Continuous flow multi-step organic synthesis

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Using continuous flow techniques for multi-step synthesis enables multiple reaction steps to be combined into a single continuous operation. In this mini-review we discuss the current state of the art in this field and highlight recent progress and current challenges facing this emerging area.

Introduction

The multi-step synthesis of complex organic compounds from simpler precursors is one of the outstanding accomplishments and ongoing challenges 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 considered 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 (Fig. 1(a)). Typically, after the completion of each synthetic step (A + B → C, C → D and D → 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]

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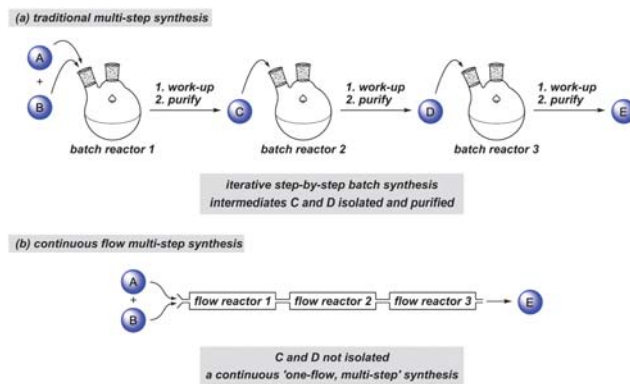
Fig. 1 Multi-step synthesis strategies.

A number of innovative strategies have been developed to increase synthetic efficiency.[3] An increasingly popular approach to streamlining multi-step syntheses is the use of continuous flow techniques[4] to combine multiple synthetic steps into a single, continuous and *uninterrupted* reactor network, thereby circumventing the need to isolate intermediate products (Fig. 1(b)). Such an approach has been called a 'one-flow, multi-step synthesis'.[5] The use of continuous flow methods for single-step transformations has been extensively reviewed elsewhere and will not be discussed in this mini-review. Here we detail some recent

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developments in the field of *multi-step* continuous flow synthesis[6] and discuss and comment upon select contemporary examples of this emerging technology.

## Multi-step flow synthesis

Solution-based approaches

The associated benefits of microreactors and continuous flow have been well documented.[4] Typically, excellent mixing and temperature control is observed meaning the technique is ideally suited for performing extremely fast and exothermic reactions. 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.[7] 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).[8] 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 time[9] (t_R) control that allows the unstable intermediates to be rapidly transferred to the next stage of the reactor before decomposition can occur.

Importantly, the ability to scale-up this technique has also been demonstrated.[10] Using the commercially available CYTOS microreactor system,[11] a two-stage system was used for the lithiation and subsequent formylation of 3-bromo-anisole (Scheme 2).
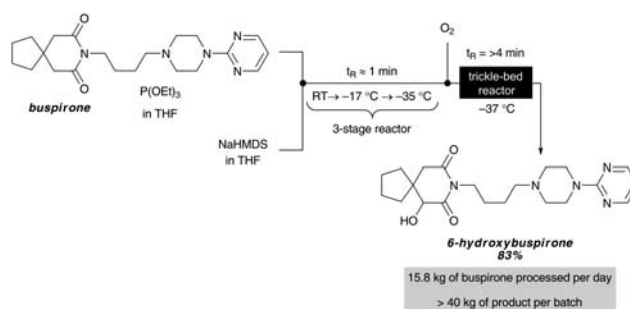
This reaction had proven difficult to reproduce on kilogram scale using batch methods (24% yield, −40 °C) owing to the long reagent dosing times that were required for effective temperature control. The efficient heat transfer properties of the microreactor system allowed the reaction to be conducted at a higher
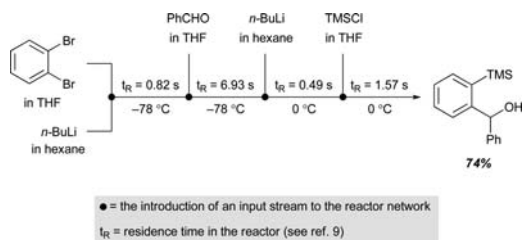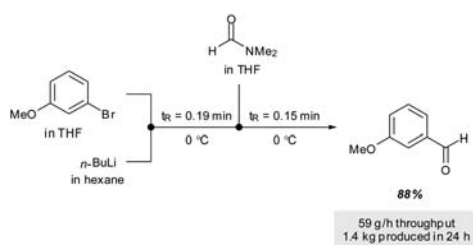
Scheme 3 Multi-kilogram scale synthesis of 6–hydroxybuspirone (LaPorte[12]).

