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TEMPO-Mediated Electrooxidation of Primary and Secondary Alcohols in a Microfluidic Electrolytic Cell

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A general procedure for the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-mediated electrooxidation of primary and secondary alcohols modified for application in a microfluidic electrolytic cell is described. The electrocatalytic system utilises a buffered aqueous *tert*-butanol reaction medium, which operates effectively without the requirement for additional electrolyte, providing a mild protocol for the oxidation of alcohols to aldehydes and ketones at ambient temperature on a laboratory scale. Optimisation of the process is discussed along with the oxidation of 15 representative alcohols.

Introduction

In recent years, microflow reactors have received a great deal of interest from synthetic chemists in both academia and industry[1] as they allow convenient synthesis on a 1 g scale with improved selectivities and reduced reaction times. Electrolysis can provide alternative routes to the synthesis of organic molecules,[2] but has never become a routine procedure in synthetic laboratories. In the belief that electrolysis in a microflow environment can provide unique opportunities for convenient synthetic procedures, we have recently initiated a programme of research in microfluidic electrosynthesis[3] with the aim of developing a range of simple, effective transformations for everyday use in the laboratory. This paper describes the modification of a known electrosynthesis for the conversion of alcohols to aldehydes and ketones, a reaction of fundamental importance in organic synthesis, so that it can be performed with high selectivity and conversion in a microflow cell.

A considerable number of methods are currently available for the oxidation of alcohols to aldehydes and ketones, but some of them involve harsh reaction conditions, low temperatures and/or the use of toxic or hazardous reagents. Conversely, stable organic nitroxyl radicals, particularly 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, **3**), have been identified as environmentally benign catalysts for the oxidation of alcohols.[4] The active species in the TEMPO-mediated oxidation of alcohols is the oxoammonium ion **4**, which is typically generated in situ with a stoichiometric co-oxidant, such as sodium hypochlorite. The coproduct of alcohol oxidation, hydroxylamine **5**, is rapidly reoxidised to the TEMPO radical (**3**) in the presence of oxygen[5] or by the cooxidant. The oxoammonium ion can also be generated from TEMPO electrochemically through a single electron transfer process at the anode (Figure 1).[6] Although there is a good deal of literature precedent for the TEMPO-mediated electrooxidation of alcohols, at present only a few preparative procedures have been reported that use TEMPO and its analogues[7] or other nitroxyl radicals[8] in a traditional batch cell. Herein, the development of a general procedure for the TEMPO-mediated electrooxidation of primary and secondary alcohols under microflow conditions, at ambient temperature, in an environmentally acceptable reaction medium is reported.[9] The protocol is intended for the conversion of alcohols with high selectivity on a laboratory scale using a microfluidic apparatus. To our knowledge, this is the first report of such a process.

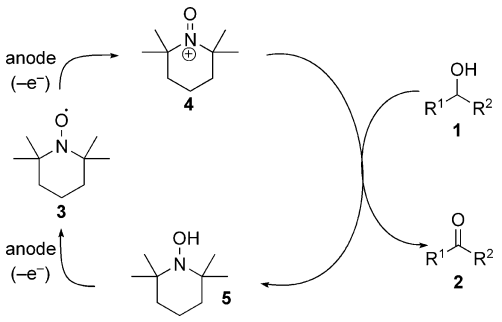

Figure 1. TEMPO-mediated electrochemical alcohol oxidation.

Results and Discussion

The microfluidic experiments were conducted by using a single channel microfluidic electrolysis cell[10] connected to a

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commercially available flow system (FRX, Syrris), which also permitted controlled heating of the cell.

