

Continuous Flow Multi-Step Organic Synthesis

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A recently developed strategy for multi-step synthesis is the use of continuous flow techniques to combine multiple synthetic steps into a single continuous operation. In this mini-review we discuss the current state of the art in this field.

Introduction

The multi-step synthesis of complex organic compounds from simpler precursors is one of the outstanding accomplishments of synthetic organic chemistry. Through the development and invention of synthesis strategies, methods and technologies, increasingly complex molecules can be assembled with designed structures and functions for a variety of medicinal, agrochemical and materials applications. However, despite significant advances, organic synthesis is still largely considered an inefficient and unsustainable practice that is highly labour- and resource-intensive.¹

The traditional pathway for multi-step synthesis proceeds by the batchwise and iterative step-by-step transformation of starting materials into desired products (Figure 1(a)). Typically, after the completion of each synthetic step ($A+B \rightarrow C$, $C \rightarrow D$ and $D \rightarrow E$), products are isolated from the reaction mixture and purified to remove any undesired components that might interfere with the subsequent synthetic transformations. Although this approach is the foundation on which modern synthesis has been built, such an approach is time-consuming, often wasteful and in stark contrast to the single-cell multi-step biosynthetic pathways found in nature.²

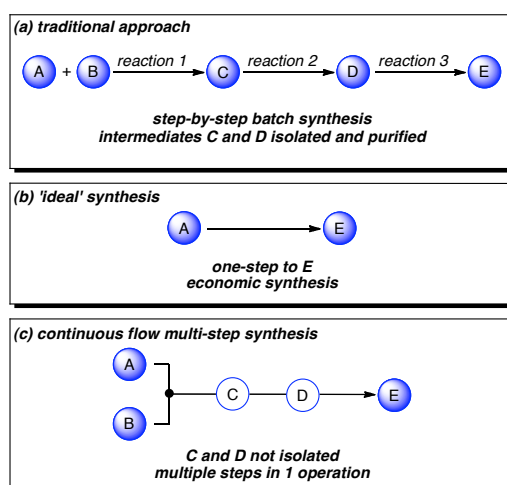


Figure 1 Synthesis strategies.

Currently, the ideal laboratory synthesis³ (Figure 1(b)) is unlikely to be achieved in practice, although a number of innovative strategies have been developed to increase synthetic efficiency.⁴ A recently introduced method for

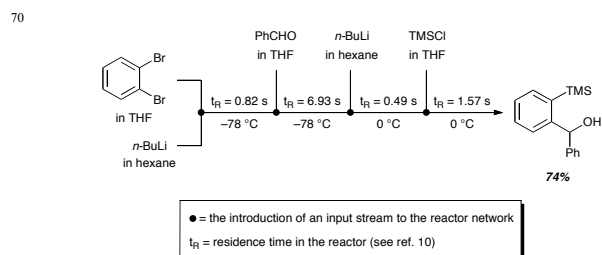
streamlining multi-step syntheses is the use of continuous flow techniques⁵ to combine multiple synthetic steps into a single continuous reactor network, thereby circumventing the need to isolate intermediate products (Figure 1(c)). In this mini-review we detail some recent developments in the field of *multi-step* continuous flow synthesis⁶ and discuss select contemporary examples of this emerging technology.

Multi-Step Flow Synthesis

Solution-based approaches

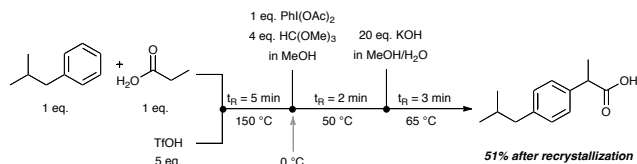
Synthetic chemists have long known that telescoping can be an effective tactic for truncating a multi-step synthesis.⁷ Telescoping reaction sequences typically involves the consecutive addition of reagents and/or catalysts to a reactor in order to initiate further transformations of intermediate products or to achieve *in situ* quenching of reactive species. This strategy is well suited to flow chemistry and a number of reports employing solution-based systems have been disclosed.

