

Application Note 17.4

Halogen-Lithium exchange



Halogen-lithium exchange is a very 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 use of *n*-Butyllithium as lithiation reagent finds widespread use in organic chemistry, but has several drawbacks. Lithiation reactions have to be conducted at strict anhydrous conditions under an inert atmosphere at low temperatures (-78°C is not uncommon), as the reagent is very sensitive to oxygen, atmospheric moisture and heat. Furthermore, good yields can be difficult to obtain, as the lithiated compound can react with any halide present in solution, or even with the used solvent.

Continuous flow solves these issues, by using short reaction times (5 to 10 seconds) at elevated temperatures (0°C to 20°C). In this method, the lithiated compound has a very short lifetime and is immediately consumed by an electrophile in almost quantitative yields.

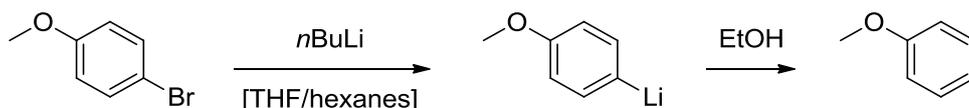


Figure 1: Halogen-lithium exchange on model substrate

To avoid the use of expensive cooling equipment, inert gasses and dosing equipment 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.
- 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 halogen-lithium exchange reaction, solution A contains the aryl bromide and solution B contains the *n*-Butyllithium reagent. The used flow setup is depicted in Figure 2.

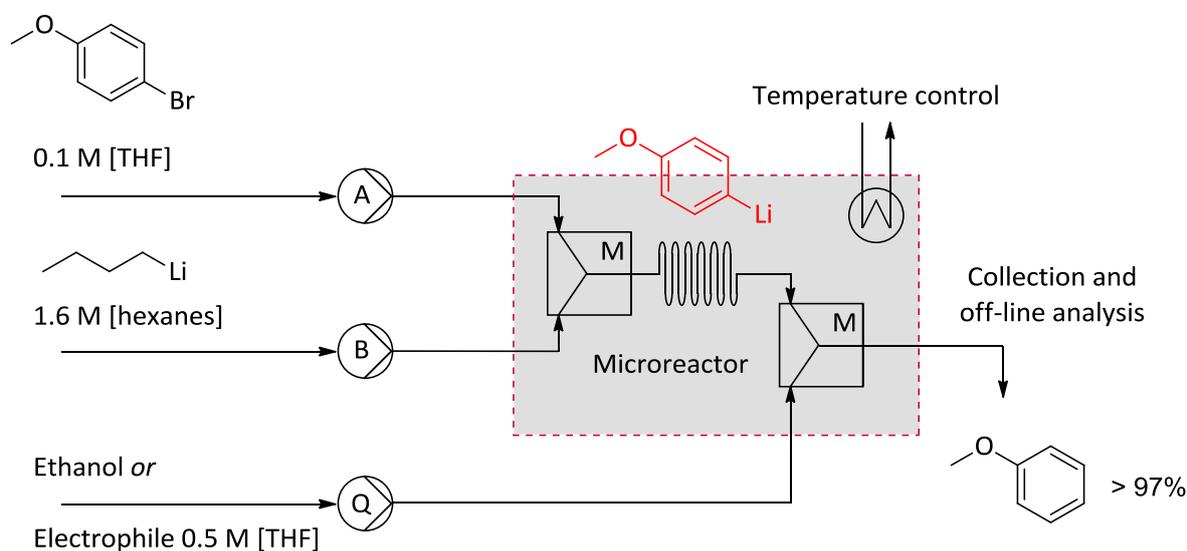


Figure 2: FlowStart Evo setup

After the aryllithium compound is formed, the lithium atom is replaced by an electrophile in solution Q. To test aryllithium formation ethanol is used, which acts as a proton donor and as co-solvent to facilitate the dissolution of the formed lithium ethoxide. The outflow of the microreactor is collected in a mixture of water and ethanol, to neutralise the ethoxide and to dissolve the corresponding hydroxide.

Between formation of the aryllithium compound and addition of the electrophile, two side reactions are common. The first is the coupling between the aryllithium compound and unreacted aryl bromide (Wurtz-Fittig coupling), which can only occur if the reaction is not complete – the halogen-lithium exchange reaction is many times faster than the coupling reaction, especially when a bromide is used instead of an iodide. The second side reaction is between the aryllithium compound and the formed butyl bromide. This reaction is mostly avoided by keeping the temperature low or reaction time short. In continuous flow chemistry, it is most convenient to use short reaction times and somewhat higher temperatures.

In the *FlowStart Evo* experiments, temperature and reaction time were varied on two levels. With a reaction time between 5 and 10 seconds, and a temperature between 0°C and 20°C, aryllithium yields were 97% to 98% for these parameter settings (the remaining 2% to 3% was butyl anisole), and the halogen-lithium exchange reaction was successfully converted from batch to flow.

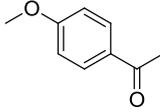
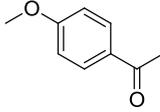
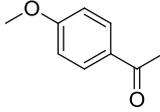
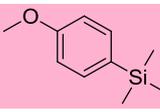
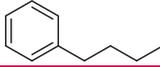
Other substrates

A variety of electrophiles was subjected to the formed aryllithium solution in continuous flow. The results are presented in Table 1. Note that anisole formation is due to the (relatively high) water or acetic acid content in the used chemicals, which were *not* purified before use. Corrected yields are to be expected when dry chemicals are used.

The yields of butyl anisole can be seen as a result of the competing Wurtz-Fittig coupling with the reaction by-product butyl bromide. Therefore, the reaction rate of the used electrophile with the aryllithium compound is inversely proportional to the corresponding butyl anisole yield. It can thus be stated that in this setup, TMS-chloride is the best electrophile, followed by the carbonyl compounds.

The use of phenyl iodide as an electrophile did not yield the desired product at all. Butyl benzene, however, was shown to be the major product. It was concluded that the use of an iodide compound led to another halogen-lithium exchange, followed by coupling to butyl bromide.

Table 1: Yields (uncorrected and corrected for water content) when using different electrophiles at a reaction time of 10 s, temperature of 0°C and electrophile molar ratio of 2.0.

Electrophile	Product	Yield (corrected yield)		
		Product	Anisole	Butyl anisole
Acetyl chloride		67% (88%)	24% (0%)	9% (12%)
Acetic anhydride		77% (89%)	12% (0%)	10% (11%)
Ethyl acetate		79% (91%)	13% (0%)	8% (9%)
TMS chloride		90% (99%)	9% (0%)	1% (1%)
Phenyl iodide		79% (93%)	15% (0%)	6% (7%)

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 . 4-Bromoanisole was used as model substrate.

Solution A (0.1 M): 4-Bromoanisole (125.5 μL , 1.00 mmol) dissolved to a total volume of 10 mL with anhydrous THF

Solution B (1.6 M): *n*-Butyllithium in hexanes (commercial solution)

Solution C (0.5 M): Electrophile (5.00 mmol) dissolved to a total volume of 10 mL with anhydrous THF

Solution C* (17.1 M): Ethanol (neat)

Three glass syringes were loaded with solutions A, B and Q respectively. For each experiment, the desired flow rates were calculated according to the known equations (*Application note 16*).

All product mixtures were analysed with GC, with retention times according to Table 2. 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 2: GC analysis retention times

Compound	Function	Retention time [min]
anisole	product (using ethanol as electrophile)	1.01
4-bromoanisole	substrate	1.61
4- <i>n</i> -Butylanisole	side-product	1.74