

Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products

Riccardo Porta, Maurizio Benaglia,* and Alessandra Puglisi*

Dipartimento di Chimica, Università degli Studi di Milano Via Golgi 19, I-20133 Milano, Italy

ABSTRACT: Recently, application of the flow technologies for the preparation of fine chemicals, such as natural products or Active Pharmaceutical Ingredients (APIs), has become very popular, especially in academia. Although pharma industry still relies on multipurpose batch or semibatch reactors, it is evident that interest is arising toward continuous flow manufacturing of organic molecules, including highly functionalized and chiral compounds. Continuous flow synthetic methodologies can also be easily combined to other enabling technologies, such as microwave irradiation, supported reagents or catalysts, photochemistry, inductive heating, electrochemistry, new solvent systems, 3D printing, or microreactor technology. This combination could allow the development of fully automated process with an increased efficiency and, in many cases, improved sustainability. It has been also demonstrated that a safer manufacturing of organic intermediates and APIs could be obtained under continuous flow conditions, where some synthetic steps that were not permitted for safety reasons can be performed with minimum risk. In this review we focused our attention only on very recent advances in the continuous flow multistep synthesis of organic molecules which found application as APIs, especially highlighting the contributions described in the literature from 2013 to 2015, including very recent examples not reported in any published review. Without claiming to be complete, we will give a general overview of different approaches, technologies, and synthetic strategies used so far, thus hoping to contribute to minimize the gap between academic research and pharmaceutical manufacturing. A general outlook about a quite young and relatively unexplored field of research, like stereoselective organocatalysis under flow conditions, will be also presented, and most significant examples will be described; our purpose is to illustrate all of the potentialities of continuous flow organocatalysis and offer a starting point to develop new methodologies for the synthesis of chiral drugs. Finally, some considerations on the perspectives and the possible, expected developments in the field are briefly discussed.

1. INTRODUCTION

Organic synthesis has traditionally been performed in batch which means in round-bottomed flasks, test tubes, or closed vessels; recently, continuous flow methodologies have gained much attention from synthetic organic chemists.¹ Until a few years ago, continuous flow processes were a prerogative of petrochemical and bulk chemicals industries, where dedicated continuous plants exist and proved as most economical; recently, application of these systems for the preparation of fine chemicals, such as natural products² or Active Pharmaceutical Ingredients (APIs) has become very popular, especially in academia. Although pharma industry still relies on multipurpose batch or semibatch reactors, it is evident that interest is arising toward continuous flow manufacturing of APIs.³

However, flow technologies have not been restricted to the synthesis of organic molecules. Researchers from the Novartis-MIT Center for Continuous Manufacturing in Cambridge reported in a spectacular work the end-to-end continuous manufacturing of an API, aliskiren hemifumarate.⁴ The described process starts from a chemical intermediate and performs the reactions and the required additional operations (quench, work up, isolation, and purification) in continuo. That means that not only chemical transformations and separations, but also crystallizations, drying, and formulation are all integrated in one single, fully automated continuous process. Impressively, the Novartis-MIT pilot plant produces 100 g/hour of aliskiren, featuring two synthetic steps, API salt formation and crystallization, and delivering as the final

products of this process the tablets containing 112 mg of free aliskiren. The continuous reactor used in the work has a volume of 0.7 L and would allow the preparation of 0.8 tons of API/year. Imaging to apply the technology to a commercial scale of 188 tons of API/year, the continuous reactor volume required would be of 136 L that very favorably compares with the actual batch reactor volume that is of about 1500 L. Moreover, while the reactions in batch require 48 h, at refluxing conditions, the continuous process is complete in 1 h only, and it operates in solvent free conditions; overall, the batch process requires a processing time of 300 h and 21 unit operations vs the 48 h and 13 unit operations of the flow process. Those figures result for the automated flow process in a lower, more convenient environmental factor and in a reduced footprint.⁴

The just mentioned example clearly testifies for the great potentialities of the flow systems; the reasons for this new interest toward continuous flow processes can be found in the intrinsic characteristics of the flow reactors. Typically, a continuous flow process is run, on laboratory scale, in the so-called "microreactor",⁵ a small-diameter device in which the reaction takes place under rigorously controlled conditions in a confined space. The great peculiarity of a flow system is a very efficient heat and mass transfer, that allows to speed the reaction rate up so that productivity is generally greatly improved with respect to the batch system.⁶ Not only heat

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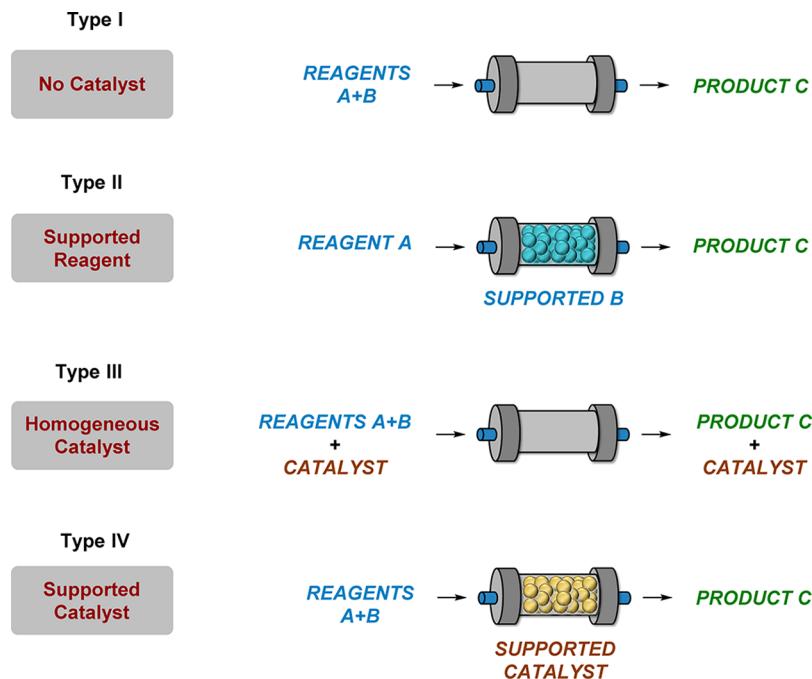


Figure 1. Types of continuous flow systems.

transfer is favored, but also the heat exchange can be precisely monitored: due to the small dimensions, it is very easy to apply and remove a heating source, thus permitting a very precise temperature control along the microreactor and avoiding uncontrolled hazardous exothermic processes. In general, reaction parameters such as temperature, pressure, and flow rate, are more easily set up and monitored with respect to a batch process, resulting in a more reliable and reproducible process.⁷ Due to the small volume required, flow processes can be used to perform a fast screening of the reaction conditions, and then, with the optimized conditions in hand, the reaction can be scaled up. Scaling up a chemical reaction often represents a challenging process since many problems may arise (e.g., runaway reactions, inefficient mixing, or byproduct formation). In principle, the reaction scale up in microreactors is easier than in batch; three different approaches can be used to produce large amount of compounds: the easiest one is to run the process longer (scaling-out). Alternatively, multi-reactors in parallel (numbering up) can be used, or the process can be performed on larger continuous reactors (scaling-up).⁸

Thanks to the small volumes of reagents that are involved in the microreactor, also some safety issues can be overcome. For example, the handling of potentially hazardous or toxic materials is limited and thus safer for the operator. Moreover, due to the short residence time in the microreactor, it is possible to perform reactions that involve transient and reactive intermediates that could not be otherwise handled or stored in traditional batch mode. Furthermore, the volume of reagents and solvents is reduced by far, so the screening of reaction conditions becomes simple and time- and cost-efficient, which implies even rapid library synthesis and an opportunity for automation. Under this light, the discovery of a potential drug candidate and its synthesis on larger scale, useful for biological tests, would become simpler.

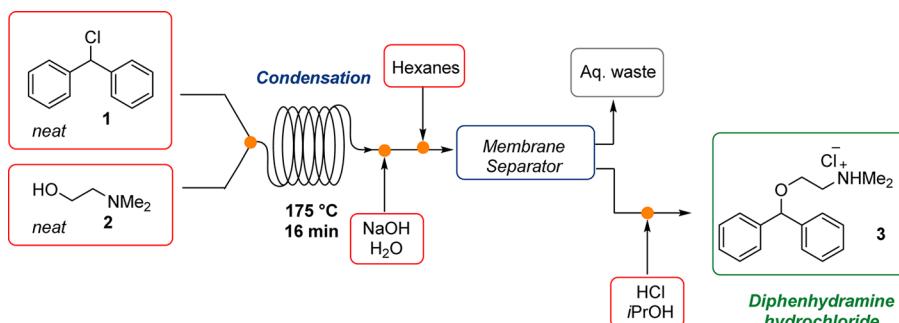
Continuous flow synthetic methodologies can also be easily combined to other enabling technologies leading to an improved efficiency.⁹ Typical enabling technologies joined to

flow chemistry are microwave irradiation, supported reagents or catalysts, photochemistry, inductive heating, electrochemistry, new solvent systems, 3D printing, or microreactor technology. This combination could allow the development of fully automated process with an increased throughput.

Given all of these advantages, it is not surprising that continuous processing is emerging as one of the techniques that can significantly impact the synthesis of APIs (or APIs intermediates). Recently, the safe manufacturing of organic intermediates and APIs under continuous flow conditions has been deeply examined in a review by Prof. Kappe and co-workers.¹⁰ As pointed out by the authors, some synthetic steps that were not permitted for safety reasons (e.g., use of potentially toxic or explosive intermediates, reactions run under high pressures, or above the boiling point of the solvent) can now be performed under flow conditions with minimum risk. For these reasons flow chemistry can be seen as a novel technology that opens the way for new synthetic routes of valuable molecules.

The continuous flow systems reported so far in the literature can be generally divided into four types, as suggested by Kobayashi and co-workers (Figure 1).¹¹ In type I, all of the reagents are flowed through the reactor, and at the end, the product is collected. In type II, one of the reactants is supported onto a solid and confined into the reactor; the substrate is passed through the reactor, and if the reaction goes to completion, the exiting reaction mixture will contain the desired product only. Both types I and II do not require the use of any catalyst during the reaction. In type III, a homogeneous catalyst is employed; the catalyst flows through the reactor together with the reactants, so, at the end, a separation step of the product from the catalyst (and possible byproducts) is required. In type IV, the catalyst resides into the reactor, while the reagents passed by of course, an immobilization step of the catalyst onto a solid support is required, but, in principle, no separation of the product from the catalyst is needed; in addition, through this typology the catalyst could be easily

Scheme 1. Continuous Flow Synthesis of Diphenhydramine Hydrochloride



recycled. The latter type is generally considered the most convenient method to perform a reaction under continuous-flow conditions, since catalytic methodologies are nowadays essential for the development of sustainable and efficient processes.¹² The examples covered in this review employ and combine all four types of reactor typologies. In the last section of this review we will discuss flow systems of type III and type IV, with a particular focus on the use of stereoselective chiral organocatalysts.

One of the possible concerns associated with the use of microreactors in the synthesis of APIs is the clogging of the (micro)reactor, that is, the blockage of the channels mainly due to precipitation of solids. This is a very common situation for a synthetic organic chemist, who constantly deals with precipitation of inorganic salts or insoluble materials during a reaction. In some case, this may represent an amenable situation, for example, when the reaction product precipitates from the reaction mixture, thus facilitating the purification process. However, it is easy to understand that this represents a problem in the case of a flow system. This is the reason why more sophisticated technologies for the handling of solids in continuous flow processes have been recently developed, although technical advances are still needed.

Since the synthesis and the manufacturing of APIs (or related advanced intermediates) have been the subject of very recent reviews,¹⁰ we have decided to focus our attention only on very recent advances in the continuous flow multistep synthesis of organic molecules which found application as APIs, especially highlighting the contributions described in the literature from 2013 to 2015, including very recent examples not reported in any published review. Without claiming to be complete, we will give a general overview of different approaches, technologies, and synthetic strategies used so far, thus hoping to contribute to minimize the gap between academic research and pharmaceutical manufacturing.

In particular, in section 2, the most significant examples appeared in the literature in 2013 and 2014 will be presented, while in section 3 only very recent works that were not previously discussed in any other review will be highlighted and deeply discussed.

In section 4, a general outlook about a quite young and relatively unexplored field of research, like stereoselective organocatalysis under flow conditions will be given and most significant examples will be described; our purpose is to illustrate all the potentialities of continuous flow organocatalysis and offer a starting point to develop new methodologies for the stereoselective synthesis of chiral drugs.

Finally, in section 5 a few general remarks on the topic will be proposed, along with some considerations on the

perspectives and the possible, expected developments in the field.

As different types of continuous flow reactors will be described, here a list of abbreviations used for common reactors materials is reported: FEP = fluorinated ethylene propylene; PEEK = polyether ether ketone; PFA = perfluoroalkoxy alkanes; PTFE = polytetrafluoroethylene.

Note to the Schemes: solid boxes in red indicate starting materials; solid boxes in green indicate products; solid boxes in yellow indicate isolated intermediate products; dashed boxes in yellow indicate nonisolated intermediates; dashed boxes in light blue indicate catalysts.

2. MULTISTEP SYNTHESIS OF ACTIVE PHARMACEUTICAL INGREDIENTS IN FLOW

In this section some selected examples about continuous flow production of Active Pharmaceutical Ingredients appeared in the literature in 2013 and 2014 will be discussed.¹³ Major breakthroughs of each example will be highlighted as well as the main synthetic route to reach the final target molecule.

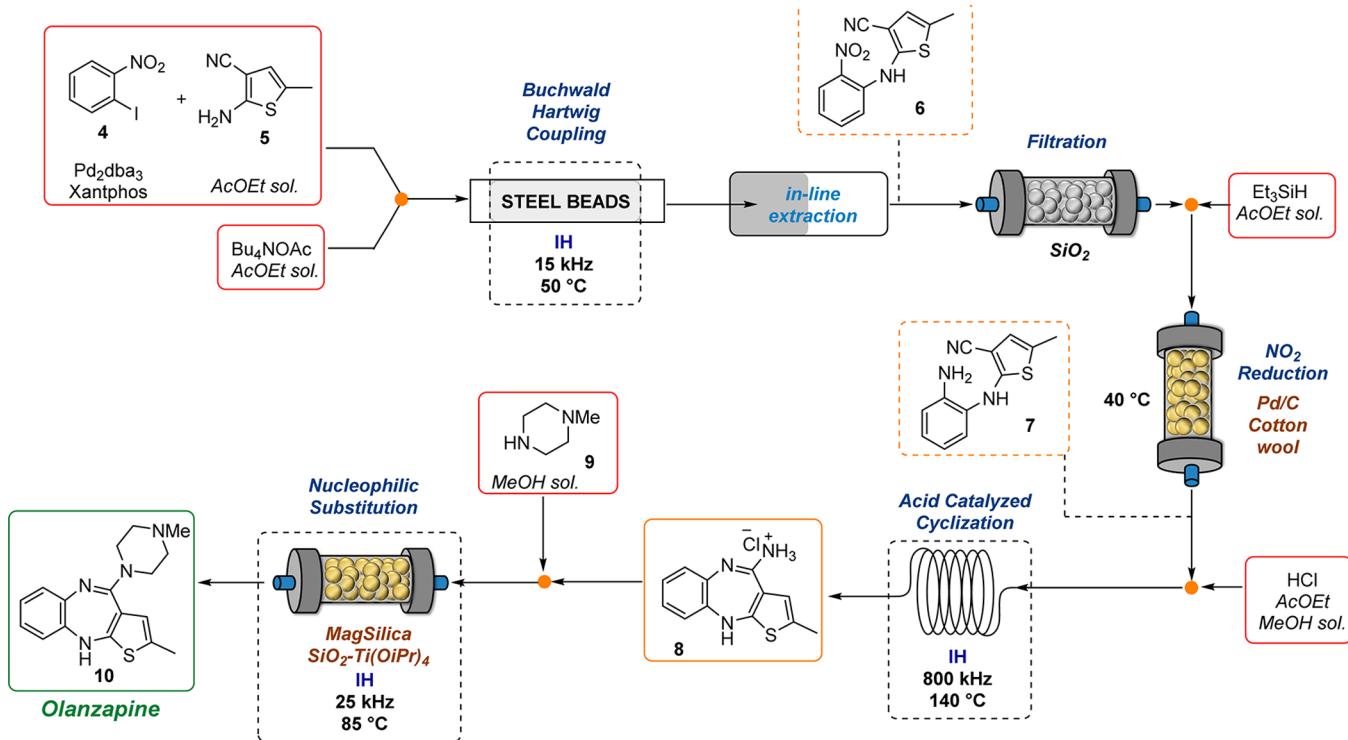
Diphenhydramine hydrochloride is the active pharmaceutical ingredient in several widely used medications (e.g., Benadryl, Zzzquil, Tylenol PM, Unisom), and its worldwide demand is higher than 100 tons/year.