Initial studies performed in a solvent mixture of acetonitrile and an aqueous carbonate buffer as a homogeneous reaction medium showed successful oxidation of benzyl alcohol (**1a**) to benzaldehyde (**2a**) with high conversion in a single pass (Table 1). The importance of a basic medium has been previously highlighted,[6d,7a,b] and the use of a partially aqueous system ensured a more balanced electrochemical process, where the desired anode transformation is given by Equation (1):

$$RCH_2OH + 2\,OH^- - 2\,e^- \rightarrow RCHO + 2\,H_2O \quad (1)$$

with Equation (2)

$$4\,OH^- - 4\,e^- \rightarrow O_2 + 2\,H_2O \quad (2)$$

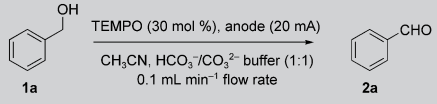
as a competing reaction. The main counter electrode reaction is given by Equation (3):

$$2\,H_2O + 2\,e^- \rightarrow H_2 + 2\,OH^- \quad (3)$$

Interestingly, production of gas bubbles in the flow channel did not impede the performance of the cell under the conditions employed, while the formed hydroxide ion ensured a pH balance in the microchannel.[11]

For the reactions conducted in CH_3CN mixtures, operating with a constant current of 20 mA ($\pm$5 mA)[12] and a 30 mol% TEMPO loading, a survey of temperature and pH indicated that high conversion and selectivity could be realised at pH 10.2[13,14] in the temperature range 22–30 °C (entries 1, 4 and 5 in Table 1). Further increase in temperature or pH generally resulted in reduced yield and selectivity, with small quantities of benzoic acid formed. However, due to concerns over the hydrolytic and electrochemical stability of CH_3CN at high pH values, subsequent electrochemistry was conducted in a more environmentally desirable *t*BuOH/aqueous buffer (1:1) mixed solvent system.[15] Further development of the TEMPO-mediated flow electrochemical oxidation was guided by the cyclic voltammetry studies described below.

Table 1. Electrolytic TEMPO-mediated oxidation of benzyl alcohol in CH_3CN/0.1 M aqueous buffer (1:1).



1a 2a

Entry	pH[a]	*T* [°C]	Conversion[e] [%]	Yield of **2a**[e] [%]	Selectivity[f] [%]
1	10.2[b]	22	71	71	100
2	11.2[c]	22	75	65	87
3	11.7[d]	22	82	61	74
4	10.2[b]	25	76	76	100
5	10.2[b]	30	85	81	95
6	10.2[b]	35	88	73	83
7	10.2[b]	50	88	70	80

[a] Measured pH of reaction mixture. [b] pH 9.16, buffer/CH_3CN (1:1), BnOH (0.1 M), TEMPO (0.03 M). [c] pH 10.14, buffer/CH_3CN (1:1), BnOH (0.1 M), TEMPO (0.03 M). [d] pH 10.83, buffer/CH_3CN (1:1), BnOH (0.1 M), TEMPO (0.03 M). [e] Yield and conversion were determined by using GC against calibration curves of BnOH and benzaldehyde. [f] Yield based on recovered BnOH.

In many media, cyclic voltammograms have been reported to show that TEMPO undergoes a reversible single-electron oxidation to the corresponding oxoammonium ion **4**.[6,7d,f] It has also been shown that in the presence of alcohols, the anodic peak becomes irreversible; a small catalytic current is observed, and the current density for the mediated oxidation of the alcohol can be increased by the addition of a base.

In this work, cyclic voltammetry at a glassy carbon disc electrode (area 0.07 cm^2) was used to select the appropriate pH for the electrosyntheses in the microflow cell. A cyclic voltammogram recorded at 22 °C for TEMPO (2 mM) alone in *t*BuOH/H_2O (1:1) at pH 9.2 shows all the characteristics of a reversible single-electron oxidation [curve (a), Figure 2]. Curves (b)–(e) are the voltammograms for solutions containing TEMPO (2 mM)

