Organic Process Research & Development

Communication

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Development and Scale-Up of the Electrochemical Dehalogenation for the Synthesis of a Key Intermediate for NS5A Inhibitors

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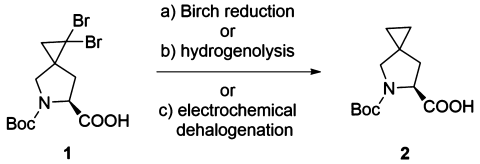
Supporting Information

ABSTRACT: The electrochemical 2-fold dehalogenation of a spirocyclopropane-proline derivative at leaded bronze was scaled-up in a divided batch-type electrolysis cell in good yield and excellent selectivity. The upscaling via a flow electrolysis cell was also successful. Conditions were elaborated employing a single cell passage for complete conversion. The keys here are the direct cooling of the cathode and ensuring a good laminar flow.

The NS5A inhibitor compounds such as Ledipasvir are highly important for the complete cure of hepatitis C.[1−5] A key intermediate for the synthesis of this drug is the spirocyclopropane-proline derivative **2**. There is a significant need for the pharmaceutical industry to have effective, sustainable, and scalable procedures in hand.[1−3] Recently, we surveyed different synthetic approaches to this particular building block.[6] The most promising one starts from chiral pool derived N-BOC-hydroxyproline which is converted in four steps into the desired proline derivative **2**. The most challenging step is the 2-fold dehalogenation of the spirocyclopropane-proline derivative **1** to key intermediate **2** (Scheme 1).

Scheme 1. Different Synthetic Strategies for the Dehalogenation

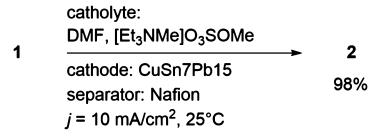


This step could be realized by a Birch reduction in 65% yield, but the reaction has the disadvantage of ring opening byproducts of the cyclopropane moiety, racemization, waste of reagents, and costly reaction conditions.[6] An alternative approach employs the hydrogenolysis at Pd/C as a catalyst. The purification of the crude product turned out to be problematic since ring-opening byproducts to the gem-dimethyl derivative are formed. Therefore, the yield after several purification steps is decreased to 48%.

Another nonconventional but promising approach is the electrochemical dehalogenation of organic substrates.[7] Since electricity can be generated via renewable sources, electro-organic synthesis represents a highly attractive and sustainable synthetic method which fulfills all requirements of "Green Chemistry".[8−15] Commonly, electrochemical dehalogenations are performed at rather simple substrates,[7,16−21] whereas for strained ring systems only a few protocols are known for monodehalogenation using lead or mercury as cathode.[22−29] However, these cathode materials are incompatible for the pharmaceutical production of intermediates since highly toxic organometallic species of lead or mercury might be formed. Nevertheless, electrolyte-stabilized lead has found recently some interest in the deoxygenation of oximes,[30−32] amides,[33,34] and sulfoxides.[34]

To circumvent these issues we developed a sustainable and efficient electrochemical protocol for this conversion using leaded bronze as novel cathode material (Scheme 2).[35] This

Scheme 2. Optimized Conditions for Highly Selective Electrolysis of 1 to 2



method has several significant advantages: First, no waste of expensive and toxic reagents are formed since the solvent and the supporting electrolyte can be recycled upon electrolytic conversion. Second, the clean conversion to a sole compound in the crude product avoids tedious separation steps. Even with an excess of electricity no distinct byproducts are formed, only decomposition of product is observed resulting in a lower yield. This simplifies the isolation strategy significantly because only an aqueous workup and a simple filtration column are necessary to obtain a highly pure product. Third, this new cathode material ensures a high selectivity and reactivity combined with a high chemical and mechanical stability. All other previously tested cathode materials are either prone to corrosion or have a significantly lower selectivity and reactivity. In particular the good performing lead led to a tremendous contamination by heavy metal salts in the product (approximately 70 mol % in respect to **2**). Additionally, the elaborated electrolytic method using leaded bronze can be applied to a broad scope of substrates containing dibromocyclopropane moieties. This method is highly tolerant of complex functionality, as demonstrated in the successful late-stage functionalization of

Received: August 24, 2015

DOI: 10.1021/acs.oprd.5b00272
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a cyclosporine A derivative.[35] Although diastereomeric mixtures of the starting materials were employed, no pronounced differences in reactivity of the respective pure diastereomers were found.

