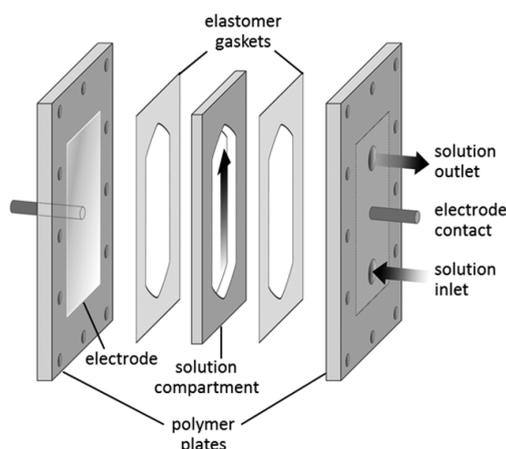
polymer sheet with its center cut away to form the electrolyte flow chamber. Leak-free operation is achieved by compression of the sandwich with a series of bolts around the edges of the plates. The dimensions of the cell are determined by the desired production rate and the cell current that can be achieved; see Table 1. As a general rule, the interelectrode gap, determined by the thickness of the spacer(s), should be as narrow as possible and 1–5 mm is readily achievable. The polymer used for the spacer will be determined by its stability to the solvent and chemicals used in the electrosynthesis. Figure 3 shows a slightly more sophisticated design based on



**Figure 3.** A simple laboratory flow cell. Shown are the components for a half-cell. The cell is completed by repeating similar components. A membrane/porous separator may be accommodated with additional gaskets. The complete cell is sandwiched between two end plates pressed together with multiple bolts.

two polymer blocks spaced by elastomer gaskets.<sup>43</sup> This design includes entry and exit lengths to the solution chamber, and this ensures a more uniform flow regime over the whole surface of the electrodes. In the absence of these entry and exit lengths, uniform flow across the electrode requires the design of solution distributors at the inlet and outlet to the cell. Elastomer sheets are available in several materials and thicknesses; the solution flow channel is created by cutting away the center of the elastomer sheet. If the electrodes are thin metal sheet or meshes, the electrodes may be laid upon the polymer blocks, and electrical contacts are readily made through tabs at the side of the cell. Alternatively, metal plate electrodes can be sunk into the polymer blocks with electrical contact from the back. The cell is sealed between two metal end plates slightly larger than the polymer blocks and a number of bolts compressing the end plates. Effective sealing of the cell may require multiple gaskets.

Other flow cell designs employ polymer blocks with centers cut away as the electrolyte chambers with elastomer gaskets between each polymer block. Figure 4 shows an undivided cell of this design. All parallel plate cells can be operated divided as well as undivided, with the additional solution compartment and ion-permeable membrane or porous polymer sheet separator sealed with additional spacers/gaskets. The interelectrode gap should always be as narrow as possible. With divided cells employing mesh electrodes, the electrodes can actually be in contact with the membrane surface with the reactant feed to the back of the mesh; this is then known as a “zero-gap” cell. In laboratory cells, typical areas are 10–100 cm<sup>2</sup>, depending on the desired rate of product formation, and typical linear flow rates are 1–20 cm s<sup>-1</sup>, with the volumetric flow rate depending on the dimensions of the electrolyte chambers. A number of papers describe parallel plate flow cell designs suitable for



**Figure 4.** A figure showing the cell structure and components of a laboratory parallel plate reactor.

laboratory electrosynthesis.<sup>43–48</sup> Such cells have also been marketed by a number of companies.<sup>12,49–51</sup>

A commercial cell used in several academic studies was the FM01-LC electrolyzer<sup>12,52–56</sup> marketed by ICI for a number of years (Figure 5). This cell has electrodes with an active area 4 × 16 cm and it could be operated with or without a separator. Data from this cell is used to illustrate the factors influencing the rate of chemical change in parallel plate flow cells. Figure 6 reports the limiting cell current densities for a mass transport controlled reaction (in fact, for the reduction of 1.0 mM ferricyanide in 1.0 M aqueous KOH) as a function of solution linear flow rate. The data are presented as plots of log(limiting cell current) vs log(linear solution flow rate) for cells with (a) a flat plate electrode, (b) a flat plate electrode with a thin plastic mesh turbulence promoter, and (c) a 4 mm thick, nickel foam electrode with flow-by configuration (the direction of current and solution flows are perpendicular). The relative limiting cell currents are proportional to the rate of chemical change/unit area for a mass transfer controlled electrosynthesis. In all configurations, it can be seen that the rate of conversion of reactant to product increases with flow rate (although the decreasing residence time of reactant in the cell with increasing flow rate will lead to a lower fractional conversion for each pass of solution through the cell).

With the flat plate electrode, the mass transfer coefficient is close to 10<sup>-3</sup> cm s<sup>-1</sup> at all flow rates used (corresponding to case b in Table 2), and a 10-fold increase in flow rate led to an approximately 3-fold increase in limiting current density. Figure 6 also shows that the rate of conversion can be further increased by including one or more thin polymer mesh turbulence promoters close to the plate electrode surface, typically by a factor of 1.5–3. This factor can be increased to >5 by inserting a stack of such meshes into the solution flow. The influence of the turbulence promoter architecture and dimensions has been investigated.<sup>44,55,57</sup> The largest increase in rate of conversion is achieved with a three-dimensional electrode, usually a foam, a felt, or a stack of mesh electrodes,<sup>43,56,58</sup> and this is illustrated in Figure 6 with data for a nickel foam cathode where the scaling factor is >20 compared to the flat plate electrode. Foam and stacked mesh electrodes as well as stacked mesh turbulence promoters are most easily incorporated into parallel plate reactors using additional polymer blocks as the electrolyte compartments;

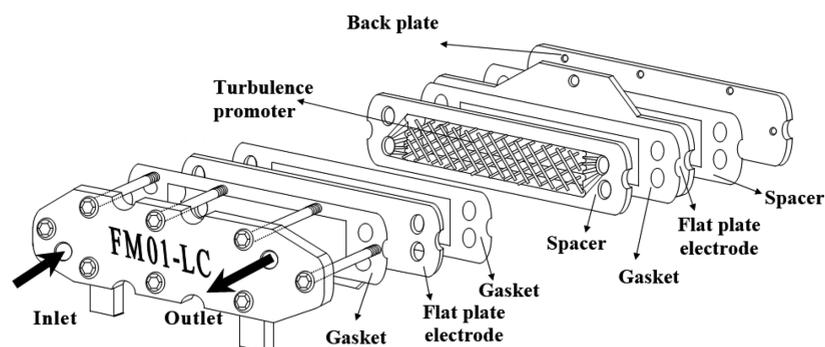


Figure 5. Design and components of the FM01-LC laboratory flow electrolyzer.

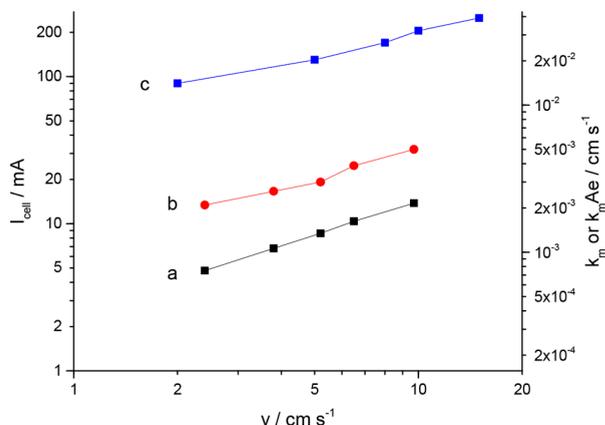


Figure 6. Variation of the cell current (cell productivity) and mass transport regime with linear flow rate for a mass transport controlled reaction, presented as log/log plots. FM01 cells with nickel cathodes (area 64 cm<sup>2</sup>). Solution was 1 mM Fe(CN)<sub>6</sub><sup>3-</sup> + a large excess of Fe(CN)<sub>6</sub><sup>4-</sup> in 1 M KOH. (a) Flat plate electrode. (b) Flat plate electrode + a fine polymer mesh turbulence promoter. (c) Foam electrode, thickness 4 mm. Data are from refs 54 and 56.

Figure 7 illustrates a cell with a reticulated vitreous carbon electrode.<sup>59</sup>

These three-dimensional electrodes benefit from an enhanced real surface area (therefore the current density scaling depends on the thickness of the structure as well as its

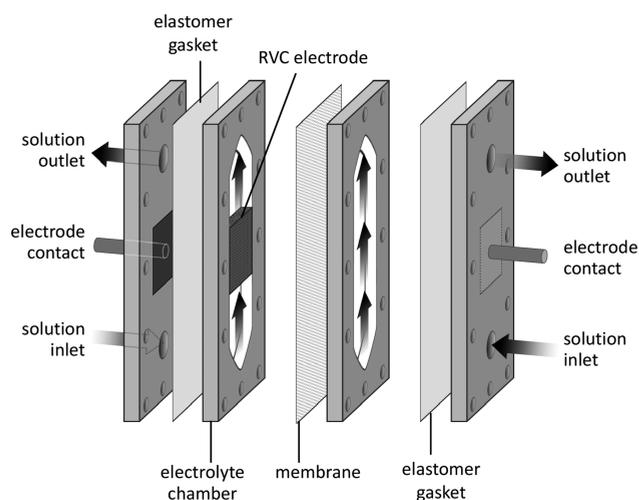


Figure 7. Flow cell with 3D foam electrode and membrane separator to illustrate a polymer block solution compartment cell.

detailed structure) in addition to the creation of turbulence in the solution flow close to the electrode. Such three-dimensional electrodes are most beneficial to the rate of conversion when the electrode reaction is occurring at low current density, a common situation in electrosynthesis. An example is the oxidation of alcohols to carboxylic acids at a nickel anode in aqueous alkali.<sup>56</sup> When the synthesis is possible at higher current density, the performance of three-dimensional electrodes becomes adversely affected by *IR* drop in the solution through the 3D structure; some of the 3D electrode depth becomes inactive and the cell productivity no longer scales with electrode thickness.

Industrial-scale parallel plate cells have electrodes with an area up to 1 m<sup>2</sup> and it is common to stack up to 100 cells with bipolar electrical connection within a filter press arrangement.<sup>12</sup> Laboratory electrolyzers are usually designed with a single pair of electrodes with areas 5–100 cm<sup>2</sup>. But as previously stressed, the literature on small parallel plate electrolyzers generally views them as a stage in the scale-up to larger electrolyzers for electrosyntheses on a commercial scale producing many kilograms/day. This, however, is not necessarily the way to view such cells and should not distract from using them in a different role, simply for laboratory synthesis. To illustrate their performance, consider an electrolyzer with 10 × 10 cm electrodes; for electrolysis of a 0.1 M solution of reactant, the initial conversion rate for a selective reaction could be 0.2 mol h<sup>-1</sup> (20 g h<sup>-1</sup> for a product with molecular weight 100 Da) and the reaction with 1 L of reactant solution should go to 95% conversion (95 mmol or 9.5 g for a product with MW = 100 Da) in under 2 h. A high current efficiency, however, requires the electrolysis to be carried out with a declining cell current (either with a programmed cell current or using a controlled potential) as the limiting current for the desired reaction decays with reactant conversion to product. Alternatively, if less than high conversion is acceptable, the electrolysis would be 50% complete in ~25 min, giving 50 mmol of product (5 g for a product with MW = 100 Da).

Parallel plate flow reactors have been much underused for laboratory organic synthesis, but reactions that have been reported include (1) the reduction of *L*-cystine to *L*-cysteine;<sup>60,61</sup> (2) the reduction of benzaldehydes to benzyl alcohols and/or diols;<sup>62,63</sup> (3) the oxidation of alcohols to carboxylic acids;<sup>56</sup> (4) the anodic coupling of *o*-hydroquinone to 4-hydroxycoumarin and 1,3-dimethylbarbituric acid to give coumestan and catecholamine, respectively;<sup>64</sup> (5) the oxidation of lignosulfonate into vanillin;<sup>65</sup> (6) the formation of 4-hydroxybenzaldehyde from sodium 4-hydroxymandelate;<sup>66</sup> (7) the solvated electron reduction of histidine methyl ester to *L*-

histidinol using ethylamine as the solvent;<sup>67</sup> and (8) the Cr(II)-mediated indirect reduction of 4-hydroxymandelic acid to 4-hydroxyphenylacetic acid.<sup>45</sup>

These examples, however, should be considered as illustrating the range of chemistry possible in parallel plate electrolysis cells rather than laboratory syntheses. Data is often reported at low conversion, and a common target is to increase current density (therefore cell productivity), at least to 50 mA cm<sup>-2</sup>.

