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In flow only

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In this Issue, we focus on reaction outcomes which are unique to flow setups and their application in synthesis.

Continuous flow is an enabling technology in synthesis, allowing a diverse range of reactions to be performed safely and efficiently across scales[1]. Many industrial manufacturing processes use flow technology to produce active ingredients, taking advantage of greater cost efficiency, lower setup footprint and potentially faster reactions compared to batch-based setups[2]. Continuous flow is defined by the performance of a reaction in a tube, as opposed to in a batch setup, where a vessel-style reactor is used[2]. Lab-scale flow setups often comprise reagent reservoirs, which feed tubing reactors connected with a series of mixers, injector valves, and outlets[3]. In an ideal scenario, reagents can be fed into a flow setup and reaction product is continuously produced and collected. Owing to the flexibility of many lab-scale flow setups, reaction performance can be optimized through setup engineering, to tailor a flow setup to the needs of a reaction[3].

As only a small portion of a reaction mixture is in the flow reactor at any one time, challenges which batch reactors encounter, such as temperature control or efficient mixing, are typically facile in flow[3]. Many reactions in flow use these technical advantages to generate and use hazardous[4] and/or sensitive[5] reagents and intermediates in a safe and controlled manner, which is often not possible in batch reactors. These processes typically produce small quantities of these species on demand and immediately react them onwards to form stable products.

Whilst a lot of flow chemistry research focuses on translating reactions from batch to flow setups to increase efficiency or perform processes safely, the engineering-based advantages that flow chemistry offers can also be used to explore new reactivity or to quickly optimize reactions. This is exemplified by the combination of flow chemistry with one or multiple other enabling technologies such as electrochemistry[6], photochemistry[7], or automation[8]. A notable example of this is the development of self-optimizing automated flow systems, where flow chemistry, analysis,

and machine learning algorithms are combined to optimize reaction conditions using minimal amounts of materials and time[9]. The power of the combination of automation and flow technologies is further highlighted in a Q&A with David Ford, who explains the challenges of using flow chemistry in process development and how automating flow systems can readily help researchers manage the flow setup.

Additionally, in a Q&A with Gabriella Oksdath-Mansilla we learn how flow- and photochemistry can combine to develop reactions which outperform previous batch-based methods in terms of efficiency and control. The challenges and advantages of transferring photochemical transformations are also discussed.

In an Article, Noël and co-workers report the development of a modular flow setup for the generation and use of gaseous sulfuryl fluoride. The process forms sulfuryl fluoride from sulfuryl chloride in flow, using a KF-filled packed-bed reactor, a reaction which is slow and unselective under batch conditions. Combining this sulfuryl fluoride generation module with a sulfur fluoride exchange (SuFEx) reaction flow module allows the generated sulfuryl fluoride to react with a series of O- and N-based nucleophiles, forming the corresponding SuFEx ligated fluorosulfates and sulfamoyl fluorides. The developed flow process can be applied to the synthesis of SuFEx ligated small molecules, peptides, and proteins.

Whilst Noël and co-workers demonstrate that proteins can be readily modified under biocompatible conditions in flow, a Q&A with Francesca Paradisi reveals how enzyme catalysts can be used in flow for synthetic transformations. Paradisi also discusses how biocatalytic and chemical transformations can be readily coupled in flow setups to enable the synthesis of natural products and some of the challenges and unique advantages of performing chemoenzymatic processes in flow setups over batch reactors.

Generating reactive intermediates and selectively using them in synthesis can be difficult in batch reactors, and switching to a flow-based system often helps. This concept is exemplified in an Article by Yorimitsu and co-workers describing the development of flow microreactor-enabled regio- and stereoselective *syn*-borylmetallation of alkynes. The method uses a flow microreactor, at low temperature, to generate a reactive *syn*-β-borylalkenyl alkali metal intermediate, which can be reacted with a range of different electrophiles to form borofunctionalised multisubstituted alkenes. In contrast, batch processes struggle to selectively use and generate this type of intermediate and are often limited by undesired side reactions.

In a Q&A with Anna Slater, we learn how the technical advantages of flow chemistry can be used to control weak and reversible reactions. Also, how flow chemistry can be used in the selective and efficient synthesis of supramolecular structures and materials that can be challenging in batch reactors.

Flow chemistry has had an increasing impact as an enabling technology across a range of scales and disciplines in recent years. This trend will likely continue as other technologies, such as photochemistry, electrochemistry, biocatalysis, automation and machine learning are used in combination with flow chemistry to develop new reactions and applications which can help tackle problems faced by the chemistry and materials science communities.

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