While the lab scale development of the reaction had been very promising, for a technical application in the pharmaceutical industry the synthesis as well as the workup for a reaction must be scalable. The problem with such an effort is typically a lack of experience since only a few electrochemical organic processed have been elaborated in this context.[19,36,37] To close this gap we developed two different approaches for upscaling the electroorganic synthesis of **2**. This includes a batch-type electrolysis cell and a flow electrolysis device.

On the basis of our previous studies, we started developing a batch-type electrochemical cell capable of conversion in the multigram range. The employed electrolyte consisted of DMF and MTES ($[Et_3NMe]O_3SOMe$). **1** was reduced at the cathode, whereas methanol was oxidized at the anode as a sacrificial compound (composition details see below). Since leaded bronze as our novel cathode material is commercially available as a pipe, we designed a cylindrical cell geometry. The pipe was cut into a tube of 20 cm length and an internal diameter of 12 cm.

As an anode we employed a cylindrical platinum net. The ceramic compartment was fixed by a Teflon cap and then immersed into the electrolysis cell (Figure 1). The applied cell voltage by this setup was 13 V. The whole cell can be kept at 25 °C by immersion into a water bath. The good thermal conductivity of the leaded bronze ensures a sufficient thermal control of the electrolysis conditions.

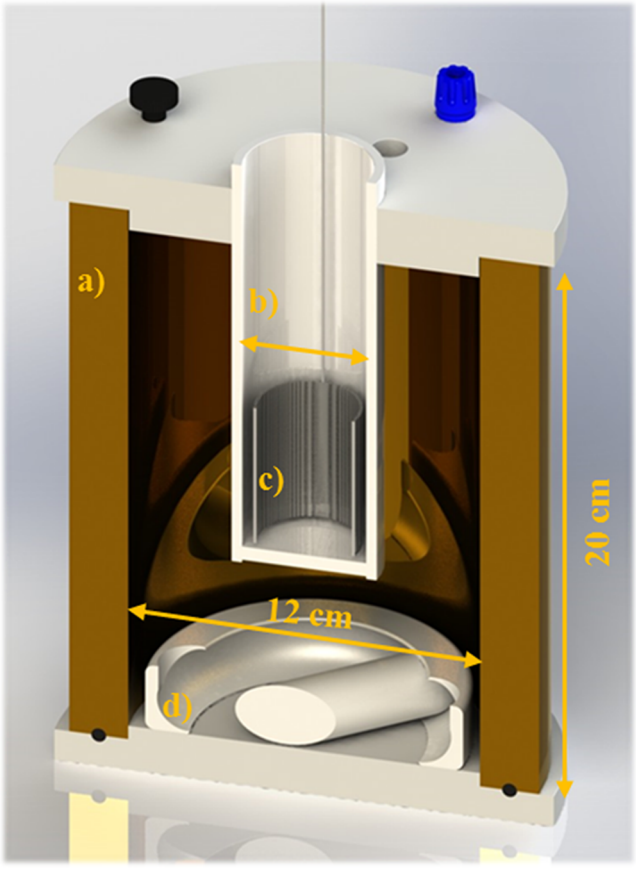
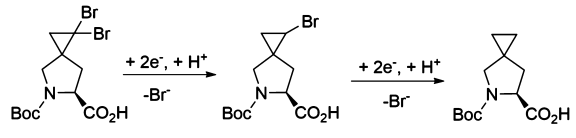


Figure 1. Scale-up electrolysis cell (batch-type) with a cathodic compartment volume of a maximum of 2 L: (a) leaded bronze cathode (CuSn7Pb15); (b) separator, porous ceramic; (c) platinum grid anode; (d) heavy duty stirring bar.

The advantages of this particular batch-type cell are the simple construction and easy operation since only a simple dc power supply and a large magnetic stirring device are required. In an emergency case, the electrolysis can be immediately stopped in order to interrupt the reaction and then be restarted again. This provides an adding degree of process safety compared to, e.g., Birch reduction.