Overall, flow cells with recycle of the reactant solution deserve consideration for laboratory synthesis. The scaling of cell productivity by attention to the flow regime, the use of turbulence promoters, and consideration of a three-dimensional electrode should be emphasized. Several designs can give high selectivity for suitable reactions, and with appropriate selection of cell dimensions and configurations, solution flow rate, and reactant concentration, various rates of product formation can be accommodated. Full/high conversion, however, requires lengthening of the electrolysis time, because the rate or conversion of reactant to product drops with time as the reactant concentration decays. Hence, flow cells with recycle of the solution are best suited to laboratory synthesis, where a low conversion is acceptable for the synthesis.

## 5. PSEUDO-PARALLEL PLATE CELLS WITH FLOW AND ELECTROLYTE RECYCLE

### 5.1. SPE Electrolyzers

A development of parallel plate electrolysis cells is the solid polymer electrolytes (SPE) (also called MEA) reactor<sup>68</sup> (Figure 8). In such cells, the electrolyte is an ion-permeable membrane

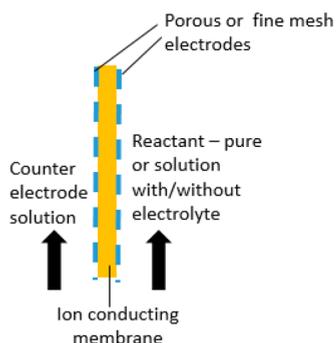


Figure 8. Design of a solid polymer electrolyte (SPE) cell.

and one or both of the electrodes are meshes or porous structures coated directly onto the surface(s) of the membrane. This has the advantage that the electrode in contact with the membrane can be fed from the back of the electrode and the feed does not need to be ion-conducting. Hence, the feed can be reactant dissolved in solvent without electrolyte, reactant dissolved in a nonpolar solvent, or even pure reactant. It is an advantageous design when the electrodes are catalytic, with the approach feeding strongly on fuel cell technology. The most common reaction is hydrogenation with substrates including decene,<sup>69</sup> acetone,<sup>69</sup> acetophenone,<sup>70,71</sup> unsaturated ketones,<sup>72</sup> nitrobenzene,<sup>73</sup> toluene,<sup>74</sup> and edible oils (such as soybean oil).<sup>75–77</sup> Other electrosyntheses reported for SPE reactors include that of *N*-acetyl-L-cysteine<sup>78</sup> and *p*-methoxybenzaldehyde,<sup>79</sup> as well as the Kolbe reaction.<sup>80</sup>

### 5.2. Pipe Cell

Although strictly not a parallel plate cell, some other cell designs share a key characteristic, the anode and cathode are separated by a uniform interelectrode gap. One design is the pipe cell (Figure 9), where the cell consists of a cylindrical graphite anode electrode inside a steel pipe cathode with a narrow interelectrode gap.<sup>81,82</sup>

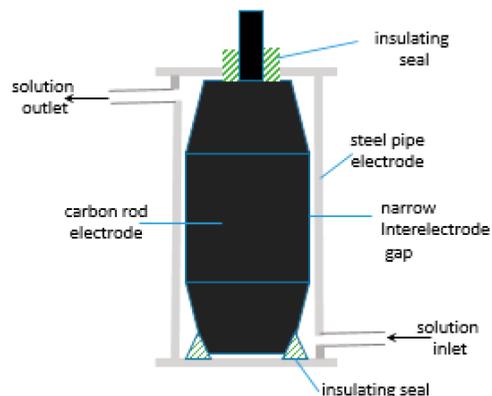


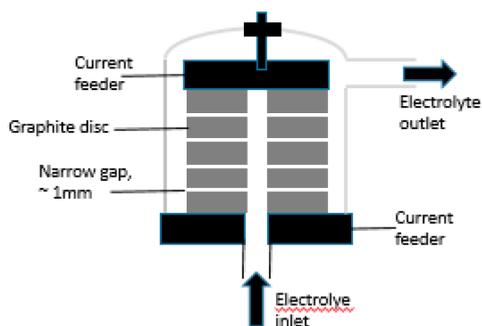
Figure 9. Design of a pipe cell.

The scale of the preparation determines the dimensions of the cell; Ebersson and co-workers,<sup>81,82</sup> describe two such cells, with anode areas of 500 and 800 cm<sup>2</sup> and interelectrode gaps 0.5 and 3 mm, respectively; smaller cells are probably easier to construct. The larger cell was used for methoxylation and acetoxylation of toluenes, alkylamides, and *N*-heterocycles, as well as dehydrocoupling of aromatic rings.<sup>41,81–83</sup> The reactions were carried out on a 1–5 mol scale with good selectivity and current efficiency, and the electrolyses were complete in 1–10 h. The residence time of the reactant for each cycle of reactant solution through the cell is, however, <1 s, allowing only a very low conversion/pass. When the cells have a narrow interelectrode gap, they also allow electrolysis with only low electrolyte concentrations, ~10 mM.

### 5.3. Bipolar Disk Stack Cell

A design of cell used successfully by BASF in Germany for pilot-scale operation and/or commercial production of adiponitrile,<sup>84</sup> dimethylsebacate,<sup>85</sup> 4-*tert*-butylbenzaldehyde,<sup>30</sup> and dimethoxyhydrofuran<sup>30</sup> is the bipolar disk stack cell.<sup>12,84,86,87</sup> It consists of a stack of graphite disks, wherein neighboring disks are kept from electrical contact by thin polymer spacers. It is a bipolar cell with electrical connections only to the two end plates. The reactant solution enters the cell through a common, central inlet and then flows outward through the narrow gaps between the disks. The industrial cell has up to 100 disks with a diameter of 0.4 m. Again, this is much too large for routine laboratory synthesis, but smaller laboratory units have been described.<sup>81,84,88</sup> One such cell consists of five graphite disks, each having an area of 31.6 cm<sup>2</sup> and an interelectrode gap of 1 mm.<sup>88</sup> It was used for the acetoxylation of *p*-methylanisole, and the monosubstituted product was obtained with a selectivity of 93%, even at high conversions (>90%), and delivers product at a rate of several grams/hour.

The bipolar disk stack is very simple to construct (Figure 10). It has the disadvantage that the linear flow rate (and, hence, the rate of mass transfer) decays as the reactant flows outward across the disks, but the influence of this on

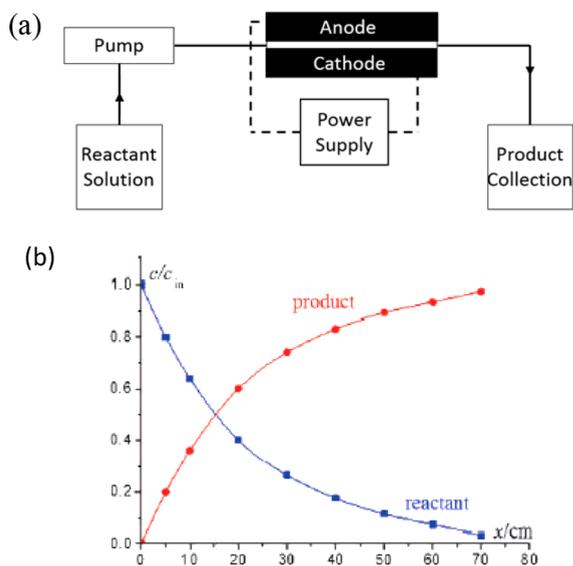


**Figure 10.** A laboratory bipolar capillary gap cell with five graphite disk electrodes in the stack.

performance is minimized by using a high flow rate of reactant solution through the cell. Certainly, excellent performance has been reported for several reactions, including the hydro-dimerization of acrylonitrile,<sup>84</sup> the synthesis of dimethylsebacate,<sup>85</sup> the dimethoxylation of 4-*tert*-butyltoluene<sup>30</sup> and the dimethoxylation of furan<sup>30</sup> on a large scale. Such cells with appropriate dimensions deserve consideration for laboratory synthesis.

## 6. FLOW REACTORS WITH HIGH CONVERSION IN A SINGLE PASS OF REACTANT SOLUTION

With the recent focus on microflow and flow technology for organic synthesis, several groups have sought to design and apply electrolysis cells that match the challenges of flow synthesis, including high conversion in a single pass of reactant solution through the cell. The laboratory arrangement for such an experiment is shown in Figure 11a, while Figure 11b stresses that a high conversion requires the reactant concentration and



**Figure 11.** (a) Laboratory arrangement for electrosynthesis using a flow cell with high conversion in a single pass. Reprinted with permission from ref 38. Copyright 2016 Academiai Kiado. (b) Concentrations of reactant and product as a function of distance through the cell under electrolysis conditions (flow rate and cell current) where the conversion is high. In ideal conditions, the local current density will be proportional to the local concentration of reactant. Reprinted with permission from ref 134. Copyright 2016 Academiai Kiado.

hence the local current density to drop (in fact, exponentially) with distance along the channel, from a high value at the inlet toward zero at the outlet. Several strategies have been used to achieve the goals with different rates of delivery of product.

### 6.1. Slowing Down the Solution Flow Rate

In principle, using a parallel plate reactor, a high conversion in a single pass can always be achieved by slowing down the flow of reactant solution through the cell. The cost is a degradation in the mass transfer regime, leading to a lower limiting current density for the desired reaction with consequences to the rate of product formation. It may also adversely affect the reaction selectivity and current efficiency. Despite these potential problems, this approach has been widely studied. A narrow interelectrode gap can be advantageous. As well as permitting electrolyses with a low electrolyte concentration, the presence of the counter electrode surface physically limits the expansion of the mass transport layer at the working electrode and thereby improves the mass transport regime.

A flow cell design using readily available components and relatively straightforward construction is based on the thin layer cell familiar in electroanalytical chemistry.<sup>89,90</sup> Thin metal films (e.g., Pt, Au, Ag) supported on glass microscope slides are separated by thin polymer tape to give a controlled and narrow interelectrode gap separation, and the cells are sealed with epoxy-resin.<sup>91</sup> The cell channel is typically 1 cm wide  $\times$  3–5 cm long, and the interelectrode gap varies between 20 and 150  $\mu$ m. Similar constructions are possible with plate electrodes. For example, Horii et al.<sup>92</sup> describe a 3  $\times$  3 cm cell with 80  $\mu$ m interelectrode gap based on glassy carbon and Pt plates. Such cells have been used for a wide variety of reactions: (1) methoxylation and acetoxylation of furan and toluenes,<sup>92,93</sup> (2) coupling of activated alkenes with benzyl bromides,<sup>94</sup> (3) cathodic dimerization of 4-nitrobenzyl bromide,<sup>95</sup> (4) cathodic coupling of benzyl bromide and acetic anhydride,<sup>96</sup> (5) the monoalkylation of methyl phenylacetate,<sup>97</sup> (6) electrogeneration of *o*-benzoquinone and coupling to benzenethiols,<sup>98</sup> (7) anodic phenol-arene coupling,<sup>99</sup> (8) conversion of benzylamine to dibenzylamine,<sup>95</sup> (9) paired electrosynthesis of diaryl ethers,<sup>100</sup> and (10) cathodic carboxylation of benzyl halides with CO<sub>2</sub>.<sup>101</sup>

Table 3 summarizes the performance of some of the above reactions. Typically, good conversions, yields, and selectivity can be achieved, but this requires relatively low flow rates, limiting productivity to a few milligrams/hour. Additionally, the low currents required to drive the transformation, along with micrometer interelectrode dimensions, mean that in most cases no additional conducting salts (electrolyte) are required, making the isolation of pure product easier.

More recently, modifications to the cell design has allowed more complex transformations to be achieved. Amemiya et al. described a sequential paired redox process, where benzylamine (12) was oxidatively dimerized to imine 13 and then reduced to amine 14 (Scheme 6).<sup>102</sup> This was achieved by switching cathode materials from Pt to graphite halfway through the cell. The anode remained Pt. In practice, mixed products were obtained, but the conversion is a demonstration of an interesting concept.

