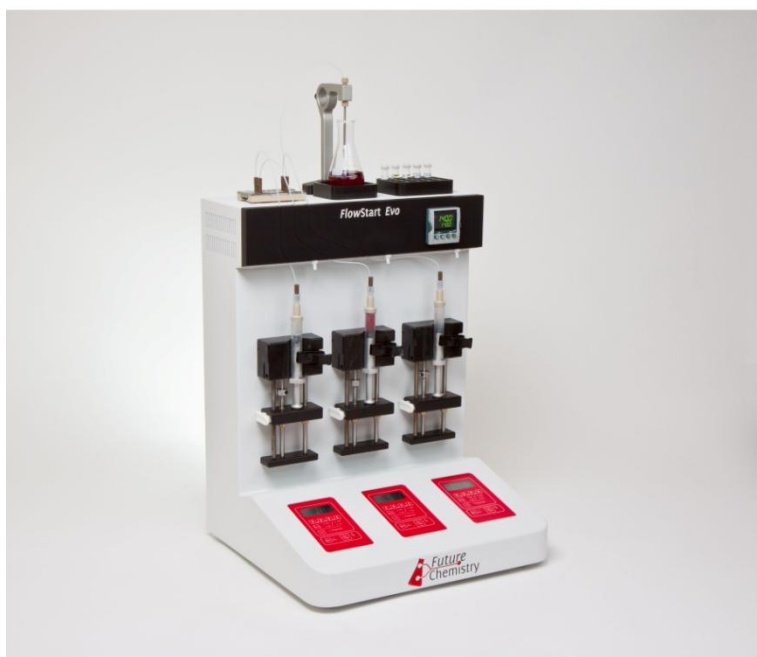


# Application Note 7.4

## *Swern-Moffatt oxidation*



The Swern-Moffatt oxidation is a highly valuable reaction, as it selectively oxidises alcohols to the corresponding aldehydes or ketones. In batch, the reaction requires a temperature of  $-78^{\circ}\text{C}$ . The reaction was successfully translated from batch to continuous flow in the *FlowStart Evo* microreactor platform, providing an improvement over the conventional batch process by raising the temperature to  $20^{\circ}\text{C}$  while keeping high yields.

## Introduction

The Swern-Moffatt oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones is a useful reaction in organic chemistry, as it provides a selective pathway towards aldehydes and ketones. This reaction is difficult to control due to its fast reaction rate and exothermic character, and is therefore traditionally performed at  $-78^{\circ}\text{C}$ . At elevated temperatures, side product formation becomes dominant, except when very short reaction times are used. These short reaction times can be perfectly controlled in a continuous flow microreactor, and a minimum of 300 ms was obtained using the Short Quench Microreactor.

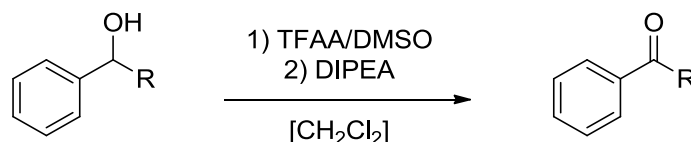


Figure 1: Swern-Moffatt oxidation of model substrates (R = H, CH<sub>3</sub>)

To avoid the use of low temperatures and controlled reagent addition, FutureChemistry has translated this reaction from a batch process to a continuous flow process. FutureChemistry's typical three-tier approach led to a protocol which can be adapted to any viable alcohol substrate:

- 1) Translation of batch process to continuous flow process:
  - a) Stock solutions approach, yielding a homogeneous reaction mixture.
  - b) Quenching solution to follow the reaction in time.
  - c) Flow markers approach to accurately assess reaction parameters.
- 2) Automated reaction optimisation.
- 3) Out scaling to preparative synthesis.

This *application note* describes the translation of the batch process to the continuous flow process using the *FlowStart Evo B-401*.

## Batch to flow conversion

In contrast to batch chemistry, reactions in continuous flow are conducted from stock solutions. These solutions should remain inactive after preparation, but react when combined. In the Swern-Moffatt oxidation, solution A contains the alcohol substrate and dimethyl sulfoxide (DMSO), solution B contains the trifluoroacetic anhydride (TFAA) reagent and solution Q is *di*iso-propylethylamine (DIPEA) without solvent. The used flow setup is depicted in Figure 2.