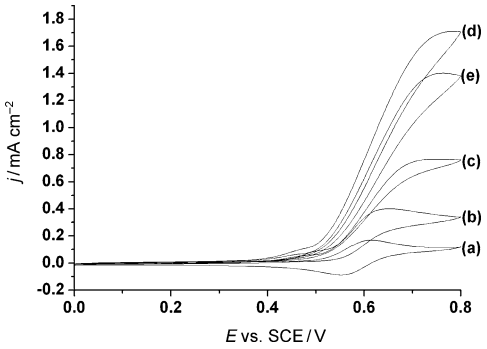


Figure 2. Cyclic voltammograms for solutions of TEMPO (2 mM) in *t*BuOH/H_2O containing Na_2CO_3/$NaHCO_3$ at a scan rate of 50 mV s^{-1} at 22 °C. (a) pH 9.2 without added BnOH; (b) pH 9.2, BnOH (16 mM); (c) pH 10.6, BnOH (16 mM); (d) pH 11.5, BnOH (16 mM); (e) pH 11.6, BnOH (16 mM).[14]

and benzyl alcohol (BnOH, 16 mM) at four pH values in the range 9.2–11.6. In voltammograms (b)–(e), there is no cathodic peak for the reduction of the oxoammonium ion on the reverse scan, which confirms a chemical reaction of the oxoammonium ion with the alcohol. Also, the anodic peak for the oxidation of TEMPO in the presence of BnOH has become a sigmoidal wave, where the limiting currents are significantly larger than the anodic peak in the absence of alcohol. Such responses are characteristic of a mediated oxidation of the alcohol, for which the catalytic cycle leading to the regeneration of the electroactive species is relatively slow. Certainly, the limiting currents are low compared to that estimated for the mass transport-controlled oxidation of the alcohol, if the mass transfer coefficient used was measured using the reduction of ferricyanide as the model reaction.[10] The key observation from Figure 2, however, is that the limiting current increases with increasing pH, and the variation is a factor of five (Figure 3). This represents a significant increase in the turnover rate of the TEMPO catalyst and, hence, formation of aldehyde product, and this is important in the context of microflow electrolysis.

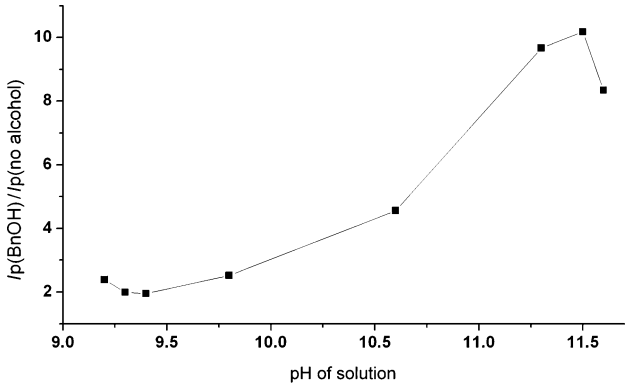


Figure 3. Graph showing the effect of the pH value on the peak current for the electrochemical TEMPO-mediated oxidation of BnOH in *t*BuOH/H_2O.

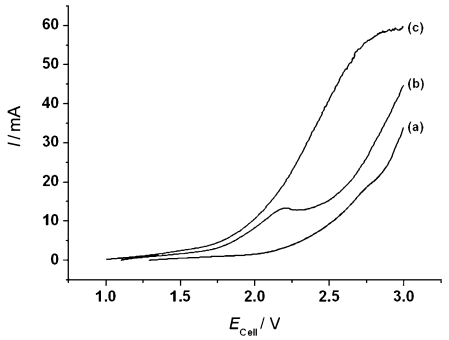


Figure 4. Cell current vs. cell voltage curves in the microflow cell for (a) *t*BuOH/H_2O containing Na_2CO_3/$NaHCO_3$, pH 11.5, after the addition of (b) TEMPO (30 mM), and (c) TEMPO (30 mM) and BnOH (100 mM). Temperature: 298 K. Solution flow rate: 0.1 mL min^{-1}.