temperature (0 °C) and with short residence times (0.19 and 0.15 min), providing the desired product in 88% yield. A 24 h experiment afforded 1.4 kg of product at a throughput of 59 g h^{-1}.

Workers at Bristol-Myers Squibb recently described the development of a pilot plant process for the continuous enolisation and oxidation of buspirone (Scheme 3).[12] Again, the use of a microreactor system allowed the reactions to be conducted at elevated temperatures compared to the batch synthesis (−38 °C *vs.* −80 °C), which contributed to a faster and more reliable reaction. The reaction volume for the continuous process was estimated to be three orders of magnitude smaller than the batch process, which offers considerable safety benefits. Finally, scale-up of the process was achieved by 'numbering-up' the trickle-bed oxidation reactor. The researchers demonstrated that simply increasing the diameter (and hence the volume) of the reactor led to a dramatic loss of temperature control within the column and increased levels of impurities from the reaction were observed.

Synthetic chemists have long known that telescoping can be an effective tactic for truncating a multi-step synthesis.[13] 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. Recently, the McQuade group reported a synthesis of the non-steroidal anti-inflammatory drug ibuprofen using continuous flow methods (Scheme 4).[14] The three-step synthesis (Friedel–Crafts acylation, 1,2-migration and ester hydrolysis) was linked into a single continuous system and provided racemic ibuprofen in 51% isolated yield following off-line workup and crystallisation of the exiting flow stream. It is important to note that this multi-step telescoping sequence would be especially difficult (and unsafe!) to replicate using batch methods. The rapid change in reaction temperature (150 °C → 50 °C) would require considerable energy expenditure. Additionally, the pH adjustment from 1 →

Scheme 1 Generation and reaction of *o*-bromophenyllithium species using flow chemistry (Yoshida[8]).

Scheme 2 Generation of kilogram quantities of 3-methoxybenzaldehyde using flow chemistry (Schwalbe[11]).
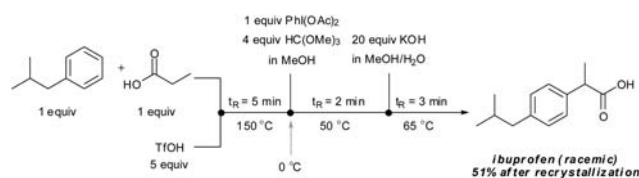

Scheme 4 Continuous flow synthesis of ibuprofen (McQuade[14]).

14 is a highly exothermic reaction and is rendered manageable only by the high surface area and efficient heat transfer properties of the microreactor system.

The ability to perform multi-step reactions in an uninterrupted continuous fashion may also be beneficial for medicinal chemistry applications.[15] Cosford recently described a continuous two-step synthesis of a focused 13-membered library of imidazo[1,2-a]pyridine-2-carboxamides (Scheme 5).[16] No isolation of the carboxylic acid intermediates 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.[17] For the example shown is Scheme 5 an impressive improvement in yield was observed for the flow synthesis compared to the original two-step batch method (46% *vs.* 16%).
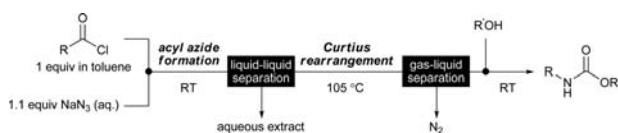
Continuous separation and distillation

