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Expanding chemistry's horizon with continuous-flow reactors

Abstract
Continuous-flow micro- and mesofluidic reactors come with inherent properties that can be advantageously utilized for expanding the horizon of preparative chemistry. Accurate control over local process parameters, even under extreme conditions, inherent safety, production homogeneity and seamless scale-up are amongst the most important assets of continuous-flow chemistry. Besides, flow chemistry enables the design of efficient multistep processes with significantly reduced footprints. In this note, we discuss some of the most fascinating aspects of continuous-flow micro- and mesofluidic reactors in the specific context of preparative organic chemistry.

Keywords
Continuous-flow chemistry, enabling technology, unusual conditions, reaction telescoping

1. Introduction

For centuries, chemists have utilized macroscopic batch reactors (MBRs, Figure 1a and Table 1) for the transformation of raw chemicals into high value-added products. MBRs are characterized by internal dimensions typically greater than 10^4 μm, by internal volumes ranging from mL to kL, and processing capabilities ranging from mg to t. Chemists usually learn chemistry in lab-scale MBRs, such as classical glass round-bottomed flasks (Figure 1a). These MBRs are extremely versatile and relatively affordable, accounting for their omnipresence in labs. They are compatible with virtually all branches of chemistry, from polymers to nanoparticle synthesis, from peptide modifications to total synthesis. Large MBRs are compatible with mass production of an incredibly large amount of commodity and specialty chemicals (Table 1).

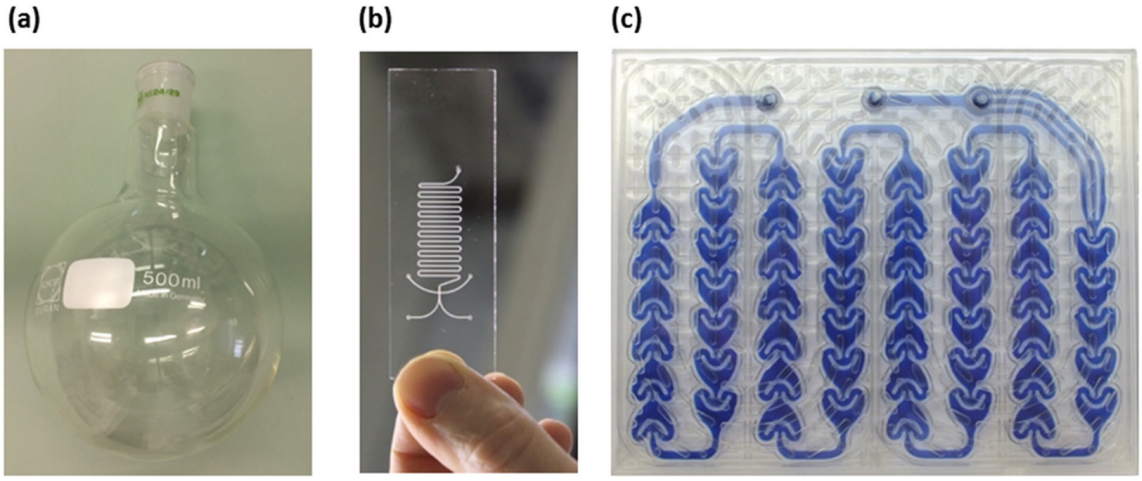


Figure 1: **(a)** Macroscopic batch reactor (MBR); **(b)** Microfluidic continuous-flow reactor; **(c)** Mesofluidic continuous-flow reactor (Courtesy of Corning®)

Despite their popularity, the inherent specifications of MBRs drastically limit the chemical space accessible, hence markedly impacting the way chemical strategies are designed. For instance, the upper temperature limit is usually dictated by the boiling point of the solvent, and pressures greater than 2 bar are difficult to access in standard glass MBRs. Chemical manufacturing in MBRs also comes with additional drawbacks such as poor mixing efficiency and heat transfer, with a dramatic impact not only on reaction purity, process efficiency and productivity, but also on process safety.

Scale-up is notoriously time-consuming in MBRs: each increase in production scale often requires multiple re-optimizations and suffers from batch variability. Most importantly, many organic processes that require the handling of toxic, hazardous or rapidly decaying molecules in MBRs at large scales remain problematic. Accessing advanced molecular architectures according to MBRs strategies often requires stepwise approaches (Figure 2) relying on manual interruption, large chemical intermediate inventories and transportation of synthetic intermediates or active ingredients, which not only result in low global efficiency and productivity, but also often account for quality deficiency. Large internal volumes are also poorly compatible with greener alternative processing technologies such as photochemistry.

The last decade has witnessed the emergence of a new chemical process technology based on micro- and/or meso-structured continuous flow reactors (aka micro- and mesofluidic reactors, MFRs, Figure 1b,c and Table 1) [1-5]. MFRs are characterized by channels with internal dimensions smaller than 10^3 μm (typically 100-800 μm) and by internal volumes ranging from μL to mL, yet capable of processing large amount of chemicals due to their continuous nature [4, 5]. Chemicals flow through well-defined channels and are processed under strictly controlled conditions [4, 5].