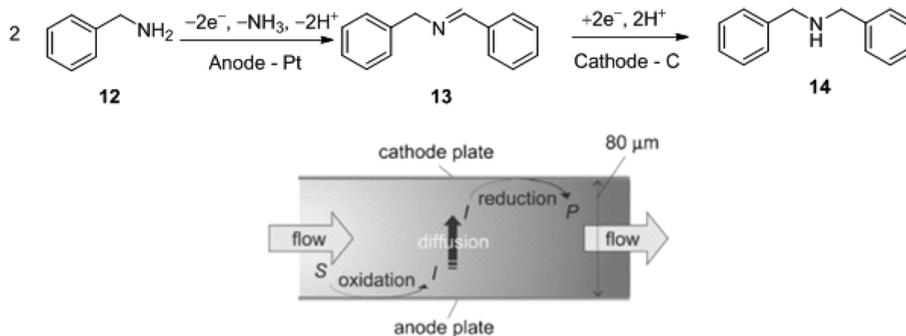
Atobe and co-workers have introduced the concept of using “parallel laminar flow” within such narrow gap reactors to separate the anolyte and catholyte streams without a physical separator;<sup>103,104</sup> this includes the separation of two different phases.<sup>105</sup> The cell design is as described above, except for the

Table 3. Performance Summary of Synthetic Examples Performed in Short Path Length Microfluidic Flow Electrolysis Cells

| reaction | flow rate (mL min <sup>-1</sup> ) | yield (%)             | productivity (mg h <sup>-1</sup> ) | no. of substrates | interelectrode gap (μm) | refs   |
|----------|-----------------------------------|-----------------------|------------------------------------|-------------------|-------------------------|--------|
| 1        | 0.010                             | 7–85 <sup>a</sup>     | 10                                 | 5                 | 80                      | 92, 93 |
| 2–4      | 0.015                             | >95 <sup>b</sup>      | 3                                  | 16                | 120                     | 94–96  |
| 5        | 0.100                             | up to 88 <sup>a</sup> | 20                                 | 3                 | 80                      | 97     |
| 6        | 0.020                             | up to 90 <sup>b</sup> | 20                                 | 5                 | 20                      | 98     |
| 9        | 0.600                             | 52–98                 | 51                                 | 4                 | 20                      | 101    |

<sup>a</sup>Yield determined by HPLC. <sup>b</sup>Yield determined by GC, using an internal standard.

Scheme 6. Conversion of Benzylamine to Dibenzylamine by a Paired Reaction in a Thin Layer Cell



requirement for two inlets and two outlets (Figure 12). The two solutions are fed to the cell from different inlets, each with

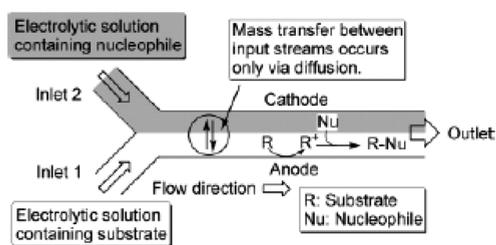


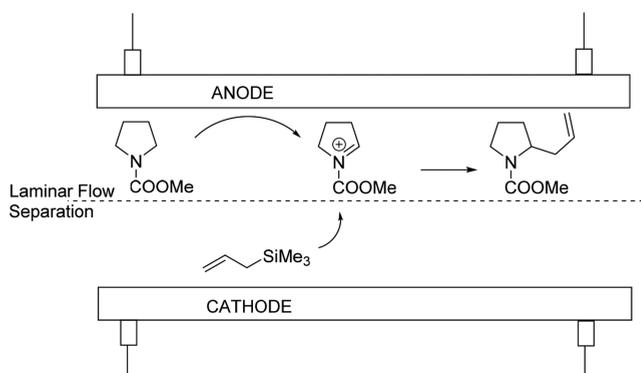
Figure 12. Principle of parallel laminar flow in a microflow reactor illustrated with an anodic substitution reaction. The substrate is introduced via the inlet to the anode and the nucleophile via the inlet to the cathode. Reprinted with permission from ref 103. Copyright 2007 American Chemical Society.

a flow rate typically 0.1 cm<sup>3</sup> min<sup>-1</sup>, and the channel dimension ensures that the two flows remain unmixed, stable, and linear. The separation of the two flows allows separation of the anode and cathode chemistries and the introduction of one reactant through the counter electrode feed. For example, the reaction shown in Scheme 7 becomes possible in moderate yield when the allyltrimethylsilane is fed from the cathode stream, despite the nucleophile being the more readily oxidized reactant.<sup>105,104</sup>

The separated flows can also be used to determine which of a pair of electroactive reactants is reduced/oxidized. In the example shown in Scheme 8, the regioselectivity for the coupling of allyl halides and aldehyde/ketones (formation of  $\gamma$ -adduct vs  $\alpha$ -adduct)<sup>106–108</sup> is controlled by fixing which of the reactants is reduced at the cathode and which is introduced from the anolyte.

Again, the very thin interelectrode gap also makes possible electrolysis without added electrolyte, as demonstrated with an example of paired electrosynthesis, to generate two products.<sup>107</sup> At the anode 1-phenylethyl alcohol was oxidized to acetophenone and at the cathode benzyl chloride was reduced to toluene, with conversions up to 93%. Other reactions carried

Scheme 7. Allylation Using the Parallel Laminar Flow Cell

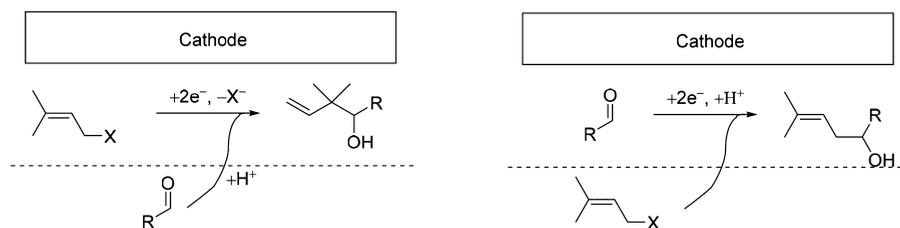


out in the cell include (1) cathodic generation of CCl<sub>3</sub><sup>-</sup> from chloroform and its addition to benzaldehyde,<sup>109</sup> (2) cathodic generation of base for the monoalkylation of methyl phenylacetate,<sup>97</sup> and (3) cross-coupling of toluenes and naphthalene.<sup>110</sup>

Parallel laminar flow is clearly an interesting and clever concept and it certainly allows the demonstration of novel syntheses. Unfortunately, the slow flow rate of solution limits the cell productivity to a few milligrams/hour. Moreover, it is difficult to see how the separation of flows can be maintained if the flow rate is increased or the cell channel extended, especially if there is gas evolution from one of the electrodes.

Clearly, cells based on glass microscope slides are not robust, and Watts et al.<sup>111</sup> have developed an alternative design with a narrow gap channel. On the basis of easily mounted, circular end plates, the cell with a PTFE body had a solution channel 0.3 cm wide × 3 cm long × 254 μm deep interelectrode gap. The cell has been used for several syntheses, with moderate to good yields and with productivities of several milligrams/hour, including (1) methoxylation of furan,<sup>111</sup> (2) Kolbe reaction of phenylacetic acid,<sup>111</sup> (3) synthesis of diaryliodonium salts,<sup>111</sup> (4) Kolbe electrolyses with CHF<sub>2</sub>COO<sup>-</sup> and CF<sub>3</sub>COO<sup>-</sup>,<sup>112</sup>

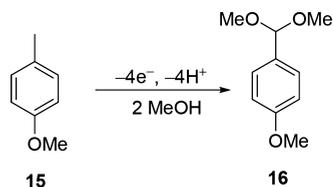
## Scheme 8. Controlling the Regioselectivity Using the Concept of Parallel Laminar Flow



and (5) cleavage of the isonicotinylloxycarbonyl group from carbonates and thiocarbonates.<sup>113</sup>

Several groups have described flow cells designed to increase the productivity of such narrow interelectrode gap cells. He et al.<sup>114</sup> suggested two approaches to extend the throughput of their single channel reactor with two Pt electrodes.<sup>94,95</sup> The designs had multiple, parallel channels and gave high conversions, but the cell productivity remains only milligrams/hour. Simms et al.<sup>115</sup> used soft lithography and micromolding techniques to fabricate a device with multiple parallel solution channels. It was used for the methoxylation of 2-pyrrolidone, but again, the total flow rates and cell productivity remain very low.

Attour et al.<sup>116</sup> described a parallel plate cell that achieved significantly increased throughput of reactant. It had a single channel, 1 cm wide  $\times$  10 cm long  $\times$  50–100  $\mu\text{m}$  deep interelectrode gap, and the anode was divided into 10 independently controllable sections so that the current density could be reduced as reactant was converted to product along the cell. This sectioned anode greatly improved the conversion of 4-methylanisole (**15**) to the dimethoxylated product (**16**) (Scheme 9) in methanol/KF, reaching a conversion of 90% in a

Scheme 9. Anodic Methoxylation of 4-Methylanisole (**15**)

single pass with a selectivity of 87%. The paper reports the influence on both conversion and selectivity of flow rate (0.05–2  $\text{cm}^3 \text{min}^{-1}$ ), electrolyte concentration (2.5–100 mM), and cell current (0.1–2 times the theoretical charge for full conversion). This work is supported by two further papers reporting design calculations with the objective of further scaleup.<sup>117,118</sup>

An even greater scaleup was reported by Küpper and co-workers,<sup>119</sup> who report a parallel plate configuration with electrodes 18.9 cm long  $\times$  9.8 cm wide spaced by a PEEK foil 30–40  $\mu\text{m}$  thick that is machined so as to divide the interelectrode gap into 75 parallel microchannels each with width 0.8 mm. The key component is shown in Figure 13.

This cell could give good, but not complete, conversions at flow rates up to 10  $\text{cm}^3 \text{min}^{-1}$ , and the productivity could be further enhanced by placing multiple cells in a bipolar stack. It could also be operated in the divided mode by employing an ion-permeable membrane as the separator and at pressures up to 35 bar to compress the hydrogen bubbles formed at the cathode and hence reduce the cell voltage. The performance of the cell was established using the methoxylation of 4-

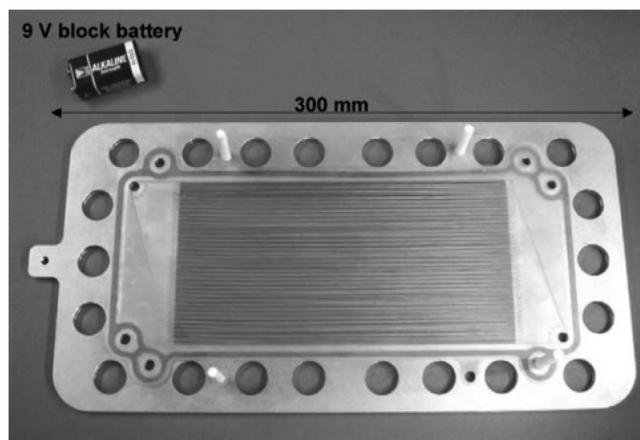


Figure 13. Image of the spacer, with multiple channels, reported by Küpper et al. Reproduced with permission from ref 119. Copyright 2003 Elsevier.

methylanisole (Scheme 9), but the cell was designed for the oxidation of gluconate to arabinose, and the latter reaction was used for model calculations for a combined electrolysis/liquid chromatography separation process.<sup>120</sup>

A smaller version of this cell has been described.<sup>22,121</sup> It has plate dimensions 5.7  $\times$  5.7 cm and 27 parallel channels with a length of 2.95 cm and width of 0.8 mm; the interelectrode gap was 100  $\mu\text{m}$  (Figure 14). It was again designed for high-pressure operation (up to 27 bar) and tested with the methoxylation of 4-methylanisole. With a flow rate of 0.2  $\text{cm}^3 \text{min}^{-1}$ , conversions were 85% with selectivity over 90% employing the theoretical cell current.

