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Stereoselective organocatalysis and flow chemistry

Abstract: Organic synthesis has traditionally been performed in batch. Continuous-flow chemistry was recently rediscovered as an enabling technology to be applied to the synthesis of organic molecules. Organocatalysis is a well-established methodology, especially for the preparation of enantioenriched compounds. In this chapter we discuss the use of chiral organocatalysts in continuous flow. After the classification of the different types of catalytic reactors, in Section 2, each class will be discussed with the most recent and significant examples reported in the literature. In Section 3 we discuss homogeneous stereoselective reactions in flow, with a look at the stereoselective organophotoredox transformations in flow. This research topic is emerging as one of the most powerful method to prepare enantioenriched products with structures that would otherwise be challenging to make. Section 4 describes the use of supported organocatalysts in flow chemistry. Part of the discussion will be devoted to the choice of the support. Examples of packed-bed, monolithic and inner-wall functionalized reactors will be introduced and discussed. We hope to give an overview of the potentialities of the combination of (supported) chiral organocatalysts and flow chemistry.

Keywords: stereoselective synthesis, stereoselective catalysis, organocatalysis, supported catalysts, flow chemistry, catalytic reactors, microreactors, mesoreactors

1 Introduction

Continuous-flow processes were recently rediscovered as an enabling technology [1] to be applied to the synthesis of organic molecules [2, 3]. Kirschining has defined Enabling technologies as "various traditional as well as new techniques which have been developed to speed up synthetic transformations and importantly ease workup as well as isolation of products" [4]. The merits of flow chemistry both on a micro- and on a meso-scale have been reviewed [5–10] a number of times, but can be shortly summarized here: (1) *efficient heat and mass transfer*: this is particularly emphasized in narrow-channel system, where heat and concentration profiles are homogeneous along the reactor. (2) An easy *combination*

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with other enabling technologies such as microwave irradiation, inductive heating, photochemistry, electrochemistry, which opens the door to efficient and fast synthetic transformations. (3) An *improved safety* of the process: this is mainly due to the accurate control of the reaction parameters (temperature, pressure) in the (micro)reactor. In addition, the possibility of using and reacting small amounts of potentially toxic and/or dangerous reagents at a given time drastically expands the pool of reagents available to the synthetic organic chemist. Safety issues are particularly important in the case of massive production and are generally concerns of big industries. Pharmaceutical companies have recently started to adopt continuous technologies thanks to the great benefits associated: the possibility to develop a fully automatic process while analyzing the data *in continuo*, using low-cost equipment. Food and Drug Administration (FDA) and European Medicines Agency (EMA) on their side recommend the massive use of continuous-flow technologies to meet high-quality standards and green chemistry principles [11, 12]. The equipment necessary to run a reaction *in continuo* is by far more flexible and cheaper than the common equipment used to run the same process in batch. The immediate benefit is that the optimization campaign for the active pharmaceutical ingredient (API) synthesis is much shorter and the synthetic organic chemist can produce the desired amount of the API in a very short time. Consequently, the risk and the cost associated with the development and production of and API is greatly reduced, due to reduced investment. The specific topic of the application of continuous-flow processes to the synthesis of pharmaceuticals intermediates was broadly reviewed in the past few years and will not be specifically discussed in this chapter [13–21].

All these discussed features contribute to have faster reactions and lead to an implementation of the existing processes. Some common problems related to the reaction scale-up can be more easily tackled in flow rather than in batch: this is the case of runaway reactions, inefficient mixing, and byproduct formation that benefits from the use of microreactors. The small dimension of microreactors allows to better control the reaction parameters and, therefore, possible problems that may arise. Accordingly, the reaction scale-up in small reactors is easier than in batch, at least in principle. There are three reported methods to produce large amounts of a compound *in continuo*: (i) the scaling-out, which is the easiest method and consists on running the process for long time, (ii) the numbering up, which is used in many reactors in a parallel manner, and (iii) the scaling-up, where the process is performed on larger continuous reactors [22].

Finally, we can observe a considerable increase in the complexity of the continuous-flow processes published in the literature; this is particularly true for the applications toward APIs. We assisted to a rapid evolution of flow chemistry, from single-step reactions to multistep processes, often completely integrated, comprising advanced downstream purification and formulation [23].