Microfluidic reactors usually have internal dimensions below 500 μm, and internal volumes of up to several hundred μL (Figure 1b), while mesofluidic reactors have larger internal diameters (up to 1000 μm) and

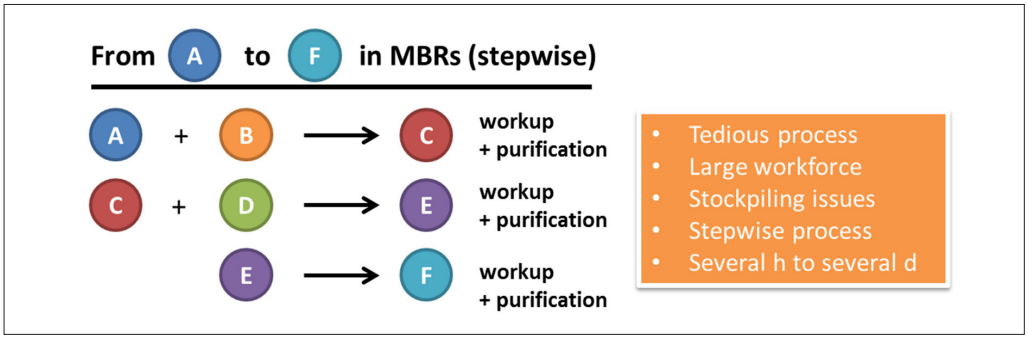


Figure 2: Classical stepwise approach using MBRs. The individual steps are spatially and temporally disconnected

KEY FEATURES	MBRs	MFRs
	3D internal structure >> 10^4 μm	3D internal structures < 10^3 μm
	mL < internal volume < kL	μL < internal volume < mL
	mg < productivity < t	mg < productivity < t
	Scale-dependent processes	Scale-independent processes
	Low surface/volume ratio	High surface/volume ratio
	Production variability	Homogeneous production
	Conventional conditions	Expansion of chemical space
	Safety concerns	Inherently safer
	Significant footprint	Reduced footprint
	Resource/time consuming scale-up	Fast transfer from R&D to production
	Robust, versatile, common cost-efficient technology	New technology with still scarce know-how, high starting costs
	Compatible with gas, solids & liquids	Processing solids is challenging
	Product traceability (batch #)	Product traceability to be redefined

Table 1: Comparative features of macroscopic batch and continuous-flow reactors

larger internal volumes, up to several mL (Figure 1c). MFRs offer a wide range of advantages for processing chemicals: precise control over the local reaction conditions, fast mixing and efficient heat transfer, inherent safety, and homogeneity of the production are amongst the most important [1, 6, 7]. Extreme conditions of temperature and pressure are readily implemented in MFRs to boost chemical reactivity, yet keeping full control on process parameters [6]. Additionally, MFRs enable a fast transfer between R&D and production using scale-out or numbering-up strategies. MFRs enable faster, cleaner and safer chemical transformations, and hence more reliable, reproducible and efficient processes [8-10].

2. Flow chemistry: key concepts and principles

Continuous-flow chemistry is a term widely utilized to describe the performance of a chemical reaction in a MFR, rather than in a MBR. Flow chemistry exploits the inherent properties of MFRs to enable the continuous production of chemicals within a strictly controlled environment [4, 5]. The behavior of fluids in macroscopic environments differs significantly from that in micro-/mesofluidic systems [1, 4, 5]: in MBRs, fluid dynamics is mostly dominated by pressure and gravity, while in MFRs, surface tension, energy dissipation and fluidic resistance start to dominate the system. [1] Consequently, one can expect very different behaviors for chemical reactions when performed in MBRs or MFRs (Figure 3).

Another striking difference between MBRs and MFRs is their intrinsic surface-to-volume (S/V) ratio (Table 2). Since reaction heat is primarily evacuated through the wall of the reactor, the S/V ratio has a huge impact on the heat exchange phenomenon. Smaller S/V ratios account for less efficient heat exchange, which can have dramatic consequences for large-scale exothermic reactions. In the best case scenario, a poor heat exchange results in a wider temperature distribution and/or hot spots in the reaction vessel that could trigger side reactions and deplete purity profiles; in the worst case scenario, a poor heat exchange can lead to a runaway. MBRs come with fairly small S/V ratios as a consequence of their large internal volumes, while MFRs usually have much larger S/V ratios, and are therefore more efficient for accurately controlling the temperature profile. Obviously, other parameters intervene in heat transfer such as the nature of the reactor wall (material and thickness) and the design of the heat exchanger. Many examples in the literature illustrate the benefits of MFRs either for the implementation of highly exothermic reactions under safe continuous-flow conditions or the suppression of hot-spots related side-reactions [1, 4, 5].