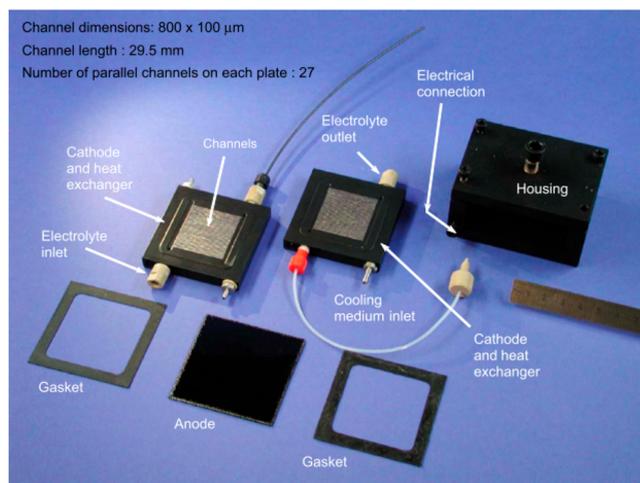
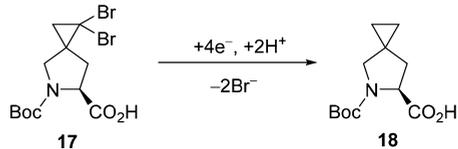


Figure 14. Components for microflow cell described by Attour et al. Reproduced with permission from ref 121. Copyright 2011 Elsevier.

Gütz et al.<sup>122</sup> have reported the application of a traditional membrane divided flow cell with 80 cm<sup>2</sup> electrodes for the cathodic debromination of dibromo-spirocyclopropane-proline derivative **17** to form intermediate **18**, for the synthesis of NSSA inhibitors (Scheme 10). By combining a slow flow rate

**Scheme 10. Debromination of 17 To Give 18, a Step in the Synthesis of NSSA Inhibitors**

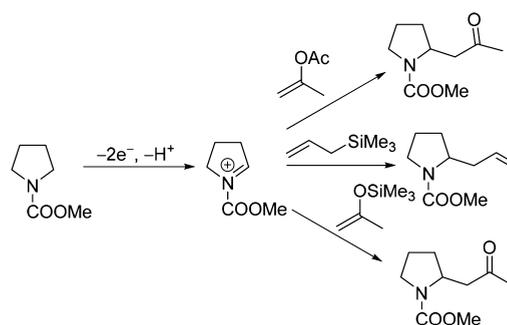


(0.6 cm<sup>3</sup> min<sup>-1</sup>) and a high charge input (20 e<sup>-</sup>/molecule), they were able to achieve a yield of 70% for an electrolysis carried out with 6.4 g of starting material. This paper emphasizes that flow rate is an important parameter in laboratory electrolyses; although a slow flow rate degrades the mass transfer regime and hence restricts the limiting current density (rate of conversion/unit area) for the conversion, it does, however, allow a reaction to be carried out towards full conversion.

### 6.2. Using a Three-Dimensional Electrode

A compact cell (Figure 15a) with a carbon felt anode has been described by Yoshida and co-workers.<sup>123–126</sup> In this cell, the carbon felt anode (7 × 7 × 5 mm) is separated from another carbon felt or Pt wire cathode by a porous PTFE diaphragm. The flow of reactant solution is into the cell through the anode and then passing through the separator to the cathode before leaving the cell. In the early design, the solution entered the cell at one side of the anode, leading to a nonuniform flow distribution across the anode. Later the design of the anode compartment was modified to have a defined and tortuous flow channel<sup>123</sup> (width 1.5 mm, depth 4 mm, length 57 mm) (Figure 15b,c); this improved the performance significantly. Despite a rather low flow rate (a few cubic centimeters/hour) leading to a low rate of product formation, the cells have been used for a rich variety of chemistry<sup>127–129</sup> largely based around their “cation flow” methodology, where metastable organic cations are generated at low temperature (down to 201 K) in the cell and then reacted with nucleophiles exterior to the cell. Typical reactions were the oxidation of carbamates to *N*-acyliminium cations and subsequent reaction with nucleophiles, such as allylsilanes, enol acetates, and enol silyl ethers (Scheme 11).

**Scheme 11. Examples of Syntheses Using the Cation Flow Methodology**

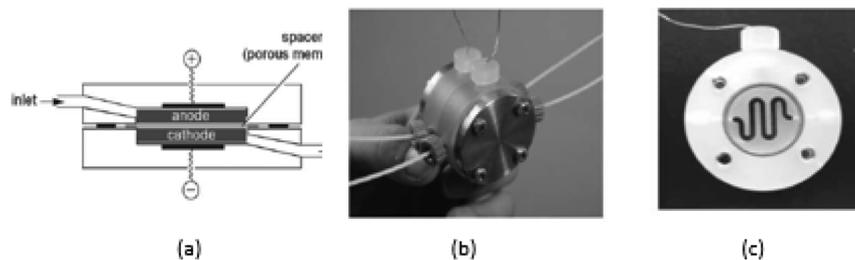


In another version of the cell, there were separate inlets to the anode and cathode compartments, and this cell was used for a paired synthesis, where a cation formed at the anode and a nucleophile formed at the cathode were coupled external to the cell in the presence of an acid (Scheme 12).<sup>123</sup>

Particularly impressive is the ability of the cell to carry out electrolyses at very low temperatures and its integration into sequences of operations to allow complex chemical changes and a combinatorial approach to electrosynthesis (the cation can be reacted with a series of nucleophiles exterior to the cell). In general, good reaction selectivity (67–100%) was achieved, although at only moderate conversions (50–75%) and slow product formation rates (5–50 mg/h).

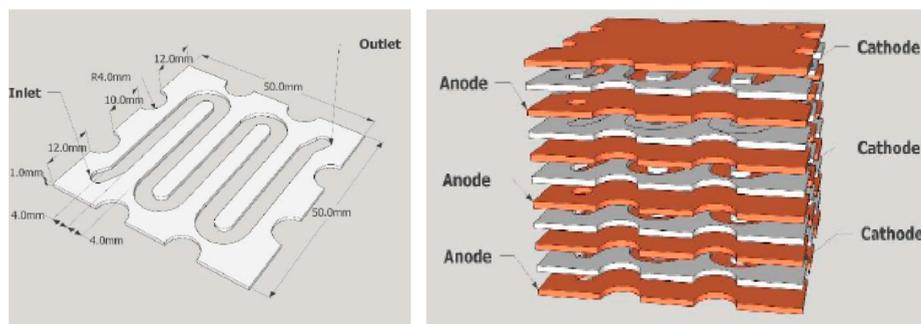
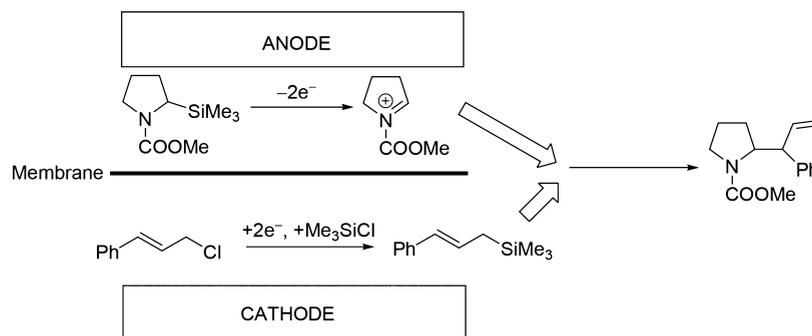
When a synthesis includes a chemical step external to the electrolysis cell, the selectivity of the synthesis is influenced by the mixing regime in the reactor following the cell. Nagaki et al.<sup>130</sup> reported the reaction of *N*-acyliminium ions electro-generated at low temperature with aromatic molecules in an external reactor. In the case of 1,3,5-trimethoxybenzene, it was shown that both mono- and disubstituted products were formed. Introducing the cell effluent into the solution of 1,3,5-trimethoxybenzene with very rapid stirring using a micromixer improved the fractional selectivity for the monoalkylated product from 0.37 to 0.92.

A flow cell with a cylindrical geometry and a three-dimensional electrode has been described.<sup>131,132</sup> It is formed by filling a porous glass tube (Vycor), internal diameter 8 mm, with a tightly packed bundle of carbon fibers (length 5 cm) and surrounding the tube by a Pt wire or carbon cloth counter electrode. The cell was used for the reduction of quinones and the oxidation of cholesterol to cholesta-4,6-dien-3-one. The latter reaction was carried out at controlled potential using a dilute solution (200 μM) of cholesterol in acetonitrile and a flow rate of 2.5 cm<sup>3</sup> min<sup>-1</sup>; it was possible to obtain 90%



**Figure 15.** Yoshida microflow cell: (a) basic design (Reproduced with permission from ref 124. Copyright 2005 the Royal Society of Chemistry.), (b) a complete cell (Reproduced with permission from ref 125. Copyright 2005 the Royal Society of Chemistry.), and (c) improved, extended flow channel (Reproduced with permission from ref 123. Copyright 2005 John Wiley and Sons.).

## Scheme 12. Cation Flow Paired Electrosynthesis



**Figure 16.** A monopolar stack cell: (a, left) gasket with “snaking” channel and (b, right) structure of the stack with six Cu electrodes. Figures reproduced with permission from the Supporting Information of ref 135. Copyright 2015 the Royal Society of Chemistry.

consumption of the cholesterol and a 42% yield (3.3 mg) of product. The Vycor separator, however, has a significant resistance, and this probably limits this cell design to electrolyses at low current densities.

### 6.3. Using an Extended Reactor Channel Length

The cells described by Attour and co-workers<sup>116</sup> and K pper et al.<sup>119</sup> and discussed in section 6.1 have already demonstrated the possibility of obtaining a high conversion in a single pass of the reactant through the cell by increasing the length of the electrode in contact with the solution. Hence, it is to be expected that very high conversions even at increased flow rates (reduced residence time) could be achieved by developing cells with a more extended length of contact between electrode and reactant solution. This concept was confirmed using a cell with two disk electrodes (diameter 10 cm) spaced by a Viton spacer (thickness 0.5 mm) with a star shaped channel (length 60 cm and width 1 mm) cut into it.<sup>133</sup> Using the methoxylation of *N*-formylpyrrolidine (Scheme 5) as the model reaction, the cell achieved a conversion of 96% with a flow rate of 0.1 cm<sup>3</sup> min<sup>-1</sup>, delivering product at a rate of 78 mg h<sup>-1</sup>. At higher flow rates the conversion dropped, but the delivery of product could be much higher, approaching 1 g h<sup>-1</sup> with a flow rate of 3.5 cm<sup>3</sup> min<sup>-1</sup>.

In cells with an extended channel length, it is important to recognize that the local current density must drop along the electrode length, from a high value at the inlet to approaching zero at the outlet, as the conversion of reactant to product decreases the local reactant concentration in solution<sup>38,134</sup> (see Figure 11b). Hence, the cell current is the integral of the local current densities along the channel, and the cell current must be high enough for the charge passed to be sufficient to convert all the reactant to product during the residence time of the reactant in the cell. Assuming a 100% current efficiency for the

desired reaction, the cell current ( $I_{\text{cell}}$ ) for a fractional conversion ( $X$ ) is readily estimated using Faraday's law, i.e.

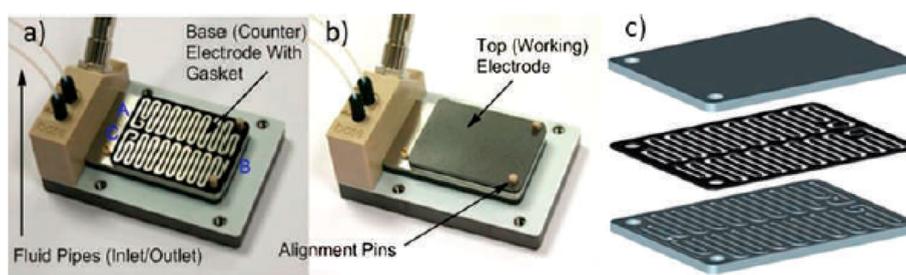
$$I_{\text{cell}} = nFQ_v c_{\text{in}} X \quad (5)$$

where  $n$  is the number of electrons required for the conversion of reactant to product at the working electrode,  $F$  is the Faraday constant,  $Q_v$  is the volumetric flow rate of reactant solution, and  $c_{\text{in}}$  is the reactant concentration at the cell inlet. For the current efficiency to be 100%, the mass transfer regime must be sufficiently efficient that the limiting current for the desired reaction under mass transfer control consumes all the charge passed. In this desirable situation, the length of electrode and solution channel needed for a fractional conversion ( $X$ ) may be estimated using the equation<sup>38,134</sup>

$$X = 1 - \frac{c_{\text{out}}}{c_{\text{in}}} = 1 - \exp\left[-\frac{k_m w L}{Q_v}\right] \quad (6)$$

where  $c_{\text{in}}$  and  $c_{\text{out}}$  are the inlet and outlet concentrations of reactant,  $k_m$  is the mass transfer characterizing the mass transfer regime in the cell, and  $w$  and  $L$  are the width and length of the solution channel, respectively. An advantage of a narrow interelectrode gap is that it determines a minimum value of the mass transfer coefficient.

