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N-Heterocyclic Carbene-Mediated Oxidative Electrosynthesis of Esters in a Microflow Cell

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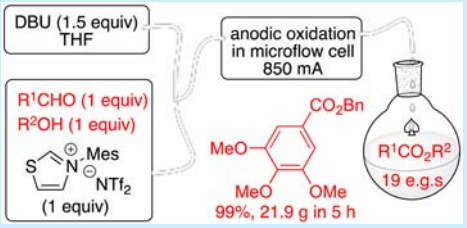
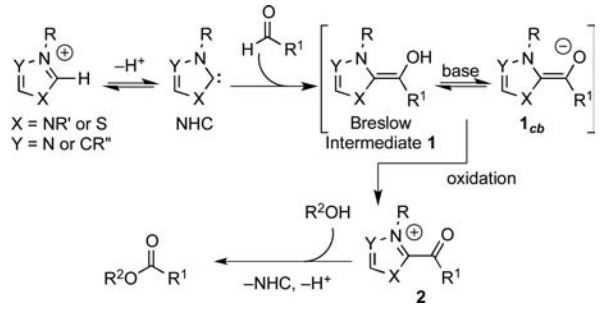
Supporting Information

ABSTRACT: An efficient N-heterocyclic carbene (NHC)-mediated oxidative esterification of aldehydes has been achieved in an undivided microfluidic electrolysis cell at ambient temperature. Productivities of up to 4.3 g h^{-1} in a single pass are demonstrated, with excellent yields and conversions for 19 examples presented. Notably, the oxidative acylation reactions were shown to proceed with a 1:1 stoichiometry of aldehyde and alcohol (for primary alcohols), with remarkably short residence times in the electrolysis cell (<13 s), and without added electrolyte.



Esters are ubiquitous in natural and synthetic organic molecules and materials, with applications spanning all areas of science, engineering and medicine. Despite the success of traditional synthetic approaches to esters through carboxylate activation,[1] substantial effort has been devoted to alternative methodologies, particularly those that may increase atom efficiency, avoid toxic reagents, reduce waste, and occur under mild conditions.[2] N-Heterocyclic carbenes (NHCs) have been identified as powerful organic catalysts for a range of reactions, including the oxidative conversion of aldehydes to esters (Scheme 1).[3] The majority of NHC-mediated oxidative esterification reactions require the addition of external stoichiometric chemical oxidant or utilize a substrate containing an internal redox system (e.g., halide or alkene),[4] to transform Breslow intermediate **1** to activated acyl species **2**. Intermediate **2** then reacts with an alcohol, typically in stoichiometric excess, to afford an ester. Anodic oxidation was first applied to the conversion of **1** to **2** by Diederich and co-workers, who reported a thiazolium/flavin dual-catalyst electrochemical conversion of aldehydes to methyl esters in batch.[5] More recently, Finney et al.[6] disclosed a direct electrochemical NHC-catalyzed synthesis of esters from aldehydes in an undivided batch cell.

Scheme 1. NHC-Mediated Oxidative Esterification of Aldehydes



Microfluidic electrolysis cells provide a simple-to-use platform for electrosynthesis, and with appropriate channel design, they can lead to improved mass transfer at the electrode surface and increased productivity compared with batch reactors.[7] We have described an undivided microfluidic cell wherein high conversions can be achieved in a single pass at rates of product formation commensurate with preparative application.[8,9] Here we report an NHC-promoted oxidative esterification of aldehydes in an undivided electrochemical flow cell that delivers high rates of product formation and excellent yields in many cases.

The oxidative esterification of methyl 4-formylbenzoate (**4**) with MeOH was selected as a trial reaction (Figure 1). The optimized conditions consisted of in-flow mixing of two

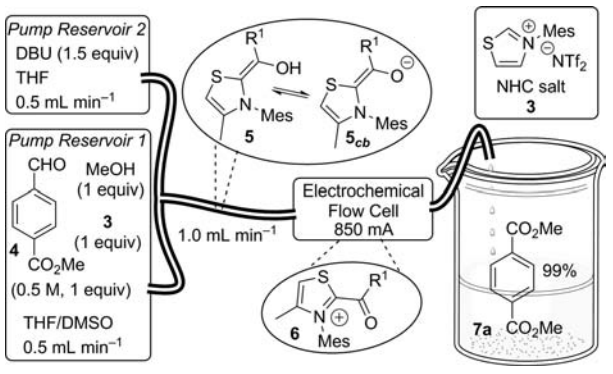


Figure 1. Schematic of the flow arrangement used for the oxidative esterification of aldehydes.

