Novel Organic Synthesis through Ultrafast Chemistry

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The transfer of organic reactions from batch to flow has a long history, although only recently has this field of chemistry received more attention, which is mainly due to the availability of commercial flow equipment for synthesis laboratories.[1] The progress of a batch reaction can typically be followed over time in the reaction flask after the reagents **A** and **B** have been added at the start of the reaction (time = 0) until the end of the reaction (time = 1). Conversely, the progress of a reaction performed in flow chemistry can be monitored at various positions of the flow reactor. The position at the flow reactor where the reagents **A** and **B** are mixed corresponds to the time = 0, while the exit of the reactor where the reaction is finished or quenched corresponds to the end of the reaction (time = 1) (Figure 1). The distance in the reactor from the initial mixing point is therefore directly correlated to the reaction time. Many researchers have taken advantage of this time resolution in a flow reactor either to directly monitor or intercept reaction products or intermediates.

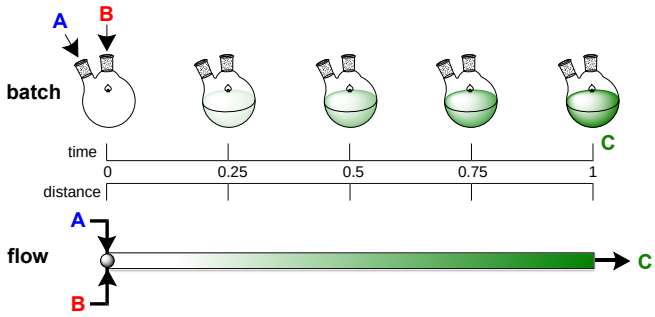


Figure 1. Progress of batch and flow chemistries with time.

Depending on the reaction rate, the quality of mixing of reagents **A** and **B** can be important. In batch processes, mixing is typically achieved by stirring, while in flow systems it takes place at the point where reagents **A** and **B** meet. Although smaller volumes are handled in flow synthesis, mixing devices can be used to reduce mixing times. This is particulary important for fast or very fast reactions, where the quality of the mixing of **A** and **B** has to be considered carefully.

The safe generation of hazardous intermediates and their handling in subsequent reactions is one of the prime benefits of closed flow chemistry systems. Similarly, the generation of short-lived intermediates has been successfully achieved in flow systems as the space / time resolution can allow a subsequent reaction after a short and defined time (Figure 2). This concept has been labeled 'Flash Chemistry' by J.-i. Yoshida and is used by various researchers.[2]

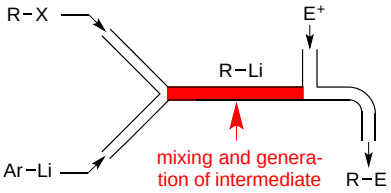
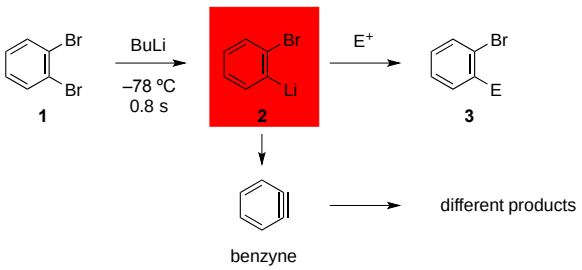


Figure 2. Generation of short-lived intermediates R-Li in flow reactors.

Using suitably designed flow reactors, short-lived intermediates can be generated and reacted very rapidly before these intermediates decompose or react in a different reaction pathway. There are several experimental prerequisites for successful transformations of this type. Halogen-lithium exchange reactions are highlighted here as the lithiated products (R-Li) can be very unstable. A classical example for this in flash chemistry is the lithiation of 1,2-dibromobenzene **1** as shown in Scheme 1.[3] The lithiated intermediate **2** is efficiently generated within approx. 0.8 s at –78 ºC, before it is trapped with an electrophile to generate addition products of type **3**. At higher reaction temperatures (or longer reaction times), intermediate **2** can eliminate LiBr generating a benzyne, which will subsequently decompose, dimerize or react to other products. Only through the adjustment of flow rates in the device shown in Figure 2 to a residence time in the red part of the tube reactor to 0.8 seconds, the intermediate **2** can be formed selectively and subsequently reacted with the electrophile E^+.



Scheme 1. Trapping of the short-lived intermediate **2** with electrophiles in continuous processes.