For a faster catalytic cycle, a shorter channel will suffice to give high conversion. Inspection of Figure 3 also implies that the highest rate for the oxidation of BnOH occurs at pH 11.5, which is the pH value used in most electrosyntheses. A similar pattern is observed for the cyclohexanol/TEMPO system. A comparable trend in the kinetics of the catalytic cycle with pH was reported by Yamauchi et al. using a fully aqueous system.[16] However, they used lower concentrations of TEMPO and alcohols and failed to recognise that at pH 13, the reaction of the oxoammonium ion with hydroxide, is fast compared to that with low concentrations of alcohol.[17]

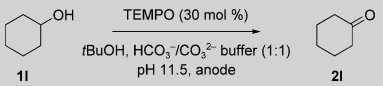
The influence of temperature was also determined by using cyclic voltammetry. Voltammograms were recorded for TEMPO (2 mM) and BnOH (16 mM) at pH 11.5. Over the temperature range 24–45 °C, the limiting current increased by a factor of 6.

Cell current vs. cell voltage plots were recorded directly in the microflow cell. Although these remain instructive, it is important to recognise that these are not traditional voltammograms: the current vs. potential response will vary along the channel as the concentrations of TEMPO and alcohol change, and the current will decrease towards zero as the exit is approached if a full conversion is achieved. Hence, the responses are the integral of the currents along the channel plotted as a function of applied cell voltage.

Such current vs. cell voltage responses (Figure 4) were recorded in the microflow cell for (a) a solution of the *t*BuOH/H_2O containing buffer, pH 11.5; (b) the buffer solution also containing 30 mM TEMPO; and (c) the buffer solution also containing 30 mM TEMPO+100 mM BnOH. In each case, the electrolyses were allowed to proceed for approximately 120 s prior to recording the responses to achieve a steady state distribution of both TEMPO and alcohol along the flow channel before the cell current vs. cell voltage response was obtained by varying the cell voltage at a rate of 25 mV s^{-1}. In this experiment, the responses were recorded for a flow rate of 0.1 mL min^{-1} and a temperature of 25 °C. In the absence of TEMPO, no current is observed until the cell voltage reaches 2.5 V, when oxygen evolution commences and thereafter, with further increase in cell voltage, the current increases steeply. When TEMPO is present in solution, a well-formed oxidation wave is observed at a cell voltage of approximately 2 V, and this corresponds to the oxidation of TEMPO to the oxoammonium ion. With the solution containing both TEMPO and BnOH, the wave at 2.0 V has an increased limiting current (from 14 to 58 mA) resulting from the regeneration of TEMPO by reaction with the alcohol. The oxidation wave is, however, drawn out along the cell voltage axis due to the unavoidable IR drop in this two electrode cell, as well as the overpotentials at the two electrodes. In further experiments, the limiting current increased with an increase in either (a) solution flow rate or (b) temperature. Hence, these experimental parameters may be used with other alcohols to achieve full conversions in preparative electrolyses when the rate of the TEMPO-mediated oxidation is lower.

Preparative electrolyses were performed by applying a constant current below the limiting current seen in the above current vs. voltage experiments to achieve a high current efficiency; for example, for electrolyses with a flow rate of 0.1 mL min^{-1} at 25 °C, the cell current was 20 mA. Further experimental support for operating the cell at a constant current of 20 mA can be seen for a series of oxidations of cyclohexanol (**1l**), for which a good balance of conversion and selectivity was achieved (entry 2, Table 2).[18] Conversion is dependent on the passage of charge, and at 10 mA a correspondingly low conversion was obtained (entry 1, Table 2), whereas at higher currents decreased yields and selectivities were observed (en-

Table 2. Influence of current on the conversion and selectivity for the TEMPO-mediated oxidation of cyclohexanol measured at a constant flow rate.[a]



1l 2l

Entry	Current [mA±5 mA]	Conversion[b] [%]	Yield of **2l**[b] [%]	Selectivity[c] [%]
1	10	54	41	76
2	20	86	85	99
3	30	82	72	88
4	40	89	72	81

[a] Reagents and conditions: flow rate = 0.1 mL min^{-1}, 25 °C, *t*BuOH, $NaHCO_3$/Na_2CO_3 buffer solution (pH 11.5). [b] Yield and conversion were determined by using GC against calibration curves of cyclohexanol and cyclohexanone. [c] Yield based on unreacted cyclohexanol.

