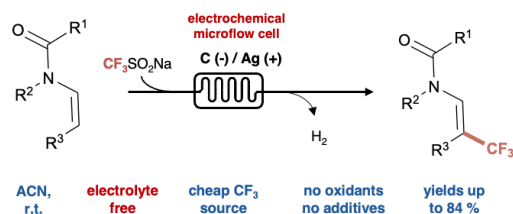


Electrochemical trifluoromethylation of enamides under microflow conditions

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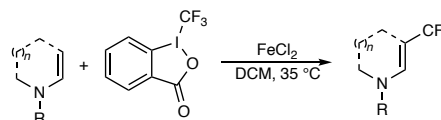


ABSTRACT: The development of sustainable trifluoromethylations of enamides is of great interest to the pharmaceutical industry. Herein, we demonstrate a sustainable direct electrochemical trifluoromethylation method in a microflow cell, using Langlois reagent, without the need of a supporting electrolyte, oxidants or any additive under mild conditions. This method can be applied to various substrates with a yield up to 84%.

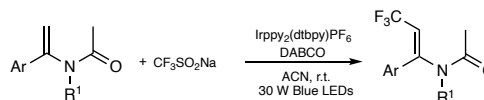
The synthesis of trifluoromethylated compounds is a long-standing objective in organic chemistry due to their significant applications in agrochemicals and pharmaceuticals, comprising about 20% of the marketed drugs.¹⁻⁸ The introducing of fluorinated groups can enhance the drug's acidity, lipophilicity and metabolic stability.⁹ Additionally, functionalized enamides, found in numerous natural products,¹⁰ and pharmaceuticals,^{11,12} are key building blocks for complex amino derivatives.¹³⁻¹⁶ They offer greater stability and reduced reactivity compared to enamines due to the electron-withdrawing *N*-acyl group.^{13, 15, 17} Several approaches to synthesize trifluoromethylated enamides are documented in the literature. Togni's reagent was used in combination with copper catalysis by the Loh group¹⁸, and with iron catalysis by the Gillaizeau group.¹⁹ The Masson group demonstrated photoredox oxytrifluoromethylation of enecarbamates using Togni's reagent in the presence of a photocatalyst.²⁰ The Yang group developed visible-light promoted olefinic trifluoromethylation of enamides by Langlois' reagent in the presence of a photocatalyst and DABCO.²¹ The Yu group introduced visible-light promoted trifluoromethylation using Umemoto's reagent in the presence of a photocatalyst,²² and without photocatalyst in the presence of a base.¹¹ Nevertheless, all these methods employed high-cost or unstable trifluoromethylating reagents, additional metal catalysts, photocatalysts or oxidants. Thus, alternative methods towards direct trifluoromethylation of enamides are desirable, with an electrochemical approach being particularly promising.²³ A series of significant trifluoromethylation methodologies using electrochemistry²⁴ and Langlois reagent (LR) has been developed, for instance trifluoromethylation of unactivated alkenes,²⁵ quinolinones,²⁶ 2-pyridones,²⁷ and allylic alcohols.²⁸ However, a direct trifluoromethylation of enamides remains challenging. Interestingly, a

Scheme 1: Recent representative examples of trifluoromethylation of enamides

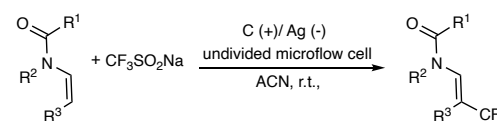
1) Iron-catalyzed trifluoromethylation of enamides (2016):



2) Visible-light-promoted trifluoromethylation of enamides (2021):



This work:



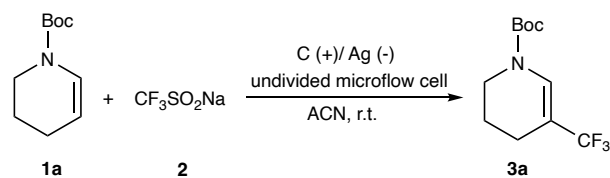
double functionalisation of enamides is more feasible when the trifluoromethylated carbocation intermediate is attacked by a nucleophile.²⁹⁻³¹ For instance, in the presence of water, an oxytrifluoromethylation product can be obtained³² and with an alcohol, the corresponding alkoxytrifluoromethylation product can be formed.³³ The Luo group demonstrated the difficulty of direct trifluoromethylation with a method involving H₂SO₄ in DMF in an electrochemical batch reactor and based on *N*-benzyl-*N*-(1-phenylvinyl) acetamides.³⁴ Earlier this year, Chausset-Boissarie group reported the trifluoromethylation of enamides

by LR with a supporting electrolyte with poor yields and a limited scope.³³

The challenges stem from LR's and the formed sodium salts limited solubility in the organic solvents which hinder the double functionalisation and have a large electrochemical potential window, such as ACN. This results in a decrease in yield, especially due to electrode passivation when no additional solvent, e.g. MeOH or water is used. We present a straightforward method for direct trifluoromethylation of enamides in a microflow cell, eliminating the need for a supporting electrolyte or additives due to the small interelectrode distance within the cell. This approach reduces waste and simplifies product purification, making electrolyte-free electrochemical synthesis highly desirable yet underexplored.^{27, 35-39}

We started our study with model substrate **1a** and LR (**2**), aiming to optimise reaction conditions in an undivided microflow cell (Table 1). The initial reaction in ACN with 3 equiv. of **2**, graphite electrodes, constant current (cc) 10 mA ($j = 1.5 \text{ mA/cm}^2$) and a flow rate of 155 $\mu\text{L/min}$, corresponding to a residence time of 52 s and an applied charge of 2 F resulting in a moderate yield (entry 1), which also proved to be an optimal production rate (for detail information see ESI: Table 1). Adding a supporting electrolyte (LiClO_4 , entry 2) even reduced the yield. Increasing the channel height (larger interelectrode distance) compared to the initial one (54 μm vs. 127 μm), while keeping the applied charge constant, slightly decreased the yield (entry 3). Since LR precipitated in the syringe, we next used 2 equiv. of **2** (entry 4) which led to an increase in yield. Further decreasing the equiv. of LR decreased further the yield (entries 5 and 6). Increasing the applied charge to 2.5 F (entry 7) did not affect the yield, while a higher applied charge of 3 F (entry 8) led to a decrease in yield, as did applying a lower charge of 1.5 F (entry 9). Evaluating various solvents showed that in HFIP (entry 7) just traces of product were detected, while other solvent mixtures (entry 8-11) failed, as they led to yield decrease and several side products. The reaction proceeded best in ACN, but electrode fouling was observed on the cathode (see the ESI, Figure 1). Alternating and rapid alternating polarity were evaluated as strategies to prevent fouling.⁴⁰ Although these methods reduced electrode fouling, evaluated by measuring electrode weights before and after the reaction (see the ESI, Table 5 for details), yields dropped significantly, with mostly starting product present in the reaction mixture (entry 15-17). This drop in yield is likely due to the high electrode capacitance of graphite, where electricity is consumed by charge-discharge cycles of the electrical double layer.^{40, 41} Longer pulses and higher currents only slightly improved the yields (entry 18 and 19). Additionally, different cathodes were tested, stainless steel (SS, entry 23) and silver (Ag, entry 24). To our delight, using a silver electrode, the reaction yield increased to 82% and had less fouling (8.5 mg vs. 21.4 mg for carbon). Adding a back pressure regulator (since gas is produced) reduced the yield significantly. No reaction occurred without electricity. Different channel geometries did not significantly affect the yield compared to a simple channel design (see ESI, Table 2). Interestingly, in batch reactor, the highest achieved yield was 51% and a high overpotential was present. Addition of several tested supporting electrolytes, to reduce the overpotential, decreased the yields (for details see ESI, Table 4).