2 Catalytic flow reactors: classification, tools and parameters

"Continuous-flow chemistry" is the common and wide term used to describe the performance of a reaction in a continuous manner, within the channels of a fluidic reactor. It collects a variety of process technologies, tools and strategies now routinely used in many research groups both for explorative and preparative purposes. Intuitively, we can describe a flow reactor as a vessel with an inlet and an outlet, in which the reagents are fed continuously and the products are continuously removed. Figure 1 depicts the different types of flow reactors that will be discussed in this chapter.

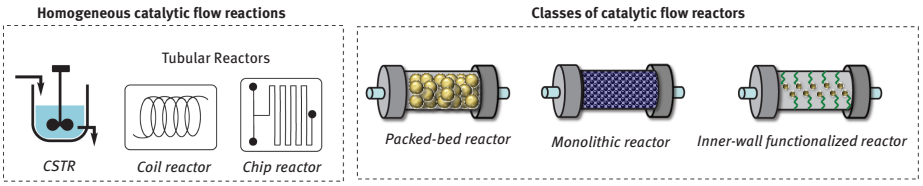

Figure 1: Types of flow reactors discussed in this chapter.

There are two main classes of flow reactors: the continuous stirred-tank reactor (CSTR) and the tubular reactor (TR). On a laboratory scale, TRs are commonly used.

Catalytic reactors can be defined as those in which the catalyst permanently resides inside. They can be divided into three main classes, according to the method used to incorporate the immobilized (organo)catalyst into the device: (i) packed-bed; (ii) monolithic; and (iii) inner wall-functionalized. These types of catalytic reactors will be discussed in Section 4.

Johnston et al. [24] have reported an example of a homogeneous Brønsted acid – base catalyzed aza-Henry reaction performed in a CSTR. This work was developed in collaboration with Eli Lily researchers to testify the interest of big pharmaceutical industries to the development of continuous-flow processes. Due to the absence of (micro)channels, CSTRs are more suitable for handling the solids in flow with respect to TRs; thus, heterogeneous reactions with solid precipitation can be run in flow using a CSTR. The initial goal of the project was to translate the enantioselective aza-Henry reaction from batch to continuous flow, to accelerate the large-scale production of diamine building blocks. During the reaction, the formation of a less-soluble product prevented the use of a typical tubular flow reactor for the initial investigations. The presence of solids usually leads to plugging and clogging of the (micro)reactors. The authors selected an automated intermittent flow-stirred tank reactor, an equivalent process to continuous flow. Under the optimized operating conditions, the aza-Henry product continuously crystallized from the reaction mixture; this solid was intermittently filtered, while the mother liquor, containing the soluble catalyst, returned to the reactor. The sequence separation-catalyst recycling allowed to achieve

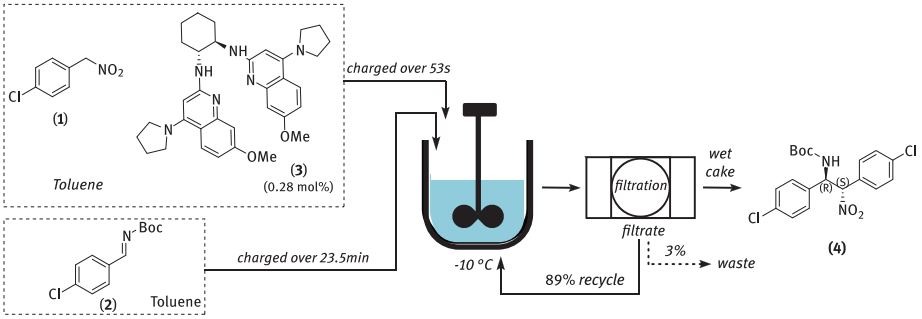

Figure 2: Homogeneous Brønsted acid–base catalyzed aza-Henry reaction performed in a CSTR.

a high-catalyst concentration in the reactor, thus leading to a faster organocatalytic reaction. The reaction setup is illustrated in Figure 2. The benchmark reaction was the aza-Henry reaction between 1-chloro-4-(nitromethyl)benzene **1** and *N*-Boc-4-chloro-benzaldimine **2** promoted by the diamine catalyst **3** to afford compound **4**. Overall, the development of an automated process allowed to improve the safety of the process, since small amounts of reactive nitroalkane were present at any given time. In comparison to the batch reaction, the reaction in flow was run with a higher output with a reduced time (40 min for a single cycle in flow *vs* 22 h for the batch process). Moreover, it turned out that the aza-Henry reaction was highly reproducible, thanks to the precise control over the parameters, and the scale-up required minimum optimization. The authors applied this process to the multigram synthesis of chiral nitro amines, direct precursors to differentially protected diamines.