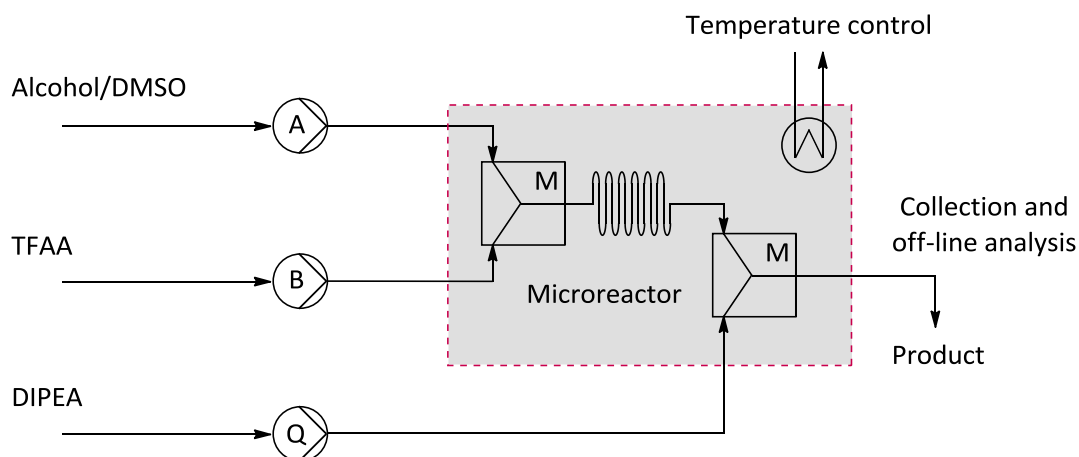


Figure 2: FlowStart Evo setup

To stop the reaction at a certain point in time a quenching agent is needed, which reacts with the reagent many times faster than the reaction itself. In the Swern-Moffatt oxidation, DIPEA is used to neutralise the formed trifluoroacetic acid, and also provides the second step in the reaction.

## Benzy alcohol oxidation

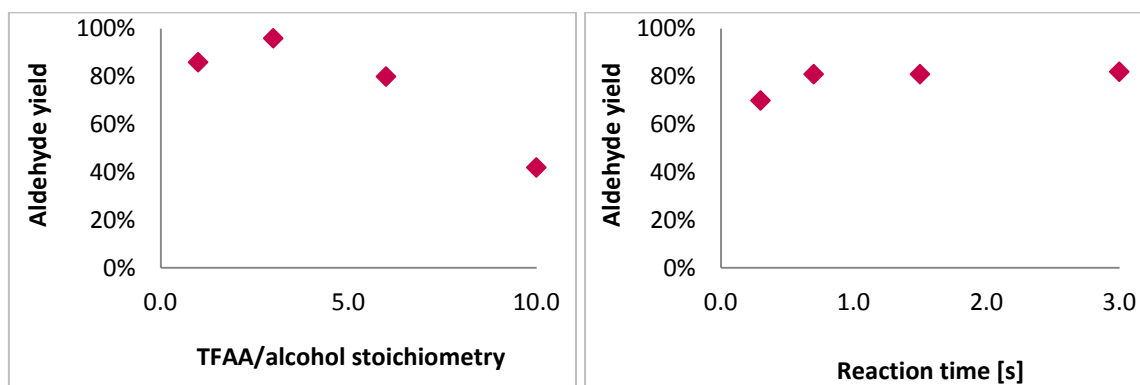


Figure 3: Results of the benzyl alcohol oxidation (R = H)

Left: Benzaldehyde yield vs. TFAA/alcohol stoichiometry (temperature 20°C, reaction time 1.0 s)

Right: Benzaldehyde yield vs. reaction time (temperature 20°C, TFAA/alcohol stoichiometry 6.0)

In the *FlowStart Evo* experiments, temperature, TFAA/alcohol stoichiometry and reaction time were varied. A standard reaction was defined as having a temperature of 20°C, reaction time of 1.0 s and TFAA/alcohol stoichiometry of 6.0, around which all univariate screening experiments were performed.

The univariate screening of the benzyl alcohol oxidation (Figure 3) showed an optimal TFAA/alcohol stoichiometry of 3.0 and an optimal reaction time around 1.0 s. The temperature effect from 0 to 60°C was minimal (yield deviations < 5%).