Although the telescoping processes described above are effective, they are not without limitations. A significant drawback is that excess reagents are often needed to quench leftovers from previous transformations, whilst the requirement for a holistic and careful route design (to ensure downstream reagent compatibility) is an added challenge. The integration of solution-based work-ups, 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 6).[18] A microseparator incorporating a hydrophobic membrane was designed and used to successfully remove the aqueous stream and thus any water-soluble components.[19]
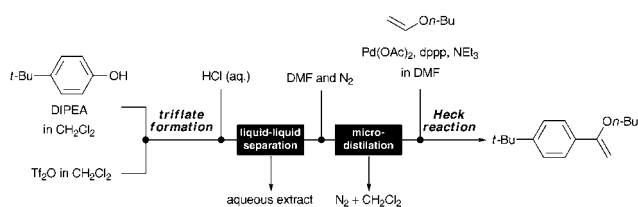
The Jensen group added a further instrument to the flow toolbox with the development of a microfluidic distillation unit capable of performing an in-line solvent switch. Working in conjunction with the Buchwald laboratory, a two-step flow
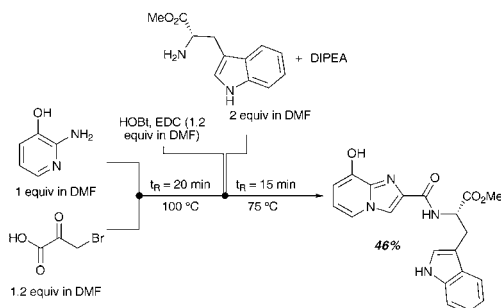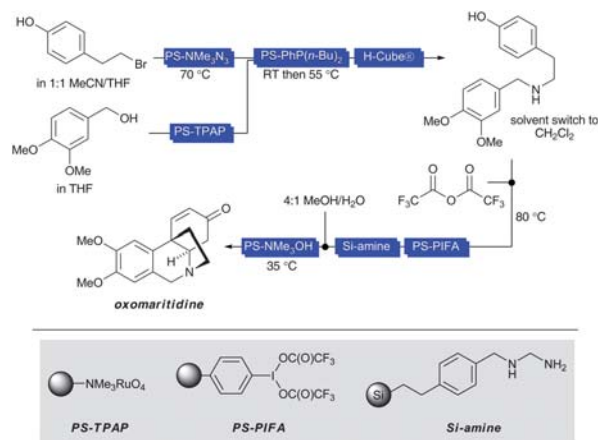
Scheme 7 Continuous synthesis of an enol-ether involving liquid–liquid separation and continuous solvent exchange (Jensen and Buchwald[20]).

sequence to prepare enol ethers was developed (Scheme 7).[20] A bespoke silicon device was employed to carry out a continuous distillation of a binary solvent mixture (dichloromethane–DMF).[21]

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.[22] The combination of immobilized reagents with flow reactors[23] has great potential for revolutionising the synthesis process.[24]

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.[25] Indeed, the group's 2006 synthesis of the complex natural product oxomaritidine is the most elaborate example of continuous flow multi-step synthesis to date (Scheme 8).[26] Employing a variety of supported reagents, catalysts and scavengers, including the commercially available H-Cube hydrogenator,[27] *seven* synthetic steps were orchestrated into a single reactor network to afford the target in excellent yield (>40%). No traditional work-up or purification procedures were required to produce the natural product with >90% purity. Impressively, the entire sequence is completed in approximately six hours whilst performing the synthesis using traditional solid-phase assisted methods would take around four days of work. The labour savings are even more impressive when one considers that the system is automated, therefore releasing the researcher to undertake further tasks.

Scheme 5 Synthesis of a Mur ligase inhibitor using multi-step continuous flow synthesis (Cosford[16]).

Scheme 6 Continuous carbamate synthesis involving multiple reactions and separations (Jensen[18]).
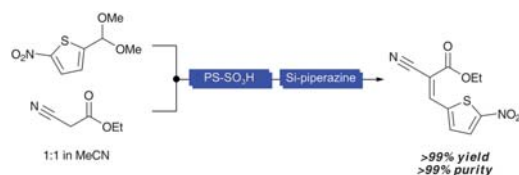
Scheme 8 Continuous flow synthesis of racemic oxomaritidine (Ley[26]). PS = polymer supported.