Reactor type	Surface/volume ratio (cm^2/cm^3)
100 mL MBR	1
1 m^3 MBR	0.06
MFR 100 µm channel	200

Table 2: S/V ratios for representative MBRs and MFRS

Mixing also occurs according to different phenomena depending on the process technology. In MBRs, mixing occurs mainly through macromixing (fluid circulation through mechanical agitation) and micromixing (diffusion), with typically transitional

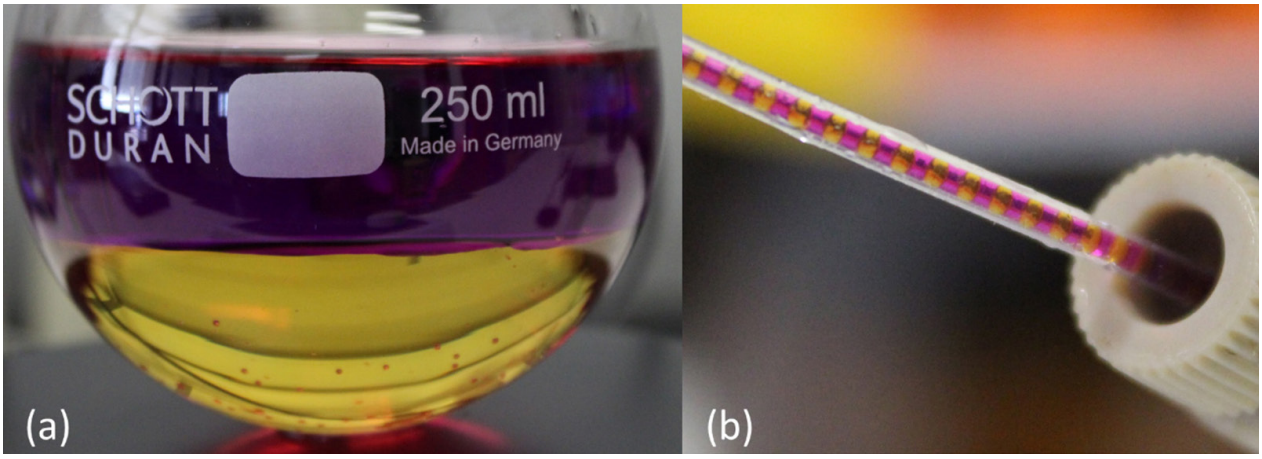


Figure 3: Cyclohexane extraction of iodine from an aqueous solution of potassium triodide. **(a)** In MBRs, phase separation occurs according to density and gravity; **(b)** in MFRs, surface tension, energy dissipation and fluidic resistance dominate, resulting in segmented fluidic systems (channel diameter: 500 µm)

or turbulent flow patterns. Macromixing strongly depends on an external energy input (*i.e.* the rotation speed of the impeller), and the design of the stirrer. Achieving homogenous solution in MBRs can be time consuming, hence leading to local excess of chemicals that can trigger side-reactions. Contrastingly, in MFRs, mixing occurs mainly through passive micromixing: in straight micrometric channels, flow patterns are usually laminar, and mixing occurs through diffusion only. Various static micromixers (Figure 4) can be implemented to induce multilamellation or the formation of vortices, and hence increase mixing efficiency. Active micromixing can also be implemented, but requires an external source of energy such as ultrasonic transducers.

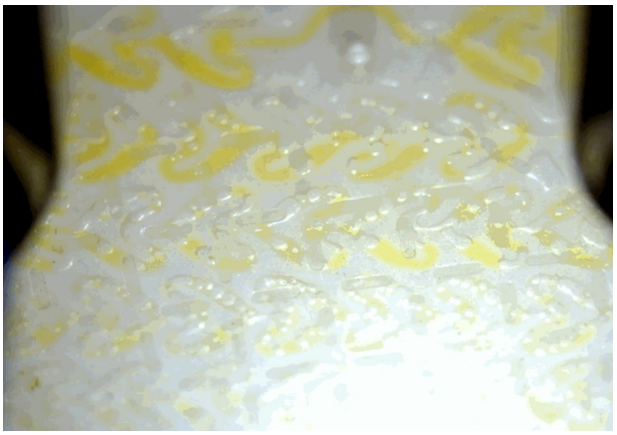


Figure 4: Gas-liquid reaction under continuous-flow conditions in a mesofluidic device showing details of heart-shaped static mixers (Courtesy of Corning®)

Transposing a chemical process from a MBR to a MFR setup is not obvious, and requires some important adaptations. Shifting from batch to continuous-flow processes imposes a new paradigm (Figure 5): high-precision dosing pumps, flow meters, connectors, micro/mesofluidic assemblies and pressure regulators replace the usual chemist's spatula, pipette, magnetic stirrer, round-bottomed flask and septa. Flow chemists work rather with flow rates (usually mL min^{-1}), local molar ratios, residence times (usually min) and outputs (usually mmol or g min^{-1}) than finite quantities, equivalents, reaction times and yields [4, 5].

A challenging aspect of flow chemistry is inherently related to the concept of flowing chemicals within narrow channels; it requires the selection of appropriate dosing pumps or flow meters, and is paramount for a successful continuous-flow process. The most common pumps utilized in flow chemistry are pressure-driven, although other technologies such as electro-osmotic systems do exist. An accurate control of the flow rate in the well-defined environment of a MFR adds a significant layer of control for chemical processes [4 5].

Beyond the selection of pumping devices, appropriate connectors to convey the chemicals towards the reactor are paramount, and should sustain the mechanical stress imposed by the process conditions. The MFR itself is another essential part of a continuous-flow setup. Various materials can be selected for machining MFRs, such as glass, metals, polymers and ceramics, and their internal features have to be carefully designed for a perfect match. Chemical and mechanical compatibility must obviously be assessed prior to carrying out any experiments [4, 5].

