CONTINUOUS-FLOW CHEMISTRY FOR MULTISTEP SYNTHESIS

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INTRODUCTION

Meaningful progress in research into bioactive small molecules demands that useful quantities (milligram to gram scale) are available. Despite complete biosynthetic access to numerous biologically relevant compounds, many exist without the benefit of such a source. Although total synthesis is powerful in its versatility, scaling of syntheses to production levels is often non-trivial. Accordingly, attention is increasingly devoted to streamlining synthetic routes. The recent extension to synthetic labs of a common chemical engineering technique, continuous-flow chemistry, is poised to accelerate progress in this area.

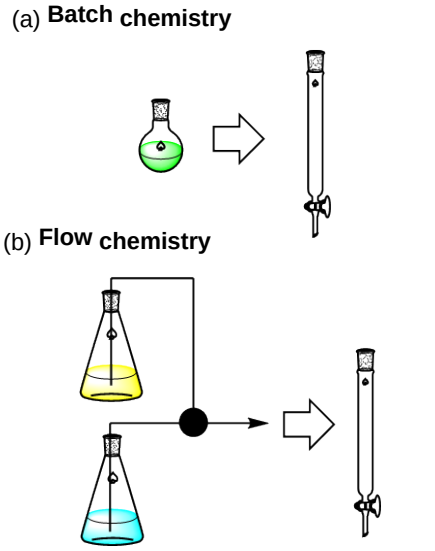

Fig. 1. (a) Batch chemistry scales with volume; (b) flow chemistry scales with time.

AN ENABLING TECHNOLOGY FOR TANDEM REACTIONS

The merits, realities, and pitfalls of continuous-flow synthesis have been discussed extensively.[1] However, the use of flow chemistry for multistep processes is less developed than its use for single transformations. Essentially, flow chemistry benefits from a combination of precise experimental variable control, predictable behavior at all scales, and improvements in step economy. Yoshida reported the protecting group-free lithiation and electrophilic quenching of aryl ketones; this methodology was applied to the total synthesis of pauciflorol F.[2] Jamison and Webb reported a general method for telescoped 2-carbon ester homologation operating via a precisely controlled DIBAL reduction.[3] These two reports demonstrate scalable, reproducible use of reaction sequences that are often capricious in batch chemistry.

Despite promising theoretical advantages, the use of flow chemistry to streamline multistep syntheses is limited by substantial technical and chemical challenges. Unlike in batch processes, phase separation is difficult in continuous flow due to the dominance of surface tension forces over gravity; this renders in-line purification problematic. Jensen and coworkers have developed continuous liquid-liquid separators relying on a phase-selective fluoropolymer membrane; this technology was applied to the synthesis of carbamates from acyl chlorides with excellent selectivity.[4] Extension of the principle to gas-liquid separation enables continuous distillation; Buchwald and Jensen employed this approach for the tandem generation and cross-coupling of aryl triflates from phenols with an in-line solvent switch from CH_2Cl_2 to DMF.[5] However, although industrial-scale uses of other continuous techniques such as chromatography and crystallization are known, robust lab-scale applications merit further development.

The nature of microfluidic systems employed in flow chemistry also make heterogeneous reactions problematic. Microfluidic plug-flow regimes, for instance, result in good intra-phase but poor inter-phase mixing. The use of solid packed-bed reactor systems addresses this limitation by promoting turbulent flow while maintaining favorable microfluidic properties. Buchwald and coworkers have accordingly used a combination of packed-bed reactors and continuous extraction for the development of Suzuki-Miyaura and Buchwald-Hartwig couplings.[6] McQuade and coworkers have reported the easy functionalization of a macroporous non-swelling packed-bed resin for the immobilization of reagents and catalysts; this system allows efficient solid-liquid heterogeneous reactivity without microreactor clogging.[7] Such developments enhance and expand the reactivity available in continuous systems.

Complex syntheses inevitably require the use of diverse reagents; this presents a problem when incompatible reagents must be combined in one reactor system. A general and powerful strategy is the use of solid-immobilized reagents as a means of spatially separating inimical reaction components or to remove troublesome byproducts from the flow stream. This approach was utilized by Ley and coworkers in the first two reported flow-only syntheses of natural products: grossamide and (±)-oxomaritidine.[8] Although this approach is flexible, the need to periodically replace reagent/scavenger cartridges is non-ideal. Nonetheless, a resin-based strategy has been employed in medicinal chemistry efforts wherein the newly-prepared derivatives could be biophysically characterized on-line prior to isolation or scale-up.[9]

SUMMARY AND OUTLOOK

Multistep flow synthesis is a young field, but efforts in this area are continuous. Although academic adaptations are yet developing and commercially-available platforms have only recently become broadly available, flow processes have already begun to find use in solving world-scale problems. For instance, a flow reactor enabled the low-cost semisynthetic photochemical production of artemisinin, an anti-malarial drug which is currently subject to a volatile supply and pricing market.[10] With the development of broadly useful reactions and separation techniques, continuous flow strategies have the potential to streamline access to complex targets, enabling rapid diversification and scale-up.

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