Using this approach we tested reaction conditions which were promising during our screening at very small scale.[35] It has been shown that the solvent and the current density are essential parameters for the electrolysis. In DMF, it was possible to obtain in a single electrolysis run 25.9 g of the desired product in an excellent yield of 93% and 99% ee (Table 1, entry 1).Thus, we achieved comparable results at large (115.8 mmol) as well as at small lab scale (2.6 mmol). The electrolysis time was 7 h. Since DMF is a Substance of Very High Concern (SVHC) by the European Chemical Agency (ECHA), its use is discouraged on scale, especially in the pharmaceutical industry. Consequently, we tested several other solvents as electrolyte component including acetone, propylene carbonate, γ-butyrolactone, and acetonitrile. Among them only DMF and acetonitrile provided either sufficient conductivity or cathodic conversion in the electrolyte. However, cathodic dehalogenation in acetonitrile is less powerful since the only product observed is the monodehalogenated species **1a** (almost no stereoselectivity has been observed in the mono dehalogenation). However, these conditions with a low current density selectively provide the monobromo derivative on the preparative scale (Table 1, entry 2). Increasing the current density did not improve the situation for the dehalogenation in acetonitrile, as the evolution of hydrogen became more prominent and led to an inferior result (Table 1, entry 3). Therefore, only in DMF a stable and reliable process for the 2-fold dehalogenation was achieved.

Table 1. Optimized Electrolysis Parameters for the Batch Approach



entry	solvent	Q [F][a]	j [mA/cm²][b]	product
1	DMF	8	10	**2** (25.9 g, 93%)
2	CH_3CN	9	5	**1a** (23.4 g, 64%)
3	CH_3CN	11	10	**1** + **1a**

[a]Q = applied electricity. [b]j = current density.

However, for the batch-type cell, significant manual operations are required and this particular cell design is only suitable for electrolyte volumes up to a few liters. A further scale-up of such an electrolysis cell forces an increase of the distance between the electrodes. Thus, the ohmic resistance will heat up the cell, and in addition an inferior rate of electrode surface to electrolyte volume is created. This will inevitably result in lower energy efficiency and prolonged electrolysis times.

DOI: 10.1021/acs.oprd.5b00272
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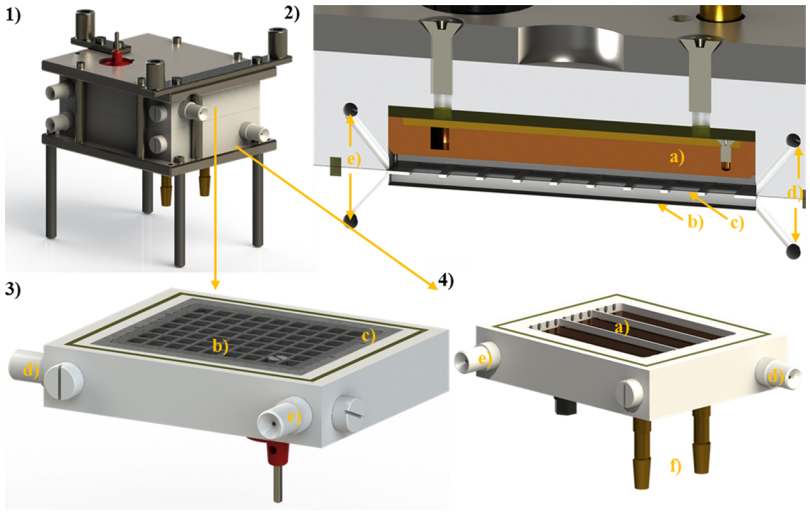

Figure 2. (1) Total view of the flow cell, (2) cross section of the hole cell, (3) anodic half-cell and Nafion separator, (4) cathodic half-cell: (a) cathode, CuSn7Pb15; (b) anode, graphite; (c) Nafion membrane; (d) inlets for electrolyte; (e) outlets for electrolyte; (f) contacts for cooling media.

Therefore, we designed an electrochemical flow cell. The main advantages of this cell are the excellent ratio of electrode surface to reaction volume, better control of reaction parameters such as temperature or the retention period of the substrate at the electrode and, of course, a continuous operation mode.

The newly developed flow cell and the complete setup are presented in Figures 2 and 3 (for more details and exploded

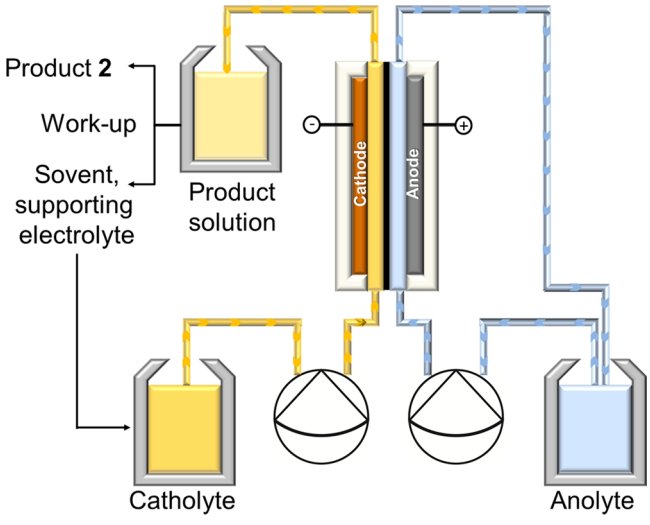

Figure 3. Schematic setup of the newly developed electrochemical flow cell and the recycling streams.