In an extended channel length cell giving a high conversion, the rate of product formation is determined by the inlet concentration of reactant and the flow rate of solution. There is, however, a maximum flow rate where a very high conversion can be achieved (eq 6). At the expense of conversion, the product formation rate can usually be increased by increasing the flow rate; optimum conversion and product formation rate, as with other cells, require the application of different flow rates, although always with a correctly chosen cell current.



**Figure 17.** Photographs of the Syrris microflow cell and its components: (a) internal view of the cell to show the grooved electrode and inset elastomer gasket to form extended tortuous channel within a small device, (b) cell after the inclusion of the plate electrode, and (c) the arrangement of the grooved electrode, gasket, and plate electrode. Figure reproduced with permission from ref 134. Copyright 2015 Academiai Kiado.

Chapman et al.<sup>135</sup> have described a cell with two copper plate electrodes (dimensions  $22 \times 5$  cm and separation 2.5 mm) separated by a PTFE spacer with a linear flow channel (19 cm long and 4 mm wide) cut into it, and it was used for the preparation of a Cu(I) complex. Both electrodes are used in the chemistry; a *N*-heterocyclic carbene is generated by reduction of an imidazolium ion at the cathode and combined with copper(I) formed by dissolution of the copper anode. A higher throughput and more compact cell<sup>135</sup> (Figure 16) was based on a stack of six copper plate electrodes (dimensions  $5 \times 5$  cm and separation 1 mm) with a spacer between each pair of plates. In this cell, however, a channel (20 cm long and 4 mm wide) was achieved with the much smaller plates by cutting a “snakelike” channel. The solution flow through the five interelectrode gaps was in series and the channel length can be extended by increasing the number of electrode plates in the stack. The electrical connection was monopolar so that the copper plates in the stack were alternatively anode and cathode. The stack cell allowed a faster overall flow of reactant solution or a higher conversion by using a slower flow rate through each individual gap. The narrower interelectrode gap lowered the cell voltage and improved the selectivity to the Cu(I) complex vs the formation of the imidazolinone byproduct.

Two commercially available, extended channel length cells are now on the market. They seek to provide a maximum length of channel within a compact unit. The first commercial, extended channel length flow cell<sup>136</sup> was described in 2012.<sup>137</sup> It is a parallel plate cell with the two rectangular electrodes separated by a polymer spacer with a complex “snaking” channel cut into it; see Figure 17. The spacer is held in place by a groove cut into one of the electrodes. The cell unit has the overall dimensions  $10 \times 7 \times 4$  cm. Internally, it has a channel 70 cm long  $\times$  1.5 mm wide and an interelectrode gap of  $\sim 200$   $\mu\text{m}$ . Again using the methoxylation of *N*-formylpyrrolidine as the model reaction (Scheme 5), a conversion  $>95\%$  was obtained with a flow rate of  $1 \text{ cm}^3 \text{ min}^{-1}$  decreasing to 80% at  $3 \text{ cm}^3 \text{ min}^{-1}$  when product was formed at a rate of  $2 \text{ g h}^{-1}$ . The cell has been used for a number of other conversions and syntheses: (1) the  $\alpha$ -methoxylation of *N*-Boc-protected pyrrolidine as an intermediate in the synthesis of nazoline,<sup>40</sup> (2) the TEMPO-mediated oxidation of alcohols to aldehydes,<sup>138</sup> (3) the oxidation of activated toluenes to benzaldehydes,<sup>38,139</sup> (4) the oxidation of quinone derivatives to quinone ketals,<sup>38</sup> (5) the monofluorination of  $\text{PhCH}_2\text{COOEt}$ ,<sup>38</sup> (6) the Kolbe reaction for the formation of dimethyl adipate,<sup>38</sup> (7) the generation of Ce(IV) and its reaction with toluene to give benzaldehyde,<sup>38</sup> (8) the conversion of aldehydes to esters mediated by *N*-heterocyclic carbenes,<sup>140</sup> (9) the conversion of aldehydes to amides

mediated by *N*-heterocyclic carbenes,<sup>141</sup> and (10) the oxidation of drugs as a method to prepare drug metabolites.<sup>142</sup>

Table 4 summarizes the impressive performance of some of the reactions performed in the Syrris microflow reactor.

**Table 4. Summarizing the Performance of the Syrris Flux Reactor**

| reaction | flow rate<br>( $\text{mL min}^{-1}$ ) | yield (%) <sup>a</sup> | productivity<br>( $\text{g h}^{-1}$ ) | no. of<br>substrates | ref |
|----------|---------------------------------------|------------------------|---------------------------------------|----------------------|-----|
| 1        | 0.12                                  | 89–98                  | 0.1                                   | 9                    | 40  |
| 2        | 0.10                                  | 21–94                  | 0.1                                   | 15                   | 138 |
| 8        | 1.00                                  | 39–99                  | 4.1                                   | 19                   | 140 |
| 9        | 1.20                                  | 71–99                  | 2.5                                   | 19                   | 141 |

<sup>a</sup>Isolated yield.

Generally excellent conversion and yields are achieved, and productivity can be tailored to the users needs, giving milligrams to multigrams per hour. Furthermore, these high productivities were maintained over several hours of operation.

More recently, Ammonite cells have become available.<sup>143</sup> In order to fit the maximum length of the reaction channel into a compact design, in these cells the reactant solution flows through a spiral channel formed by a polymer gasket/spacer between two disk electrodes. The spacer is again held in position in a spiral groove machined into one of the electrodes. Two sizes have been described.<sup>39,144</sup> In the smaller cell<sup>144</sup> (Figure 18), the electrodes are disks with radius 8.5 cm and the channel is 2 mm wide and 1 m long, while the spacer thickness and groove depth lead to an interelectrode gap of 0.5 mm. The overall dimensions of the cell unit are 11 cm diameter and 6 cm height. Convenient electrode materials are stainless steel for the cathode and carbon/PDVF polymer composite or Pt for the anode, while the spacer material, Kalrez perfluoroelastomer, ensures good sealing and resistance to chemical attack by likely electrolysis media. The cell gives high conversions with flow rates up to  $3 \text{ cm}^3 \text{ min}^{-1}$ , allowing product formation at a rate  $>1 \text{ g h}^{-1}$ , over many hours, and has been tested using two reactions, the methoxylation of *N*-formylpyrrolidine<sup>144</sup> and the cleavage 4-methoxybenzyl groups from ethers to form deprotected alcohols.<sup>145</sup> The larger cell had a very similar design,<sup>39</sup> but was based on disk electrodes with a diameter of 14.9 cm allowing a spiral channel 2 m in length and 5 mm in width. The interelectrode gap was again usually 0.5 mm. This larger cell was designed to permit the use of higher flow rates ( $2\text{--}16 \text{ cm}^3 \text{ min}^{-1}$ ) with high conversions, and good selectivity was again achieved for the methoxylation of *N*-formylpyrrolidine. Productivity reached  $>20 \text{ g/h}$  and the cell was conveniently operated with batches of 20–50 g of reactant.



**Figure 18.** Ammonite 8 cell with spiral solution channel: (a) the key components and (b) the complete cell. Reproduced with permission from ref 144. Copyright 2016 Elsevier.

The cell was also used to produce 350 g of methoxylated *N*-formylpyrrolidine in three 8 h electrolyses.

## 7. CONCLUSIONS AND FUTURE TRENDS

While beaker cells are constructed from components readily available in most laboratories, they allow only slow conversion of reactant to product, and this can degrade reaction selectivity. In addition, descriptions of such cells that lack precise information on electrode geometry, position, and dimensions as well as mass transport conditions within the cell lead to the irreproducibility of performance from laboratory to laboratory. At first sight, flow cells are more complex and require planning in their design, but they often give significantly improved performance and reproducibility. Laboratory flow cells are generally based on “parallel plate” geometry and can be operated in two limiting ways, (i) with recycle of the reactant solution between the cell and a reservoir and (ii) with high conversion in a single pass of reactant through the cell.

When recycling reactant solution between the cell and a reservoir, this mode of operation benefits from a high linear flow rate of solution and use of turbulence promoters to give efficient mass transport. The cell design seeks uniform chemistry and rate of chemistry over the whole surface of the electrode. At the beginning of electrolyses, it gives the highest current density and rate of conversion of reactant to product (in terms of mole/unit area of electrode), but this drops with time as the concentration of reactant decreases; a high fractional conversion requires a long electrolysis time. The high rate of conversion can be maintained by continuous addition of reactant, but the fractional conversion then remains low. Pipe cells and carbon disk stack cells, discussed in section 5, are viable alternatives to traditional parallel plate reactors when operating in reactant recycle mode. The absolute productivities of the cells depend on their dimensions, but electrode areas of 10–100 cm<sup>2</sup> will meet the needs of many laboratory syntheses.

Cell designs with high conversion in a single pass of reactant through the cell operate with a decreasing current density with passage of reactant solution along the cell. In general, the flow rate is low in order to achieve a high fractional conversion, but this is at the cost of poorer mass transport and, hence, of a lower average current density. Consequently, the rate of conversion (in terms of mole/unit area of electrode) is lower. With many cell designs easily constructed in the laboratory, it is possible to obtain very high conversion but with a very low productivity; the cells are only able to deliver product at a rate of milligrams/hour. The productivity can be increased to multigrams/hour, but this requires more sophisticated cell

design. Cells with narrow interelectrode gaps often allow operation with a low/zero electrolyte concentration.

Both types of cell have a role in laboratory synthesis. The choice depends on the objectives of the synthesis; the cell design and dimensions will be determined by how much product is targeted and the relative importance of rapid product formation vs a high conversion (and therefore high yield).

It should be recognized that a cell with particular design and dimensions is only capable of product formation rates within a limited range. Some increased productivity can be achieved by increasing the reactant concentration, but larger increases in product formation rate require the use of a larger cell. Unfortunately, the possibility to increase cell size is often limited by the availability of electrode materials in the necessary shape/form in larger sizes. The cost and stability of electrode materials also become more important issues with larger cells. While cells and, in particular, electrodes can be expensive, the essential, auxiliary equipment (power supply, pumps etc.) can be relatively cheap.

Laboratory synthetic chemists should welcome the availability of flow cells on the market but ensure that purchased cells meet their specific needs. They should also recognize that the literature on flow electrolysis cells is not always focused on laboratory-scale synthesis, but this should not disguise the impact that the change from beaker cells to flow electrolysis cells could have on the reputation of organic electrosynthesis in the laboratory.

Operated with suitable control parameters (cell current, flow rate, reactant concentration, medium), all flow electrolysis offers the possibility of higher selectivity and productivity than can be achieved with beaker cells. Indeed, fractional selectivities approaching 1.0 can be achieved. The flow cells described in section 6 additionally offer a high conversion of reactant to product (>0.95) in a single pass of solution through the cell and fractional yields close to 1.0. Moreover, some such cells allow the preparation of multigrams/hour and the development of highly convenient laboratory syntheses. They are also well-suited for the integration of electrolysis into multistage flow syntheses.

The prospects for flow electrolysis are exciting, and it is to be expected that flow electrolysis cells can contribute much to overcoming the barriers and prejudices that have prevented electrosynthesis from being a routine procedure in the organic synthesis laboratory.

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## Notes

The authors declare no competing financial interest.

## Biographies

Derek Pletcher was born in London in 1943. He received B.Sc. and Ph.D. degrees from the University of Sheffield and has been a member of the Electrochemistry Group in Southampton since 1967. He was elected a Fellow of the Electrochemistry Society in 2005 and awarded their Henry B. Linford Distinguished Teaching Award in 2006 and the Vittorio de Nora Medal in 2010 for contributions to electrochemical technology. He is the author of 5 books and more than 350 papers.

Robert A. Green obtained his M.Chem. and Ph.D. degrees from the University of Southampton in 2010 and 2014, respectively. His interest in flow electrosynthesis started during his Ph.D. studies, under the guidance of Profs. Richard Brown and Derek Pletcher, with the development of novel electrochemical methodologies. A postdoctoral position at Southampton allowed him to continue these developments, and he is now working in the pharmaceutical sector.