Table 1: Selected optimization data for the electrochemical trifluoromethylation of enamide **1a to product **3a****



Entry	2a equiv.	solvent	current density [mA/cm ²]	anode/cathode	applied charge [F]	Yield ^b [%]
1	3	ACN	1.5	C/C	2	65
2 ^c	3	ACN	1.5	C/C	2	47
3 ^d	3	ACN	1.5	C/C	2	54
4	2	ACN	1.5	C/C	2	74
5	1.5	ACN	1.5	C/C	2	63
6	1.1	ACN	1.5	C/C	2	38
7	2	ACN	1.8	C/C	2.5	77
8	2	ACN	2.2	C/C	3	51
9	2	ACN	1.1	C/C	1.5	54
10	2	HFIP	1.5	C/C	2	3
11	2	MeOH	1.5	C/C	2	9
12	2	ACN:MeOH 4:1	1.5	C/C	2	17
13	2	ACN:H ₂ O 4:1	1.5	C/C	2	8
14	2	ACN:H ₂ O 1:1	1.5	C/C	2	3
15 ^e	2	ACN	1.5	C/C	2	9
16 ^f	2	ACN	1.5	C/C	2	9
17 ^g	2	ACN	1.5	C/C	2	22
18 ^g	2	ACN	2.9	C/C	4	14
19 ^h	2	ACN	2.9	C/C	4	0
20	2	ACN	1.5	C/SS	2	68
21	2	ACN	1.5	C/Ag	2	82
22 ⁱ	2	ACN	1.5	C/Ag	2	56
23 ^j	2	ACN	0	C/Ag	0	0

^aReaction conditions in an undivided flow electrolysis cell (Analytical Sales, Inc.): **1a** (0.2 mmol, 1 equiv.), **2a** (1.1 – 3 equiv.), solvent (10 mL), plate electrodes, current, r.t., flow rate 155 $\mu\text{L/h}$ (corresponds to residence time 52 s) for 65 minutes (time to convert 0.2 mmol). ^bYield was evaluated by ¹⁹F-NMR spectroscopy of the crude reaction mixture using trifluorotoluene as an internal standard. ^cSupporting electrolyte LiClO_4 (0.1 M). ^dChannel height 254 μm instead of 127 μm . Alternating polarity ^e0.2 Hz; ^f0.05 Hz; ^g0.01 Hz. ^hRapid alternating polarity, 10 Hz. ⁱWith back pressure regulator. ^jNo current.

Having established the optimized reaction conditions, the substrate scope of the trifluoromethylation reaction of enamides was explored. As shown in Scheme 2, various substrates, including carbamates, endocyclic, exocyclic and acyclic enamides, were tested. The effect of different protecting groups was evaluated, *N*-Boc and *N*-Cbz protected substrates led to similar yields (**3a**, **3b**), while the methoxycarbonyl protected substrate led to a slightly lower yield (**3c**). Next, the effect of various substituents was evaluated. For the enamide with a methyl group (electron donating) in the 4-position (**3e**), the desired product was obtained in a slightly lower yield than with a methyl group in the 2-position (**3d**), though the yield remained above 80%, likely due to steric hindrance. Considerably lower yields were observed for **3f**, likely due to the lower affinity of the CF₃ radicals to electron deficient substrates. The ring size had a significant effect on the reaction success. A moderate yield was obtained for the 7-membered ring (**3g**), while poor yields were obtained with 5-membered rings (**3h**, **3i**). The CV showed that the oxidation potential of the 5-membered ring substrates is lower than the oxidation potential of LR (1.22 V compared to 1.27 V, vs Ag/AgCl) leading to primarily oxidation of the substrate and resulting in a large amount of side products. To our delight, good yields were obtained for endocyclic 5-membered enamides (**3j**, **3k**), but a significant drop in yield was observed for the 7-membered endocyclic enamide (**3l**). Additionally, the desired products were obtained in good yields for acyclic enamides (**3m**, **3n**). In summary, several new trifluoromethylated enamides (**3c**, **3d**, **3e**, **3g**, **3k**, **3m**, **3n**) were obtained in good yields.