The Yoshida group has published several examples outlining the use of highly reactive and unstable organolithium compounds for multi-step synthesis under continuous flow conditions.⁸ For example, *o*-dibromobenzene could be effectively coupled with two different electrophiles *via* sequential halogen–lithium exchange reactions in an extremely fast yet controlled manner (Scheme 1).⁹ The authors used flow reactors constructed from stainless steel micromixers and tubes, whilst the reagent streams were driven by syringe pump devices. The success of these protocols is attributed to effective temperature and residence time¹⁰ (t_R) control that allows the unstable intermediates to be rapidly transferred to the next stage of the reactor before decomposition can occur.



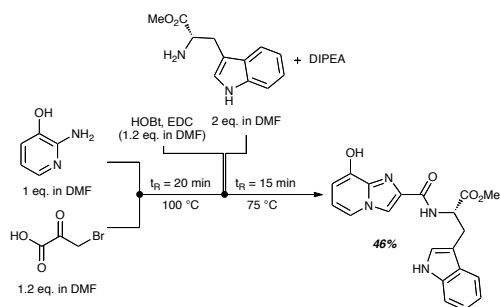
Scheme 1 Generation and reaction of *o*-bromophenyllithium species using flow chemistry (Yoshida).

Recently, the McQuade group reported a synthesis of the non-steroidal anti-inflammatory drug ibuprofen using continuous flow methods (Scheme 2).¹¹ The three-step synthesis (Friedel–Crafts acylation, 1,2-migration and ester hydrolysis) was linked into a single continuous system and provided ibuprofen in 51% isolated yield following off-line workup and crystallisation of the exiting flow stream.



Scheme 2 Continuous flow synthesis of ibuprofen (McQuade).

The ability to perform multi-step reactions in an uninterrupted continuous fashion may also be beneficial for medicinal chemistry applications.¹² Cosford recently described a continuous two-step synthesis of a focused 13-membered library of imidazo[1,2-a]pyridine-2-carboxamides (Scheme 3).¹³ No isolation of the carboxylic acid intermediate was required and a final off-line purification of the crude reaction mixture provided the targets. For their work the authors used the commercially available Syrris AFRICA flow system.¹⁴

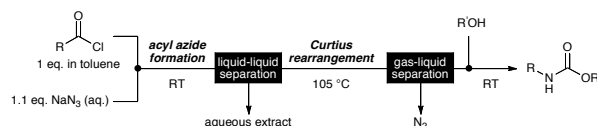


Scheme 3 Synthesis of a Mur ligase inhibitor using multi-step continuous flow synthesis (Cosford).

Continuous separation and distillation

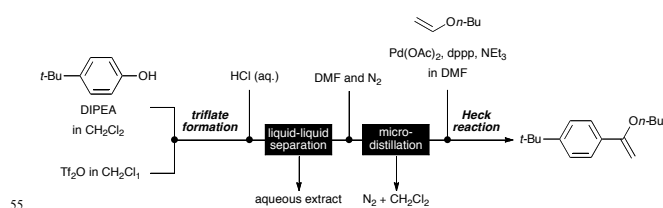
Although the telescoping processes described above are effective, they are not without limitations. A significant drawback is that excess reagents are often required, whilst the requirement for careful route design to ensure downstream reagent compatibility is an added challenge. The integration of solution-based quenching with subsequent phase separation operations into flow systems would therefore greatly expand the utility of this new technology.

The Jensen group reported the integration of microfluidic biphasic extraction systems with microreactors for the multi-step synthesis of carbamates (Scheme 4).¹⁵ A microseparator incorporating a hydrophobic membrane was designed and used to successfully remove the aqueous stream and thus any water-soluble components.¹⁶



Scheme 4 Continuous carbamate synthesis involving multiple reactions and separations (Jensen).

The Jensen group added a further instrument to the flow toolbox with the development of a microfluidic distillation unit capable of performing an in-line solvent switch. Working in conjunction with the Buchwald laboratory, a two-step flow sequence to prepare enol ethers was developed (Scheme 5).¹⁷ A bespoke silicon device was employed to carry out a continuous distillation of a binary solvent mixture (dichloromethane/DMF).¹⁸