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

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## REFERENCES

- (1) Shono, T. *Electroorganic Synthesis*; Academic Press: New York, 1991.
- (2) *Organic Electrochemistry*, 4th ed.; Hammerich, O., Lund, H., Eds.; Marcel Dekker: New York, 2001.
- (3) *Organic Electrochemistry*, 5th ed.; Hammerich, O.; Speiser, B., Eds.; CRC Press: Boca Raton, FL, 2015.
- (4) Fuchigami, T.; Atobe, M.; Inagi, S. *Fundamentals and Applications of Organic Electrochemistry*; Wiley: New York, 2014.
- (5) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008**, *108*, 2265–2299.
- (6) Waldvogel, S. R.; Janza, B. Renaissance of Electrosynthetic Methods for the Construction of Complex Molecules. *Angew. Chem., Int. Ed.* **2014**, *53*, 7122–7123.
- (7) Pletcher, D. Organic Electrosynthesis. In *Developments in Electrochemistry: Science Inspired by Martin Fleischmann*; Pletcher, D., Tian, Z.-Q., Williams, D. E., Eds.; Wiley: Chichester, U.K., 2014; pp 77–94.
- (8) Frontana-Urbe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. Organic Electrosynthesis: A Promising Green Methodology in Organic Chemistry. *Green Chem.* **2010**, *12*, 2099–2119.
- (9) Francke, R.; Little, R. D. Redox Catalysis in Organic Electrosynthesis: Basic Principles and Recent Developments. *Chem. Soc. Rev.* **2014**, *43*, 2492–2521.
- (10) Horn, E. J.; Rosen, B. R.; Baran, P. S. Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method. *ACS Cent. Sci.* **2016**, *2*, 302–308.
- (11) Navarro, M. Recent Advances in Experimental Procedures for Electroorganic Synthesis. *Curr. Opin. Electrochem* **2017**, *2*, 43–52.
- (12) Pletcher, D.; Walsh, F. C. *Industrial Electrochemistry*, 2nd ed.; Chapman and Hall: London, 1990.
- (13) Pütter, H. Industrial Electroorganic Chemistry. In *Organic Electrochemistry*; Hammerich, O., Lund, H., Eds.; Marcel Dekker: New York, 2001; pp 1259–1307.
- (14) Walsh, F. C. *A First Course in Electrochemical Engineering*; The Electrochemical Consultancy: Romsey, U.K., 1993.
- (15) *Chlorine: Principles and Industrial Practice*; Schmittinger, P., Ed.; Wiley-VCH: Chichester, U.K., 2000.
- (16) *Handbook of Chlor-Alkali Technology*; O'Brien, T. F., Tilak, B. V., Hine, F., Eds.; Springer: New York, 2005; Vols. 1–5.
- (17) Yoshida, J. *Flash Chemistry: Fast Organic Synthesis in Microsystems*; Wiley-VCH: Weinheim, Germany, 2008.
- (18) *Chemical Reactions and Processes under Flow Conditions*; Luis, S. V., Garcia-Verdugo, E., Eds.; Royal Society of Chemistry: Cambridge, U.K., 2009.
- (19) *Microreactors in Organic Synthesis and Catalysis*, 2nd ed.; Wirth, T., Ed.; Wiley-VCH: Weinheim, Germany, 2013.
- (20) *Microreactors in Preparative Chemistry*; Reschetilowski, W., Ed.; Wiley-VCH: Weinheim, Germany, 2013.
- (21) Watts, K.; Baker, A.; Wirth, T. Electrochemical Synthesis in Microreactors. *J. Flow Chem.* **2014**, *4*, 2–11.
- (22) Ziogas, A.; Kolb, G.; O'Connell, M.; Attour, A.; Lopicque, F.; Matlosz, M.; Rode, S. Electrochemical Microstructured Reactors: Design and Application in Organic Synthesis. *J. Appl. Electrochem.* **2009**, *39*, 2297–2313.
- (23) Atobe, M. Organic Electrosynthesis in Flow Microreactor. *Curr. Opin. Electrochem.* **2017**, *2*, 1–6.
- (24) Pletcher, D. *A First Course in Electrode Processes*, 2nd ed.; Royal Society of Chemistry: Cambridge, U.K., 2009.
- (25) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods—Fundamentals and Applications*, 2nd ed.; Wiley: New York, 2001.
- (26) Sata, T. *Ion Exchange Membranes—Preparation, Characterisation, Modification and Application*; Royal Society of Chemistry: Cambridge, U.K., 2004.
- (27) Strathmann, H. *Ion Exchange Membranes Separation Processes*; Elsevier: Amsterdam, 2004.
- (28) Tanaka, Y. *Ion Exchange Membranes: Fundamentals and Applications*; Elsevier: Amsterdam, 2015.
- (29) Paddon, C. A.; Atobe, M.; Fuchigami, T.; He, P.; Watts, P.; Haswell, S. J.; Pritchard, G. J.; Bull, S. D.; Marken, F. Towards Paired and Coupled Reactions for Clean Organic Microreactor Electrosynthesis. *J. Appl. Electrochem.* **2006**, *36*, 617–634.
- (30) Steckhan, E.; Arns, T.; Heineman, H. R.; Hilt, G.; Hoormann, D.; Jörissen, J.; Kroner, L.; Lewall, B.; Pütter, H. Environmental Protection and Economization of Resources by Electroorganic and Electroenzymatic Syntheses. *Chemosphere* **2001**, *43*, 63–73.
- (31) Moraleda, I.; Llanos, J.; Sáez, C.; Rodrigo, M. A.; Canizares, P. Integration of Anodic and Cathodic Processes for the Synergistic Electrochemical Production of Peracetic Acid. *Electrochem. Commun.* **2016**, *73*, 1–4.
- (32) Karakus, C.; Zuman, P. Electrosynthesis of Nitrosobenzenes Bearing Electron Withdrawing Substituents. *J. Electrochem. Soc.* **1995**, *142*, 4018–4025.
- (33) Lamoureux, C.; Moinet, C.; Tallec, A. An Electrolysis Cell with Close Consecutive Flow-through Porous Electrodes for Particular Organic Electrosynthesis. *J. Appl. Electrochem.* **1986**, *16*, 819–824.

- (34) Sock, O.; Troupel, M.; Perichon, J. Electrosynthesis of Carboxylic Acids from Organic Halides and Carbon Dioxide. *Tetrahedron Lett.* **1985**, *26*, 1509–1512.
- (35) Silvestri, G.; Gambino, S.; Filardo, G.; Gulotta, A. Sacrificial Anodes in the Electrocarboxylation of Organic Chlorides. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 979–980.
- (36) Chaussard, J.; Troupel, M.; Robin, Y.; Jacob, B.; Juhasz, J. P. Scale-up of Electrocarboxylation Reactions with a Consumable Anode. *J. Appl. Electrochem.* **1989**, *19*, 345–348.
- (37) Chaussard, J. Electrochemical Synthesis of Fenoprofen. In *Electrosynthesis—From Laboratory to Pilot to Production*; Genders, D. J., Pletcher, D., Eds.; The Electrosynthesis Co.: Buffalo, NY, 1990; pp 165–176.
- (38) Green, R. A.; Brown, R. C. D.; Pletcher, D. Electrosynthesis in Extended Channel Length, Microfluidic Electrolysis Cells. *J. Flow Chem.* **2016**, *6*, 191–197.
- (39) Green, R. A.; Brown, R. C. D.; Pletcher, D.; Harji, B. A Microflow Electrolysis Cell for Laboratory Synthesis on the Multigram Scale. *Org. Process Res. Dev.* **2015**, *19*, 1424–1427.
- (40) Kabeshov, M. A.; Musio, B.; Murray, P. R. D.; Browne, D. L.; Ley, S. V. Expedient Preparation of Nazlinine and a Small Library of Indole Alkaloids Using Flow Electrolysis as an Enabling Technology. *Org. Lett.* **2014**, *16*, 4618–4621.
- (41) Nyberg, K.; Servin, R. Large Scale Laboratory Electrolysis in Organic Systems. III. Synthesis of Alpha-Methoxyalkamides - Cyclic Acylimmonium Precursors. *Acta Chem. Scand.* **1976**, *30b*, 640–642.
- (42) Palasz, P. D.; Utley, J. H. P.; Hardstone, J. D. Electro-Organic Reactions. Part 23. Regioselectivity and the Stereochemistry of the Anodic Methoxylation of *N*-Acylpiperidines and *N*-Acylmorpholines. *J. Chem. Soc., Perkin Trans. 2* **1984**, 807–813.
- (43) Lipp, L.; Pletcher, D. Extended Area Electrodes Based on Stacked Expanded Titanium Meshes. *Electrochim. Acta* **1997**, *42*, 1101–1111.
- (44) Gonzalez-Garcia, J.; Frias, A.; Exposito, E.; Montiel, V.; Aldaz, A.; Conesa, J. A. Characterisation of an Electrochemical Pilot-Plant Filter-Press Reactor by Hydrodynamic and Mass Transport Studies. *Ind. Eng. Chem. Res.* **2000**, *39*, 1132–1142.
- (45) Ingles, M.; Bonete, P.; Exposito, E.; Gonzalez-Garcia, J.; Montiel, V. Indirect Electrochemical Synthesis of *p*-Hydroxyphenylacetic Acid. *Ind. Eng. Chem. Res.* **2000**, *39*, 1–6.
- (46) Ralph, T. R.; Hitchman, M. L.; Millington, J. P.; Walsh, F. C. Mass Transport in an Electrochemical Laboratory Filterpress Reactor and Its Enhancement by Turbulence Promoters. *Electrochim. Acta* **1996**, *41*, 591–601.
- (47) Recio, F. J.; Herrasti, P.; Vazquez, L.; Ponce de Leon, C.; Walsh, F. C. Mass Transport to a Nanostructured Nickel Deposit of High Surface Area in a Rectangular Flow Channel. *Electrochim. Acta* **2013**, *90*, 507–513.
- (48) Gutz, C.; Stenglein, A.; Waldvogel, S. R. Highly Modular Flow Cell for Electroorganic Synthesis. *Org. Process Res. Dev.* **2017**, *21*, 771–778.
- (49) Electrocell home page. [www.Electrocell.com](http://www.Electrocell.com) (accessed June 7, 2017).
- (50) C-Flow electrochemical cells home page. [www.c-flow.co.uk](http://www.c-flow.co.uk) (accessed June 7, 2017).
- (51) Continuous flow cell. ElectraSyn flow. [www.ikaprocess.de/Products/Continuous-Flow-Cell-Cph-45/](http://www.ikaprocess.de/Products/Continuous-Flow-Cell-Cph-45/) (accessed June 7, 2017).
- (52) Rivera, F. F.; de Leon, C. P.; Nava, J. L.; Walsh, F. C. The Filter-Press FM01-LC Laboratory Flow Reactor and Its Applications. *Electrochim. Acta* **2015**, *163*, 338–354.
- (53) Griffiths, M.; de Leon, C. P.; Walsh, F. C. Mass Transport in the Rectangular Channel of Filter Press Electrolyser (the FM01-LC Reactor). *AIChE J.* **2005**, *51*, 682–687.
- (54) Brown, C. J.; Pletcher, D.; Walsh, F. C.; Hammond, J. K.; Robinson, D. Studies of Space-Averaged Mass Transport in the FM01 Electrolyser. *J. Appl. Electrochem.* **1993**, *23*, 38–43.
- (55) Brown, C. J.; Pletcher, D.; Walsh, F. C.; Hammond, J. K.; Robinson, D. Local Mass Transport Effects in the FM01 Laboratory Electrolyser. *J. Appl. Electrochem.* **1992**, *22*, 613–619.
- (56) Brown, C. J.; Pletcher, D.; Walsh, F. C.; Hammond, J. K.; Robinson, D. Studies of Three Dimensional Electrodes in the FM01-LC Laboratory Electrolyser. *J. Appl. Electrochem.* **1994**, *24*, 95–106.
- (57) Gonzalez-Garcia, J.; Frias, A.; Exposito, E.; Montiel, V.; Aldaz, A.; Conesa, J. A. Characterisation of an Electrochemical Pilot-Plant Filter-Press Reactor by Hydrodynamic and Mass Transport Studies. *Ind. Eng. Chem. Res.* **2000**, *39*, 1132–1142.
- (58) Montillet, A.; Comiti, A.; Legrand, J. Application of Metallic Foams in Electrochemical Reactors of the Filter Press Type: Part II Mass Transport Performance. *J. Appl. Electrochem.* **1994**, *24*, 384–389.
- (59) Friedrich, J. M.; de Leon, C. P.; Reade, G. W.; Walsh, F. C. Reticulated Vitreous Carbon as an Electrode Material. *J. Electroanal. Chem.* **2004**, *561*, 203–217.
- (60) Ralph, T. R.; Hitchman, M. L.; Millington, J. P.; Walsh, F. C. The Importance of Batch Electrolysis Conditions during the Reduction of L-Cystine Hydrochloride. *J. Electrochem. Soc.* **2005**, *152*, D54–D63.
- (61) Ralph, T. R.; Hitchman, M. L.; Millington, J. P.; Walsh, F. C. The Electrochemistry of L-Cystine and L-Cysteine 2. Electrosynthesis of L-Cysteine at Solid Electrodes. *J. Electroanal. Chem.* **1994**, *375*, 17–27.
- (62) Guena, T.; Pletcher, D. Electrosynthesis from Aromatic Aldehydes in a Flow Cell. Part I. The Reduction of Benzaldehyde. *Acta Chem. Scand.* **1998**, *52*, 23–31.
- (63) Guena, T.; Pletcher, D. Electrosynthesis from Aromatic Aldehydes in a Flow Cell. Part II. The Cross Coupling of Benzaldehydes to Unsymmetrical Diols. *Acta Chem. Scand.* **1998**, *52*, 32–36.
- (64) Szanto, D.; Trinidad, P.; Walsh, F. C. Evaluation of Carbon Electrodes and Electrosynthesis of Coumestan and Catecholamine Derivatives in the FM01-LC Electrolyser. *J. Appl. Electrochem.* **1998**, *28*, 251–258.
- (65) Smith, C. Z.; Utley, J. H. P.; Hammond, J. K. Electro-Organic Reactions. Part 60 The Electro-Oxidative Conversion at a Laboratory Scale of a Lignosulfonate into Vanillin in an FM01 Filter Press Flow Reactor: Preparative and Mechanistic Aspects. *J. Appl. Electrochem.* **2011**, *41*, 363–375.
- (66) Gomis, J. A.; Garcia-Garcia, V.; Gonzalez-Garcia, J.; Montiel, V.; Aldaz, A. Electrosynthesis of 4-Hydroxybenzaldehyde from Sodium 4-Hydroxymandelate. *J. Appl. Electrochem.* **1999**, *29*, 265–270.
- (67) Beltra, A. P.; Bonete, P.; Gonzalez-Garcia, J.; Garcia-Garcia, V.; Montiel, V. Electrochemical Synthesis of L-Histidinol Using Solvated Electrons. *J. Electrochem. Soc.* **2005**, *152*, D65–D68.
- (68) Jörissen, J. Ion Exchange Membranes as Solid Polymer Electrolytes (SPE) in Electro-Organic Syntheses without Supporting Electrolyte. *Electrochim. Acta* **1996**, *41*, 553–562.
- (69) Benziger, J.; Nehlsen, J. A Polymer Electrolyte Hydrogen Pump Hydrogenation Reactor. *Ind. Eng. Chem. Res.* **2010**, *49*, 11052–11060.
- (70) Sáez, A.; Garcia-Garcia, V.; Solla-Gullon, J.; Aldaz, A.; Montiel, V. Electrochemical Synthesis at Pre-Pilot Scale of 1-Phenylethanol by Cathodic Reduction of Acetophenone Using a Solid Polymer Electrolyte. *Electrochem. Commun.* **2013**, *34*, 316–319.
- (71) Sáez, A.; Garcia-Garcia, V.; Solla-Gullon, J.; Aldaz, A.; Montiel, V. Electrocatalytic Hydrogenation of Acetophenone Using a Polymer Electrolyte Membrane Electrochemical Reactor. *Electrochim. Acta* **2013**, *91*, 69–74.
- (72) Kunugi, A.; Fujioka, M.; Yasuzawa, M.; Inaba, M.; Ogumi, Z. Electroreduction of 2-Cyclohexene-1-One on Metal-Solid Electrolyte Composite Electrodes. *Electrochim. Acta* **1998**, *44*, 653–657.
- (73) Jiang, J.; Wu, B. Promotion of the Electrochemical Hydrogenation of Nitrobenzene at Hydrogen Storage Alloys Studied Using a Solid Polymer Electrolyte Method. *J. Appl. Electrochem.* **2006**, *36*, 733–738.
- (74) Takano, K.; Tateno, H.; Matsumura, Y.; Fukazawa, A.; Kashiwagi, T.; Nakabayashi, K.; Nagasawa, K.; Mitsushima, S.; Atobe, M. Electrocatalytic Hydrogenation of Toluene Using a Proton Exchange Membrane Reactor. *Bull. Chem. Soc. Jpn.* **2016**, *89*, 1178–1183.