In 2013, Jamison and co-workers developed a continuous flow process for the synthesis of 3 minimizing waste and reducing purification steps and production time with respect to existing batch synthetic routes (Scheme 1).¹⁴ In the optimized process, chlorodiphenylmethane 1 and dimethylethanamine 2 were mixed neat and pumped into a 720 μL PFA tube reactor (i.d. = 0.5 mm) at $175\text{ }^{\circ}\text{C}$ with a residence time of 16 min. Running the reaction above the boiling point of 2 and without any solvent resulted in high reaction rate. Product 3, obtained in the form of molten salt (i.e., above the melting point of the salt), could be easily transported in the flow system, a procedure not feasible on the same scale under batch conditions.

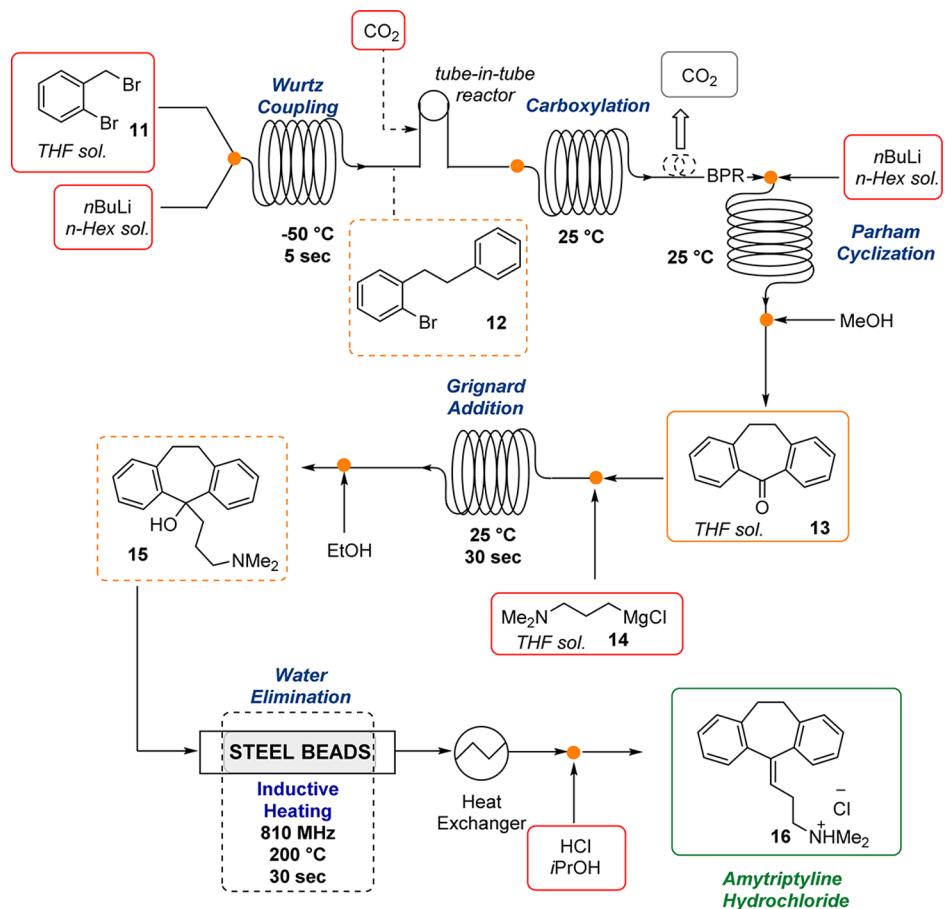
The reactor outcome was then combined with preheated NaOH 3 M to neutralize ammonium salts. After quenching, neutralized tertiary amine was extracted with hexanes into an inline membrane separator. The organic layer was then treated with HCl (5 M solution in iPrOH) in order to precipitate diphenhydramine hydrochloride 3 with an overall yield of 90% and an output of 2.4 g/h.

Atypical antipsychotic drugs differ from classical antipsychotics because of less side effects caused (e.g., involuntary tremors, body rigidity, and extrapyramidal effects). Among atypical ones, olanzapine 10,¹⁵ marketed with the name of

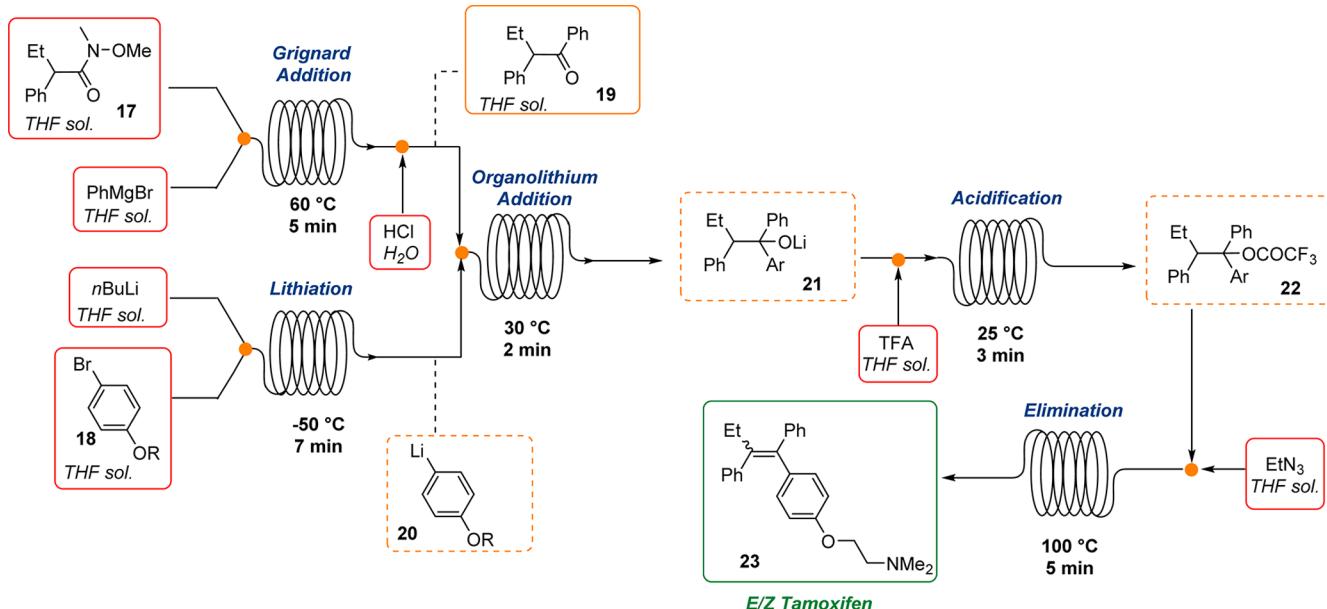
Scheme 2. Continuous Flow Synthesis of Olanzapine



Scheme 3. Continuous Flow Synthesis of Amitriptyline Hydrochloride



Scheme 4. Continuous Flow Synthesis of Tamoxifen



Zyprexa, is used for the treatment of schizophrenia and bipolar disorders.

In 2013 Kirschning and co-workers developed the multistep continuous flow synthesis of olanzapine **10** using inductive heating (IH) as enabling technology to dramatically reduce reaction times and to increase process efficiency.¹⁶ Inductive heating is a nonconventional heating technology based on the induction of an electromagnetic field (at medium or high frequency depending on nanoparticle sizes) to magnetic nanoparticles which result in a very rapid increase of temperature.¹⁷ As depicted in Scheme 2 the first synthetic step consisted of coupling aryl iodide **4** and aminothiazole **5** using Pd₂dba₃ as catalyst and Xantphos as ligand. Buchwald–Hartwig coupling took place inside a PEEK reactor filled with steel beads (0.8 mm) and heated inductively at 50 °C (15 kHz). AcOEt was chosen as solvent since it was compatible with following reaction steps. After quenching with distilled H₂O and upon in-line extraction in a glass column, crude mixture was passed through a silica cartridge in order to remove Pd catalyst. Nitroaromatic compound **6** was then subjected to reduction with Et₃SiH into a fixed bed reactor containing Pd/C at 40 °C. Aniline **7** was obtained in nearly quantitative yield, and the catalyst could be used for more than 250 h without loss of activity. The reactor outcome was then mixed with HCl (0.6 M methanol solution) and heated under high frequency (800 kHz) at 140 °C. Acid catalyzed cyclization afforded product **8** with an overall yield of 88%. Remarkably, the three step sequence did not require any solvent switch, and the total reactor volume is about 8 mL only.

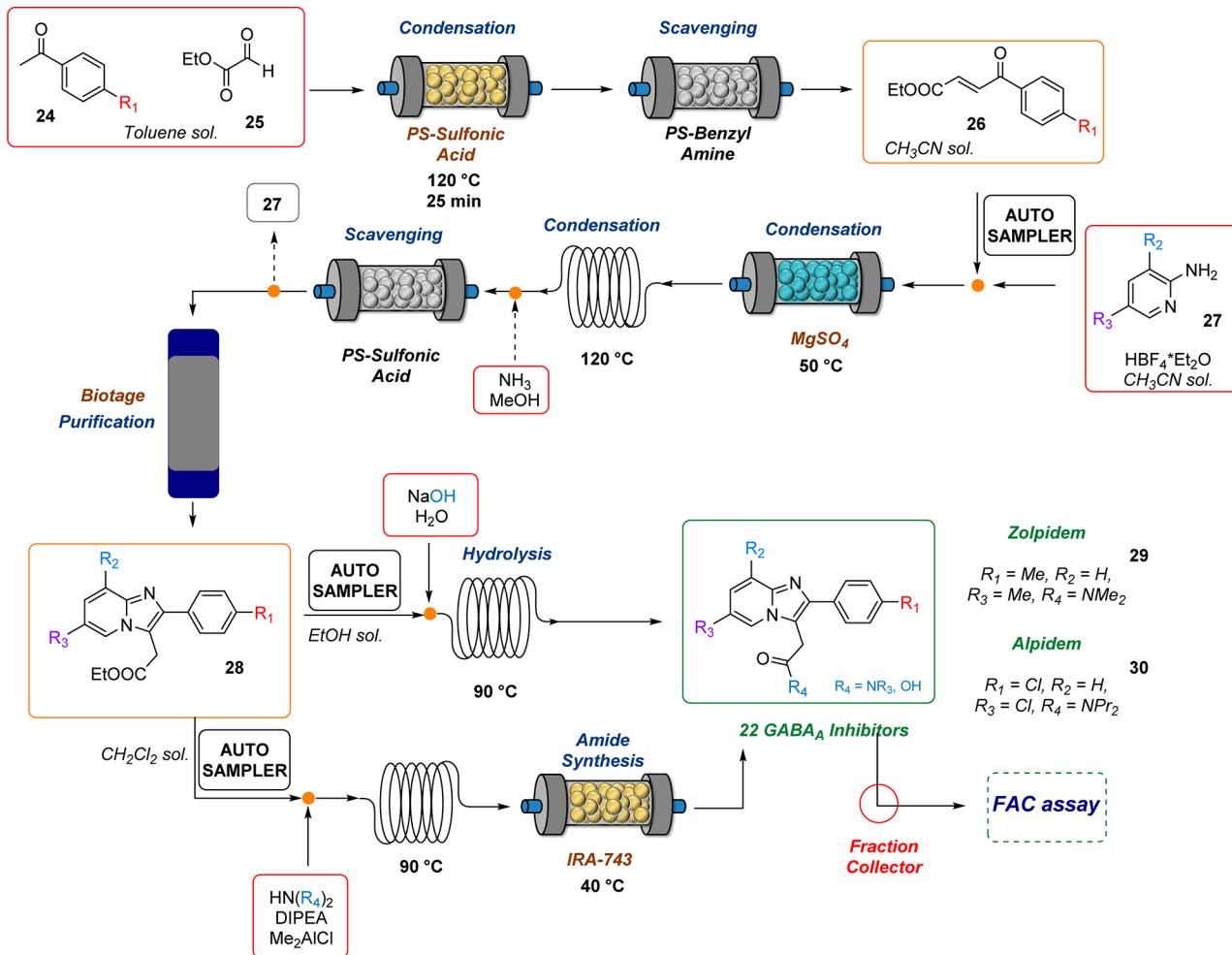
The final substitution of compound **8** with piperazine **9** was carried out using a 3 mL of PEEK reactor containing MAGSILICA as inductive material and silica-supported Ti-(O*i*Pr)₄ as Lewis acid. Heating inductively the reactor at 85 °C with a medium frequency (25 kHz) gave Olanzapine **10** in 83% yield.

Amitriptyline is a tricyclic antidepressant (TCA) that acts as a sodium, calcium, and potassium channel blocker. Among many medical uses, it finds applications against migraines, tension headaches, anxiety attacks, and some schizophrenic

symptoms. The most used synthetic procedures for its preparation involve the synthesis of dibenzosuberone **13** starting from lithiated benzyl bromide **11** by Wurtz dimerization followed by one-pot Parham cyclization using CO₂ as electrophile. Ketone **13** was then reacted with Grignard reagent **14**; the following water elimination resulted in API target **16**.

Kirschning and Kupracz, in 2013, following this established synthetic strategy developed a new protocol for the synthesis of Amitriptyline **16** under continuous flow conditions (Scheme 3).¹⁸ Carrying out the multistep synthesis of **16** in continuo features great advantages over traditional batch procedure considering the use of highly reactive intermediates (i.e., aryl- and alkyl lithium compounds) as well as reagents in gas phase (i.e., CO₂). The first lithiation reaction between benzyl bromide **11** and *n*BuLi was performed into a 0.5 mL steel reactor coil (i.d. = 1.0 mm) at -50 °C. Upon quenching with MeOH, the desired aryl bromide **12** was isolated in 79% yield after 5 s only. Having established the best reaction conditions for initial Wurtz coupling, the telescoped synthesis of ketone **13** was studied. Taking advantage of tube-in-tube reactor technology developed by S. V. Ley,¹⁹ CO₂ was directly introduced in the crude stream of reactants. Carboxylation step took place in a 0.5 mL of PFA reactor coil (i.d. = 0.8 mm) at 25 °C. After gas removal, a second stream of *n*BuLi was added to reaction mixture, and the final cyclization step was performed using a 0.5 mL PFA reactor coil (i.d. = 0.8 mm) at 25 °C. After MeOH addition, dibenzosuberone **13** was isolated in 76% yield with an overall residence time of about 30 s. Superior performances of the flow methodology can be understood considering that the corresponding batch synthesis of **13** required 2 h reaction time at -100 °C, with an isolated yield of 56% only.

Once pure ketone **13** was isolated from multistep flow synthesis, it was dissolved in THF and reacted with Grignard reagent **14** employing a 0.5 mL PFA reactor coil (i.d. = 1.0 mm) at 25 °C with a residence time of about 30 s. Crude reaction mixture was protonated with EtOH, and the resulting carbinol **15** was subjected to H₂O elimination using inductive heating technology: a 0.3 mL cartridge steel reactor (i.d. = 4.0

Scheme 5. Continuous Flow Synthesis of GABA_A Inhibitors

mm) filled with steel beads (i.d. = 0.8 mm) was encased into a high frequency field (810 Hz). After 30 s of residence time at 200 °C, the starting material was completely converted into amitriptyline. The presence of a heat exchanger was necessary to cool the crude mixture to room temperature. Finally, by addition of HCl (1 M solution in isopropanol) and after recrystallization from EtOH/Et₂O mixture, amitriptyline hydrochloride salt **16** was isolated in 71% yield.