drawings see the Supporting Information). The design is a divided gap cell. The chassis is made of two Teflon blocks which are mechanically connected by two stainless steel plates. Inside of each Teflon block there is a small space to accommodate the electrodes and the reaction chambers. We used leaded bronze (15% Pb) as cathode and graphite felt as anode. The anodic and cathodic compartments are separated by a Nafion membrane. The applied cell voltage was 11 V. For reliable results, two features of the cathodic compartment turned out to be crucial: First, the temperature has to be kept at 25 °C by cooling. A precooling of the electrolyte was not efficient enough and therefore, the external cooling was directly attached onto the backside of the cathode. The high thermal conductivity of leaded bronze enabled sufficient control of electrolysis conditions. Second, dead volumes have to be strictly avoided and a laminar flow is beneficial. The inlet has a feeder with sufficiently large holes over the width of cathode. The outlet exhibits the same geometry. In order to avoid contact of the membrane to the cathodic surface by pressure instabilities of the pumps employed, cross-pieces were installed. Thereby, this approach provides a laminar flow and a controlled cavern (total volume 40 cm^3) with a much better surface to volume ratio compared to the batch-type cell.

Using this gap cell, the anolyte is pumped in a cycle, whereas the catholyte is collected after passage through the flow cell (setup see Figure 3). The anodic reaction is the oxidation of methanol. The isolated yield for the dehalogenated product **2** in the continuous approach is 70% with 99% ee. Essential factors, which influence the selectivity and the yield, are current density, applied electricity and the flow per minute (Table 2). First, we started to optimize the applied electricity. It turned out that an applied electricity of 10 or 15 F results in a product mixture with the starting material **1** as the major compound (Table 2, entry 1 and 2). In contrast, a complete conversion was achieved with 20 F (Table 2, entry 5). Since the three parameters are interconnected, a fixed applied electricity leads to two possibilities for the current density and the flow per minute: First, a high flow and a high current density or second, a low flow and a low current density. The first possibility results in a very short residence time within the gap cell and, therefore, in

Table 2. Optimized Electrolysis Parameters for the Flow Cell

entry	flow rate [mL/min]	applied electricity [F]	j [mA/cm^2]	product
1	1.5	10	20	product mixture (**1** + **2**)
2	0.5	15	10	product mixture (**1** + **2**)
3	1.14	20	30	product mixture (**1** + **2**)
4	0.38	20	10	product mixture (**1** + **2**)
5	0.6	20	15	**2** (2.7 g, 70%)

DOI: 10.1021/acs.oprd.5b00272
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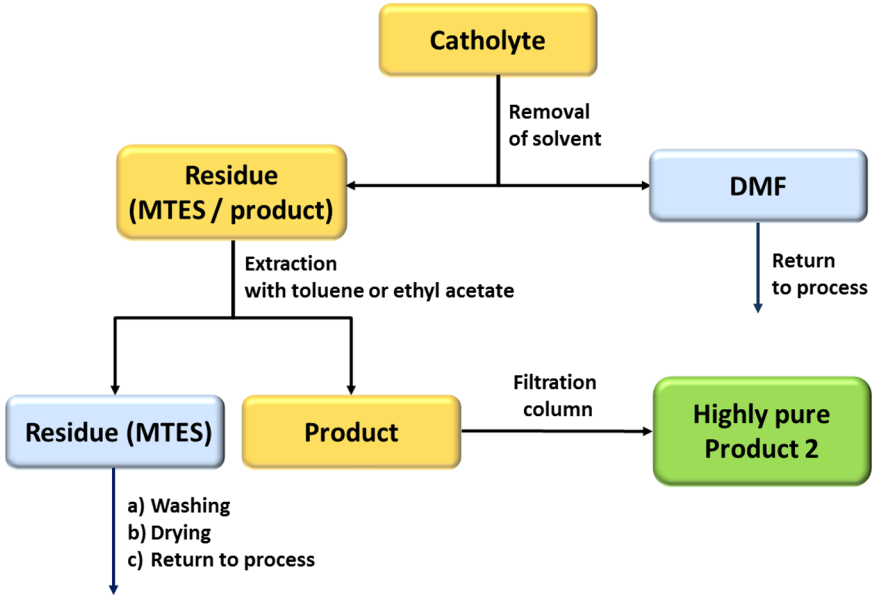