While in batch, precipitation is never a problem and is often used to shift chemical reactions toward completion, the appearance of a solid precipitate, or an increase in viscosity can be very challenging to manage under continuous-flow conditions. Such processes have to be adapted to avoid clogging or rupture of the MFR. On the other hand, the implementation of unusual conditions such as quick exposure to high

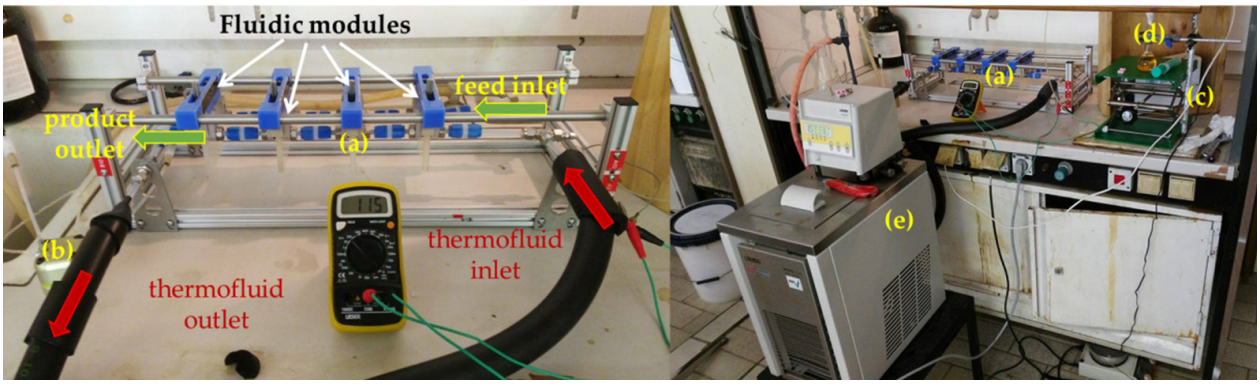


Figure 5: Illustration of a typical lab-scale continuous-flow MFR setup. (a): reactor (Corning® Advanced-Flow™ Low-Flow) configuration showing 4 fluidic modules, (b): back-pressure regulator (BPR), (c): HPLC pump, (d): feed solution, (e): thermostat

temperatures or controlled irradiation with light sources is very easy. Additionally, the precise control on residence time enables to quench reactions within millisecond time-frames, and hence access short-lived species before their decomposition [1, 4, 5].

Other less conventional processes than just thermal also tremendously benefit from a development in MFRs. For instance, continuous-flow organic photochemistry is a blooming research area with arguably a huge industrial impact. Indeed, photochemistry in MBRs on large scale is mainly hampered by low light penetration in large reaction vessels, restricting photochemical transformations to small scale, highly-diluted and time-consuming processes. Contrastingly, the narrow channels of MFRs, and the precise control of residence, and thus, exposure time are game changers that led to successful applications for organic photochemistry at a production scale under continuous-flow conditions (Figure 6) [4, 5, 11-16].

Complex molecular architectures require multistep processes that are carried out stepwise in conventional MBRs (see above), coming with significant safety issues related to large inventories of chemical intermediate and/or the transportation of synthetic intermediates. An appealing aspect of continuous-flow chemistry for multiple step chemical process is the integration of multiple steps, including purifications, into an uninterrupted continuous reactor network (*i.e.* reaction telescoping), rather than being performed individually (Figure 7) [17]. Reaction telescoping is of particular interest for reaction sequences involving hazardous, unstable or transient species: rather than being stockpiled, these hazardous/unstable/transient species are immediately reacted inside the MFR network, therefore avoiding degradation and decreasing chemical risk [7, 17].

Despite their small internal volumes, MFRs are readily utilized for industrial-scale production. Most importantly, MFRs enable a fast and seamless transfer from lab-scale R&D to production: reaction conditions are optimized on a small scale in microfluidic reactors, and then transferred to mesofluidic reactors to increase production scale (*i.e.* scale-out, see Figure 10). This often comes with minimal reoptimization, which drastically reduces the timeframe for increasing the production scale. Another option for increasing the productivity consists in working with several identical MFRs operated in parallel (*i.e.* numbering-up) [4, 5]. Besides, their extremely small footprint and versatility drastically reduce operating costs, and could lead to mobile production units [18]. Since 2007, continuous-flow chemical processing has become a top research priority, and an increasing number of continuous-flow applications are currently exploited in industrial facilities [19-21].

