Selective α-ketone bromination is a useful reaction in organic chemistry, but can be performed in a microreactor for added safety and reaction control. The reaction was successfully translated from batch to continuous flow in the FlowStart Evo microreactor platform, providing a viable alternative to the conventional batch process.
**Introduction**

The synthesis of α-ketone bromides is a useful reaction in organic chemistry, as it provides a good pathway towards α-substituted ketones through bromide substitution. Traditionally, this reaction is difficult to control due to its fast reaction rate and exothermic character. As a result, the brominated ketone easily reacts further to the double-brominated product. In batch, side product formation is largely overcome by controlled reagent addition and the use of mild bromination reagents (instead of bromine) such as N-bromosuccinimide, whose synthesis again requires the use of bromine. Direct α-ketone bromination with bromine limits batch scale-up, but has been shown to be possible in continuous flow. The latter has the added advantage of handling all toxic and corrosive reagents inside a closed system.

![Figure 1: Bromination of model substrate](image)

To avoid the use of expensive bromination reagents while keeping a high throughput at the same time, 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 ketone 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*. 
Selective α-ketone bromination

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 α-ketone bromination, solution A contains the ketone substrate and solution B contains the bromine reagent. To avoid self-catalysis, hydrobromic acid is added to solution A. The used flow setup is depicted in Figure 2.

![FlowStart Evo setup](image)

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 synthesis reaction itself. In the α-ketone bromination, an activated alkene (2-methoxypropene) is used to remove all leftover bromine by forced alkene addition.

![Figure 3](image)

In the FlowStart Evo experiments, temperature, bromine stoichiometry and reaction time were varied. With the above parameter values, yields up to 95% were observed (Figure 3), and selective α-ketone bromination was successfully converted from batch to flow.
Selective α-ketone bromination

Method

All experiments were conducted in a standard FutureChemistry B-401 FlowStart Evo setup, using the Basic Quench Microreactor with internal volume of 92 µL. Acetophenone was used as model substrate. The solvent was degassed at low pressure to keep the reaction mixture in liquid phase.

Solution A (0.2 M): Acetophenone (233 µL, 2.00 mmol) and hydrobromic acid (33% in acetic acid, 173 µL, 1.00 mmol) dissolved to a total volume of 10 mL with 1,4-dioxane

Solution B (0.2 M): Bromine (103 µL, 2.00 mmol) dissolved to a total volume of 10 mL with 1,4-dioxane

Solution Q (0.6 M): 2-Methoxypropene (555 µL, 6.00 mmol) dissolved to a total volume of 10 mL with 1,4-dioxane

Three glass 5.0 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:

\[
\text{Total flow} = \frac{\text{microreactor volume}}{\text{reaction time}}
\]

\[
\text{Flow A} = \frac{\text{total flow}}{1 + \text{bromine stoichiometry}}
\]

\[
\text{Flow B} = \text{Flow Q} = \text{Flow A} \times \text{bromine stoichiometry}
\]

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, H2 60 mL/min, Air 400 mL/min), using a temperature program (0-0.5 min 60°C, 0.5-2.2 min 60-230°C, 2.2-2.7 min 230°C) and 1.0 µL injection with split ratio 200.

Table 1: GC analysis retention times

<table>
<thead>
<tr>
<th>Compound</th>
<th>Function</th>
<th>Retention time [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetophenone</td>
<td>substrate</td>
<td>1.43</td>
</tr>
<tr>
<td>phenacyl bromide</td>
<td>product</td>
<td>1.98</td>
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