Figure 4. Overview of the workup protocol. Color code: green = final product, blue = pure reagent for further use, orange = reagent mixture. MTES = $[Et_3NMe]O_3SOMe$.

an incomplete conversion (Table 2, entry 3). A low current density and flow also resulted in a product mixture. A possible reason could be a higher diffusion rate of H^+ between anolyte and catholyte resulting in H^2 evolution as a side reaction (Table 2, entry 3). Instead, it turned out that a current density of 15 mA/cm^2 and a flow of 0.6 mL/min are optimal parameters for the conversion of **1** to **2** in this flow cell (Table 2, entry 5).

Additionally, for recycling of the electrolyte and isolation of pure product, we developed an efficient and simple workup protocol. This procedure can be applied for both approaches, batch-type and continuous flow, and is schematically represented in Figure 4. First, DMF is removed at reduced pressure for possible recycling. Next, the product is isolated from the solid residue by extraction with toluene or ethyl acetate, which is then removed under reduced pressure. This crude product exhibits a trace metal content lower than 10 ppm thus meeting the tight residual requirements and demonstrating the suitability for the production of pharmaceuticals. Finally, in order to guarantee high purity the product is filtered through a short silica gel column using toluene and ethyl acetate (3:1) as eluent. Furthermore, to achieve a directly reusable supporting electrolyte, the solid residue after toluene extraction is washed by ethyl acetate and then dried under reduced pressure (reuse of the supporting electrolyte was tested for five times without loss of conductivity and performance).

In summary, we established two different approaches for the scale-up of electrochemical debromination of a pharmaceutically relevant spirocyclopropane-proline building block. The electrolysis can be performed in a batch-type cell or in a continuous flow gap cell. The latter allows an almost unlimited scale up. The workup strategy is easy to perform. The protocol allows an efficient recycling of both electrolyte components, solvent, and supporting electrolyte for further use in this electrolytic conversion. For obtaining pure cathodic product, good thermal control and laminar flow within the cell are essential. By design adaptions, these requirements can be fulfilled. This electroorganic conversion is an example for the sustainable use of electric current as reagent and should inspire other process development projects given the demonstrated scalability of the electrochemical reaction conditions coupled with the inherent advantages of continuous chemistry.

EXPERIMENTAL SECTION

General Information. Power source: Genesys 30-50 (TDK Lambda, Achern, Germany); dc output 0−30 V (±0.01 V) and 0−50 A (±10 mA). The electric current was adjusted for the given current density, whereas the voltage was set freely. Membrane pumps: "Dosierpumpe Ritmo R 033" (Fink Chem +Tec GmbH & Co.KG, Leinfelden-Echterdingen, Germany). Column chromatography was performed on silica gel 60 M (0.040−0.063 mm, Macherey-Nagel GmbH & Co, Düren, Germany) with a maximum pressure of 1.6 bar. As eluent a mixture of toluene and ethyl acetate 3:1 was used. Silica gel 60 sheets on glass (F254, Merck, Darmstadt, Germany) were used for thin layer chromatography. Spectroscopy and spectrometry: ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C by using a Bruker AV II 400 or a AV III HD 300 (Bruker, Germany). Chemical shifts (δ) are reported in parts per million (ppm) relative to traces of $CHCl_3$ in the corresponding deuterated solvent. Mass spectra and high-resolution mass spectra were obtained by using a QTof Ultima 3 (Waters, Milford, MA) apparatus employing ESI+, a micrOTOF-Q-spectrometer (Bruker), a MAT 95XL (Finnigan) EI mass spectrometer or a MAT 95 (Finnigan) FD mass spectrometer. HPLC chromatography was performed as reaction control on a Prominence UFLC System (Shimadzu Europa GmbH, Duisburg, Germany). Column specification: Chromolith Reversed Phase (Merck), polymer; monolithic; macropore 2 μm; mesopore 13 nm; pore volume 1 mL/g, porosity >80%, surface 300 m^2/g. Method: solvent A = H_2O/CH_3CN 95:5 + 0.1% H_3PO_4, solvent B = CH_3CN; flow rate 0.7 mL/min, gradient: A/B = 1:0 to 1:9 until t = 7.5 min (gradient), A/B = 1:9 until t = 10 min (constant), A/B = 1:9 to 1:0 until t = 15 min (gradient). Trace analysis: ICP-OES spectrometer (Spectro; Arcos-EOP); results of trace analysis Cu, 4 ppm; Pb, 5 ppm; Sn, 1 ppm. All solvents were used in analytical grades. Starting material **1** and triethylmethylammonium methyl sulfate were synthesized according to the literatue.[6,38]