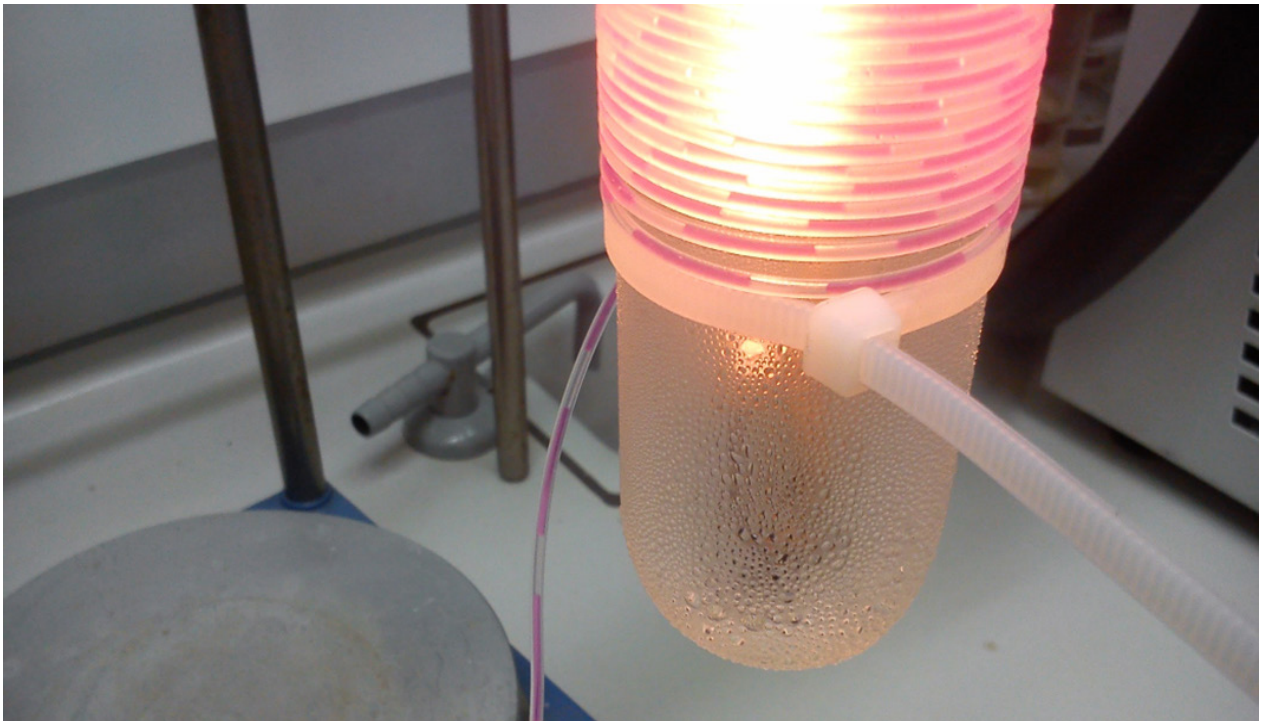


Figure 6: Illustration of a photochemical reaction under segmented gas/liquid continuous-flow conditions (oxygen/water, substrate and rose Bengal). The PFA capillary is wrapped around a thermostatized halogen light source

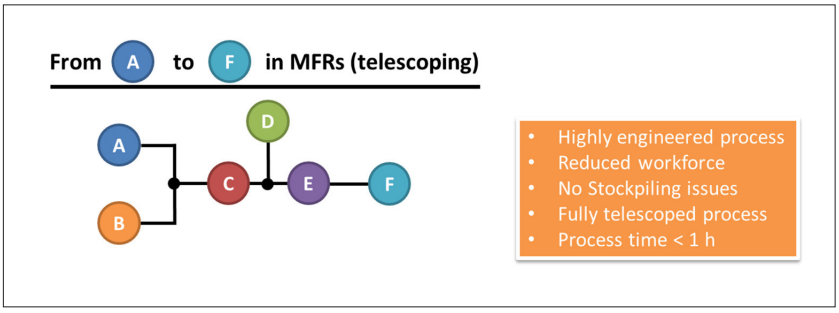


Figure 7: Illustration of multistep reaction telescoping in MFRs. The individual steps are spatially and temporally connected

3. Flow chemistry @ ULg

3.1. The Center for integrated Technology and Organic Synthesis

The Center for Integrated Technology and Organic Synthesis (CiTOS, more details at www.citos.ulg.ac.be) was created in 2013 as a part of the Department of Chemistry and of the Molecular Systems Research Unit (MolSys) at the University of Liège. Current research projects revolve around the implementation of micro- and mesofluidic reactors and the development of innovative strategies for accessing high-value added organic molecules under unconventional conditions. CiTOS also organizes a series of lectures to teach the fundamental as well as the practical aspects of continuous-flow chemistry to Master students [22]. This series of lectures offers a very unique opportunity to acquire the necessary theoretical background, to convey the subject matter at hand through practice in the lab, as well to visit industrial facilities using MFRs and flow chemistry equipment.

3.2. Representative case studies

Some of our ongoing projects exploit the benefits of continuous-flow chemistry for handling hazardous, toxic, rapidly decaying or transient species as reactive chemical intermediates. In particular, the handling of carbenes and diazo species in MFR setups was studied. We recently reported a method that uses the inherent properties of MFR devices to simplify the preparation of common *N*-heterocyclic carbenes (NHCs) from stable imidazol(in)ium precursors such as compound **1** (Figure 8) [23]. NHCs are highly reactive, oxygen- and moisture-sensitive species, and telescoping their preparation and use in the controlled and confined environment of a MFR setup could therefore drastically simplify their handling. The microfluidic setup we designed in this context enabled the generation of free nucleophilic carbenes under homogeneous conditions and their use as organocatalysts further downstream. NHC generation was next telescoped with benchmark NHC-catalyzed reactions such as transesterification and amidation reactions.