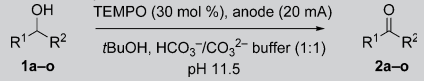
tries 3 and 4, Table 2), suggesting the occurrence of competing reactions as the current is increased. At pH 11.5, the temperature had a modest influence on the conversion and selectivity, and further oxidations were performed at 25 °C. However, secondary aliphatic alcohols are known to be more difficult to oxidise in TEMPO-mediated systems;[4] here, cyclohexanone is produced in 85% yield and 99% selectivity.

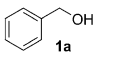
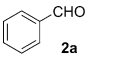
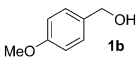
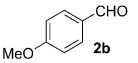
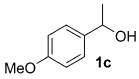
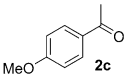
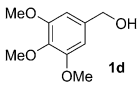
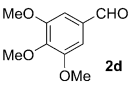
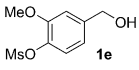
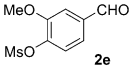
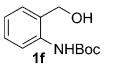
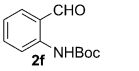
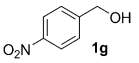
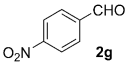
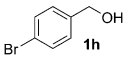
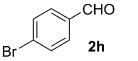
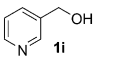
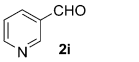
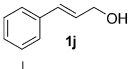
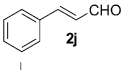
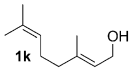
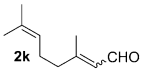
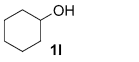
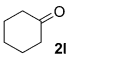
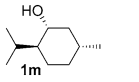
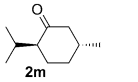
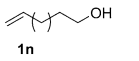
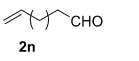
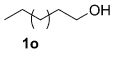
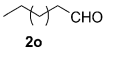
Under the same conditions, benzyl alcohol was oxidised to benzaldehyde in 87% yield and 98% conversion (entry 1, Table 3). 30 mol% of TEMPO was required to achieve a favourable rate of product formation (30–100 mg h^{-1}), conversion, and selectivity for the TEMPO-mediated oxidation of benzyl alcohol in the flow cell. Reducing the amount of TEMPO led to lower conversions and selectivities at the same current and flow rate. The decreased selectivity observed at lower TEMPO loading is likely to be a consequence of the observed increase in cell potential under these conditions. Approximately 60% of the catalyst could be recovered at the end of the reaction, and future work will focus on the identification of nitroxyl radical-mediated systems that may operate at lower catalyst loadings, and/or facilitate catalyst recovery. Alternatively, high rates of conversion and selectivity may be achieved at lower TEMPO loadings by using a microfluidic cell with a longer path length (increased electrode area).

A range of primary and secondary alcohols were oxidised under the preferred conditions (see Table 3). In general, benzylic and allylic alcohols are more easily oxidised. Despite the slower chemistry,[4] secondary alcohols were also oxidised with high conversion and selectivity. In particular, more electron-rich benzylic alcohols were oxidised very efficiently in the flow cell with excellent yields and selectivities. The more sterically hindered and electron-poor benzylic alcohols (entries 6 and 7, Table 3, respectively) show lower conversion, but still high selectivities (100 and 85%, respectively). Examples of substrates containing other electrochemically active functionalities were also included in our study. Although reduced selectivities were observed for the oxidation of compounds **1g–i** (entries 7–9, Table 3), their corresponding aldehydes **2g–i** were obtained in acceptable isolated yields. The nitro and halogen groups present in **1g** and **1h,** respectively, may react at the cathode in an undivided cell such as this, although no other products were isolated from the reactions. The benzylic alcohol **1e** containing a methanesulfonate ester was oxidised with high selectivity at 81% conversion (entry 5, Table 3).