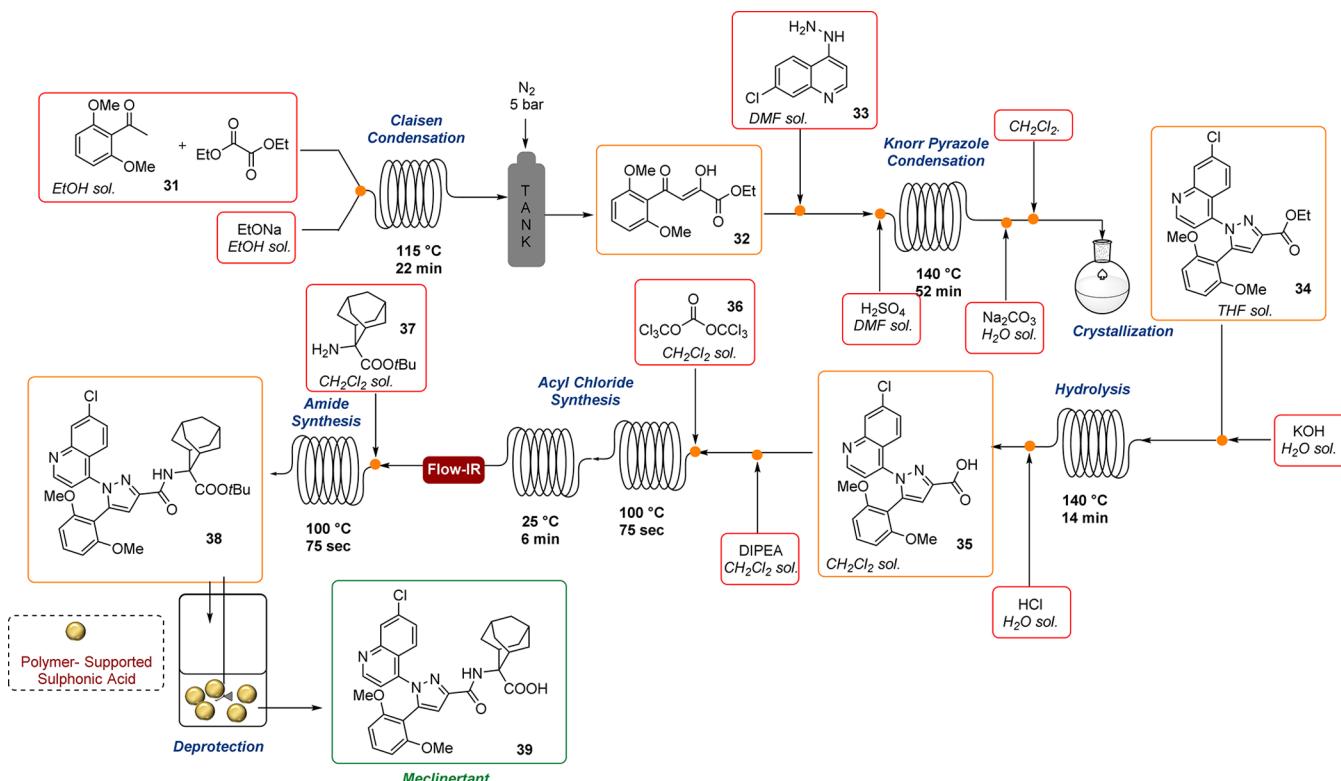
Flow chemistry technology offers the possibility of using organometallic reagents with many benefits over traditional batch procedures including precise temperature control of potentially exothermic reactions, safe handling of highly reactive organometallic intermediates, and rapid and stoichiometric mixing of substrates and reagents.²⁰ Within this context, Steven Ley's research group explored the use of a new flow platform, based on fluoropolymer peristaltic pumps, ideal for operating with highly reactive and air-sensitive compounds such as organolithium and Grignard reagents. In 2013 they demonstrated the applicability of this technology to the multistep synthesis of tamoxifen **23**, an antagonist prodrug used in the treatment of all stages of breast cancer.²¹ This procedure combined four different chemical transformations into one stream and minimized manual intervention reducing risks associated with the handle of organometallic reagent (Scheme 4).

The first step in the flow synthesis of the tetrasubstituted target alkene **23** consisted of Grignard addition of PhMgBr to

Weinreb amide **17** in a 10 mL PFA reactor coil at 60 °C. After a residence time of 5 min and upon quenching with HCl aq., ketone **19** was isolated in 97% yield. Simultaneously, aryl bromide **18** was lithiated with *n*BuLi at -50 °C employing a 10 mL PFA reactor coil. After 7 min of reaction, resulting aryl lithium compound **20** was mixed with a THF solution of ketone **19** and pumped into a 0.4 mL PFA reactor coil at -50 °C with a residence time of 10 s and then heated in a second PFA reactor coil (5 mL) at 30 °C for 2 min. The crude lithium alkoxide **21** was combined with TFA into a 10 mL PFA reactor coil at 25 °C for 3 min. Trifluoroacetate **22** was then subjected to elimination with triethylamine into 2 PFA reactor coils (10 mL) at 100 °C with an overall residence time of 5 min. The telescoped synthesis afforded tamoxifen **23** as *E/Z* mixture (25:75) in 84% yield starting from aryl bromide **18**. Running continuously the flow process for 80 min gave access to 12.4 g of pure API; this amount is sufficient for one patient's treatment for over 900 days (equivalent to one daily dose every 5 s).

Drug discovery in pharmaceutical research sometimes suffers from disconnection between chemical and biological sciences resulting in waste of time and poor flow of information. The development of a tool able to integrate both chemical synthesis and biological assays²² of drug candidates was investigated by Ley's research group in 2013. They combined a flow chemistry platform for organic synthesis and frontal affinity chromatography (FAC) as inline screening device.²³ A small library of 22

Scheme 6. Continuous Flow Synthesis of Meclenertant



analogues of GABA_A inhibitors were synthesized and tested in continuo (Scheme 5). Among them, two agonists of GABA_A receptors are currently employed as active pharmaceutical ingredients: in particular zolpidem is a drug prescribed for the treatment of insomnia and some brain disorders, while alpidem is used against anxiety. These molecules belong to imidazopyridines, a class of molecules which possesses anticancer, antiviral, and antimicrobial activity.

Continuous flow synthesis of imidazopyridines began with the acid catalyzed condensation between ketone 24 and ethyl glyoxalate 25. The reaction took place at 120 °C in a reactor packed with 2 g of polymer supported sulfonic acid with 25 min as a residence time. The crude mixture was then passed through a cartridge containing 3 g of polymer supported benzyl amine which scavenges the excess of 25. Neither workup nor further purifications were needed, and three products 26 were recovered in good yield ranging from 76% to 85%. By means of an auto sampler, three α,β -unsaturated ketones 26 were collected, combined with three aminopyridines 27, and pumped into a reactor packed with MgSO₄ as dehydrating agent at 50 °C. Under superheating conditions the corresponding imines were rapidly formed, and then they were subjected to 5-exo cyclization into a 14 mL reactor coil at 120 °C. The crude reaction mixture then passed through a column packed with polymer supported sulfonic acid which trapped the excess of aminopyridine 27. This could be recovered later by injecting NH₃ in MeOH to release the bound material. After in-line chromatographic purification with Biotage system, eight imidazopyridines were collected. The last synthetic step served to introduce molecular diversity into imidazopyridine scaffold using an auto sampler to control two distinct processes: the first one involved the saponification of the ester moieties of 28 using NaOH aq. into a 14 mL reactor coil at 90 °C; the second one involved the conversion of esters 28 into corresponding amides

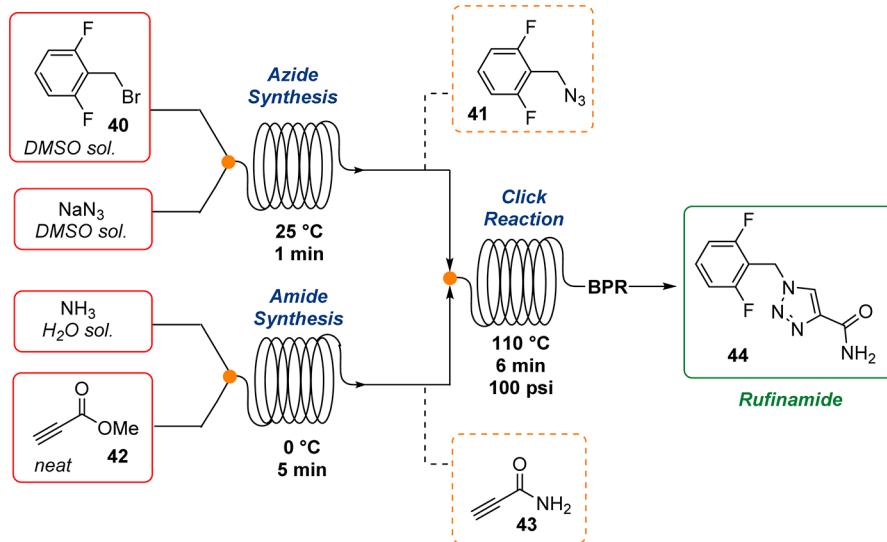
by using Me₂AlCl and two different secondary amines (HN(R₄)₂). The reaction mixture was heated at 90 °C into a 14 mL reactor coil and then passed through a cartridge containing a polyol resin (IRA-743) to remove Al derivatives.

Using this flow procedure, a library of 22 imidazopyridine derivatives could be obtained in a relatively short period of time (4 days). At the end of the synthetic platform a fraction collector was introduced: automatically aliquots of 10 μ L for each reaction output were taken and subjected to FAC analysis, upon proper dilution.

Although batch processes remain the most used procedure for running chemical reactions, the use of machine-assisted flow methodologies²⁴ enables an improved efficiency and high throughput. A direct comparison between conventional batch preparation and flow multistep synthesis of selective neuropeptide SR48692 (Meclenertant) was reported by Ley and co-workers in 2013 (Scheme 6).²⁵ In this case study, the authors investigated whether flow technology could accelerate a multistep synthesis (i.e., higher yields or lower reaction times) and overcome many synthetic issues (i.e., solid precipitation or accumulation of byproducts). The initial Claisen condensation between ketone 31 and ethyl glyoxalate in the presence of NaOEt as base and EtOH as solvent in batch is run at room temperature and product 32 is obtained in 60% yield after 3 h stirring. Superheating (heat above solvent boiling point) the reaction in flow provided a faster alternative: using a 52 mL PFA reactor coil at 115 °C with a residence time of 22 min gave the corresponding product 32 in 74% yield. In order to solve some problems of solid accumulation an ad-hoc pressurized stainless-steel tank (5 bar, nitrogen) was designed; it allowed to run the reaction continuously without any precipitation or blockage.

The following reaction between 32 and commercially available hydrazine 33 was performed in DMF in the presence

Scheme 7. Continuous Flow Synthesis of Rufinamide



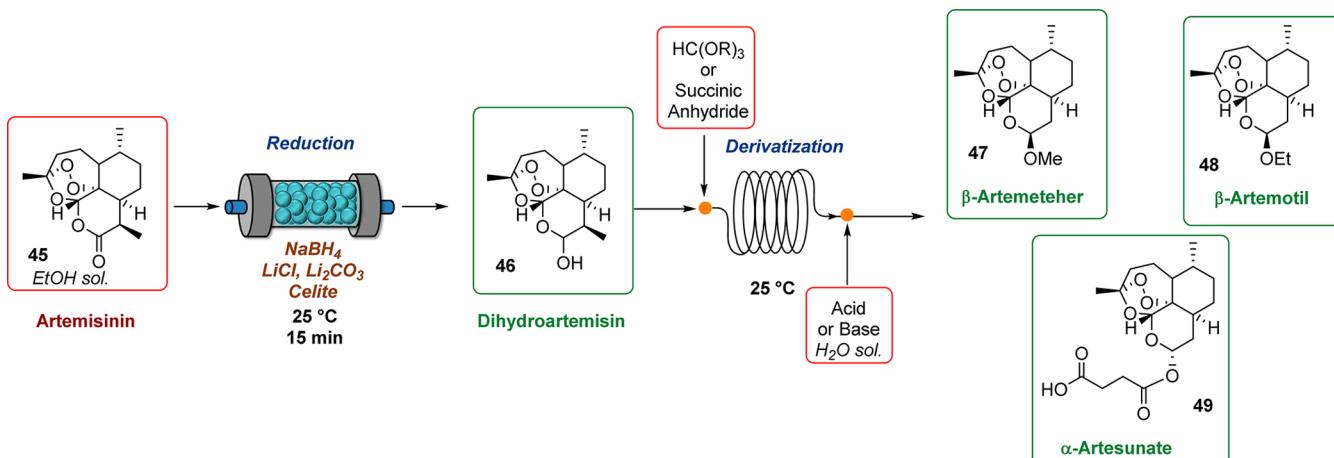
of concentrated H₂SO₄. After 52 min of residence time at 140 °C into a 52 mL PFA reactor coil the crude mixture was treated with an Na₂CO₃ aq. and then inline extracted through a semipermeable membrane with CH₂Cl₂. After crystallization, pyrazole ester 34 was isolated in 89% yield. The corresponding reaction in batch was conducted in DMF under microwaves irradiation at 140 °C for 2 h. Running the reaction in batch on the same scale as in flow (3.58 mmol) gave product 34 in a lower yield (70%). The subsequent hydrolysis was performed combining a THF solution of ester 34 and 3 M aqueous KOH. The reaction was performed inside a 14 mL PFA reactor coil heated at 140 °C with a residence time of 14 min. Upon treatment with 3 M HCl aq., acid 35 precipitated, and it was isolated by filtration in 90% yield. In this case, the corresponding batch hydrolysis afforded product 35 with the same yield (90%); however, a longer reaction time (1.5 h) was required. The final amide formation was performed by reacting acid 35 (activated as acyl chloride) and protected amino alcohol 37 through a telescoped synthesis. Triphosgene 36 (a safer substitute for phosgene) was found to be the best acid activator. Triphosgene decomposition occurred in the presence of DIPEA at 100 °C into a stainless steel heat exchanger, where phosgene was generated. The crude mixture, containing also acid 35, then passed into a 2.5 mL stainless steel reactor coil at 25 °C, to complete the formation of the corresponding acyl chloride. An inline Flow-IR spectrometer²⁶ was used to monitor the formation of phosgene without exposing the operator to the toxic gas during analysis. As soon as acyl chloride was formed it was reacted with protected amino alcohol 37. The amide formation took place into a 14 mL stainless steel reactor coil at 100 °C with a residence time of 75 s. Amide 38 was isolated in 85% yield after quenching with NH₄Cl and extraction with AcOEt. For obvious safety concerns, avoiding the handling of phosgene and the isolation of highly reactive acyl chloride intermediate represent a remarkable improvement with respect to batch procedure. Finally, meclintertant 39 was obtained after deprotection of ester 38 by using a polymer-supported sulfonic acid. The last synthetic step was conducted in batch on a small scale; however, it could be easily transferred to flow mode by using a column packed with commercially available polymer-supported sulfonic acid.

1,2,3-Triazoles are very important five-membered ring heterocycles present in many compounds possessing biological activity. The easiest way to prepare these molecules is the 1,3-dipolar cycloaddition reaction between organic azides and alkynes developed by Huisgen and also known as “click reaction”.²⁷ Unfortunately, organic azides are compounds prone to detonation upon exposure to even slight energy sources (e.g., heat, pressure, or light). Moreover, their synthesis could generate hydrazoic acid, an explosive and toxic chemical. For these reasons, their application on a preparative scale, especially at industrial level, is substantially limited by safety and regulatory issues. From this point of view flow chemistry would be the ideal technology to minimize the hazardous handling of organic azides. In this context, in a paper of 2014, Jamison reported the continuous flow synthesis of organic azides and their application in the multistep synthesis of antiepileptic API rufinamide 44 (Scheme 7).²⁸ Benzyl azide 41 was synthesized starting from the corresponding aryl bromide 40 and NaN₃ in DMSO into a 40 μL PFA microreactor at room temperature.