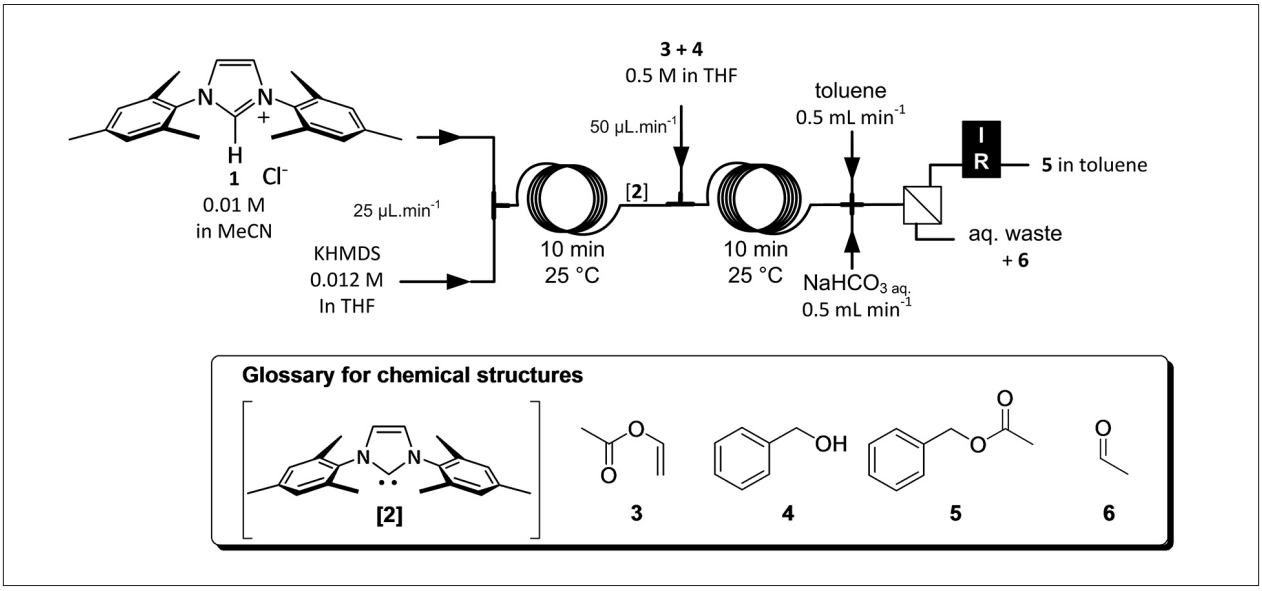


Figure 8: *In situ* generation of free nucleophilic NHCs and organocatalysis under continuous-flow conditions featuring in-line IR spectroscopy (simplified flow-chart). For details, the reader is refereed to ref. [23]

These reactions proceeded with total conversion, and excellent yields were achieved, showcasing the first examples of continuous-flow organocatalysis with NHCs, such as a transesterification of vinyl acetate **3** with benzyl alcohol **4** in the presence of NHC **2** (Figure 8). It turned out that this microfluidic setup enabled the fast scouting of reaction parameters and the screening of various NHC precursors to determine structure-activity relationships for free nucleophilic NHCs. In-line reaction monitoring, downstream quench, and liquid-liquid extraction/separation techniques were implemented as well.

The successful implementation of organocatalytic applications with free carbenes under continuous-flow conditions led us to consider other carbene-based reactions. In particular, the peculiar reactivity of carbene species toward activated C-H bonds was investigated for the preparation of a pharmaceutical ingredient. Two strategies involving either inter- or intramolecular activated C-H carbene insertions were developed under continuous-flow conditions, and their performances were assessed for the production of methylphenidate hydrochloride (Ritalin®, **10**) [24, 25]. Both inter- and intramolecular strategies imply the telescoping of multiple processing steps, including reactions and purifications. The carbene species were obtained by thermal, photochemical or catalytic decomposition of diazoester or diazoamide precursors (Figure 9).

The MFR setup for the intermolecular pathway telescoped the preparation of an explosive organic azide (**7**), a diazo transfer reaction towards methyl phenyldiazoacetate (**8**) and an unprecedented continuous-flow Rh-catalyzed intermolecular C-H carbene insertion, providing methylphenidate hydrochloride **10** in up to 38% (3.9 g d^{-1}) isolated yield after Boc-deprotection (Figure 9a).