The concept of generating reactive lithiated intermediates has recently been extended to the selective functionalization of biselectrophiles as shown in Scheme 2.[4] Due to the controlled generation and the short lifetime of the lithiated intermediates **4**

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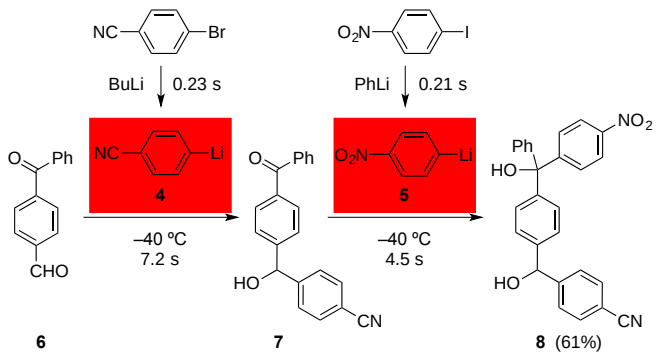
and **5**, protecting groups are obsolete and the straightforward synthesis of the functionalized derivative **8** demonstrates the potential of the approach. By modifying the substrates to carbamoyl chlorides (R_2N-CO-Cl), even unstable carbamoyl anions (R_2N-CO-Li) can be generated by lithiation at low temperatures and used for reactions with various electrophiles.[5]



Scheme 2. Controlled generation of intermediates **4** and **5** and reaction with biselectrophile **6** in flow.

The technique has now been developed further and extended towards intermediates which have lifetimes in the range of milliseconds. This requires a rapid flow of reagents through the device shown in Figure 2 and, in addition, a volume reduction of the red area whereby the intermediate is generated. This has been recently achieved by D.-P. Kim and J.-i. Yoshida by designing a chip microreactor where the mixing area consists of a 3D serpentine channel for efficient mixing with a total internal volume of 25 nL (dotted area) as shown in Figure 3.[6] It was constructed using a layer approach where different layers of fluoroethylene propylene-polyimide films were patterned by UV laser ablation and then thermally bonded together.[7,8] Applying a total flow rate of 4.5 mL/min leads to a residence time of approx. 0.33 ms.

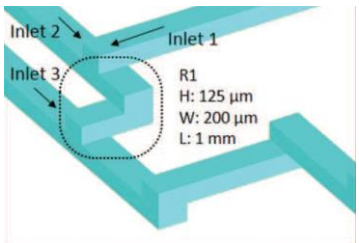
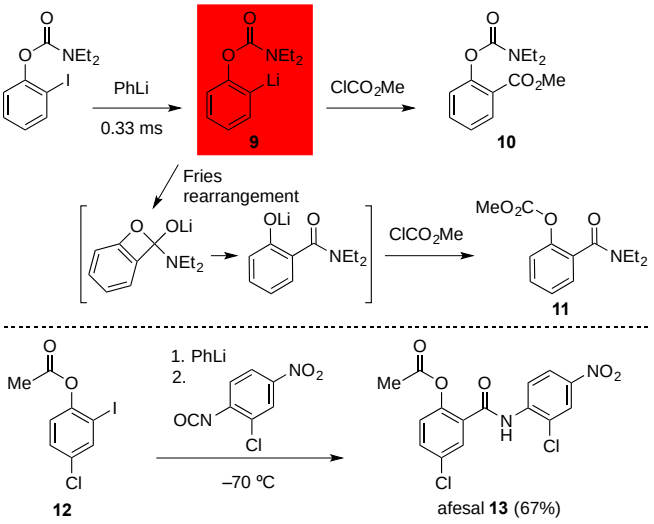


Figure 3. 3D channel system for ultrafast reactions. From *Science* **2016**, *352*, 691. Reprinted with permission from AAAS.

This device now allows the generation and trapping of extremely short-lived intermediates. The lithiated compound **9**, immediately formed by mixing the starting material and phenyllithium, can be trapped within 0.33 ms with methyl chloroformate to give the reaction product **10** in 91% yield. If the intermediate **9** is left on its own for more than 628 ms, it will undergo the Fries rearrangement to compound **11**, which is then the only product and also obtained in 91% yield. If the Intermediate **9** is left for 220 ms after its generation, approximately half of the compound rearranges before reacting with methyl chloroformate and equal amounts of **10** and **11** are formed (Scheme 3).



Scheme 3. Submillisecond chemistry of intermediate **9** in flow and application in the synthesis of afesal **13**.

By conducting the reaction of **9** in a submillisecond time frame it is possible to outpace the Fries rearrangement. Even the more reactive ester derivative **12** can be lithiated and trapped with an isocyanate without rearrangement. Such a process would not be achievable in batch operation mode. The direct synthesis of the anthelmintic compound afesal **13** was possible in 67% yield. Although the physical dimensions of the flow device are small, its productivity with 5.3 g/h is reasonable.

Synthetic access to very short-lived intermediates is now possible and their use in scalable synthesis within reach. This new flow technology will enable the design of novel synthetic routes and a faster approach to valuable compounds.

Keywords: flash chemistry • flow chemistry • Fries rearrangement • microreactors • organolithium compounds

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