Apart from few exceptions, in the course of this chapter, when we refer to "flow reactor," we usually consider a TR. TRs are typically characterized by narrow and well-defined channels with internal dimensions in the 10^2–10^3 μm range, and by internal volumes ranging from a few microliters to several milliliters. Based on internal diameters and volumes, they are referred to as micro- or mesofluidic reactors. They can be "chips" or "coils" according to the geometry (see Figure 1).

In a TR, no mixing is performed along its length, but usually the reagents are premixed before entering the reactor. There are many flow systems available on the market, with their costs variable from high to exorbitant, depending on the features and equipment. The high price of the commercially available systems has encouraged the researchers to engineer their own homemade flow setup, using some common laboratory tools. It is worth mentioning here that 3D-printing technology is becoming increasingly available and is significantly contributing to the field [25].

A list of tools for developing flow chemistry devices is reported here. (For a complete dissertation, see ref [10].)

PUMP: It ensures a constant flow rate. There are several possibilities, but it is commonly a syringe pump or an HPLC pump.

TUBING: It represents the connections and the real TR. There are several materials that can be used; the most common materials are PTFE, (stainless) steel, glass, and PEEK.

TEE: It is usually made by PEEK and it serves to connect different streams. It is used also for the reactants mixing at the inlet of the reactor.

The combination of these three pieces is sufficient to build a basic flow setup. Other devices that help the operator and complete the system are listed below.

CHECK VALVE: It is a device that ensures a unidirectional flow.

BACK-PRESSURE REGULATOR (BPR): It is a device that allows having and maintaining pressure in the reactor. It is used with gases and low-boiling solvents, to avoid the formation of bubbles.

LIQUID-LIQUID SEPARATOR: It is a device used for in-line reaction work-up that allows to separate two liquids based on their polarity.

IN-LINE MONITORING: It is an instrument that can be connected to the flow setup. It allows obtaining real-time information about the reaction progress by operating on the flow stream, without stopping the system. Commonly, it is a FLOW-IR, although other devices are becoming available (FLOW-NMR).

When dealing with continuous-flow systems, some important parameters need to be considered, besides the common parameters used to describe batch reactions such as temperature, pressure, concentration and molar ratios. Vr is the reactor volume; the flow rate ϕ is the rate at which the reagents are fed into the reactor. The flow rates are additive, so, if two reagents are pumped independently, the flow rate inside the reactor will be the sum of the two flow rates. The residence time τ is the time in which the reagents reside into the reactor. Intuitively, it corresponds to the reaction time for batch reactions. The relationship that connects the three parameters is:

$$\tau = \mathrm{Vr}/\phi \tag{1}$$

In the case of packed-bed reactor (see below) the volume to consider is the void volume V_0, determined by Vr minus the volume occupied by the catalyst:

$$V_0 = \mathrm{Vr} - \mathrm{Vcat} \tag{2}$$

In case of catalytic reactors, it is important to assess the efficiency of the catalyst to evaluate the overall convenience of the flow process. Different parameters have been proposed and are reported in the literature for a given transformation. However, it must be pointed out that it is not trivial to compare two different flow processes or a flow process to its corresponding batch version. The most common parameters found in the literature are listed below.

Mole hourly space velocity (MHSV): It represents the substrate feed to the reactor per unit mole of the catalyst and time unit.

Space–time yield (STY): It is defined as the amount of product obtained per unit time and reactor (or catalyst bed) unit volume.

Productivity: It is defined as the amount of product (obtained per amount of catalyst) in the unit time.

Time on stream (TOS): It is the overall duration of the process; it indicates the temporal stability of the catalyst inside the reactor.