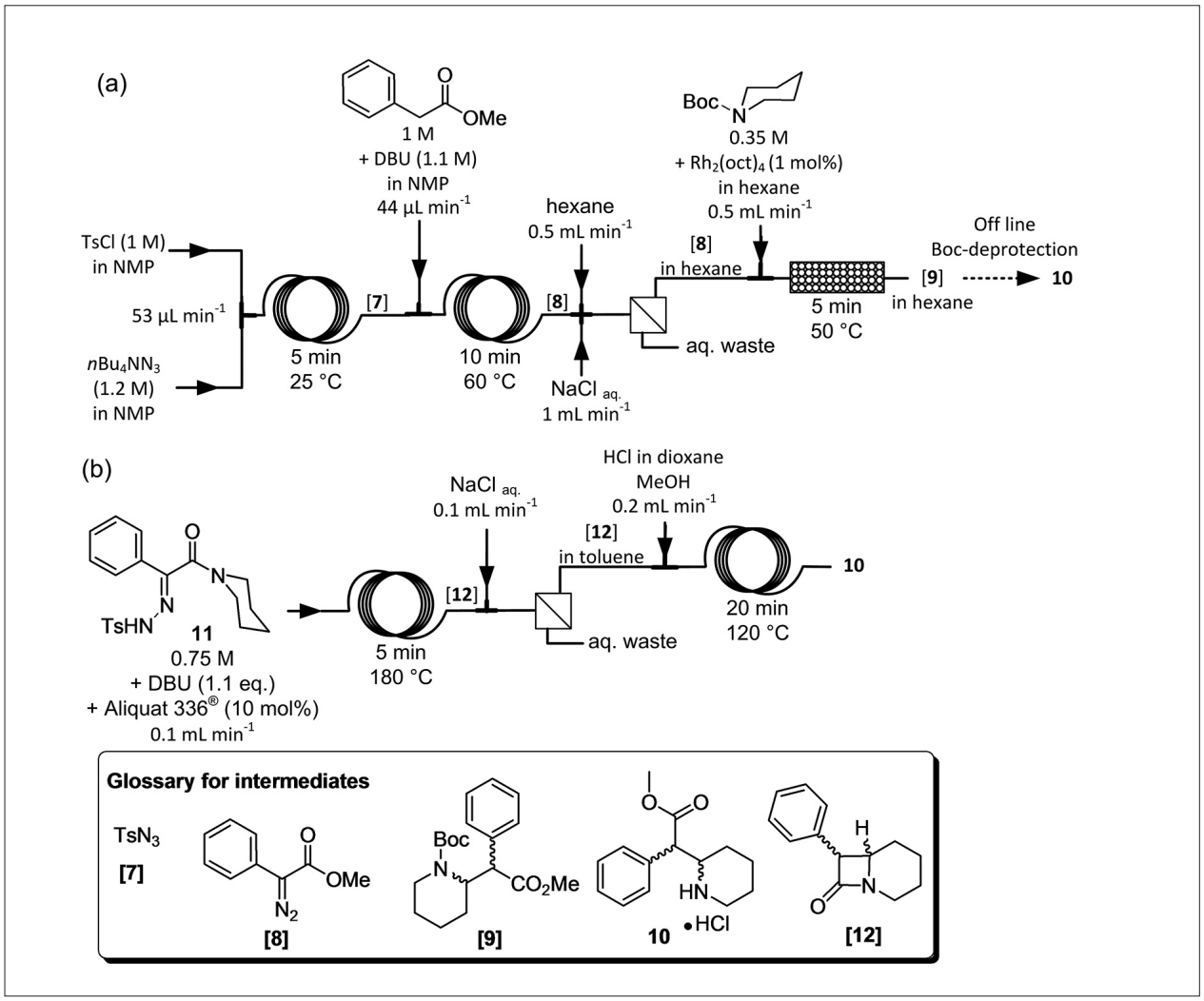


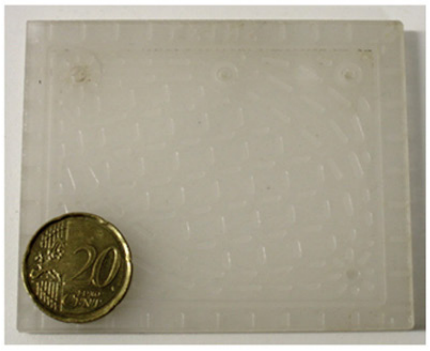
Figure 9: Illustration of reaction telescoping for the continuous-flow production of methylphenidate hydrochloride (**10**). **(a)** Fully telescoped intermolecular strategy (simplified flow-chart); **(b)** Fully telescoped intramolecular strategy (simplified flow-chart). For details, the reader is refereed to ref. [25]

The MFR setup for the intramolecular pathway formally telescoped several process steps (Figure 9b): (a) the thermal decomposition of tosylhydrazone **11** giving a β-lactam intermediate **12** through a C-H carbene insertion, (b) an in-line purification and (c) a methanolysis under acidic catalysis. The fully telescoped intramolecular process (25 min total residence time) gave methylphenidate hydrochloride (**10**•HCl) in 70% isolated yield with a 2.2:1 threo/erythro ratio, corresponding to a daily productivity of about 1400 doses.

The scalability of the most promising intramolecular thermal process was next assessed, and the critical formation of β-lactam intermediate **12** was implemented in glass mesofluidic reactors following a scale-out strategy [25]. The production scale was significantly improved starting with 21.7 g day^{-1} in a microfluidic PFA coil reactor (0.5 mL internal volume), to 86.9 g day^{-1} with a mesofluidic glass reactor (Corning® Advanced-Flow™ Low-Flow Reactor, 2 mL internal volume) and to a remarkable 4.25 kg day^{-1} with a pilot-scale mesofluidic reactor (Corning® Advanced-Flow™ G1™ Reactor, 36 mL internal volume), while keeping a minimal footprint (Figure 10).