CV experiments were conducted to gain further insight into the mechanism. Enamide (**1a**) showed a higher oxidation potential than CF₃SO₂Na (1.31 V vs 1.27 V, vs Ag/AgCl), indicating that CF₃SO₂Na is more easily oxidized at the anode. A plausible reaction mechanism for the electrochemical trifluoromethylation of enamide is illustrated in Figure 1. Initially, the CF₃ radical is generated from CF₃SO₂Na by anodic oxidation and emission of SO₂. The addition of this radical to the enamide leads to the formation of a carbon radical intermediate. This intermediate is further oxidized at the anode to form a carbon cation, which, after loss of a proton, results in the desired trifluoromethylated product. As a counter reaction, protons are reduced to hydrogen gas at the cathode. This mechanism is consistent with previous literature reports.⁴²

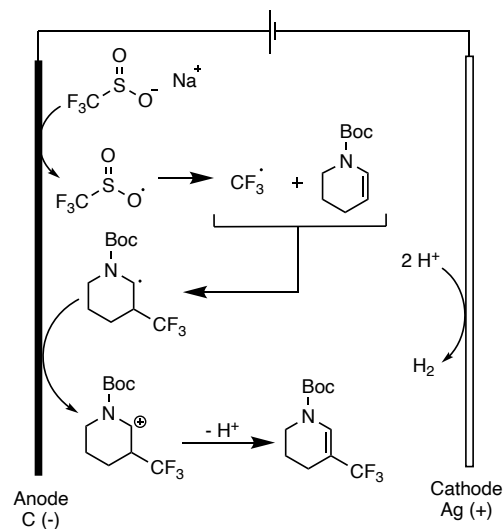
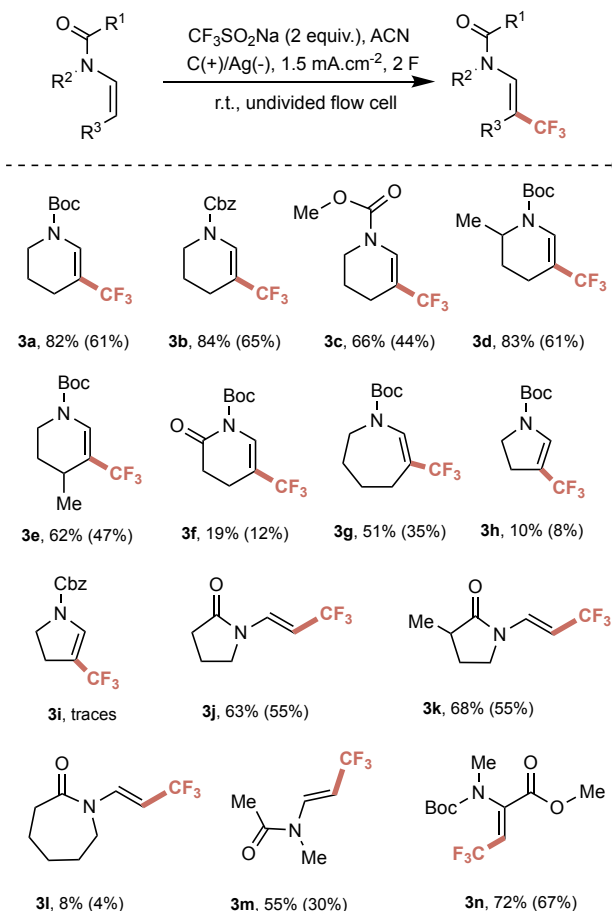


Figure 1: Proposed reaction mechanism

Scheme 2: Electrochemical synthesis of trifluoromethylated enamides in the flow cell