Total turnover number (TTON): It is given by the molar ratio between the substrate converted into the expected product and the initial catalyst amount; it indicates the total amount of product that can be obtained by the process.

Accumulated TON: it is given by the product of catalyst TOF by operation time.

In a catalytic flow process, the catalyst can be homogeneous, so it flows through the reactor (chip or coil) together with the reactants; in this case, at the end of the reaction, a separation step of the product from the catalyst (and possible by-products) is required. On the contrary, the catalyst can be heterogeneous, that is, supported on a solid matrix. The solid catalyst resides into the flow reactor while the reactants pass by; at the end of the reaction there is no additional separation step required. The types of catalytic reactors are discussed in Section 4.

3 Homogenous organocatalysis in flow

Despite the great popularity of continuous-flow processes in the last decades, the use of homogeneous stereoselective organocatalysts in flow is still underdeveloped. This is mostly due to the fact that, in a homogenous catalytic continuous-flow process, the catalyst flows in the (micro)reactor together with the reactants, leading to a process in which, at the end, a separation step is required in order to purify the product and, possibly, recover and recycle the catalyst. This technique does not seem very appealing if compared to the use of supported catalysts that will be discussed in the next section. However, homogeneous catalysts are usually more active than their supported counterpart, so a continuous-flow process with an integrated catalyst separation and recovery would be amenable (see below).

Microfluidic technology allows for a fast screening of different reaction parameters, such as temperature, solvent, reactants concentration, reaction times, catalyst loading, and catalyst/reagents combinations just to name a few. The great benefit is the quick identification of the best reaction conditions that guarantee high chemical and stereochemical efficiency. The reactions developed under continuous-flow conditions favorably compare with those carried out in a flask only if reduced reaction times and improved productivity can be achieved.

Among the possible advantages of the use of continuous process, there is the possibility of heating the reaction, in a very controlled manner, in order to speed up the reaction; however, in the presence of a homogeneous chiral organocatalyst, heating while maintaining a high level of enantioselectivity can be challenging. Odedra and Seeberger [26] reported the 5-(pyrrolidin-2-yl)tetrazole-catalyzed aldol reaction between acetone and different aromatic aldehydes in a glass chip reactor. The reaction

was run in a 1:1 acetone:DMSO mixture at 60 °C; with a residence time of 40 min, they obtained the desired product in shorter time than the corresponding reaction in batch, with similar yield and enantiomeric excess. With 4-nitrobenzaldehyde **6** yield and enantioselectivity were superior than those of the same reaction performed in batch in the same conditions (60 °C, 20 min, 79 % yield, 75 % ee, Figure 3(a)). They extended the scope to different aldehydes and cyclohexanone. They also applied the same catalyst **5** and the same flow set-up for studying the Mannich reaction between cyclohexanone and *N*-PMP protected α-imino ethylglyoxylate. Performing the reaction at 60 °C allowed to obtain the desired product in short reaction time maintaining high yield and high diastereo- and enantioselectivity. The authors showed that the continuous process allowed to lower the catalyst loading with respect to the batch (5–10 mol %).

Luisi et al. [27] reported the use of the same catalyst **5** to promote the Michael addition of cyclohexanone to differently substituted β-nitrostyrenes to yield the products with moderate to good levels of enantioselectivity. The system was then implemented by adding a second microreactor and the set-up was thus modified: the first chip was dedicated to perform a Michael addition, leading to an intermediate that react in a second chip with a different Michael acceptor (e.g. an α,β-unsaturated carbonyl compound). This second organocatalyzed process afforded the corresponding adduct with up to four consecutive stereogenic centres. As an example, cyclohexanone **8** and *trans*–β–nitrostyrene **9** reacted in the presence of catalyst **5**; the output of the first microreactor, containing **5** and adduct **10**, was fed to the second microreactor with a solution of cinnamaldehyde **11** and DIPEA. The multifunctionalized adduct **12**, with six stereogenic centers, was obtained in 73 % yield, 66:34 dr and 84 % ee for the major isomer, thus demonstrating the ease of realizing multi-step stereoselective organocatalytic continuous-flow processes (Figure 3(b)).