Allylic alcohols **1j** and **1k** (entries 10 and 11, Table 3) were oxidised in 77 and 72% yields, with excellent selectivities for aldehyde products, whereas aliphatic alcohols, with the exception of cyclohexanol (**1l**, entry 12, Table 3), were slower to oxidise under these conditions (entries 14 and 15, Table 3). Generally, the selectivity remained excellent, with only traces of the corresponding carboxylic acids observed during the oxidation of aliphatic alcohols **1n** and **1o**. The conversion of (−)-menthol (**1m**), a particularly hindered secondary alcohol, not surprisingly showed poor conversion to the respective ketone **2m** (entry 13, Table 3). Current efficiencies were commonly approaching 100%, although for a few alcohols that were oxidised more slowly the current efficiency dropped to 40–60%.

Table 3. TEMPO-mediated oxidation of a range of primary and secondary alcohols in the electrolysis flow cell.[a]



Entry	Alcohol	Product	Conv.[b] [%]	Yield[b] [%]	Selectivity[c] [%]
1			98%[d]	87[d]	89
2			88%	88	100
3			100%	92	92
4			94%	94	100
5			81%	81	100
6			60%	60	100
7			59%	50	85
8			79%	68	85
9			68%	50	50
10			80%	77	96
11			73%	72[e]	99
12			86%[d]	85[d]	99
13			29%	21	72
14			52%	48	92
15			62%	57	92

[a] Conditions: flow rate = 0.1 mL min^{-1}, 20 mA (±5 mA), ROH (0.1 M), TEMPO (0.03 M), 25 °C. [b] Yields are reported for purified isolated products. Conversions are based on isolated recovered starting material. [c] Yield based on recovered starting material. [d] Yield and conversion were determined by using GC. [e] Olefin isomerisation was observed [ratio (*E*/*Z*) = 1.8:1, ^{1}H NMR spectroscopy].

Increasing the residence time in the electrolysis cell by reducing the flow rate to 0.05 mL min^{-1} led to reduced selectivities at the same current (20 mA), with overoxidation to the corresponding acids becoming more prominent for alcohols **1f**, **1n** and **1o**. A higher yield of ketone **2m** could be achieved in this manner (38%), but the selectivity of the reaction was reduced significantly. This can be understood by the rate-limiting reaction of the alcohol with oxoammonium ion **4**; an increase in total cell potential was observed, extending into the range, where side reactions become more prevalent as was evident from the cell current vs. cell voltage studies described above

(Figure 4). Despite the slightly lower conversion for some of the examples, the oxidation protocol allows for the production of approximately 30–100 mg of aldehyde or ketone per hour, depending on the substrate. The reactions do not require added tetraalkylammonium salts as electrolyte and are very clean, with generally only starting material and catalyst present in crude reaction mixtures in addition to the desired product.

Conclusions

An electrocatalytic TEMPO-mediated process has been developed for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, in a microfluidic electrolysis cell. This alcohol oxidation allows a mild and convenient laboratory scale synthesis in an aqueous *t*BuOH system at ambient temperature. The scope of the process has been evaluated through the oxidation of 15 representative alcohols, many of which delivered high conversions and selectivities in a single pass through the cell.