The development of catalytic processes is integral to the future of synthesis[28] 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 9).[29] The heterogeneous nature (and hence spatial-isolation) of the acidic and basic catalysts ensures their mutual compatibility and removes the need for any work-up or purification procedures.
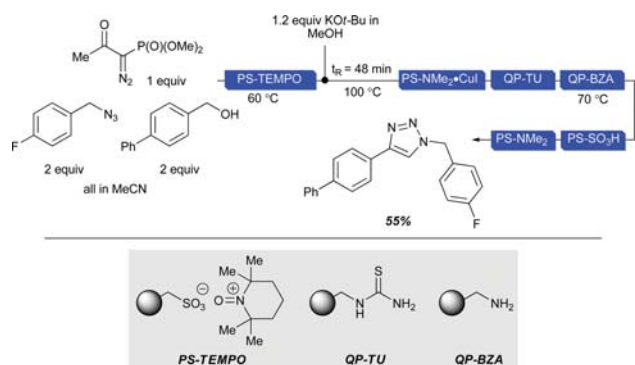
In many instances, such as the synthesis of pharmaceuticals, the quality of the final product of a synthetic route must meet stringent purity standards. An effective method for achieving in-line purification in flow-mode is the integration of solid-supported scavengers to selectively remove unwanted components of the flow stream.

The Ley group recently reported on the multi-step synthesis of triazoles[30] using the commercially available flow system from Vapourtec[31] (Scheme 10). 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. These scavengers effectively purged the flow stream of any leached copper (QP-TU), excess aldehyde (QP-BZA), basic (PS-SO₃H) and acidic components (PS-NMe₂), to provide the desired product in excellent purity and without recourse to traditional column chromatography.[32]
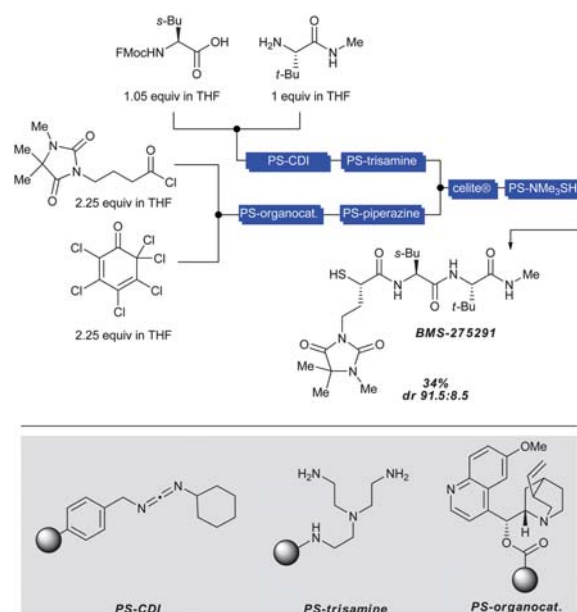
The Lectka group has described the use of sequentially linked jacketed glass columns for catalytic and enantioselective multi-step flow synthesis and reported a continuous route to the metalloproteinase inhibitor BMS-275291 (Scheme 11).[33] The use of scavenger columns eliminated the need for batch purification of the eluting flow stream. In their approach the flow streams were
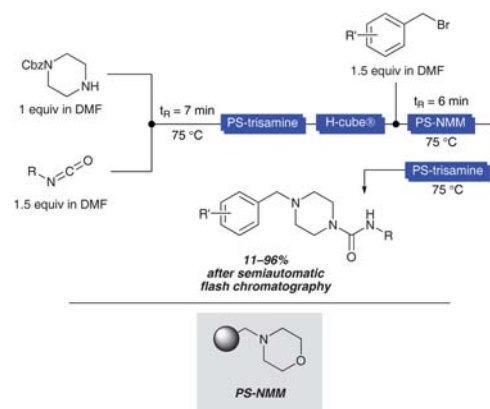

Scheme 11 Synthesis of BMS-275291 using a column-based system incorporating resin-bound reagents and scavengers (Lectka[33]).

purely gravity-driven and Celite® was employed to control the reactor residence times. Remarkably impressive yields and selectivities were observed.