The same catalyst **5** was used by Nakashima and Yamamoto [28] in a completely different approach for the use of nonsupported organocatalyst in flow. They packed proline tetrazole catalyst **5** into an empty column, thus realizing a reactor to be used with low-polarity organic solvents. The resulting heterogeneous system was studied in continuo without consumption and loss of catalytic activity. The column was used in the aldol reaction between ketones and different aromatic aldehydes using ethyl acetate as nonpolar solvent; the addition of 3 % water was beneficial for improving the ee. Notably, the packed-bed column was repeatedly used for reactions on 10 mmol scale and for different reactions, such as Mannich and *ortho*-nitro aldol reactions. Products were obtained in high yield (generally more than 70 %) and ee. Although the nonsupported proline tetrazole showed lower efficiency with respect to other solid-supported organocatalysts, this approach proved to be simple and efficient in the aldol reactions (Figure 3(c)).

Benaglia et al. [29] reported the stereoselective synthetic strategy for the preparation of trifluoromethylamine mimics of retro thiorphan, an inhibitor of metalloproteinase NEP (neutral endopeptidase). The crucial step is the stereoselective,

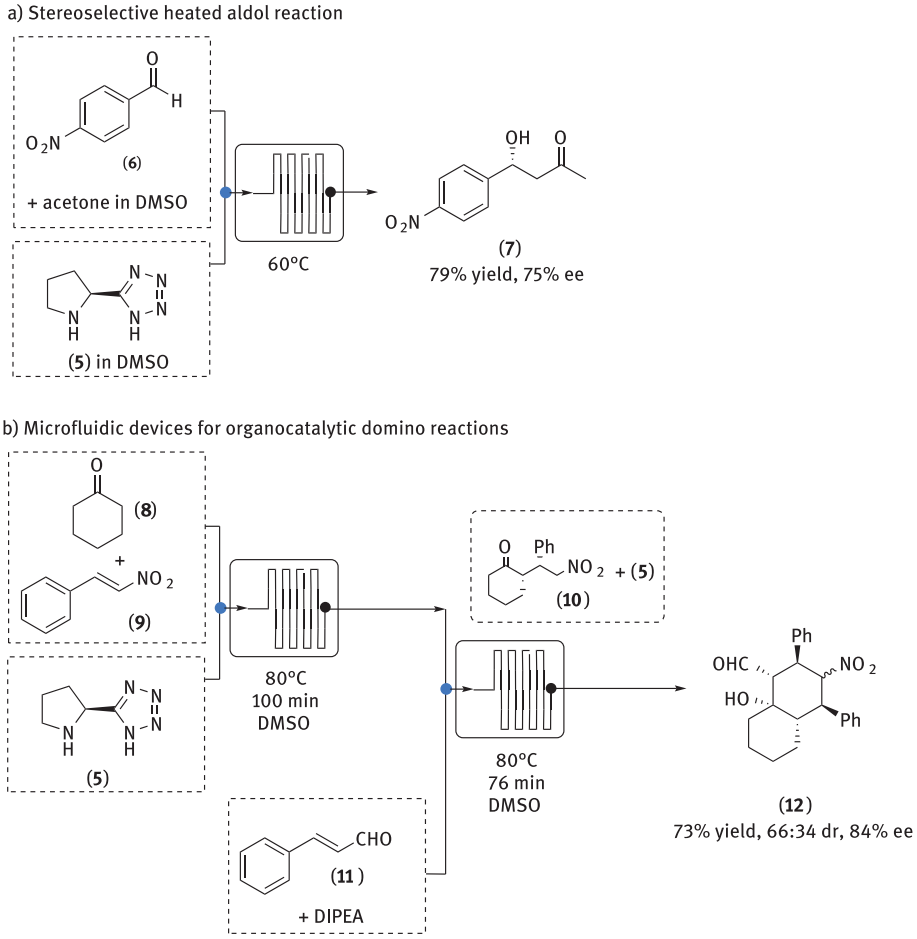

Figure 3: Examples of homogenous organocatalytic reaction under flow conditions using chip reactors (examples a and b) and packed bed reactor (example c).