Unusual conditions such as flash thermolysis of sensible organic substrates are easily accessible under continuous-flow conditions. For instance, we developed a robust and convenient continuous-flow mesofluidic device for the thermolysis of sensitive methionine sulfoxide derivatives **13** (Figure 11) [26]. The design of the mesofluidic reactor enabled accurate control of reaction time and conditions, affording a convenient scale-independent procedure for the production of *N*,*C*-protected vinylglycine derivatives **14**. Thermolysis was effective at 270 °C under 1000 psi of pressure in superheated toluene. Under these conditions, total conversion was usually reached after less than 2 min, with daily outputs ranging from 11 to 46 g day^{-1} with excellent selectivity and enantiomeric excess (>97%). Process efficiency was greatly improved in comparison with the batch process, and in-line purification unit was inserted downstream to remove water-soluble impurities.

Controlled flash chemistry at high temperatures on biosourced organic substrates is currently investigated in mesofluidic reactors in the context of a project supported by the European Regional Development Fund (Intense4Chem). Researchers at CiTOS currently develop scalable and intensified processes for the valorization of biomass. The project includes various partners in Wallonia such as the Centre of Technological Resources in Chemistry (Certech), and is supported by major Walloon industrial partners. For instance, glycerol is studied as a bio-sourced platform molecule for the production of a variety of relevant industrial building blocks such as glycerol carbonate, glycidol, allyl alcohol or acrolein. The project includes other bio-sourced platform molecules such as hydroxymethylfurfural (HMF) and furfural. The aim of this project is to develop a compact, versatile and intensified production unit.



Mesoscale (Corning® LowFlow™)
86.9 g day^{-1}

Mesoscale-pilot (Corning® G1™)
4.25 kg day^{-1}

Figure 10: Process scale-out for the preparation of chemical intermediate **12** showing details of mesofluidic modules (Courtesy of Corning)

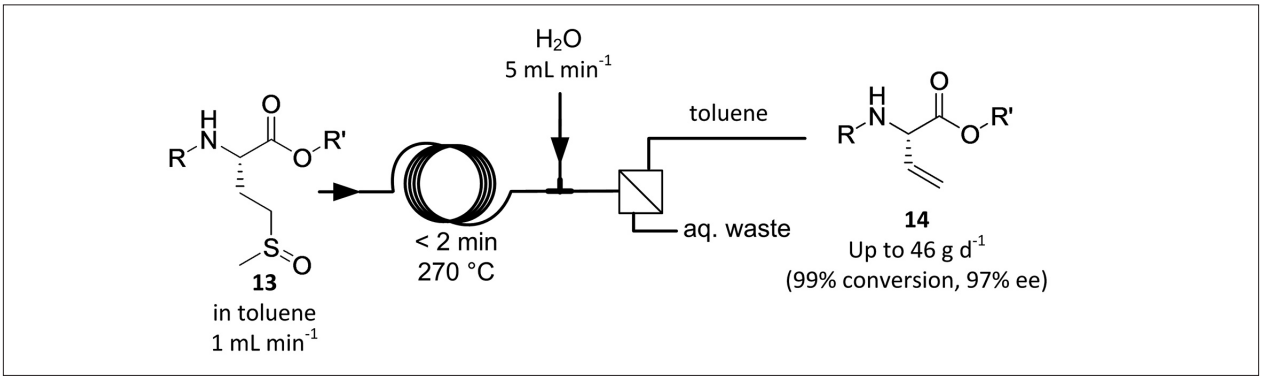


Figure 11: Continuous-flow flash thermolysis of methionine sulfoxide derivatives (simplified flow-chart). For details, the reader is refereed to ref. [26]

As mentioned in the introduction of this note, photochemical processes can also benefit from the inherent properties of MFRs. In some of our ongoing projects, we develop photocatalytic processes that combine multiple assets of flow reactors, including improved light penetration, accurate control of the exposure time and the efficient generation and handling of short-lived reactive species such as singlet oxygen. This project combines various areas of expertise from organic chemists, chemical engineers and physicists. It aims at the development of integrated photocatalytic microreactors for the continuous synthesis of high value-added organic molecules, such as active pharmaceutical ingredients, through the efficient *in situ* generation and handling of singlet oxygen.

4. Perspectives

Continuous-flow chemistry drastically expands the horizon of what is achievable in chemistry. Not only it enables the access to unconventional conditions such as high temperatures and pressures, but it also enables the efficient processing of unstable or rapidly decaying molecules, and accelerates the transition from lab scale to production scale. Complex reaction sequences can be literally telescoped within uninterrupted continuous-flow reactor networks, leading to compact, mobile and extremely versatile processes.

Current challenges are mostly dedicated to increasing molecular and process complexity. Flow chemists are currently developing new tools for the implementation of complex unit operations such as in-line (re) crystallization, resolutions, advanced purifications and in-line analysis. Further technology challenges deal with in-line testing or purification of large biomolecules through specific affinity, as well as the development of advanced automation tools and the miniaturization of auxiliaries. Flow chemistry also brings up new regulatory challenges that are currently evaluated by the authorities. Most importantly, flow chemistry should be included in early chemistry curriculum to provide the new generations with the fundamental as well as the practical aspects of this enabling technology.

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