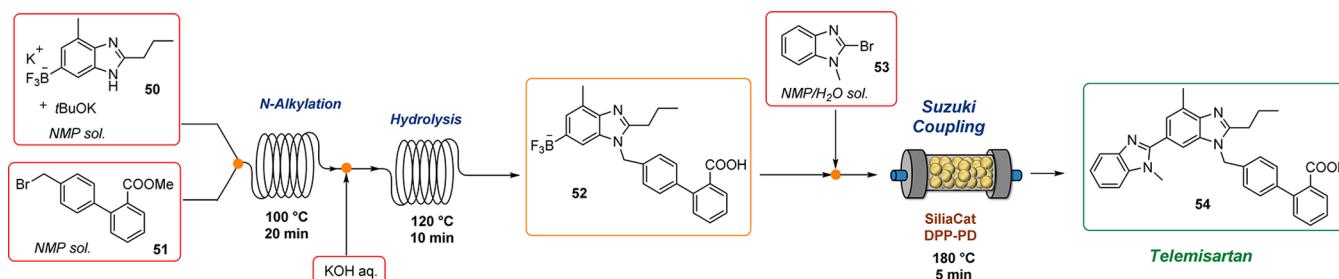
A residence time of 1 min only was sufficient to quantitatively generate azide 41. In parallel, into a 57 μL PFA microreactor, methyl propiolate 42 and NH₃ aq. were reacted at 0 °C with a residence time of 5 min. The resulting propiolamide 43 was formed in 95% yield, and polymerization byproducts were minimized. As soon as hazardous azide 41 and highly reactive and unstable amide 43 were formed, they were not isolated, stored, or handled, but they were immediately mixed and transferred into a 431 μL copper tubing reactor where azide–alkyne cycloaddition took place at 110 °C and 100 psi. After 6 min of residence time rufinamide 44 was obtained with an overall yield of 92%.

Malaria represents a major worldwide health problem affecting hundreds of thousands people every year. The most effective drug against malaria disease is Artemisinin, an organic molecule extracted from *Artemisia annua* plant. In 2012 Seeberger and co-workers reported for the first time the multistep continuous flow synthesis of artemisinin 45 starting from dihydroartemisinic acid through a photooxidation process.²⁹ Recently, in 2014 they extended this methodology and developed a divergent synthesis in continuo of four

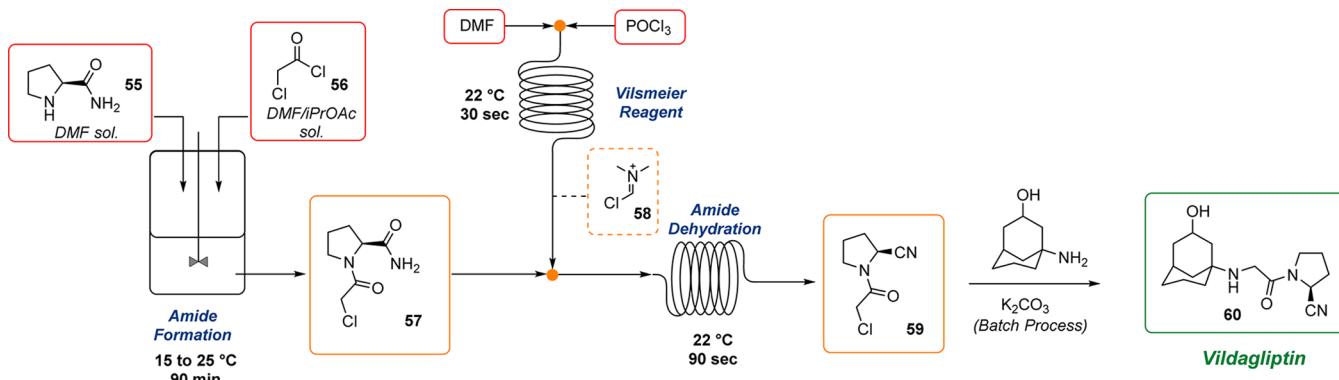
Scheme 8. Continuous Flow Synthesis of Four Antimalaria APIs



Scheme 9. Continuous Flow Synthesis of Telemisartan



Scheme 10. Continuous Flow Synthesis Vildagliptin



antimalaria APIs (46–49) that are key components in Artemisinin Combination Therapies (ACT, Scheme 8).³⁰

Starting from the previously synthesized artemisinin 45, the first step consisted of a reduction into a column packed with NaBH_4 and Celite, and LiCl and Li_2CO_3 as additives. A complete conversion into API 46 was obtained with a residence time of 15 min at 25°C . API 46 could be further converted into APIs 47–49. The reaction with trimethylorthoformate followed by a basic workup (i.e., NaHCO_3 aq.) gave β -aremethe 47; the same procedure, employing triethylorthoformate afforded β -artemotil 48; treatment of dihydroartemisinin 46 with succinic anhydride gave α -artesunate 49, upon acid workup. Besides the synthetic steps required to prepare the four APIs, this work highlighted great potential offered by continuous flow processes: by combining or interchanging different reaction modules a divergent

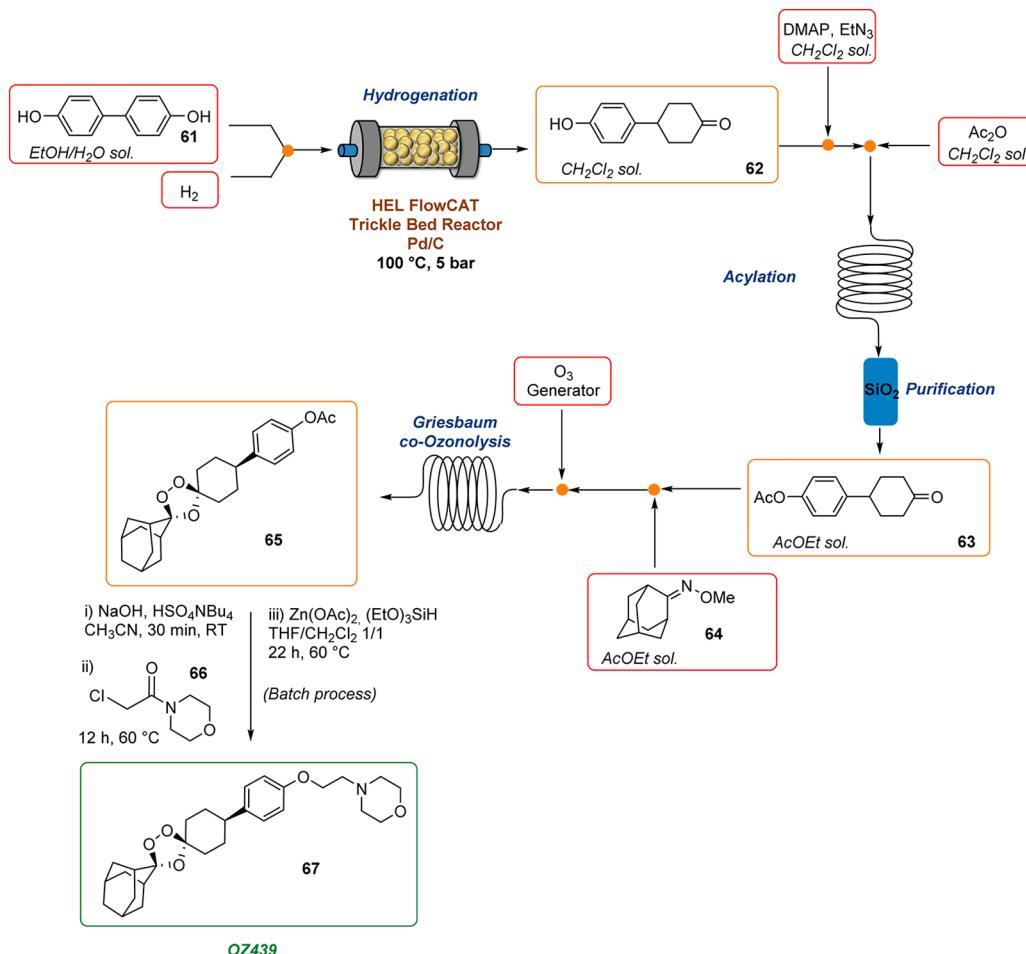
multistep synthesis of a small library of drugs is easily accomplished. The same procedure under batch conditions would be much more labor intensive.

3. LATEST DEVELOPMENTS IN THE CONTINUOUS FLOW MANUFACTURING OF API

Since continuous flow synthetic methodologies represent a rapidly expanding research area, many scientific publications of the field appear every week in the literature, both from academia and industry.³¹ This section will cover only the most recent examples of continuous manufacturing of Active Pharmaceutical Ingredients which have not been previously discussed anywhere else.

Telemisartan 54 is the active pharmaceutical ingredient present in the antihypertensive drug Micardis (Scheme 9). It is an angiotensin receptor antagonist and, compared to other

Scheme 11. Continuous Flow Synthesis of OZ439



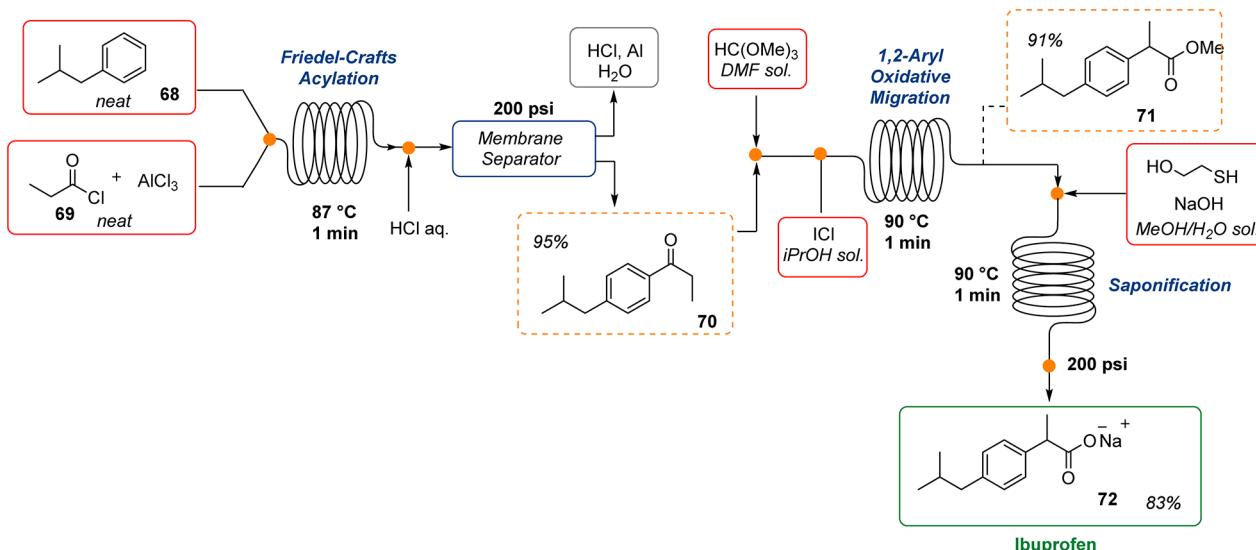
drugs of this class, has a longer half-life, higher protein binding affinity, and lower daily dosage. Gupton and co-workers developed a continuous flow convergent multistep synthesis of telemisartan³² which did not required any intermediate purification or solvent switching (Scheme 9). This fully automated process represents a significant improvement over traditional batch procedure since it reduces waste and unit operations.³³ The three-step synthesis involved an initial alkylation of benzimidazole **50** with bromide **51** in the presence of *t*BuOK as a base into a 10 mL reactor coil at 100 °C with a residence time of 20 min. *N*-methylpyrrolidone (NMP) was the solvent of choice since it is miscible with H₂O (necessary in the following step) and did not cause any solid precipitation. The reactor outlet was then combined with an excess of KOH water solution and the resulting mixture was introduced into a 10 mL reactor coil heated at 120 °C. Ester hydrolysis was accomplished with a residence time of 10 min. The crude compound **52** was then collected into a reservoir and mixed with a NMP/H₂O solution of **53**. The combined mixture was introduced into a cartridge containing 0.1 g of Pd-catalyst (SiliaCat DPP-Pd) at 180 °C. Suzuki cross-coupling took place with a residence time of 5 min only. Upon base–acid workup pure telemisartan **54** was isolated with an overall yield of 81% (97% HPLC purity) and with a production rate of 1 mg/min.

Vildagliptin **60** is an antihyperglycemic drug belonging to dipeptidyl peptidase-4 (DPP-4) inhibitor family (Scheme 10). Its chemical synthesis involves as key step amide dehydration promoted by Vilsmeier reagent (VR, dimethyl chloroiminium

ion **58**). VR is a highly reactive and moisture sensitive reagent, and the risks associated with its use are well-known. The application on a large productive batch scale remains problematic since special precautions are required. As well as health issues upon exposure, major hazards are related to very rapid increase of pressure and temperature. In a recent work, Sedelmeier reported the continuous flow synthesis of Vildagliptin with the aim of increasing the safety of the processes associated with the use of VR (Scheme 10).³⁴

The rapid generation of **58** and its instantaneous consumption by reaction with amide **57** had many benefits: the closed flow reactor avoided the handling of the hazardous reagent and sheltered the operator from the exposure; the use of small reaction volumes, compared to conventional batch vessels minimized pressure or temperature increases. The formation of amide **57** was performed into a 250 mL double jacketed batch reactor combining prolinamide **55** and chloroacetyl chloride **56** for 90 min. VR **58** was prepared by mixing neat POCl₃ and DMF (1.5 equiv) into a 4.5 mL PFA reactor coil (i.d. = 1.6 mm) with a residence time of 30 s at 22 °C. The resulting chloroiminium ion **58** was immediately combined with preformed DMF solution of amide **57** and mixed into a 50 mL PFA reactor coil (i.d. = 5.0 mm) filled with glass beads for improved mixing. Optimal reaction conditions were found to be 22 °C and a residence time of 90 s; cyanopyrrolidine **59** was obtained in 79% overall yield upon crystallization of the crude flow stream. Multigram quantities of intermediate **59** were generated by running the flow apparatus

Scheme 12. Continuous Flow Synthesis of Ibuprofen



for 60 min, and no system fouling or blockage was observed. Final conversion to Vildagliptin **60** was accomplished by combining pure compound **59** with hydroxyaminoadamantane (HAAD) in the presence of K₂CO₃ as a base.

OZ439 (**67**) is currently undergoing phase IIa trials after having successfully completed phase I clinical trials. As soon as it will be approved by World Health Organization (WHO), **67** would represent a valuable and more economical alternative to Artemisinin and its derivatives. In spite of a promising activity exhibited by drug candidate OZ439 (**67**), its chemical synthesis is still troublesome: indeed the existing synthetic process involves the use of commercially available expensive or genotoxic reagents.³⁵

Moreover, large quantities of organic solvents are employed, and as a consequence, many wastes are produced. In order to overcome these issues, Steve Ley and co-workers developed a machine-assisted protocol for the continuous flow synthesis of **67** (Scheme 11).³⁶ The continuous flow hydrogenation of dihydroxybiphenyl **61** was performed exploiting HEL Flow-CAT platform for liquid/gas reactions under trickle heterogeneous catalysis conditions.³⁷ By using 20% of Pd/C catalyst at 100 °C and 5 bar ketone **62** was obtained as the major product and it was isolated in 58% upon crystallization. Compound **62** was then mixed with *N,N*-dimethylaminopyridine (DMAP) and Et₃N₃ in CH₂Cl₂ and acylated with Ac₂O into a 10 mL PFA reactor coil at room temperature. Upon inline purification through a column containing silica gel, compound **63** was isolated in quantitative yield without further purification. Ketone **63** was then dissolved in AcOEt and mixed with oxime **64**; the mixture was combined to a stream of O₃ and mixed into a 2 mL PFA reactor coil. The outlet was collected into a flask unded Argon flow in order to remove excess of O₃. Compund **65**, resulting from Griesbaum co-ozonolysis, was isolated in 70% yield after recrystallization of crude mixture from Et₂O. Final conversion into drug candidate **67** was performed under batch conditions though a three-step reaction sequence involving ester hydrolysis, O-alkylation with N-chloroacetylmorpholine **66**, and amide reduction with Zn(OAc)₂ and Et₃SiH (73% yield over 3 steps).