Experimental Section

The microfluidic electrolytic cell was supplied by Syrris Ltd[19] and was intended for application alongside its range of microflow equipment. In consequence, the cell holder had similar dimensions, solution connections, etc. to other Syrris microreactors. The electrolysis cell was constructed from two rectangular electrode plates (5.3 cm × 4.0 cm × 0.2 cm thick). The anode was carbon-filled polyvinylidene fluoride (PVDF, type BMA5, Wilhelm Eisenhuth GmbH, Germany, electrical resistivity in plane 180 $\mu\Omega\,m^{-1}$), and the cathode was stainless steel (grade 316 L, Castle Metals UK Ltd). The perfluoroelastomer (FFKM, TRPlast 330B, 500 μm thick) spacer had a 'snaking', microchannel of designed pattern cut into it to give an extended channel length and to enhance the convection within the channel. The steel electrode had a patterned, recessed channel (depth 250 μm) machined into it to allow it to accept the patterned spacer and thereby permit facile alignment of the inter-electrode spacer; it also incorporated two fluid inlet/outlet holes. The design provided a channel path length of 70 cm, combined with a channel depth of approximately 200 μm (with the spacer fitted into the recessed channel of the electrode and the cell compressed) and a channel width of 0.15 cm, giving a cell volume of approximately 0.21 cm^3. The total electrode surface area in contact with the fluid was 10.5 cm^2 per electrode. The pumps and sample injection loop were supplied by Syrris (FRX), and the pumps could deliver 0.01–9.99 $cm^3\,min^{-1}$ with an accuracy of 1%.

General Procedure for Oxidation Reactions

3,4,5-Trimethoxybenzaldehyde (**2d**): A solution of the alcohol **1d** (100 mg, 0.50 mmol) and TEMPO (23 mg, 0.15 mmol) in *t*BuOH (2.5 mL) and aqueous buffer solution [Na_2CO_3 (0.1 M)/$NaHCO_3$ (0.1 M) = 8:2; 2.5 mL) was passed through the electrolytic cell at a flow rate of 0.1 $mL\,min^{-1}$. The electrolysis was performed under a constant current of approximately 20 mA, and the cell temperature was maintained at 25 °C. The reaction solution was collected, 2 M HCl (10 mL) was added, and the resulting mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by performing flash column chromatography on silica gel (eluent EtOAc/hexane = 1:4) affording the title compound **2d** (92 mg, 47 mmol 94%) as a colourless solid. Physical and spectroscopic data were consistent with reported values.[20] m.p. 74–75 °C (lit.[20] 71–72 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.87 (s; 1H, CH), 7.13 (s; 2H, CH), 3.94 (s; 3H, OCH_3), 3.94 ppm (s; 6H, 2× OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 191.0 (C=O), 153.6 (2× C), 143.6 (C), 131.7 (C), 106.7 (2×CH), 61.0 (CH_3), 56.3 ppm (2× CH_3); IR (Neat): $\tilde{\nu}_{max}$ = 1681 cm^{-1} (C=O). Additionally, alcohol **1d** (6 mg, 0.03 mmol, 6%) was recovered.

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Keywords: alcohols · aldehydes · electrolysis · flow chemistry · oxidation

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[9] Other nitroxyl radicals were evaluated, but under the conditions described proved less effective than TEMPO.

[10] A comprehensive study on the cell performance will be reported elsewhere.

[11] An in depth discussion of the effect of gas bubbles on the performance of the electrolytic flow cell is outside the scope of the current article and will be published separately.

[12] In an effort to develop an accessible system, a less expensive power supply was used for the experiments as opposed to a more expensive potentiostat. Consequently, there is an inherent error in the reported current as a result of the accuracy of the unit.

[13] Sodium carbonate/bicarbonate buffer solutions were made up according to Delroy: G. E. Delory, *Biochem. J.* **1945**, *39*, 245 – 245. Details are provided in the Supporting Information.

[14] The reported pH values for the reaction mixtures were measured by using a pH meter.

[15] A recently published green chemistry solvent guide classifies acetonitrile as a "useable" solvent, whereas *t*BuOH is considered to be a "preferred" solvent on the basis of safety and environmental considerations (see Ref. [4f]).

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[17] An in depth discussion of the mechanism of the TEMPO oxidation will be reported elsewhere.

[18] Although there is a significant error in the applied current and the use of a more sensitive power supply may allow for a more accurate determination of the optimal current, it was considered that the overall effect on the efficiency of the reaction would be very small. As a result, no further current dependency studies were conducted.

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