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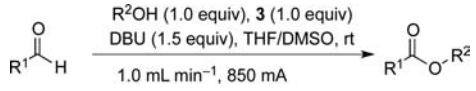
solution streams to generate reactive intermediates: reservoir 1 contained aldehyde **4** (1 equiv), MeOH (1 equiv), thiazolium salt **3** (1 equiv), and DMSO (5 equiv) in THF, and reservoir 2 contained 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 equiv) in THF. Each solution flowed at 0.5 mL min^{-1} into a mixing T-piece, whereupon a change in color of the exiting solution to red indicated the formation of Breslow intermediate **5**/conjugate base $\mathbf{5}_{cb}$. Passage through the undivided electrolysis cell with a current of 850 mA resulted in oxidation of $\mathbf{5}_{cb}$ to acylthiazolium **6**,[10] which reacted with MeOH to give methyl ester **7a** in excellent yield (99%) at a high rate of productivity (2.9 g h^{-1}).

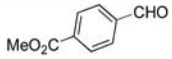
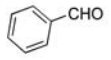
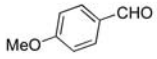
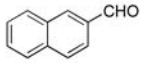
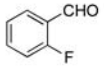
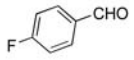
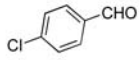
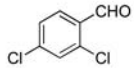
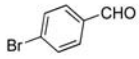
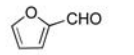
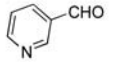
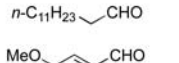
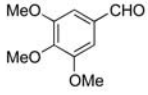
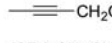
The optimized conditions were then applied to a range of aldehydes and alcohols (Table 1). In many cases, isolated yields in excess of 90% were realized, with productivities of up to 4.3 g h^{-1} and current efficiencies in the range of 80−100%. Examples include electron-rich and electron-poor aromatic aldehydes as well as heteroaromatic substrates reacting in equimolar ratios with primary alcohols such as MeOH, BnOH, *n*-BuOH, and but-2-yn-1-ol. Oxidative esterification of an enolizable aliphatic aldehyde was demonstrated through the formation of benzyl dodecanoate (**7l**). Secondary alcohols (*i*-PrOH, *i*-BuOH) returned higher yields of the corresponding esters **7r** (82%) and **7s** (62%) when used in excess (5 equiv). The electron-deficient secondary alcohol hexafluoroisopropanol afforded the corresponding benzoate **7q** in reduced yield, and the result was little influenced by the alcohol stoichiometry. For this example, the current efficiency was also low, indicative of other competing electrochemistry.

The optimization of the conditions to achieve high conversions and productivities in a single pass of the electrochemical microflow reactor was informed by a combination of approaches. For oxidative esterification of aldehyde **4** with MeOH, design of experiment identified that no benefit was gained from using MeOH in stoichiometric excess, while 5 equiv of DMSO improved the solubility of thiazolium salt **3** and the resulting yields.[11] The use of bistriflimide (Tf_2N^-) as the counterion in **3** was important in achieving reproducibility compared with others such as BF_4^-. We believe that this is due to the increased hydrophobicity of bistriflimide salt **3** and its reduced tendency to absorb moisture during manipulation and storage.

The significance of the loading of DBU on the success of the reaction is illustrated in a collection of cyclic voltammograms (CVs) with progressively increased loadings of DBU (Figure 2). The electrochemical oxidation of Breslow intermediates has been reported to involve two reversible single-electron transfers ($\mathbf{5}_{cb} \rightarrow \mathbf{9} \rightarrow \mathbf{10}$; Figure 3),[6a,12] which are observed as two well-formed peaks in the CVs when an excess of DBU is present (pink and green lines). These peaks are not visible when substoichiometric loadings of DBU are present (red and black lines). The CV data are also consistent with the results of the synthetic experiments, where the yields improved up to 1.5 equiv of DBU. A control experiment where thiazolium salt **3** was absent (with Et_4NBF_4 added as an electrolyte) showed only recovered starting materials. For electrolyses in undivided cells, it is also important to consider the reaction at the counter electrode. In the present case, hydrogen gas is produced by cathodic reduction of protic species in the medium (e.g., $MeOH/[DBUH]^+ \rightarrow MeO^-/DBU + {}^1/_2H_2$), which compensates for protons generated in the anodic electrochemistry that would otherwise reduce the concentration of $\mathbf{5}_{cb}$ as the reaction progressed.