### 1-Phenyl ethanol oxidation

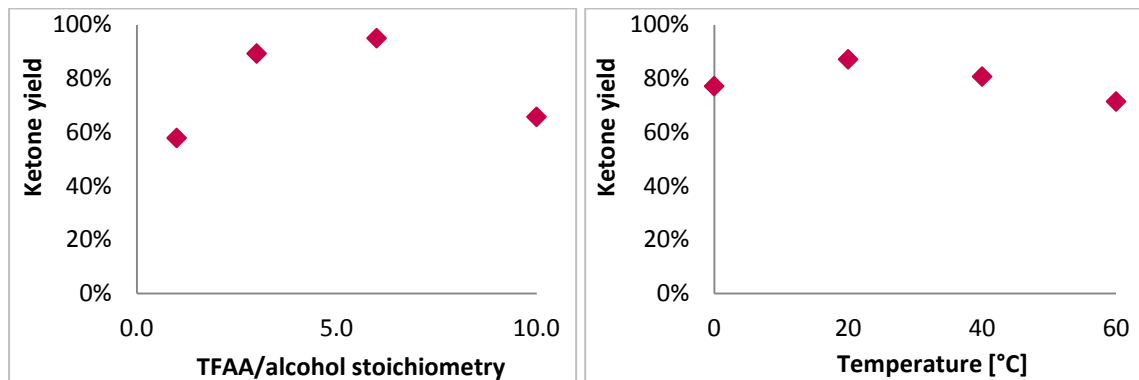


Figure 4: Results of the 1-phenyl ethanol oxidation (R = CH<sub>3</sub>)

Left: Acetophenone yield vs. TFAA/alcohol stoichiometry (temperature 20°C, reaction time 1.0 s)

Right: Acetophenone yield vs. reaction time (temperature 20°C, TFAA/alcohol stoichiometry 6.0)

The univariate screening of the 1-phenyl ethanol oxidation (Figure 4) showed an optimal TFAA/alcohol stoichiometry of around 5.0 and an optimal temperature around 20°C. Reaction time was varied as well, but no significant changes in yield were observed from 0.3 s to 3.0 s.

### General results

With the above optimal parameter values, yields up to 95% were observed, and the Swern-Moffatt oxidation was successfully converted from batch to flow. The reaction temperature was thereby raised by around 100°C.

## Method

All experiments were conducted in a standard FutureChemistry B-401 *FlowStart Evo* setup, using the Short Quench Microreactor with internal volume of 1.0  $\mu\text{L}$ . Benzyl alcohol and 1-phenyl ethanol were used as model substrates.

**Solution A (0.2 M):** Alcohol substrate (2.00 mmol) and dimethyl sulfoxide (1.29 mL, 18.0 mmol) dissolved to a total volume of 10 mL with dichloromethane

**Solution B (1.2 M):** Trifluoroacetic anhydride (1.67 mL, 12.0 mmol) dissolved to a total volume of 10 mL with dichloromethane

**Solution Q (6.0 M):** *Diiso*-propylethylamine (neat)

Three glass 1.0 mL syringes were loaded with solutions A, B and Q respectively. For each experiment, the desired flow rates were calculated according to the following equations:

$$\text{Total flow} = \text{microreactor volume} / \text{reaction time}$$

$$\text{Flow A} = \text{total flow} / (1 + \text{TFAA/alcohol stoichiometry} / 6)$$

$$\text{Flow B} = 2.5 * \text{Flow Q} = \text{Flow A} * (\text{TFAA/alcohol stoichiometry} / 6)$$

All product mixtures were analysed with GC, with retention times according to Table 1. Analysis was performed on a Shimadzu GC2010 using a Quadrex 007 1701 apolar column (L 15.0 m, ID 0.10 mm) and flame ionisation detector (T 325°C, H<sub>2</sub> 30 mL/min, Air 400 mL/min), using a temperature program (0-0.85 min 98°C, 0.85-1.76 min 98-235°C, 1.76-1.86 min 235°C) and 1.0  $\mu\text{L}$  injection with split ratio 300.

**Table 1: GC analysis retention times**

| Compound     | Function                       | Retention time [min] |
|--------------|--------------------------------|----------------------|
| Benzaldehyde | product (R = H)                | 0.85                 |
| Acetophenone | product (R = CH <sub>3</sub> ) | 1.15                 |