- (75) An, W.; Hong, J. K.; Pintauro, P. N.; Warner, K.; Neff, W. The Electrochemical Hydrogenation of Edible Oils in a Solid Polymer Electrolyte Reactor. Part I Reactor Design and Operation. *J. Am. Oil Chem. Soc.* **1998**, *75*, 917–925.
- (76) Pintauro, P. N.; Gil, M. P.; Warner, K.; List, G.; Neff, W. Electrochemical Hydrogenation of Soybean Oil with Hydrogen Gas. *Ind. Eng. Chem. Res.* **2005**, *44*, 6188–6195.
- (77) An, W.; Hong, J. K.; Pintauro, P. N. Current Efficiency for Soybean Oil Hydrogenation in a Solid Polymer Electrolyte Reactor. *J. Appl. Electrochem.* **1998**, *28*, 947–954.
- (78) Montiel, V.; Sáez, A.; Exposito, E.; Garcia-Garcia, V.; Aldaz, A. The Use of MEA Technology in the Synthesis of Pharmaceutical Compounds: The Electrosynthesis of *N*-Acetyl-*L*-Cysteine. *Electrochem. Commun.* **2010**, *12*, 118–121.
- (79) Jiang, J. H.; Wu, B.-L.; Cha, C. S. Electrosynthesis of 4-Methoxybenzaldehyde on Graphite/Nafion Membrane Composite Electrodes. *Electrochim. Acta* **1998**, *43*, 2549–2552.
- (80) Ogumi, Z.; Yamashita, H.; Nishio, K.; Takehara, Z.; Yoshizawa, S. Application of the Solid Polymer Electrolyte (SPE) Method to Organic Electrochemistry. 3. Kolbe Type Reactions on Pt-SPE. *Electrochim. Acta* **1983**, *28*, 1687–1693.
- (81) Cedheim, L.; Ebersson, L.; Helgee, B.; Nyberg, K.; Servin, R.; Sternerup, H. Large Scale Laboratory Electrolysis in Organic Systems. 2. Construction and Performance of an Undivided 800 cm<sup>2</sup> Concentric Capillary Gap Cell. *Acta Chem. Scand.* **1975**, *29b*, 617–621.
- (82) Ebersson, L.; Nyberg, K.; Sternerup, H. A Simple Cell for Large-Scale Laboratory Electrolysis in Organic Systems. *Chem. Scr.* **1973**, *3*, 12–14.
- (83) Ebersson, L.; Hlavaty, J.; Jonsson, L.; Nyberg, K.; Servin, R.; Sternerup, H.; Wistrand, L. G. Large Scale Laboratory Electrolysis in Organic Systems. 4. Anodic Methoxylation and Acetoxylation. *Acta Chem. Scand.* **1979**, *33b*, 113–115.
- (84) Beck, F. Electrosynthesis of Adiponitrile in Undivided Cells. *J. Appl. Electrochem.* **1972**, *2*, 59–69.
- (85) Beck, F. Kolbesynthese von Sebacinsäure in Der Kapillarspaltzelle. *Electrochim. Acta* **1973**, *18*, 359–366.
- (86) Beck, F.; Guthke, H. Entwicklung Neuer Zellen Für Elektroorganische Synthesen. *Chem. Ing. Tech.* **1969**, *41*, 943–950.
- (87) Hoormann, D.; Jörisen, J.; Pütter, H. Elektrochemische Verfahren - Neuentwicklungen Und Tendenzen. *Chem. Ing. Tech.* **2005**, *77*, 1363–1376.
- (88) Fankhauser, A.; Ouattara, L.; Griesbach, U.; Fischer, A.; Pütter, H.; Comminellis, C. Investigation of the Anodic Acetoxylation of 4-Methylanisole in Glacial Acetic Acid Using Graphite and BDD Electrodes. *J. Electroanal. Chem.* **2008**, *614*, 107–112.
- (89) Hubbard, A. T.; Anson, F. C. The Theory and Practice of Electrochemistry with Thin Layer Cells. In *Electroanalytical Chemistry*; Bard, A. J., Ed.; Marcel Dekker: New York, 1970; Vol. 4, pp 169–171.
- (90) Hawkridge, F. M. Electrochemical Cells. In *Laboratory Techniques in Electroanalytical Chemistry*; Kissinger, P. T., Heineman, W. R., Eds.; Marcel Dekker: New York, 1984; pp 355–365.
- (91) Paddon, C. J.; Pritchard, G. J.; Thiemann, T.; Marken, F. Paired Electrosynthesis: Micro-Flow Cell Processes with and without Added Electrolyte. *Electrochem. Commun.* **2002**, *4*, 825–831.
- (92) Horii, D.; Atobe, M.; Fuchigami, T.; Marken, F. Self-Supported Methoxylation and Acetoxylation Electrosynthesis Using a Simple Thin-Layer Flow Cell. *J. Electrochem. Soc.* **2006**, *153*, D143–D147.
- (93) Horii, D.; Atobe, M.; Fuchigami, T.; Marken, F. Self-Supported Paired Electrosynthesis of 2,5-Dimethoxy-2,5-Dihydrofuran Using a Thin Layer Flow Cell without Intentionally Added Supporting Electrolyte. *Electrochem. Commun.* **2005**, *7*, 35–39.
- (94) He, P.; Watts, P.; Marken, F.; Haswell, S. J. Self-Supported and Clean One-Step Cathodic Coupling of Activated Olefins with Benzyl Bromide Derivatives in a Micro Flow Reactor. *Angew. Chem., Int. Ed.* **2006**, *45*, 4146–4149.
- (95) He, P.; Watts, P.; Marken, F.; Haswell, S. J. Electrolyte Free Electro-Organic Synthesis: The Cathodic Dimerisation of 4-Nitrobenzylbromide in a Micro-Gap Flow Cell. *Electrochem. Commun.* **2005**, *7*, 918–924.
- (96) He, P.; Watts, P.; Marken, F.; Haswell, S. J. Electrosynthesis of Phenyl-2-Propanone Derivatives from Benzyl Bromides and Acetic Anhydride in an Unsupported Micro-Flow Cell Electrolysis Process. *Green Chem.* **2007**, *9*, 20–22.
- (97) Matsumura, Y.; Kakizaki, Y.; Tateno, H.; Kashiwagi, T.; Yamaji, Y.; Atobe, M. Continuous in Situ Electrogeneration of a 2-Pyrrolidone Anion in a Microreactor: Application to Highly Efficient Monoalkylation of Methyl Phenylacetate. *RSC Adv.* **2015**, *5*, 96851–96854.
- (98) Kashiwagi, T.; Amemiya, F.; Fuchigami, T.; Atobe, M. Continuous In Situ Electrogeneration of *o*-Benzoquinone in Microreactor: Application to High Yield Reaction with Benzenethiols. *J. Flow Chem.* **2013**, *3*, 17–22.
- (99) Kashiwagi, T.; Elsler, B.; Waldvogel, S. R.; Fuchigami, T.; Atobe, M. Reaction Condition Screening by Using Electrochemical Microreactor: Application to Anodic Phenol-Arene C-C Cross-Coupling Reaction in High Acceptor Number Media. *J. Electrochem. Soc.* **2013**, *160*, G3058–G3061.
- (100) Kashiwagi, T.; Fuchigami, T.; Saito, T.; Nishiyama, S.; Atobe, M. Sequential Paired Electrosynthesis of a Diaryl Ether Derivative Using an Electrochemical Microreactor. *Chem. Lett.* **2014**, *43*, 799–801.
- (101) Tateno, H.; Matsumura, Y.; Nakabayashi, K.; Senboku, H.; Atobe, M. Development of a Novel Electrochemical Carboxylation System Using a Microreactor. *RSC Adv.* **2015**, *5*, 98721–98723.
- (102) Amemiya, F.; Kashiwagi, T.; Fuchigami, T.; Atobe, M. Electrochemical Conversion of Benzylamine to Dibenzylamine Using a Microreactor: Analogous System of Photocatalytic Redox Combined Synthesis. *Chem. Lett.* **2011**, *40*, 606–608.
- (103) Horii, D.; Fuchigami, T.; Atobe, M. A New Approach to Anodic Substitution Reaction Using Parallel Laminar Flow in a Micro-Flow Reactor. *J. Am. Chem. Soc.* **2007**, *129*, 11692–11693.
- (104) Horii, D.; Amemiya, F.; Fuchigami, T.; Atobe, M. A Novel Electrosynthetic System for Anodic Substitution Reactions by Using Parallel Laminar Flow in a Microflow Reactor. *Chem. - Eur. J.* **2008**, *14*, 10382–10387.
- (105) MacDonald, S. M.; Watkins, J. D.; Gu, Y.; Yunus, K.; Fisher, A. C.; Shul, G.; Opallo, M.; Marken, F. Electrochemical Processes at a Flowing Organic Solvent/Aqueous Electrolyte Phase Boundary. *Electrochem. Commun.* **2007**, *9*, 2105–2110.
- (106) Amemiya, F.; Fuse, K.; Fuchigami, T.; Atobe, M. Chemo-selective Reaction System Using a Two Inlet Micro-Flow Reactor: Application to Carbonyl Allylation. *Chem. Commun.* **2010**, *46*, 2730–2732.
- (107) Amemiya, F.; Horii, D.; Fuchigami, T.; Atobe, M. Self-Supported Paired Electrosynthesis Using a Microflow Reactor Without Intentionally Added Electrolyte. *J. Electrochem. Soc.* **2008**, *155*, E162–E165.
- (108) Amemiya, F.; Matsumoto, H.; Fuse, K.; Kashiwagi, T.; Kuroda, C.; Fuchigami, T.; Atobe, M. Product Selectivity Control Induced by Using Liquid-Liquid Parallel Laminar Flow in a Microreactor. *Org. Biomol. Chem.* **2011**, *9*, 4256–4265.
- (109) Matsumura, Y.; Yamaji, Y.; Tateno, H.; Kashiwagi, T.; Atobe, M. In Situ Generation of Trichloromethyl Anion and Efficient Reaction with Benzaldehyde in an Electrochemical Flow Microreactor. *Chem. Lett.* **2016**, *45*, 816–818.
- (110) Arai, T.; Tateno, H.; Nakabayashi, K.; Kashiwagi, T.; Atobe, M. An Anodic Aromatic C-C Cross-Coupling Reaction Using Parallel Laminar Flow Mode in a Flow Microreactor. *Chem. Commun.* **2015**, *51*, 4891–4894.
- (111) Watts, K.; Gattrell, W.; Wirth, T. A Practical Microreactor for Electrochemistry in Flow. *Beilstein J. Org. Chem.* **2011**, *7*, 1108–1114.
- (112) Arai, K.; Watts, K.; Wirth, T. Difluoro- and Trifluoromethylation of Electron-Deficient Alkenes in an Electrochemical Microreactor. *ChemistryOpen* **2014**, *3*, 23–28.
- (113) Arai, K.; Wirth, T. Rapid Electrochemical Deprotection of the Isonicotinylloxycarbonyl Group from Carbonates and Thiocarbonates in a Microfluidic Reactor. *Org. Process Res. Dev.* **2014**, *18*, 1377–1381.