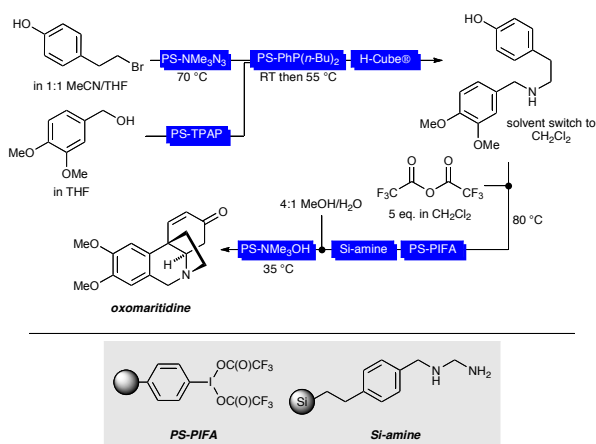


Scheme 5 Continuous synthesis of an enol-ether involving liquid–liquid separation and continuous solvent exchange (Jensen and Buchwald).

Solid-supported multi-step flow synthesis

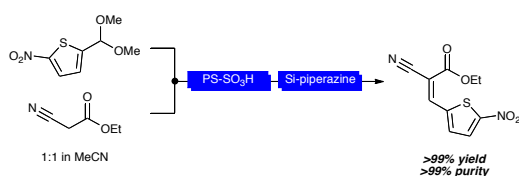
The use of supported reagents, catalysts and scavengers in synthesis is well documented and has proven to be an extremely advantageous technology in the modern laboratory.¹⁹ The combination of immobilized reagents with flow reactors²⁰ has great potential for revolutionising the synthesis process.²¹

The Ley group has pioneered the use of solid-supported reagents, catalysts and scavengers to facilitate organic synthesis and has an expanding portfolio of work in the area of continuous flow multi-step synthesis.²² Indeed, the group's 2006 synthesis of the complex natural product oxamaritidine is currently the most elaborate example of continuous flow multi-step synthesis to date (Scheme 6).²³ Employing a variety of supported reagents and catalysts, including the commercially available H-Cube hydrogenator,²⁴ seven synthetic steps were orchestrated into a single reactor network to afford the target in excellent yield (>40%) and purity (>90%).



Scheme 6 Continuous flow synthesis of oxomaritidine (Ley). PS = polymer supported.

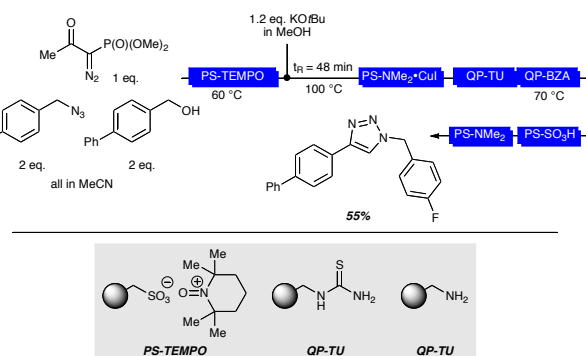
The development of catalytic process is integral to the future of synthesis²⁵ and so the use of solid-supported catalysts for multiple steps in flow systems is particularly attractive. Using an electroosmotic flow-driven miniaturized flow reactor, Watts recently reported the use of two solid-supported catalysts in series for the two-step synthesis of analytically pure α,β -unsaturated compounds (Scheme 7).²⁶



Scheme 7 Continuous two-step synthesis of α,β -unsaturated compounds using supported catalysts (Watts).

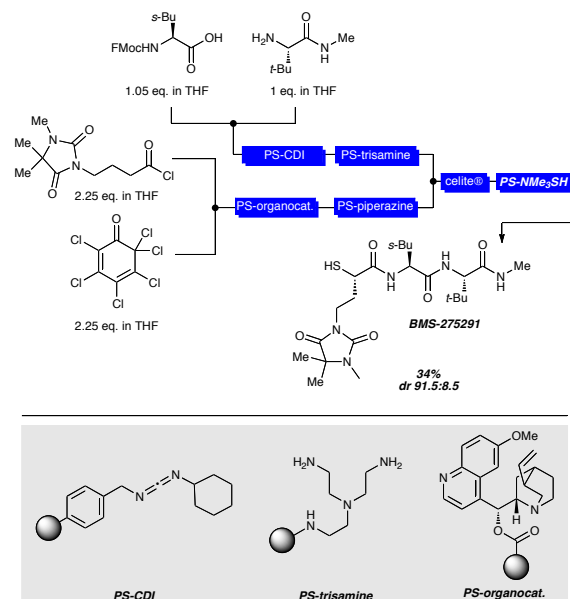
In many instances, such as the synthesis of pharmaceuticals, the quality of the final product of a synthetic route must meet stringent purity standards. An effective method for achieving in-line purification in flow-mode is the integration of solid-supported scavengers to selectively remove unwanted components of the flow stream.