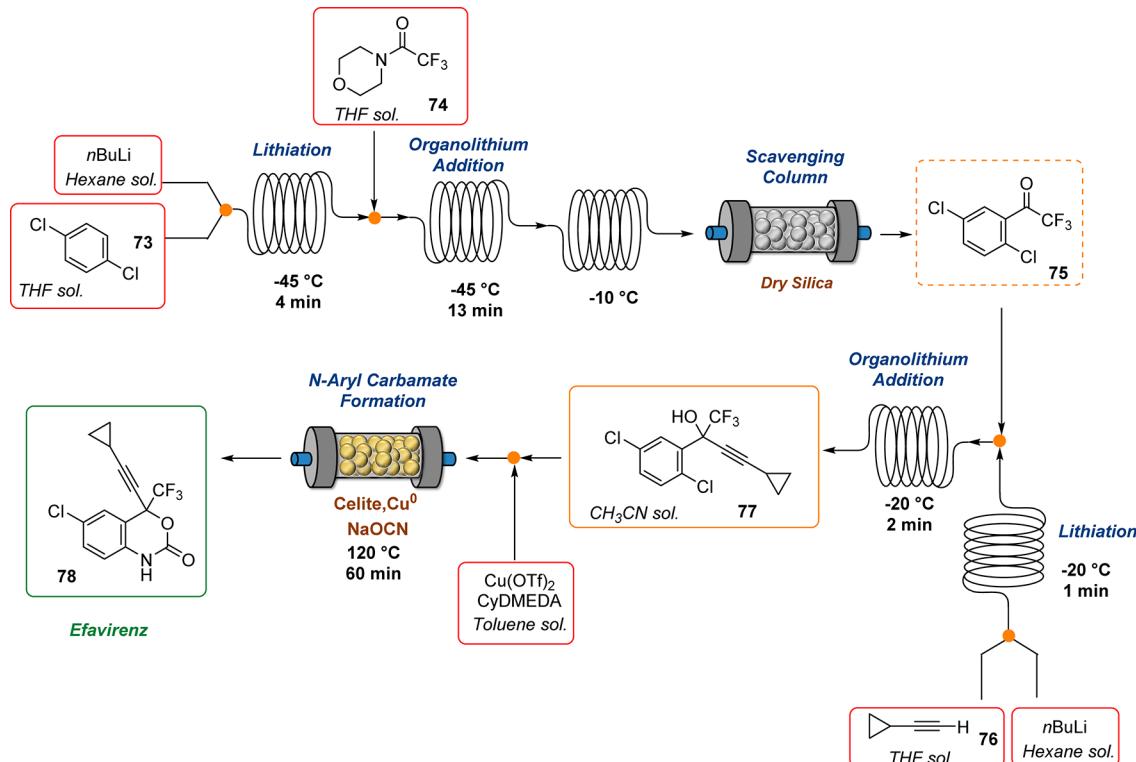
Among several benefits ensured by continuous flow operations, there is the possibility of speeding up a chemical

process achieving high throughput. In this context, Jamison and co-workers demonstrated how to “push the limits” of flow methodologies.³⁸ Extending a previously reported procedure developed by McQuade in 2009,³⁹ in this paper the authors discussed the continuous flow synthesis of a very important generic pharmaceutical, ibuprofen **72**. In 3 min only, API **72** was prepared starting from very simple building blocks and inexpensive reagents with an overall yield of 83% (three bond-forming steps, one workup, and one inline extraction, Scheme 12). Even though highly reactive chemicals (i.e., AlCl₃, ICl) and harsh reaction conditions were employed, the flow methodology guaranteed a high level of safety (no system failure or uncontrolled exothermic processes were observed).

The continuous flow Friedel–Crafts acylation of isobutylbenzene **68** with propionyl chloride **69** was performed with AlCl₃ as a Lewis acid using a 250 μL PFA reactor coil heated at 87 °C with a residence time of 60 s. The outlet was treated with aqueous HCl, and the crude mixture was extracted through an inline membrane separator operating at 200 psi. Aryl ketone **70** was formed in 95% yield and then mixed with a DMF solution of trimethylorthoformate (TMOF) and subjected to 1,2-aryl oxidative migration using ICl as promoter. Oxidation to ester **71** took place into a 900 μL PFA reactor coil at 90 °C with a residence time of 60 s. The final synthetic step involved a simultaneous quench of excess ICl and saponification of ester **71**. Crude mixture exiting from oxidation reactor was combined with a H₂O/MeOH mixture containing NaOH and 2-mercaptopropanoic acid and heated at 90 °C for 60 s into a 3.9 mL PFA reactor coil. Upon quenching with HCl aq. and extraction with hexanes, pure compound **72** was obtained in 83% yield. Ibuprofen **72** could be produced under flow conditions for several hours with an output of 8.1 g/h.

The global availability of critical medicines depends on their prices which are closely related to the complexity of the chemical synthesis. Efavirenz, an essential drug for the treatment of HIV, is currently manufactured by Merck⁴⁰ and Lonza⁴¹ through batch procedures involving five or four synthetic steps, respectively. In a very recent work,⁴² Seeger and co-workers developed a concise flow protocol for the preparation of efavirenz **78** leading to a shorter (three steps), cleaner, and safer synthetic pathway avoiding the use of toxic

Scheme 13. Continuous Flow Synthesis of Efavirenz



reagents and employing a new methodology for the introduction of the carbamate core ring (Scheme 13). The lithiation of dichlorobenzene 73 occurred into a 1 mL PTFE reactor coil at $-45\text{ }^{\circ}\text{C}$ with a residence time of 4 min. The resulting product was quenched with a THF solution of morpholine 74 into a 5 mL PTFE reactor coil at $-45\text{ }^{\circ}\text{C}$, with a residence time of 45 min. The crude mixture was then warmed at $-10\text{ }^{\circ}\text{C}$ into a 0.5 mL PTFE reactor coil and the passed through a glass column containing dry silica gel as scavenger for undesired byproducts. Ketone 75 was used in the telescoped synthesis without further purification. In parallel, alkyne 76 was lithiated with *n*BuLi into a 1 mL PTFE reactor coil at $-20\text{ }^{\circ}\text{C}$ with a residence time of 1 min. The resulting flow stream was combined with compound 75. The organolithium addition took place into a 3 mL PTFE reactor coil at $-20\text{ }^{\circ}\text{C}$ in 2 min. Upon quench with brine and chromatography purification, alcohol 77 was isolated in 73% yield over two steps. An acetonitrile solution of pure alcohol 77 was mixed with Cu(OTf)₂ and *trans*-*N,N*'-dimethyl-1,2-cyclohexanediamine (CyDMEDA) and passed through a cartridge containing Cu⁰, NaOCN, and Celite at $120\text{ }^{\circ}\text{C}$ with a residence time of 1 h. The copper-catalyzed *N*-aryl carbamate formation gave efavirenz 78 in 62% yield (after extraction and purification of crude mixture). This telescoped synthesis gave the final product in 45% overall yield and required less than 2 h as a total reaction time, representing the shortest existing route for the manufacture of efavirenz.

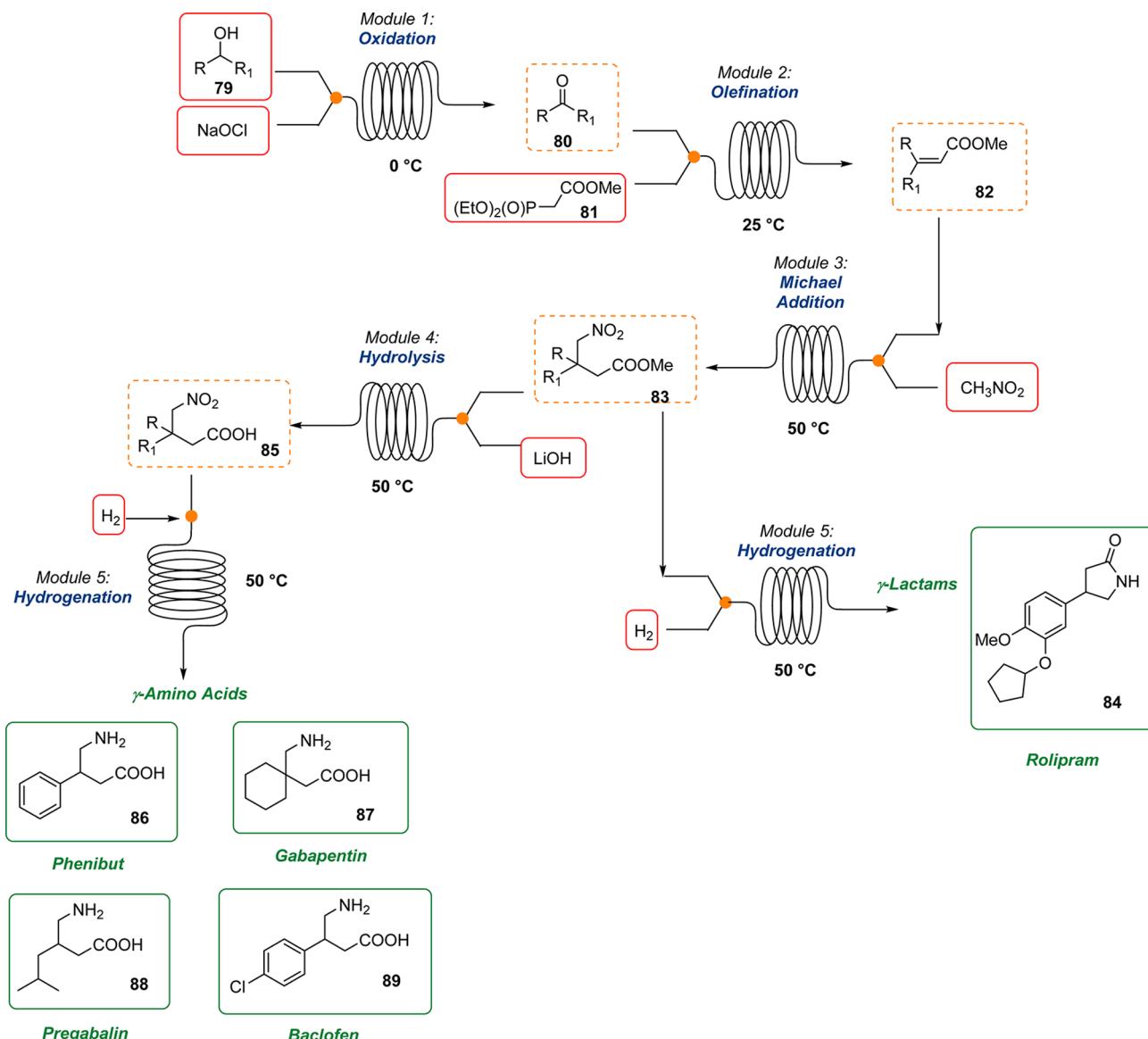
Since all pharmaceuticals are currently produced through distinct batch processes, the development of a customizable tool for the continuous manufacturing of different drugs would be a groundbreaking methodology for pharmaceutical companies. Seeberger and co-workers recently reported the continuous flow synthesis of five APIs (i.e., rolipram 84, phenibut 86, gabapentin 87, pregabalin 88, and baclofen 89) in racemic form (Scheme 14).⁴³ The flow system was based on

different modular synthetic platforms, operating under a wide range of reaction conditions. By following different linking pathways of the modules, the synthetic platform gave access to several small molecule drugs in multigram scale without requiring intermediate purification. Controlling both the starting materials and the order of reaction modules provided access to different families of compounds. The synthesis of the five APIs started with an oxidation at $0\text{ }^{\circ}\text{C}$ of alcohol 79 with NaOCl into Module 1; the resulting aldehyde 80 (or ketone, depending on R₁ structure) was then subjected to an olefination with Horner–Emmons reagent 81 providing acrylate 82. Into Module 3, a Michael addition of nitromethane to 82 occurred, and nitroester 83 was obtained. This intermediate could be alternatively employed for the synthesis of both γ -lactams and γ -amino acids. When nitroester 83 was transferred to Module 5 for a hydrogenation reaction in the presence of H₂ and Pd catalyst, a nitro group reduction followed by lactam cyclization occurred, yielding γ -lactam product. Starting from the proper alcohol 79, this synthetic route gave access to rolipram 84. On the other hand, when compound 83 was transferred to Module 4 for ester hydrolysis in the presence of LiOH, nitroacid 85 was obtained.

This compound was then converted to the corresponding γ -amino acid through Module 5 hydrogenation. The choice of the starting material (alcohol 79) could give access to four different APIs (i.e., phenibut 86, gabapentin 87, pregabalin 88, and baclofen 89).

Type IV reactors described in the introduction are the best candidates for performing multistep synthesis in flow: indeed these reactors avoid catalyst separation processes and allow the recycle of catalytic species. Furthermore, provided a good conversion (or a scavenging of unreacted starting materials) the reaction product can be further functionalized by using other catalytic reactors, without any additional operation. In this way

Scheme 14. Continuous Flow Synthesis of Five APIs



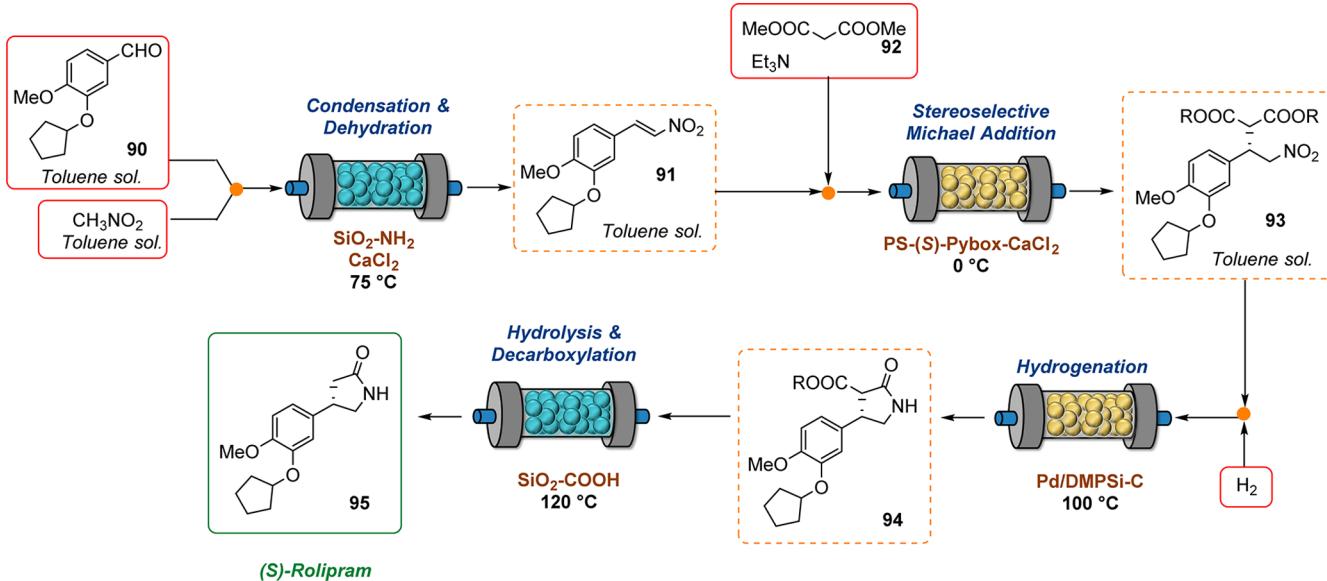
a telescoped synthesis of complex organic molecules starting from simple substrates can be accomplished in continuo. Following this principle, Kobayashi and co-workers recently reported for the first time the continuous flow multistep synthesis of (S)-rolipram **95** by using reactors containing solid supported catalyst and reagents, without requiring any intermediate operation (Scheme 15).¹¹ As a peculiarity, this work features a stereoselective Michael addition promoted by a polystyrene supported CaCl₂-(S)-Pybox as a chiral organometallic complex. This is the first time that a highly stereoselective catalytic reaction between achiral substrates is integrated into a multistep synthesis in continuo of a drug. The first reaction step involved the synthesis of nitroalkene **91** starting from aldehyde **90** and nitromethane. A toluene solution of the two reagents was flushed through a reactor containing silica-supported amine (SiO₂-NH₂) as a base and anhydrous CaCl₂ as a dehydrating agent. The system was found to be stable at 75 °C for at least 1 week, giving the products in 90% yield.