Table 1. NHC-Mediated Electrochemical Oxidative Esterification of Aldehydes[a,b]



entry	R^1CHO	R^2OH	yield of **7a–s**[c] [productivity][d]
1		Me−OH	**7a**, 99%, [2.9 g h^{-1}]
2		Bn−OH	**7b**, 89%, [2.8 g h^{-1}]
3		Bn−OH	**7c**, 94%, [3.4 g h^{-1}]
4		Bn−OH	**7d**, 95%, [3.7 g h^{-1}]
5		Bn−OH	**7e**, 93%, [3.2 g h^{-1}]
6		Bn−OH	**7f**, 93%, [3.2 g h^{-1}]
7		Bn−OH	**7g**, 94%, [3.5 g h^{-1}]
8		Me−OH	**7h**, 90%, [2.8 g h^{-1}]
9		Bn−OH	**7i**, 95%, [4.1 g h^{-1}]
10		Bn−OH	**7j**, 91%, [2.8 g h^{-1}]
11		Bn−OH	**7k**, 96%, [3.1 g h^{-1}]
12		Bn−OH	**7l**, 76%, [3.3 g h^{-1}]
13		Bn−OH	**7m**, 94%, [4.3 g h^{-1}]
14		Me−OH	**7n**, 92%, [3.1 g h^{-1}]
15		*n*-Pr−OH	**7o**, 86%, [3.3 g h^{-1}]
16			**7p**, 88%, [3.5 g h^{-1}]
17		$(CF_3)_2CH-OH$	**7q**, 39%, [1.5 g h^{-1}][e,f]
18		*i*-Pr−OH	**7r**, 82%, [3.1 g h^{-1}][e]
19		*i*-Bu−OH	**7s**, 68%, [2.7 g h^{-1}][e,g]

[a]Reactions were performed on 2.5 mmol scale. [b]The flow rate of 1.0 mL min^{-1} is the total flow rate through the electrochemical cell from mixing of two flow streams of 0.5 mL min^{-1} to form Breslow intermediates in situ. [c]Yields of purified isolated materials. [d]Productivities are based upon isolated yields from 10 mL of solution (10 min). [e]5.0 equiv of alcohol was added. [f]The yield was 44% with 1 equiv of $(CF_3)_2CHOH$. [g]The yield was 45% with 1 equiv of *i*-BuOH.

We recently reported on the application of a simple plug-flow model for use in the microflow electrosynthesis cell,[13] which allows estimation of the conversion at a given flow rate and calculation of the current required to achieve this when the mass transfer properties of the reactor are known.[14] Application of this model showed that significantly improved productivities were achieved at higher flow rates when coupled with an increased current sufficient to drive the oxidation (Table 2). In the present case, the isolated yields were also found to substantially increase under conditions of higher current and

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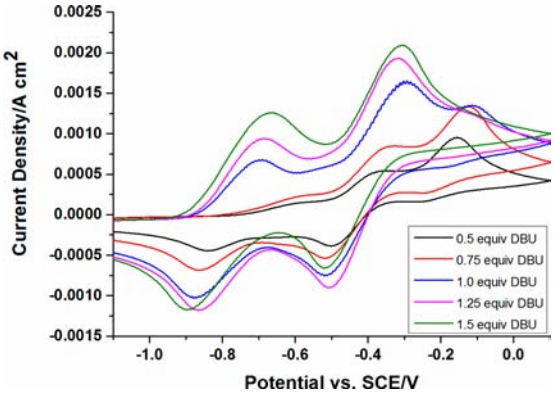

Figure 2. Cyclic voltammograms for the oxidation of Breslow intermediate **5** (R^1 = *p*-fluorophenyl) with different loadings of DBU. Conditions: thiazolium salt **3** (0.1 M), *p*-fluorobenzaldehyde (0.2 M), DBU (varied), tetrabutylammonium tetrafluoroborate (0.2 M), scan rate 100 mV s^{-1}, rt.