The Ley group recently reported on the multi-step synthesis of triazoles²⁷ using the commercially available flow system from Vapourtec²⁸ (Scheme 8). Following three chemical transformations (oxidation, homologation and 'click' triazole formation) the flowing solution was subsequently pumped through a variety of strategically positioned solid-supported scavengers to sequester any fouling components. This effectively provided the desired product in excellent purity and without recourse to traditional column chromatography.²⁹



Scheme 8 Three-step continuous flow synthesis of a triazole employing a variety of immobilized reagents and scavengers (Ley).

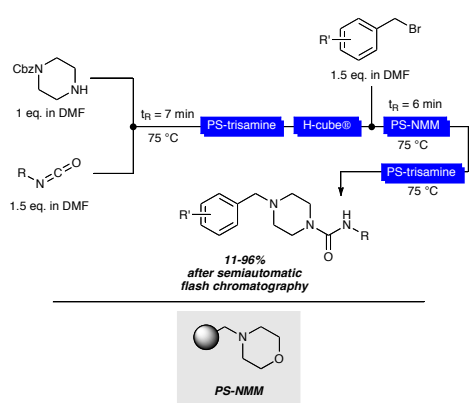
The Lectka group has described the use of sequentially linked jacketed glass columns for catalytic and enantioselective multi-step flow synthesis and reported a continuous route to the metalloproteinase inhibitor BMS-275291 (Scheme 9).³⁰ The use of scavenger columns eliminated the need for batch purification of the eluting flow stream. In their approach the flow streams were purely gravity-driven and Celite[®] was employed to control the column residence times. Remarkably impressive yields and selectivities were observed.



Scheme 9 Synthesis of BMS-275291 using a column-based system incorporating resin-bound reagents and scavengers (Lectka).

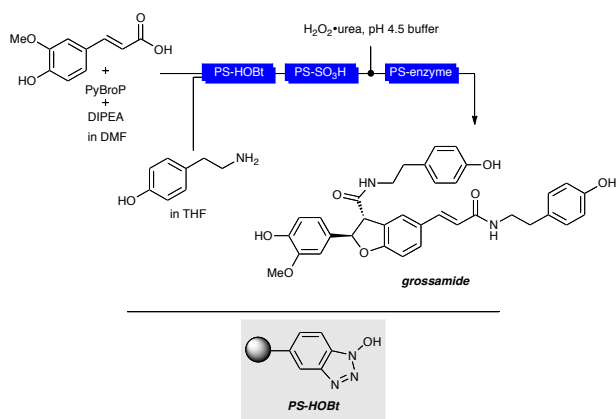
In a further example of a multiphase continuous flow system, Ulven reported the preparation of a 15-membered library of potential chemokine receptor ligands (Scheme 10).³¹ Three separate building blocks were combined in three distinct reaction steps, whilst two scavenger resins were employed to remove any unreacted substrates. Semi-automatic purification of the crude products allowed a high compound throughput, further underscoring the potential of continuous flow multi-

step synthesis as a tool for the drug discovery process.



Scheme 10 Three-step continuous flow synthesis of receptor ligands (Ulven).

Finally, immobilized enzymes have also been integrated into continuous flow systems. Ley and co-workers reported the preparation of the natural product grossamide using a continuous flow reactor system (Scheme 11).³² An initial peptide coupling protocol,³³ was followed by a peroxidase catalysed dimerization to deliver the neolignan natural product.



Scheme 11 A multi-step continuous synthesis of grossamide using an immobilised horseradish peroxidase (Ley).

Summary and Outlook

In this mini-review we hope to have demonstrated that the use of continuous flow methods for multi-step organic synthesis is a burgeoning and exciting area of research that has the potential to greatly simplify and improve the synthesis process. Indeed, with the promise of economic and safety benefits, pharmaceutical manufacturers have begun to investigate and implement continuous manufacturing as a viable alternative to the traditional batchwise synthesis of API's.³² Although many challenges remain, continuous flow multi-step synthesis may be a key breakthrough technology for enabling the efficient preparation of complex substances.

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