Once nitroalkene **91** was formed, it was combined with malonate **92** and triethylamine and transferred to a catalytic

reactor containing polymer supported (PS) (S)-pybox–calcium chloride maintained at 0 °C. The stereoselective Michael addition afforded compound **93** in 84% yield and 93% ee. The following nitro-group reduction was performed at ambient pressure and 100 °C employing a catalytic reactor containing a polysilane-supported palladium/carbon (Pd/DMPSi-C, where DMPSi is dimethylpolysilane) catalyst. γ-lactam **94** was obtained in 74% yield and 94% ee (no epimerization occurred). The final stage of this multistep synthesis of **95** involved ester hydrolysis and decarboxylation of compound **94**. The reaction was found to proceed at 120 °C into a continuous flow reactor containing silica-supported carboxylic acid (SiO₂-COOH). Enantiomerically pure (S)-rolipram **95** could be isolated upon crystallization from H₂O/MeOH of crude mixture with an overall yield of 50% (from aldehyde **90**). The flow system was stable for at least 1 week producing (S)-rolipram **95** (>99%) with an output of 1 g/d. All chemical steps were conducted without isolation of any intermediates and without the separation of any catalysts, byproducts, or excess reagents.

The author demonstrated also that, by replacing the catalytic reactor containing the supported chiral organometallic complex

Scheme 15. Continuous Flow Synthesis of (S)-Rolipram



with one containing polystyrene supported CaCl_2 -(R)-Pybox, (R)-rolipram could be obtained with the same efficiency and selectivity.

4. STEREOSELECTIVE ORGANOCATALYSIS IN FLOW

In chiral drugs usually one enantiomer (or stereoisomer) displays a different effect than the other: one may possess a desired beneficial effect, while the other could have a completely different behavior; in some cases (e.g., methorphan) this effect could be even beneficial; in other cases (e.g., thalidomide) the nonactive enantiomer could be harmful for the human body. For these reasons a general strategy for the selective synthesis of enantiomerically pure drugs is highly desirable. This methodology would be more sustainable and profitable than classical resolution of racemic mixtures, where the desired product constitutes only half of the whole production. Stereoselective catalysis represents a powerful strategy for the selective synthesis of complex chiral molecules, even starting from achiral substrates.⁴⁴

However, the application of stereoselective catalysis under continuous flow conditions is still underdeveloped.⁴⁵ The synthesis in continuo of chiral APIs through stereoselective catalysis is even more unexplored; indeed, the only example reported so far is the stereoselective multistep synthesis of (S)-rolipram described by Kobayashi and co-workers and already discussed in section 3.¹¹ Among stereoselective catalytic methodologies, asymmetric organocatalysis is a fast growing research area and represents an alternative approach to traditional organometallic and enzymatic approaches.⁴⁶

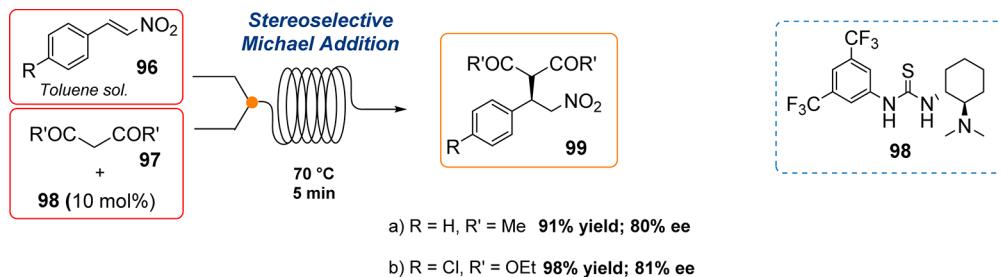
Stereoselective organocatalysis in flow is a very innovative and rapidly expanding methodology to prepare enantio-enriched (complex) molecules.⁴⁷ Since the use of potentially toxic metal species is intrinsically avoided,⁴⁸ continuous flow stereoselective organocatalysis can contribute to more sustainable processes and would be ideal for pharmaceutical applications where restrictive regulations in terms of product purity are needed.

In literature, all of the examples concerning continuous flow organocatalysis involve the use of chiral organocatalysts in quite basic reactions, usually between model substrates. Only few

examples report on the stereoselective synthesis of chiral intermediates that are API precursors (vide infra). It should be pointed out that, at the moment, no example of stereoselective reactions promoted by chiral metal-free catalysts integrated into a continuous flow multistep synthesis of pharmaceuticals exists.

As discussed in the Introduction, an organocatalytic reaction under continuous flow conditions can be performed with two different kinds of setup. In a first approach, the reaction is run under homogeneous conditions and the chiral organic catalyst is fluxed together with the reactants, typically in a microreactor. (type III, Figure 1). In the second approach, the chiral organocatalyst is incorporated into the (micro)fluidic device while the reactants flow through the reactor. (type IV, Figure 1) While this second approach is very convenient because it prevents the separation step of products from the catalyst, it is clear that an immobilization step of the chiral catalyst onto a solid support is required. Moreover, due to the fact that the catalyst has to be physically packed into the reactor, the use of microreactor is generally avoided in favor of the larger and easier to handle mini- or meso-reactors.⁴⁹ According to the method used to incorporate an immobilized catalyst into the device, catalytic (micro)reactors can be divided into three main classes: (i) packed-bed; (ii) monolithic; and (iii) inner wall-functionalized. In the packed-bed reactor the catalyst is immobilized onto an insoluble support and is randomly charged into the reactor. In a monolithic reactor the catalyst is prepared in the form of a structured material, the “monolith”, consisting of a regular or irregular network of channels. In general the monolith is built by the copolymerization of different monomers (one containing the catalyst) in the presence of a porogen inside the reactor. The main advantage of a monolithic reactor with respect to a packed-bed is that the packing is more homogeneous and a more controlled fluid dynamics is generally achieved. In an inner wall-functionalized reactor the catalyst is covalently attached onto the interior wall of the reactor. The wall-coated microreactors substantially minimize the mass transfer resistance and ensure a smooth flow of reagents without leading to any adverse pressure drop or blockage of the channels; however, their use is still very limited due to the complexity of the synthesis.

Scheme 16. Enantioselective Continuous Flow Michael Additions

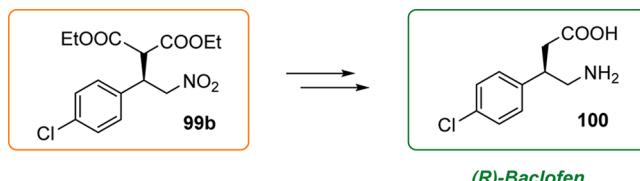


In this chapter we will cover most significant examples of stereoselective organocatalysis under continuous flow conditions: in section 4.1 the use of homogeneous chiral organocatalyst will be discussed, while in section 4.2 catalytic reactors containing solid supported chiral organocatalyst will be examined.

4.1. Homogenous Stereoselective Organocatalysis in Flow. Given the large number of chiral organocatalysts developed up to now, it is surprising that their application under continuous flow conditions is still quite limited. Indeed most of examples are limited to the use of *L*-proline (or its derivatives)⁵⁰ and chiral phosphoric acids.⁵¹

Recently, our research group has reported the use of a chiral bifunctional catalyst in glass microreactors to successfully accomplish enantioselective Michael type additions reactions⁵². The addition of acetylacetone to β -nitrostyrene promoted by Takemoto bifunctional thiourea was selected as a model reaction for the initial optimization study. The initial screening was performed in a commercially available Chemtrix Labtrix Start Standard platform equipped with two syringe pumps (Chemix Fusion 100) to deliver the reagents through two Hamilton gastight 500 μ L syringes into a glass microreactor (Chemtrix SOR 3223; 10 μ L volume). The schematic representation of the reaction is depicted in Scheme 16. After extensive optimization, it was found that, under the best reaction conditions (70 °C, 5 min residence time), the product was obtained in 91% yield and 80% ee.

This methodology was also applied to the synthesis of an advanced precursor of (*R*)-Baclofen **100** (Scheme 17).

Scheme 17. Synthesis of (*R*)-Baclofen

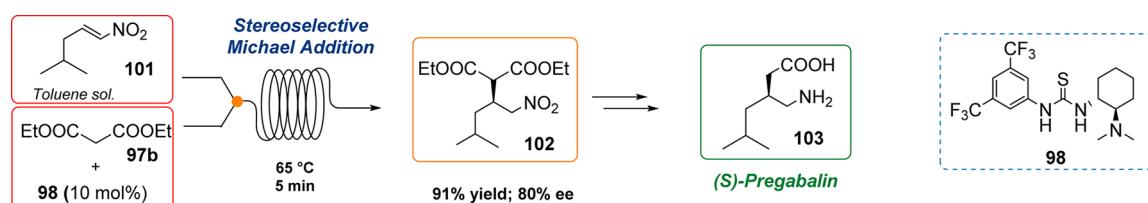
The reaction between diethylmalonate and *p*-chloro- β -nitrostyrene promoted by Takemoto bifunctional thiourea was first attempted in the standard Chemtrix Labtrix platform that allowed a fast screening of reaction conditions. In order to obtain high conversion and ee, diethyl malonate was employed neat, and 20 mol % catalyst was used; after 10 min at 80 °C, the desired product was obtained in 98% conversion and 85% ee. We then attempted a reaction scale up by using a simple fluidic module made of PTFE tubing (0.5 mm, inner diameter; 400 μ L, effective volume) coiled in a bundle and immersed in an oil bath. Two syringe pumps, equipped with two Hamilton gastight, 10 mL syringes, fed the *p*-chloro- β -nitrostyrene **96b** and the catalyst in neat diethyl malonate through a T-junction (10 μ L internal volume) into the above-mentioned PTFE tubing. Under optimized conditions (30 min residence time at 80 °C), the addition product **99b**, advanced precursor of Baclofen, was obtained in nearly quantitative isolated yield and 81% ee. Also in this case the flow system proved to be superior to the batch process, affording a productivity of 9000 h⁻¹ (productivity is measured in mmol(product) h⁻¹ mmol(catalyst)⁻¹ $\times 10^3$).

Later on, we expanded the scope of the technology by reporting the synthesis of an advanced precursor of anticonvulsant and antiepileptic drug (*S*)-Pregabalin **103** performed in a PEEK and PTFE tubing as microfluidic devices (Scheme 18).⁵³

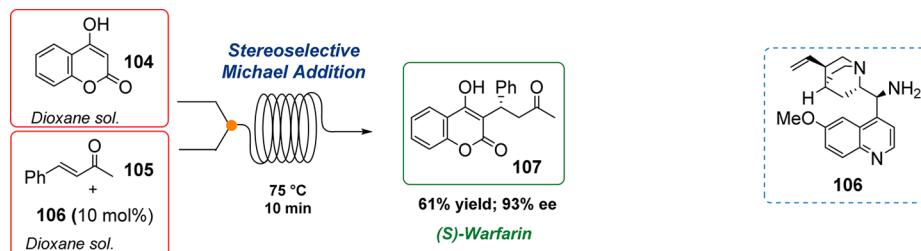
In our initial experiments we employed a PEEK microreactor with a total volume of 10 μ L in order to demonstrate the compatibility of the organocatalytic methodology with continuous flow processes. A syringe pump equipped with two syringes was used to feed the microreactor with the reagents through a T-junction. In one syringe the aliphatic nitroalkene **101** and internal standard were charged, while in a second syringe diethylmalonate **97b** and Takemoto's thiourea **98** were loaded. The microreactor was coiled in a bundle and immersed in a preheated oil bath. After a screening of reagent concentrations and reaction temperatures, it was found that product **102** was formed in 36% conversion and 79% enantiomeric excess using a residence time of 10 min.

Attempts to scale up the reaction by increasing the size of the microreactor were conducted using a PTFE microreactor

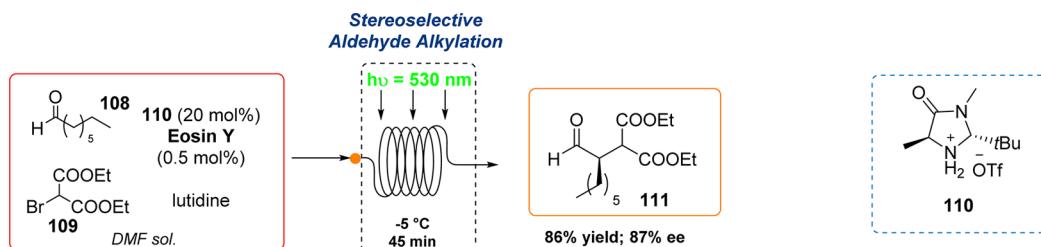
Scheme 18. Enantioselective Continuous Flow Michael Additions



Scheme 19. Enantioselective Continuous Flow Synthesis of (S)-Warfarin



Scheme 20. Stereoselective Continuous Flow Aldehyde Alkylation



(inner diameter 0.58 mm, length 189 cm, total volume 500 μL). By performing the reaction under the previously optimized reaction conditions, we were able to obtain the desired product in 40% conversion and 79% ee. We then decided to performed a gram-scale synthesis of (S)-pregabalin intermediate: under the best reaction conditions (60°C , 2 min residence time), we were able to produce 1 g of the desired product **102** in 81% ee, in 1 h only using a very simple flow apparatus.

The same flow setup was applied for the synthesis of the widely used anticoagulant (S)-warfarin **107** (Scheme 19).⁵³ We envisioned the nucleophilic addition of 4-hydroxy-coumarin **104** to benzalacetone **105** catalyzed by cinchona-derived primary amine **106**⁵⁴ in the presence of trifluoroacetic acid as cocatalyst as the most straightforward methodology compatible with flow microreactors. As in the previous example, in order to optimize the reaction conditions in flow, we employed a PEEK microreactor with a total volume of 10 μL . A syringe pump equipped with two syringes was used to feed the microreactor with the reagents through a T-junction. In one syringe 4-OH-coumarin dissolved in dioxane was charged, while in a second syringe a solution of dibenzalacetone, the chiral catalyst and trifluoroacetic acid in dioxane was loaded. The microreactor was coiled in a bundle and immersed in a preheated oil bath.

Different combinations of flow rates and reaction temperatures were investigated, and it was found that, with increasing temperature, the conversions increased and the ee remained constantly high (>90%). Optimum reaction conditions were found to be 75°C and 1 $\mu\text{L}/\text{min}$ flow rate (corresponding to 10 min residence time), which leads to the formation of the desired product (S)-warfarin **107** in 61% conversion and 93% ee. As in the synthesis of (S)-pregabalin intermediate, in an attempt of scale the reaction up, we performed the same reaction in a PTFE 500 μL volume. We observed that best reaction conditions found in the smaller microreactor were not reproducible; in particular, while the ee was satisfactory, the yields were quite low, also by increasing temperature and residence time. We then decided to explore the “numbering up” technique by connecting four microreactors of the same dimension in parallel. We used a stainless-steel splitter (two inlet and four outlet), and we performed the reaction as before.