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 12).[34] 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.

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 13).[35] An initial continuous peptide coupling protocol[36] was followed by a peroxidase catalysed dimerization to deliver the natural product.

Scheme 9 Continuous two-step synthesis of α,β-unsaturated compounds using supported catalysts (Watts[29]).

Scheme 10 Three-step continuous flow synthesis of a triazole employing a variety of immobilized reagents and scavengers (Ley[30]).

Scheme 12 Three-step continuous flow synthesis of receptor ligands (Ulven[34]).
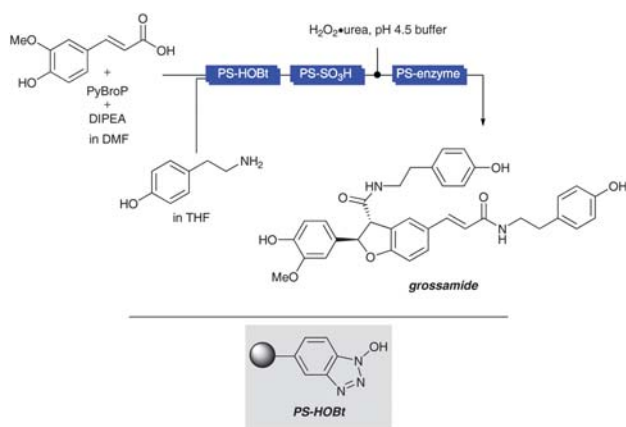
Scheme 13 A multi-step continuous synthesis of grossamide using an immobilised horseradish peroxidase (Ley[35]).

Summary and outlook

In this mini-review we hope to have demonstrated that continuous flow multi-step organic synthesis is a burgeoning and exciting area of research. Furthermore, our own experiences in this area[37] have suggested to us that this field has the potential to simplify and improve the synthesis process. Indeed, with the promise of economic, safety and time-saving benefits, pharmaceutical manufacturers have begun to investigate and implement continuous manufacturing as a viable alternative to the traditional batchwise synthesis of APIs.[38] The ultimate goal may be to consolidate all aspects of manufacturing (synthesis, finishing and packaging) into a single location, thereby miniaturizing the entire production process.[39]

However, despite much progress, in order to realise the full potential of flow chemistry a number of hurdles must still be overcome. The manipulation of solids, both as reagents and products, is still largely an unsolved problem and 'clogging' plagues much of the flow-based research currently being conducted.[40] The assembly of several reactors in series often leads to a significant build-up of system pressure, requires the precise orchestration of multiple flow streams and can lead to prohibitively dilute reaction solutions. In these instances, continuous methods for solvent removal and switching become increasingly important. Recent reports[21] of in-line distillation as part of a multi-step sequence are encouraging but may be limited to the removal of volatile solvents. A related technical challenge is reaction dispersion, particularly when heterogeneous systems are involved. As recently described by the Ley laboratory,[21b, 41] when substrate dispersion becomes significant, controlling reagent stoichiometry for subsequent reaction steps becomes a considerable challenge. In-line and real-time analytical techniques may be a solution to this problem.[41] Alternatively, catch-and-release strategies offer an ideal opportunity for product concentration, solvent switching and purification all in a single operation.[42]

Finally, a significant hurdle to the development of continuous flow organic synthesis may simply be unfamiliarity. Synthetic chemists are trained to conduct synthesis using traditional batch techniques and the technical aspects of flow chemistry may thus appear unnecessarily daunting and alien. Consequently, interdisciplinary collaborations between chemists and engineers will be essential for future developments in continuous flow chemistry.[43] 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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