DOI: 10.1021/acs.oprd.5b00272
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Synthesis of (*S*)-5-(*tert*-Butoxycarbonyl)-5-azaspiro-[2.4]heptane-6-carboxylic acid 2 in Batch Approach. In total, 46.2 g (115.8 mmol) of **1** and 60.1 g (264.4 mmol) of triethylmethylammonium methyl sulfate were dissolved in 1 L of *N*,*N*-dimethylformamide (or acetonitrile) and placed in the cathodic half-cell. For the anolyte, 4.2 g (18.5 mmol) of triethylmethylammonium methyl sulfate were dissolved in 168 mL of *N*,*N*-dimethylformamide (or acetonitrile) and 84.5 mL of methanol. As cathode material leaded bronze (CuSn7Pb15, surface in solution 340 cm^2) and as an anode material a platinum grid was used. A porous ceramic was applied as a separator (cell arrangement see Figure 1). The applied electricity and the current density were varied between 8 and 11 F and 5−10 mA/cm^2 (Table 1). A complete conversion could be obtained using *N*,*N*-dimethylformamide as solvent, an applied electricity of 8 F, and with a current density of 10 mA/cm^2. For workup see General Workup Protocol (for 115 mmol of Starting Material 1). The analytical data are in accordance to the literature.[35] For the HPLC chromatogram of the product after electrolysis, see Supporting Information.

Synthesis of (*S*)-5-(*tert*-Butoxycarbonyl)-5-azaspiro-[2.4]heptane-6-carboxylic Acid 2 in Flow Cell. In total, 6.4 g (16.0 mmol) of starting material **1** and 7.2 g (31.7 mmol) triethylmethylammonium methyl sulfate were dissolved in 120 mL *N*,*N*-dimethylformamide and placed in the catholyte storage vessel. In the anolyte storage vessel, a solution of 6.0 g (26.4 mmol) of triethylmethylammonium methyl sulfate in 80 mL of *N*,*N*-dimethylformamide and 40 mL of methanol was placed. As cathode material leaded bronze (CuSn7Pb15, cooled via cooling fins to 25 °C, surface 80 cm^2) and as anode material a graphite foil (Sigraflex, 80 cm^2) was used. A Nafion 324 sheet was applied as the separator (cell arrangement see Figures 2 and 3. For detailed views of the flow cell, see explosion drawings in the Supporting Information). However, the gap cell was operated in a vertical fashion to allow gas evolved to escape quickly from the cell compartment. The applied electricity, the flow rate, and the current density were varied between 10 and 20 F, 0.38−1.5 mL/min, and 10−30 mA/cm^2 (Table 2). A complete conversion could be obtained using an applied electricity of 20 F, a flow rate of 0.6 mL/min, and a current density of 15 mA/cm^2. For workup see General Workup Protocol (for 115 mmol of Starting Material 1). The analytical data are in accordance to the literature.[35]

General Workup Protocol (for 115 mmol of Starting Material 1). After electrolysis, the solvent from the catholyte was removed under reduced pressure. The resulting crude product (a mixture of supporting electrolyte and product) was extracted three times with 200 mL of toluene or ethyl acetate. The combined organic phases were washed twice with 200 mL of citric acid (10 wt % in H_2O) and 200 mL of brine. After drying over magnesium sulfate, the toluene or ethyl acetate was removed under reduced pressure to get the crude product (a complete removal is not necessary since ethyl acetate or toluene are used as eluent), which was purified via filtration column chromatography (silica gel; column size: diameter, 5.7 cm; height, 7 cm. Eluent: toluene/ethyl acetate 3:1).

For isolation of the supporting electrolyte, the solid residue after toluene extraction was washed with 150 mL of ethyl acetate and dried in vacuum to achieve reusable triethylmethylammonium methyl sulfate.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00272.

Explosion drawings of flow gap cell (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Malte Brutschy for the fabrication of the exploded drawings.

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DOI: 10.1021/acs.oprd.5b00272
Org. Process Res. Dev. XXXX, XXX, XXX−XXX