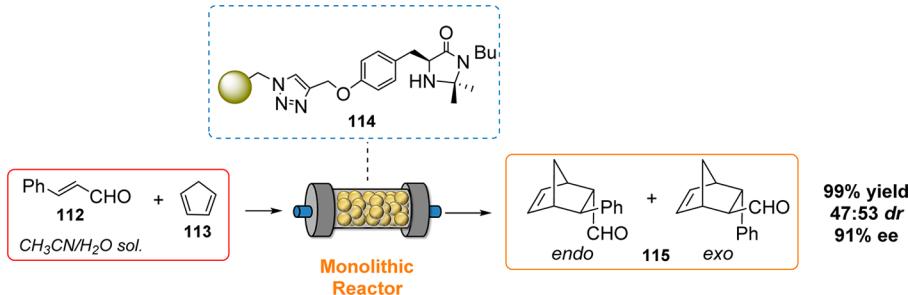
At the end, the desired product **107** was isolated in 36% yield and 91% ee.

These two works^{52,53} served as a proof that a small microreactor can be used to settle the best reaction conditions for the synthesis of interesting molecules very quickly. Then, by scaling up the reaction in a bigger reactor, it is possible to obtain larger amounts of an API intermediate or precursor in continuo by using simple flow apparatus, with equipment that can be easily found in any chemistry laboratory.

Among enabling technologies, photocatalysis is one of the most suitable for the combination with continuous flow processes; indeed performing photochemical reactions in flow systems is significantly more efficient than developing in batch: the narrow width of flow reactor coils ensures an excellent and uniform distribution of light within the entire reaction mixture, resulting in higher reaction selectivity, shorter reaction times, and lower catalyst loadings. The scale-up of a photocatalyzed reaction in flow would become easier as many flow photoreactors could be connected in parallel, and the level of efficiency would be maintained high. In addition, the irradiation of smaller volumes of flammable solvents would also reduce safety concerns with respect to batch photochemical reactions.⁵⁵ A pioneering work involving the use of both continuous flow stereoselective organocatalysis and photocatalysis was reported in 2012 by Zeitler research group (Scheme 20).⁵⁶ By using chiral imidazolidinone **110** as the organocatalyst and Eosin Y as the photoredox catalyst they developed a flow synergistic process for the continuous flow stereoselective alkylation of aldehyde **108** with bromomalonate **109**. α -Alkylated product **111** was obtained in 86% yield and 87% ee with a residence time of 45 min only. The authors demonstrated also the scale-up of the reaction by using a 4.3 mL FEP reactor tube: this flow platform afforded **111** in 92% ee with an output of about 2 mmol/h, 2 orders of magnitude higher with respect to batch process.

The reports in the literature demonstrate that microfluidic technology allows for a rapid screening of different reaction parameters, such as temperature, solvent, reactants concentration, reaction times, catalyst loading, and catalyst–reagents combinations, thus leading to a quick identification of the

Scheme 21. Monolithic Reactor for Continuous Flow Stereoselective Cycloadditions



optimized reaction conditions that guarantee high chemical and stereochemical efficiency. In general, the reactions developed under continuous-flow conditions favorably compare with those carried out in a flask, leading to an improved productivity. The microfluidic setup could be a commercial complete platform or a simple assemble of equipment (such as syringe pumps, tubing, connection, etc.) that can be easily found in any chemistry laboratory. By simple scale up of the reaction in a bigger device, it is possible to obtain grams of the desired product in a limited period of time. These studies show the great potentialities of microreactors for asymmetric catalysis; considering the great variety of organocatalysts and highly efficient metal-free synthetic methodologies developed in the past decade, a rapid growth of the use of microfluidic devices to achieve stereoselective organocatalyzed transformations can be easily predicted in a near future, especially in the field of API synthesis.

4.2. Heterogeneous Stereoselective Organocatalysis in Flow. The preparation of a solid supported chiral organocatalyst often requires a greater synthetic effort if compared to the use of the same catalysts under homogeneous conditions. However, confining the solid catalyst into a flow reactor allows to overcome the synthetic issue and give access to many advantages in terms of product purification, multistep reactivity, and catalyst recycling.

The use of supported chiral organocatalysts under continuous flow conditions to perform stereoselective reactions for the synthesis of interesting molecules dates back to 2000 with the pioneering work by Lectka and co-workers that prepared enantioenriched β -lactams by the sequential use of columns packed with supported catalysts and reagents.⁵⁷ Since then, this research area has grown very rapidly as indicated by the number of papers that appeared in the literature on this topic.^{47,49} In this chapter only very recent examples of chiral supported organocatalysts applied to the synthesis of enantioenriched organic molecules under continuous flow conditions will be discussed.

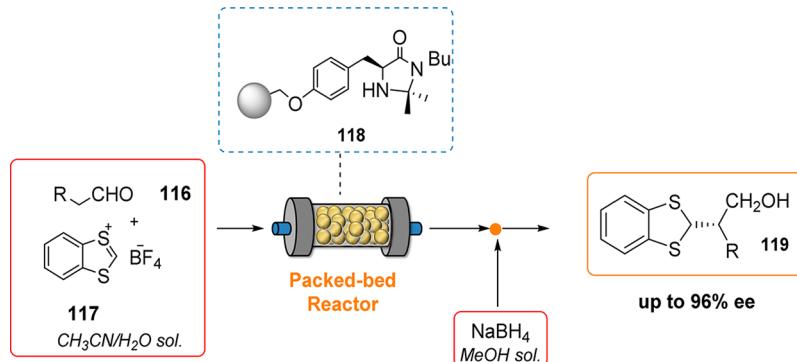
In 2013 our research group reported the continuous flow stereoselective organocatalyzed Diels–Alder reactions in a chiral catalytic “homemade” HPLC column;⁵⁸ the silica-supported MacMillan imidazolidinone was packed into an empty stainless steel HPLC column and used to efficiently promote stereoselective Diels–Alder reactions on different substrates for more than 150 h of continuous operation.⁵⁹

Short after, the same catalyst was immobilized into a monolithic system to develop the first organocatalytic monolithic reactor (Scheme 21).⁶⁰ Due to its porous structure and with respect to the packed-bed reactor, a monolith should guarantee a greater tolerance to high flow rates and efficient mass transfer through their large and small pores, allowing

higher back pressures; these features made monoliths quite popular in different fields such as chromatography.⁶¹ The use of monolithic systems as a support for catalyst to run reactions under continuous flow conditions is more limited but should, in principle, lead to higher productivities.

An ad hoc designed MacMillan type catalyst bearing a triazole spacer and a styrene moiety was easily synthesized starting from (S)-tyrosine methyl ester. This was used as a monomer in a copolymerization reaction inside an empty HPLC column (0.46 cm i.d. \times 15 cm, 2.49 mL total volume) at 70 °C in the presence of divinylbenzene (DVB) as a comonomer, AIBN as a radical initiator, 1-dodecanol and toluene as the porogenic solvents (3:1 v/v, approximately 60 vol % of the feed mixture). All of the chiral monomer was incorporated into the monolith, so it was possible to determine the absolute amount of the MacMillan derivative immobilized inside the flow device and the loading onto the polymeric support directly from the feed composition. The prepared flow devices were used in the stereoselective Diels–Alder cycloaddition between *trans*-cinnamaldehyde 112 and cyclopentadiene 113 as a model reaction. One flow device was activated by trifluoroacetic acid and tested under different flow rates. After a conditioning time of 4–6 h, a steady-state regime was reached, that allowed to produce in continuo the desired cycloadducts in 54–61% yield. In agreement with the results obtained with the nonsupported catalyst, the product was obtained as a rough 1:1 mixture of *endo/exo* isomers, both with enantioselectivities higher than 90% ee. In order to improve the chemical yield, the flow rate was reduced so as to increase the residence time: indeed with a flow rate of 2 μ L/min the product was isolated in 77% yield that was further incremented to 91%, by operating at 1 μ L/min. A different flow device was activated by tetrafluoroboric acid and used for performing the reaction in continuo between cyclopentadiene and three different aldehydes. The reaction with cinnamic aldehyde afforded the products in 75% yield and 90% ee for both isomers, thus confirming chemical and stereochemical performances comparable to the TFA-activated monolithic catalyst. Then, the column was washed and used in further cycloaddition runs with different aromatic aldehydes. By pumping a solution of 2-nitro-cinnamic aldehyde and cyclopentadiene, the catalytic column continuously produced the expected cycloadducts in up to 94% yield and 90–91% ee for both diastereoisomers. After 3 days of continuous operation the reactor was washed and used for carrying out the reaction between cyclopentadiene and crotonic aldehyde, affording the cycloadduct in yields higher than 94% and enantioselectivities up to 85% ee. Finally, in order to verify the activity of the system after a prolonged time on stream the reactor was washed once more and used to promote again the initial

Scheme 22. Continuous Flow Aldehyde Alkylation



reaction between cyclopentadiene and cinnamic aldehyde. Indeed, after 150 working hours of the catalytic reactor, the product was isolated in yields and stereoselectivities totally comparable with those of the first 24 h of activity. In order to verify the higher productivity of the monolithic reactor with respect to the packed-bed reactor and the reaction performed in batch, we performed a comparison of the three systems in the Diels–Alder cycloaddition. It was found out that the flow processes performed better than the batch system in terms of better productivity (measured in mmol(product) h⁻¹ mmol(catalyst)⁻¹ × 10³) and TON (Turn Over Number, measured in mmol(product) mmol(catalyst)⁻¹). Nevertheless, due to the long residence time that are required to achieve high yields, productivity was still quite low. However, we found that the tetrafluoroborate chiral monolithic reactor was tolerant to flow rate increase, and a remarkable level of productivity of 338 h⁻¹ was reached by using a flow rate of 18.8 μL/min.

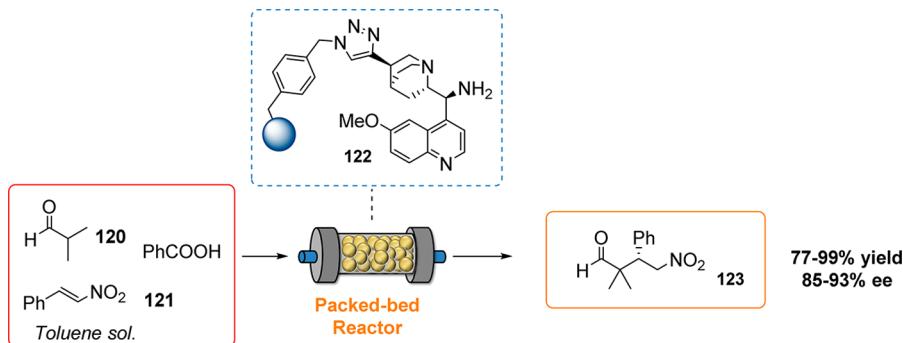
Given the very satisfied results obtained with the polystyrene-supported chiral imidazolidinone 114, we decided to apply the same system to perform a more interesting and challenging reaction: the organocatalyzed enantioselective α -alkylation of aldehydes under continuous flow conditions.⁶² Chiral, nonracemic, α -alkyl-substituted aldehydes are considerably important key substrates for the synthesis of more complex molecules; an accessible strategy to prepare them consists in the reaction of a stable carbenium ion with a saturated catalyzed by MacMillan-type catalysts as developed by Cozzi's group.⁶³ In order to verify the feasibility of the alkylation under flow conditions we prepared two catalytic reactors, one containing a silica-supported and the other containing a polystyrene-supported chiral imidazolidinone. The continuous flow stereo-selective alkylation of propionaldehyde with 1,3-benzodithiolylium tetrafluoroborate 117 performed with the silica-supported catalyst was able to continuously produce the desired alkylated compound in 82% ee (after reduction to the corresponding alcohol with NaBH₄ in MeOH), with a productivity of about 1000 h⁻¹ (Scheme 22). The second reactor, filled with polystyrene-supported imidazolidinone, produced the product with ee constantly higher than 93% and up to 95% at room temperature, totally comparable to the homogeneous nonsupported catalyst, that afforded the product in 96% ee at 0 °C in batch. Noteworthy, the reactor guaranteed high stereoselectivities at different flow rates; in particular, the excellent behavior of the reactor also at high flow rates allowed to improve the productivity of the process up to 1190 h⁻¹ always with high enantioselectivity. The two flow devices allowed to expand the scope of the reaction by using two different cations: benzylidinium and tropylidinium tetrafluoroboro-

rate. Polystyrene-supported MacMillan catalyst outperformed the analogous silica-supported catalyst, affording the products in higher ee and higher productivity. It is important to note that both reductive and oxidative removals of 1,3-benzodithiol moiety are possible; in particular, the treatment of the alkylated products with Raney nickel allows to obtain enantiomerically enriched α -methyl derivatives, key intermediates for the production of APIs and natural products.

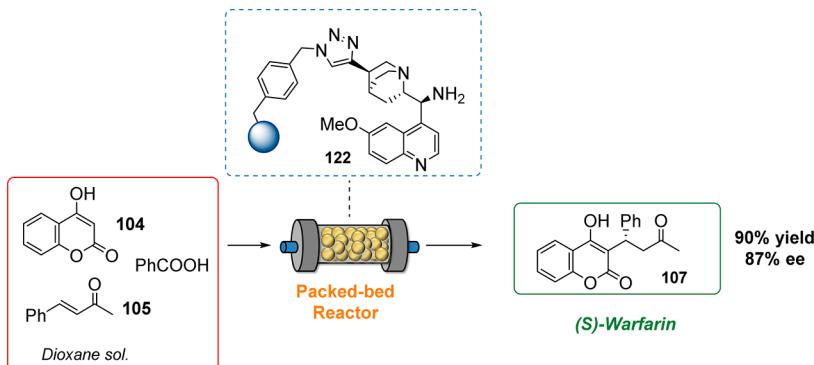
With the aim of demonstrating the applicability of our continuous flow system in the synthesis of interesting molecules, we chose different, selected aldehydes to perform stereoselective alkylations to prepare intermediates for important synthetic applications. For example, the continuous flow alkylation of octanal with 1,3-benzodithiolylium tetrafluoroborate under continuous flow conditions with polystyrene-supported catalyst, afforded, after NaBH₄ reduction, the expected alcohol in 94% ee. By using a residence time of 7 min, it was possible to obtain a productivity of 600 h⁻¹ and 90% ee. This product could be converted in (*S*)-2-methyl-octanol, a key intermediate for the preparation of natural products and antitumor antibiotic compounds. The product derived from the α -alkylation of phenylacetaldehyde with 1,3-benzodithiolylium tetrafluoroborate under continuous flow conditions with polystyrene-supported catalyst, after reduction, was obtained in 90% ee and a productivity of 970 h⁻¹ (7 min residence time). The unprotected derivative, (*S*)-2-phenylpropan-1-ol, is the precursor for bisabolanes, which are anti-inflammatory, antiviral, and antimycobacterial agents. Furthermore, the enantioselective α -alkylation of phenylacetaldehyde offers a valuable and extremely attractive approach for the preparation of enantiomerically pure α -aryl propionic acids.

The examples reported in this review and most of examples regarding heterogeneous organocatalytic continuous flow reactors deal with secondary amine-catalyzed reactions (MacMillan imidazolidinone and proline-type catalysts). Cinchona-derived primary amines-catalyzed stereoselective reactions have recently emerged as a powerful tool for the synthesis of complex molecules in enantioenriched form.⁶⁴ Surprisingly, until very recently, there was no report on the use of immobilized cinchona-derived primary amines for stereoselective reactions in flow.⁶⁵ We prepared a modified 9-amino-*epi*-quinine bearing a triazole as a linker and a styrene moiety by an ad hoc procedure starting from commercially available quinine. The immobilization step was achieved by copolymerization of the chiral monomer at 70 °C in the presence of divinylbenzene (DVB) as a comonomer, AIBN as a radical initiator, and 1-dodecanol and toluene as the porogenic solvents, as described before. The solid catalyst 122 was used

Scheme 23. Stereoselective Continuous Flow Michael Addition



Scheme 24. Continuous Flow Stereoselective Synthesis of (S)-Warfarin



to pack a stainless steel column (i.d. 0.4 cm, L 6 cm) in order to perform the stereoselective reaction of isobutyric aldehyde **120** with β -nitrostyrene **121**, originally reported by Connon,⁶⁶ under continuous-flow conditions in the presence of benzoic acid as an additive.⁶⁷ Preliminary studies were performed by flowing 2 mL of a solution of β -nitrostyrene, isobutyric aldehyde, and benzoic acid in toluene, collecting the products and washing the reactor with 1 mL of toluene before running the following run. We found out that, in the first run, the desired product was obtained in good yield but an ee lower than in the batch procedure; in the second run, when no additional amount of benzoic acid was used, the ee increased from 81% to 88%, and the ee increased further in the third and fourth run (93%), while the yield decreased. We then fluxed a solution of benzoic acid into the reactor and run the reaction again: at the end, the reactor worked for 100 h and afforded the product in 61% yield and 90% ee. It was evident that the amount of benzoic acid in the reaction environment played a crucial role in the reaction outcome; in an attempt to improve the reactor performances we decided to triturate the solid catalyst and decant it in order to get a more homogeneous packing into the reactor. Moreover, we fed the as-prepared reactor with all the reagents in toluene solution and run the reaction; a solution of benzoic acid was flushed through the flow device when the yield decreased (77% after 157 h operation). With this procedure we were able to synthesize more than 1 g of the desired product **123** in high ee (Scheme 23).