- (114) He, P.; Watts, P.; Marken, F.; Haswell, S. J. Scaling out of Electrolyte Free Electrosynthesis in a Micro-Gap Flow Cell. *Lab Chip* **2007**, *7*, 141–143.
- (115) Simms, R.; Dubinsky, S.; Yudin, A.; Kumacheva, E. A Method for Fabricating Microfluidic Electrochemical Reactors. *Lab Chip* **2009**, *9*, 2395–2397.
- (116) Attour, A.; Rode, S.; Ziogas, A.; Matlosz, M.; Lapicque, F. A Thin-Gap Cell for Selective Oxidation of 4-Methylanisole to 4-Methoxy-Benzaldehyde-Dimethylacetal. *J. Appl. Electrochem.* **2008**, *38*, 339–347.
- (117) Attour, A.; Rode, S.; Lapicque, F.; Ziogas, A.; Matlosz, M. Thin-Gap Single-Pass High-Conversion Reactor for Organic Electrosynthesis: II. Application to the Anodic Methoxylation of 4-Methoxytoluene. *J. Electrochem. Soc.* **2008**, *155*, E201–E206.
- (118) Rode, S.; Altmeyer, S.; Matlosz, M. Segmented Thin-Gap Flow Cells for Process Intensification in Electrosynthesis. *J. Appl. Electrochem.* **2004**, *34*, 671–680.
- (119) Küpper, M.; Hessel, V.; Löwe, H.; Stark, W.; Kinkel, J.; Michel, M.; Schmidt-Traub, H. Micro Reactor for Electroorganic Synthesis in the Simulated Moving Bed-Reaction and Separation Environment. *Electrochim. Acta* **2003**, *48*, 2889–2896.
- (120) Michel, M.; Schmidt-Traub, H.; Ditz, R.; Schulte, M.; Kinkel, J.; Stark, W.; Küpper, M.; Vorbrodt, M. Development of an Integrated Process for Electrochemical Reaction and Chromatographic SMB-Separation. *J. Appl. Electrochem.* **2003**, *33*, 939–949.
- (121) Attour, A.; Dirrenberger, P.; Rode, S.; Ziogas, A.; Matlosz, M.; Lapicque, F. A High Pressure Single-Pass High-Conversion Electrochemical Cell for Intensification of Organic Electrosynthesis Processes. *Chem. Eng. Sci.* **2011**, *66*, 480–489.
- (122) Gütz, C.; Bänziger, M.; Bucher, C.; Galvão, T. R.; Waldvogel, S. R. Development and Scale-Up of the Electrochemical Dehalogenation for the Synthesis of a Key Intermediate for N5SA Inhibitors. *Org. Process Res. Dev.* **2015**, *19* (10), 1428–1433.
- (123) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. Electrochemical Combinatorial Organic Syntheses Using Microflow Systems. *QSAR Comb. Sci.* **2005**, *24*, 728–741.
- (124) Horcajada, R.; Okajima, M.; Suga, S.; Yoshida, J. Microflow Electroorganic Synthesis without Supporting Electrolyte. *Chem. Commun.* **2005**, 1303–1305.
- (125) Yoshida, J. Flash Chemistry Using Electrochemical Method and Microsystems. *Chem. Commun.* **2005**, 4509–4516.
- (126) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. Cation Flow” Method: A New Approach to Conventional and Combinatorial Organic Syntheses Using Electrochemical Microflow Systems. *J. Am. Chem. Soc.* **2001**, *123*, 7941–7942.
- (127) Yoshida, J.; Suga, S. Basic Concepts of “Cation Pool” and “Cation Flow” Methods and Their Applications in Conventional and Combinatorial Organic Synthesis. *Chem. - Eur. J.* **2002**, *8*, 2650–2658.
- (128) Yoshida, J.; Ashikari, Y.; Matsumoto, K.; Nokami, T. Recent Developments in the “Cation Pool” Method. *Yuki Gosei Kagaku Kyokaiishi* **2013**, *71*, 1136–1144.
- (129) Yoshida, J.; Shimizu, A.; Ashikari, Y.; Morofuji, T.; Hayashi, R.; Nokami, T.; Nagaki, A. Reaction Integration Using Electrogenerated Cationic Intermediates. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 763–775.
- (130) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. Control of Extremely Fast Competitive Reactions Using Micromixing. Selective Friedel-Crafts Aminoalkylation. *J. Am. Chem. Soc.* **2005**, *127*, 11666–11675.
- (131) Arai, K.; Sato, T.; Tamanouchi, H.; Ohtomo, M.; Takamura, K.; Sueoka, T.; Kusu, F. Electrolysis of 2-Methyl-1,4-Naphthoquinone and 3,5-Di-Tert-Butyl-1,2-Benzoquinone Using the Flow Cell System with a Column Electrode. *Electrochim. Acta* **2000**, *45*, 3029–3034.
- (132) Hosokawa, Y.; Hakamata, H.; Murakami, T.; Kusu, F. Electrosynthesis of Cholesta-4,6-Dien-3-One from Cholesterol on a Laboratory Laboratory Synthetic Scale. *Tetrahedron Lett.* **2010**, *51*, 129–132.
- (133) Kuleshova, J.; Hill-Cousins, J. T.; Birkin, P. R.; Brown, R. C. D.; Pletcher, D.; Underwood, T. J. A Simple and Inexpensive Microfluidic Electrolysis Cell. *Electrochim. Acta* **2011**, *56*, 4322–4326.
- (134) Green, R. A.; Brown, R. C. D.; Pletcher, D. Understanding the Performance of a Microfluidic Electrolysis Cell for Routine Organic Electrosynthesis. *J. Flow Chem.* **2015**, *5*, 31–36.
- (135) Chapman, M. R.; Shafl, Y. M.; Kapur, N.; Nguyen, B. N.; Willans, C. E. Electrochemical Flow-Reactor for Expedient Synthesis of Copper-N-Heterocyclic Carbene Complexes. *Chem. Commun.* **2015**, *51*, 1282–1284.
- (136) Applications. Electrochemistry in Flow. <https://syrris.com/applications/flow-chemistry-applications/electrochemistry-in-flow/> (accessed June 7, 2017).
- (137) Kuleshova, J.; Hill-Cousins, J. T.; Birkin, P. R.; Brown, R. C. D.; Pletcher, D.; Underwood, T. J. The Methoxylation of N-Formylpyrrolidine in a Microfluidic Electrolysis Cell for Routine Synthesis. *Electrochim. Acta* **2012**, *69*, 197–202.
- (138) Hill-Cousins, J. T.; Kuleshova, J.; Green, R. A.; Birkin, P. R.; Pletcher, D.; Underwood, T. J.; Leach, S. G.; Brown, R. C. D. TEMPO-Mediated Electrooxidation of Primary and Secondary Alcohols in a Microfluidic Electrolytic Cell. *ChemSusChem* **2012**, *5*, 326–331.
- (139) Roth, G.; Stalder, R.; Long, T.; Sauer, D.; Djuric, S. Continuous-Flow Microfluidic Electrochemical Synthesis: Investigating a New Tool for Oxidative Chemistry. *J. Flow Chem.* **2013**, *3*, 34–40.
- (140) Green, R. A.; Pletcher, D.; Leach, S. G.; Brown, R. C. D. N-Heterocyclic Carbene-Mediated Oxidative Electrosynthesis of Esters in a Microflow Cell. *Org. Lett.* **2015**, *17*, 3290–3293.
- (141) Green, R. A.; Pletcher, D.; Leach, S. G.; Brown, R. C. D. N-Heterocyclic Carbene-Mediated Microfluidic Oxidative Electrosynthesis of Amides from Aldehydes. *Org. Lett.* **2016**, *18*, 1198–1201.
- (142) Stalder, R.; Roth, G. P. Preparative Microfluidic Electrosynthesis of Drug Metabolites. *ACS Med. Chem. Lett.* **2013**, *4*, 1119–1123.
- (143) The Ammonite Family of Electrolysis Cells. <http://www.cambridgereactor design.com/ammonite/> (accessed June 7, 2017).
- (144) Green, R. A.; Brown, R. C. D.; Pletcher, D.; Harji, B. An Extended Channel Length Microflow Electrolysis Cell for Convenient Laboratory Synthesis. *Electrochem. Commun.* **2016**, *73*, 63–66.
- (145) Green, R. A.; Jolley, K. E.; Al-Hadedi, A. A. M.; Pletcher, D.; Harrowven, D. C.; De Frutos, O.; Mateos, C.; Klauber, D. J.; Rincon, J. A.; Brown, R. C. D. Electrochemical Deprotection of 4-Methoxybenzyl Ethers in a Flow Electrolysis Cell. *Org. Lett.* **2017**, *19*, 2050–2053.