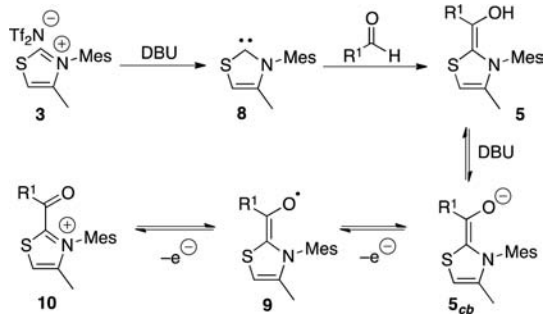

Figure 3. Formation and anodic oxidation of Breslow intermediate **5**.

Table 2. Influence of Concentration, Flow Rate, and Current upon the Productivity and Yield of Ester 7a[a]

entry	conc. (M)[b]	flow rate (mL min^{-1})	current (mA)	yield of 7a[c] [productivity][d]
1	0.1	0.1	16	80% [0.05 g h^{-1}]
2	0.5	0.1	80	89% [0.26 g h^{-1}]
3	0.5	1.0	850	99% [2.9 g h^{-1}]

[a]Reactions were performed on 0.5−2.5 mmol scale. [b]Concentration of **4** in THF/DMSO. [c]Yields of purified isolated materials. [d]Productivities are based upon isolated yields from 10 mL of solution (10 min).

flow rate. The observed increase in yield may be a consequence of a shorter residence time between T-piece mixing and oxidation of the reactive intermediate $\mathbf{5}_{cb}$ in the flow cell.

The total volume of the electrochemical flow cell is ~210 μL, leading to a residence time for the reaction mixture of <13 s (not allowing for H_2 gas evolution in the cell). These very short residence times at higher flow rates coupled with the high productivity rates of ester formation highlight the excellent mass transport characteristics of the cell. We have previously noted that hydrogen evolution, even at substantial rates, can also improve the conversion efficiency in the microfluidic electrolysis cell, which we attribute to increased turbulence and mass transfer at the electrode.[13] Even under conditions of high flow rate, where reactive intermediates are only briefly exposed to the electrodes, some modest turnover of NHC **8** was possible: reducing the loading of thiazolium salt **3** to 50 and 20 mol % afforded isolated yields of 76% and 40%, respectively, for **7i**. Furthermore, the potential to recycle the NHC/DBU solution was investigated by resubmitting a crude product solution to the flow electrolysis with the addition of a second equivalent of alcohol and aldehyde. In the case of benzyl ester **7m**, a combined, unoptimized yield of 78% was obtained.

An additional benefit of conducting electrosynthesis in flow is the ability to simply extend the run time in order to produce additional material, avoiding the requirement for a larger reactor. Therefore, to highlight the preparative value and scalability of the oxidative esterification in the microfluidic cell, the electrolysis was performed for an extended period of 5 h, yielding 21.9 g of **7m** (96%) and a productivity rate of 4.4 g h^{-1} with no significant degradation or fouling of the electrodes.

In conclusion, we have described an NHC-promoted oxidative esterification of aldehydes in an undivided electrochemical flow cell. In many cases, excellent yields and high productivity rates (up to 4.3 g h^{-1}) were achieved with high current efficiencies and selectivities using a single equivalent of alcohol. The very short residence times required for oxidation in the electrochemical cell highlight its excellent mass transfer characteristics, and the advantages of performing the reaction in flow were further demonstrated through the synthesis of >20 g of ester **7m**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and procedures, design of experiment, compound characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01459.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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(9) A closely related cell is available commercially and has been applied by others in electrosyntheses. For examples, see: (a) Roth, G.; Stalder, R.; Long, T.; Sauer, D.; Djuric, S. *J. Flow Chem.* **2013**, *3*, 34. (b) Stalder, R.; Roth, G. P. *ACS Med. Chem. Lett.* **2013**, *4*, 1119. (c) Kabeshov, M. A.; Musio, B.; Murray, P. R. D.; Browne, D. L.; Ley, S. V. *Org. Lett.* **2014**, *16*, 4618.

(10) The cell current varied during the course of the experiment: at the start of the run, the current increased from 0 to 850 mA as the channel filled with electroactive species, and then it decreased at the end of the run as the channel refilled with solvent. At steady state, the cell current was 850 mA.

(11) For details of the design of experiment, see the Supporting Information.

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(13) Green, R. A.; Brown, R. C. D.; Pletcher, D. *J. Flow Chem.* **2015**, *5*, 31.

(14) The mass transport characteristics of the electrochemical flow cell are described in ref 8a.

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