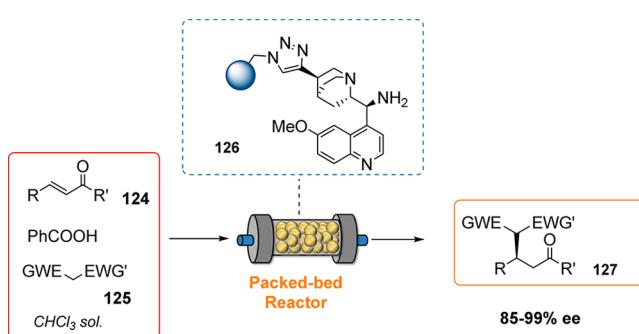
The same catalytic packed-bed reactor was used for the preparation of (S)-warfarin **107** under continuous flow conditions (Scheme 24).⁶⁸ A solution of 4-OH-coumarin **104**, benzalacetone **105**, and trifluoroacetic acid as a cocatalyst in dioxane was flowed into the reactor containing the

polystyrene-supported 9-amino-*epi*-quinine **122**. With a residence time of 5 h at 50 °C, we were able to isolate the product in up to 90% yield and up to 87% ee. Further studies are needed in order to optimize the reaction under continuous flow conditions; however, the proposed protocol already offers the possibility to extend catalyst's lifetime, longer than in batch mode, further suggesting interesting future applications for the catalytic reactors.

Almost at the same time of our work, the Pericàs group published the stereoselective Michael addition of ethyl nitroacetate to benzalacetone promoted by polystyrene-supported 9-amino-9-deoxy-*epi*-quinine **126** under continuous flow conditions.⁶⁹ It should be pointed out that the polystyrene in our hands is a highly reticulated, insoluble polymer, while the polystyrene used by the Pericàs group is a swelling resin; a careful choice of the reaction solvent should be done, as this may affect the reaction course. The functionalized resin was packed into a Teflon tube between two plugs of glass wool. The reaction was run by pumping a solution of the two reagents and benzoic acid as a cocatalyst in CHCl₃ (chosen after careful solvent screening) at 30 °C for 40 min residence time. Notably, 3.6 g (12.9 mmol) of the desired adducts were collected in 21 h of operation in roughly 1/1 dr and 97/98% ee.

The same system was used to prepare a small library of compounds by using a combination of four different aromatic enones with three nucleophiles. Each solution containing the enone **124**, a nucleophile **125**, and benzoic acid, was circulated through the system at optimized reaction conditions (Scheme 25). Between each run, the reactor was washed with CHCl₃ in order to avoid cross-contamination. At the end of the entire process, the authors found that the initial 500 mg of resin was able to afford the synthesis of five different Michael adducts **127** in high yields and high ee (>85%), generally higher than

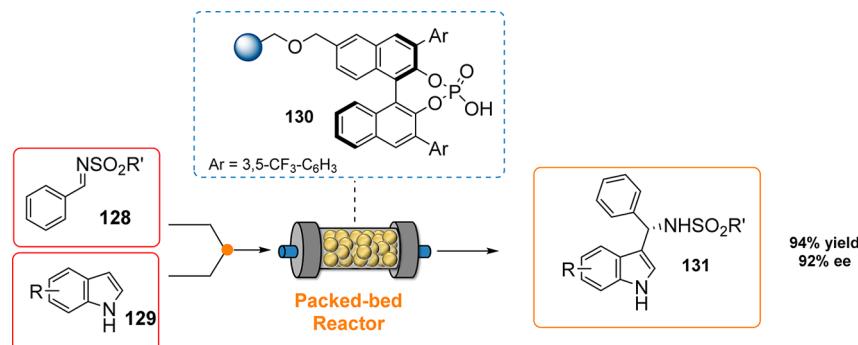
Scheme 25. Stereoselective Continuous Flow Michael Additions



the corresponding batch processes, with a remarkable productivity.

The same group reported the only example, up to date, of polymer-supported chiral phosphoric acid to be used in flow systems.⁷⁰ Despite their popularity, immobilized chiral phosphoric acids in flow are scarcely used, probably because of their complex and long preparation. Poly(styrene)-supported chiral phosphoric acid 130, prepared after several steps, was used in the Friedel-Crafts alkylation of indoles with *N*-tosyl imines; the resultant 3-indolylmethanamine derivatives are interesting molecules, since their structural motifs can be found in many biologically active natural and natural-like products. After extensive optimization in batch, the reaction was performed in a packed-bed column; the flow setup was equipped with a back-pressure regulator and integrated with an inline IR to monitor the reaction course (Scheme 26). By running a 6 h experiment with 0.2 mL/min as a flow rate, using 360 mg of the supported catalyst, it was possible to isolate 3.6 g of the desired product in 80% yield and 94% ee, with a productivity of 17.2 h⁻¹. With this strategy the preparation of a small library of five analogues was performed: by using the same continuous-flow setup, combinations of different sulfonylimines 128 and indoles 129 were passed through the packed-bed reactor in a consecutive fashion. Each solution was fluxed for 1 h, and the column was rinsed with CH₂Cl₂ between each run in order to avoid cross-contamination. Five different combination of indole and imine were used, each affording very high yield (>80%) and ee (>86%), thus guaranteeing a very high productivity. Noteworthy, the same batch of resin was used for all the continuous-flow processes performed, highlighting the great stability and robustness of the immobilized catalyst.

Scheme 26. Stereoselective Continuous Indoles Alkylation



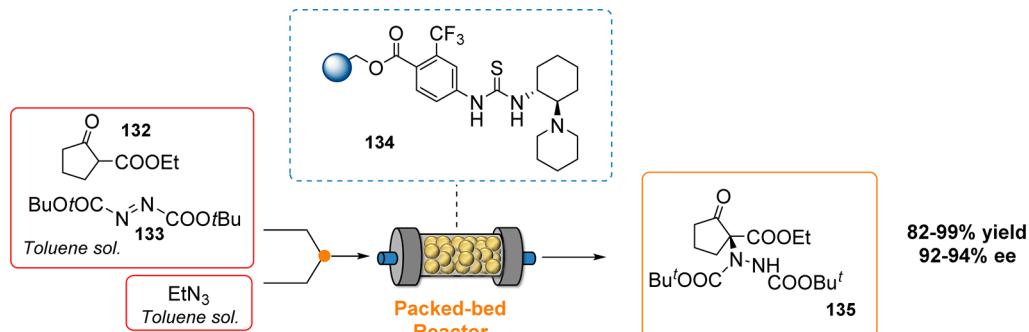
In 2015 the Pericàs group embarked on the synthesis of immobilized chiral Takemoto-like thiourea to promote the stereoselective α -amination of 1,3-dicarbonyls with azodicarboxylates (Scheme 27).⁷¹

The authors prepared two different Merrifield resin-supported thioureas, one carrying a triazole moiety and one without any linker. The immobilized catalyst with the linker proved to be unreliable, affording the desired products with nonreproducible results, so the authors switched to systems where the thiourea moiety was directly connected to the polymer chain 134; this second catalyst, with no linker, promoted the reaction with reliable results.

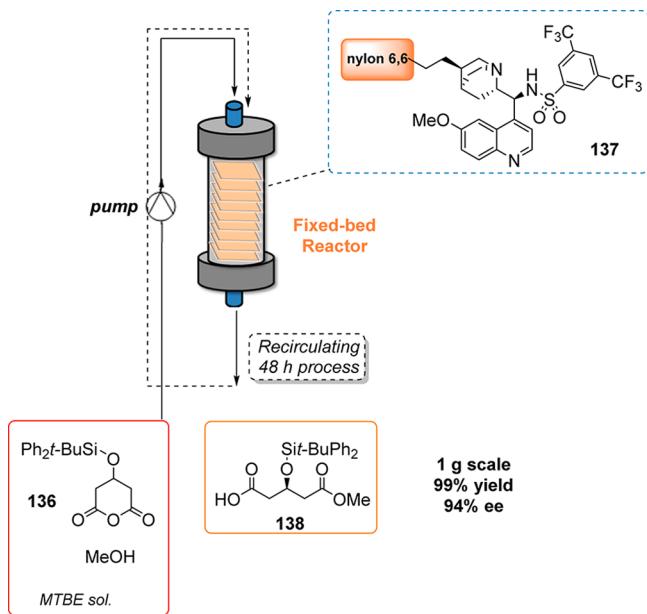
After extensive conditions screening in batch, the reaction was tested under continuous flow conditions in a packed-bed column with a pump feeding the reagents (ethyl 2-oxocyclopentanecarboxylate 132 and di-*tert*-butyl azodicarboxylate 133 in toluene solution) for a residence time of 21 min. Initial experiment showed that the catalytic reactor activity decreased after 2 h operation, mostly due to the protonation of the basic tertiary amine moiety of the catalyst. To circumvent this problem, the reactor was washed with a toluene solution of Et₃N every 2 h operation. With this improvement it was possible to isolate the product 135 in 71% overall isolated yield and 93% ee, with a productivity of 4.88 mmol mmol cat⁻¹ h⁻¹ and a TON of 37.

Last example that will be discussed in this section is the very uncommon flow setup proposed by List and co-workers.⁷² The authors chose pieces of nylon-6,6 as a solid support for the anchoring of a sulfonamide derivative of cinchona alkaloid by UV irradiation in the presence of penta-erthritol triacrylate (PETA) as a cross-linker. The obtained supported catalyst was called “organotextile catalyst” 137, and it was tested in the desymmetrization of cyclic anhydrides. Remarkably, the authors proved the robustness of the heterogenized catalyst by performing more than 300 batch recycling experiments, in which some experimental conditions were varied (amount of catalyst, amount of MeOH, concentration of the substrate). As a logical consequence, the catalyst was applied to the preparation of a valuable precursor of statin derivatives in a multigram scale by a flow synthesis using a continuous circulatory reactor packed with sheets of the catalyst (Scheme 28).

The experimental setup was very easy: 20 sheets of nylon-supported sulfonamide 137 were packed into a polypropylene cartridge of a BÜCHI-Flash System, with short fluorinated ethylene propylene connecting tubes; the system was flushed with MTBE before use. After full conversion of the starting material 136, the column was washed with MTBE reused for 10

Scheme 27. Continuous Flow Stereoselective α -Aminations

Scheme 28. Continuous Flow Anhydrides Desymmetrization



times with no loss of activity. It was possible to isolate 1 g of the desired product 138 in 99% yield and 94% ee.

5. OUTLOOK AND PERSPECTIVES

As clearly pictured in the previous sections, the continuous flow technologies offer important and attractive features exploited in the industrial process; it is not surprising that recently also the pharmaceutical companies have turned their attention to the use of flow chemistry in the preparation of APIs. It is a trend that cannot be stopped and will gain further strength in the future, enforced by the possibility to combine the synthesis of chemicals in flow with new analytical technologies for inline monitoring of the process and with enabling technologies for speeding up the isolation and purification steps.

In the case of microreactors, specific advantages comprise high surface to volume ratios and thereof, due to small dimensions, enhanced mass, and heat transfer coefficients by 1–2 orders of magnitude, high volumetric productivity, and laminar flow conditions. Furthermore, low manufacturing, operating, and maintenance costs, with low power consumption, increased safety due to small amount of materials used in the process, and scale up in parallel are all very attractive features in view of possible applications in an industrial synthesis.

However, although the technologies to manufacture microreactors in silicon, in glass and in steel, or other metals, are available, still (micro)reactors are not widely used as one may expect. One issue is they require very fast reactions and active stable catalyst (short residence times require fast reactions). A few years ago, a study by a major pharmaceutical manufacturing company⁷³ evaluated that about 50% of the reactions carried out in their synthesis would benefit from a continuous process; however 63% of those reaction could not be performed at that time in a microreactor, due to the presence of a solid. And that leads to the crucial point, the development of flexible and versatile microreactors capable of handling solids, to be used in multipurpose continuous plants. Indeed, impressive progress in this field have been made, as demonstrated by some recent multistep synthesis in flow discussed also in this review, and it is easy to foresee many other significant technological advances in the field. About economics of flow processes, it should be also considered that the time for development of such processes are usually longer than that for batch processes and investments are sometimes not trivial.

It is also true that micro reactors, due to small dimensions, are prone to fouling and clogging, leaks between channels, and their reliability and life on stream is an unknown and that may contribute to the perception of a risk factor too large to replace existing installations. Other disadvantages related to the use of catalytic reactors are possible catalyst deactivation and frequent reactor repacking or reactivation and reliability for a long time on stream.

However, an important positive feature offered by the *in flow* processes is the realization of highly flexible modules to perform on demand synthesis. That will lead to the realization of regional manufacturing and distribution network; the industrial processes which will be tailored “ad hoc”, modulating the size and the schedule of the productions, with an increased responsiveness to change in demand. For example, the (micro)reactors technology is today a viable possibility in the *In situ* preparation of hazardous and explosive chemicals, or the synthesis of special chemicals, with a reduced chance of drug shortages.

Finally, another crucial issue that will be probably the subject of many investigations in the future is the ability to perform catalytic, enantioselective reactions in flow. Stereoselective synthesis of chiral product is underdeveloped; basically, all of the examples of reactions sequence in flow discussed above and published in the very past few years are related to the synthesis of achiral compounds or the racemic form of a chiral product. Indeed, only in 2015 the Kobayashi report on Rolipram¹¹ opened the way to the use of chiral catalytic reactors to afford enantiomerically pure molecules of pharmaceutical interest. But

the problems are still numerous: activation, efficiency, lifetime, degradation, and possible reactivation of supported chiral catalysts are only a few of the topics to be studied and optimized for a successful use of catalytic reactors in an applicative process.

Integrating in a single, all in continuo process not only the synthesis of complex molecules but the whole manufacturing process is one of the future challenges. Several advantages may be envisaged: direct transfer from development to manufacturing will shorten the whole process times and will make it faster to the market. Furthermore, COGS (cost of good sold) savings, greater flexibility, small footprint, and decreased inventory may be realized through a colocation and integration of process steps in one single facility. The spectacular result reported for the production of the final tablets of aliskiren (see ref 4) has opened new avenues in this area; however it should be noted that the whole in flow manufacturing of aliskiren tablets was accomplished by studying only the two final steps of the synthesis, a condensation reaction starting from an advanced precursor of the final product where the absolute configuration of all four stereocenters has been already established. The future challenge is to accomplish efficient synthesis of enantiomerically pure products under continuous flow conditions and integrate the in flow synthesis in a single "all in flow" process featuring also in line analysis, purification, and crystallization steps, and leading to the production of the final, ready for the market drug. The road is long and full of obstacles, but, considering the impressive progress made in the continuous flow technologies in the past few years, the final goal might be accomplished in shorter times than expected.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: maurizio.benaglia@unimi.it

*E-mail: alessandra.puglisi@unimi.it

Notes

The authors declare no competing financial interest.

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