Reaction conditions: **1** (0.2 mmol, 1 equiv.), CF₃SO₂Na (0.2 mmol), ACN (10 mL), electrochemical flow cell (Analytical Sales Inc.), PFA simple channel (*h* = 127 μm), graphite plate anode (50 x 50 x 3 mm), silver plate anode (50 x 50 x 1 mm), constant current 10 mA (*j* = 1.5 mA.cm⁻²), flow rate 155 ul/h (2 F/mol) at room temperature. The yield was evaluated by ¹⁹F NMR spectroscopy of the crude reaction mixture using trifluorotoluene as internal standard. Yields reported in brackets refer to isolated and purified products.

Despite, the fouling of electrodes, a high yield of the desired product **3a** was observed (82 %) on a 0.2 mmol scale, which is comparable with scale in recent literature on trifluoromethylation functionalisation with LR, especially in the case of batch reactors.^{11, 21, 30, 33} However, electrode fouling can negatively impact the yield during prolonged production. To address this often omitted issue, the stability of the yield over time was evaluated. Eventually, the yield decreases over time due to electrode passivation. After 3 hours (corresponding to conversion of 0.6 mmol of substrate), almost no product was synthesized (Figure 2). Electrode fouling is caused by Na⁺ salts generated during the reaction with LR, which have limited solubility in ACN, but is well soluble in water. The flow setup allows for a continuous process with an incorporated flushing step. When the microflow cell was flushed with water, no decrease in yield was observed. Specifically, after 1 h of production (conversion of 0.2 mmol of substrate), the flow cell was flushed by 10 mL of H₂O (5 mL/min for 2 min). Afterwards, the reaction mixture was introduced again, and after 5 residence times (4.5 min, to

avoid presence of water and thus side product production), the reaction mixture was collected again. Additionally, the flow cell was disassembled after the flushing, and no electrode fouling was observed (see the ESI, Chapter 6 for details). The valves to switch from the flow stream of the reaction mixture or water to flush the microflow cell were switched manually, however, this process can be automated (with programmable valves and pumps) for extended production of the desired product.

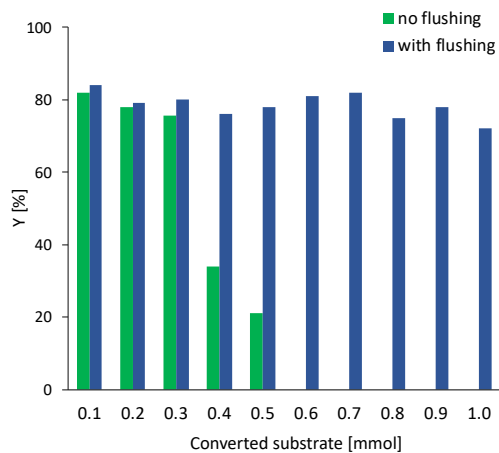


Figure 2: Stability of the production of trifluoromethylated product over time: comparing the microflow reactor performance without (green) and with (blue) flushing step, every 0.2 mmol (1 hour). Yields were evaluated by ^{19}F NMR spectroscopy of the crude reaction mixture using trifluorotoluene as an internal standard.

In conclusion, an environmentally friendly method for direct electrochemical trifluoromethylation of enamides was developed using a microflow cell and Langlois reagent as the source of the trifluoromethylated radical without the need for a supporting electrolyte. Various new trifluoromethyl enamides were produced in moderate to good yields. We demonstrated that this method is feasible exclusively in the microflow cell, and not in the batch reactor for the following reasons: i) the microflow cell allows to work without a supporting electrolyte (which otherwise reduces the yield) due to the small interelectrode distance resulting in a low Ohmic drop; ii) process intensification due to a high electrode surface-area-to-volume ratio, which increases the yield in flow; iii) the microflow cell can be easily flushed with water to prevent electrode fouling, allowing for continuous production without the yield drop, a feature unattainable in a batch reactor.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures additional optimization data and characterization for known and new compounds (PDF)

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