catalytic reduction of a fluorinated enamine with trichlorosilane as a reducing agent in the presence of a chiral Lewis base. The whole synthesis was then investigated under continuous-flow conditions: an advanced intermediate of the target molecule was synthesized in only two in-flow synthetic modules, avoiding isolation and purifications of intermediates, leading to the isolation of the target chiral fluorinated amine in up to an 87:13 diastereoisomeric ratio. The entire flow sequence is illustrated in Figure 4. The commercially available fluorinated alkyne **13** was reacted with the O-allyl protected phenyl alaninol ether **14** to afford enamine **15** with complete conversion after 10 min residence time. **15** was consequently subjected to the $HSiCl_3$-mediated diastereoselective reduction in the presence of the chiral Lewis base **16.** The reduction step required long residence times in order to have an acceptable yield: heating up the reactor to 35 °C, allowed to obtain **17** in up to 37 % isolated yield, but with lower d.r., while cooling to room temperature, the yield was below 20 %, with 95:5 d.r. Although yield and d.r. were not totally satisfactory, this work represents a multistep continuous-flow process for the synthesis of enantiomerically pure, fluorinated, pharmaceutically relevant products.

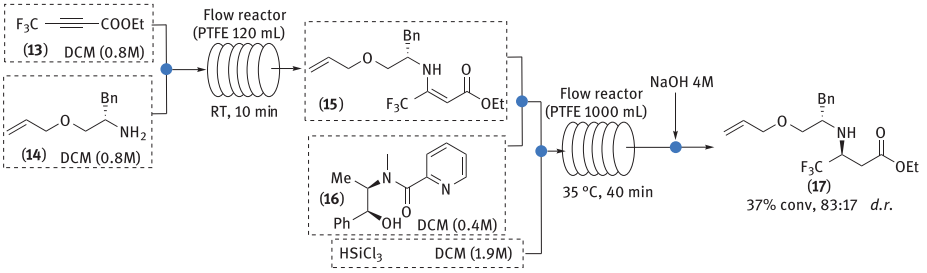

Figure 4: Continuous-flow synthesis of 17, a precursor of retrothiorphan.

Very recently, a prolinamide derivative **18** (Singh's catalyst) was used in a combination of buffer (pH 7)/2-propanol as solvent system for the stereoselective aldol reaction of 3-chloro-benzaldehyde **19** with acetone under continuous-flow conditions [30]. This is a preliminary study of a project to realize a two-step one-flow process in aqueous medium combining organo- and biocatalysis, and the first example of an organocatalytic reaction with a hydrophobic substrate in water running in flow mode. After extensive optimization, the authors were able to obtain yield and enantiomeric excess comparable to the batch reaction, opening the way to the second step. A solution of 3-chloro-benzaldehyde **19**, 2-propanol and phosphate buffer was mixed with a solution of Singh's catalyst **18** (3.6 mol %), 2-propanol, acetone and phosphate buffer and pumped into a coil Teflon tube reactor. After equilibration of the reaction, the eluted sample was collected and quenched by dropwise addition into a solution of CH_2Cl_2/2.0 M HCl; the organic materials were extracted with

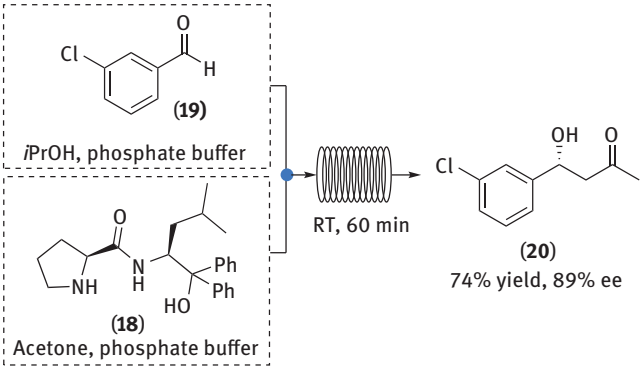

Figure 5: Stereoselective aldol reaction of 3-chloro-benzaldehyde 19 with acetone in aqueous media under continuous-flow conditions.

CH_2Cl_2, concentrated in vacuo and analysed, affording 74 % conversion and 89 % ee of product **20** (Figure 5).

Another great advantage of microfluidic techniques is the possibility of integrating in-line analytical devices with the aim of real-time monitoring of the reaction without stopping the system. Flow IR is currently the most popular analytical device for in-line monitoring, thanks to its affordable price and ease of use. In parallel, due to the urgency of new systems for in-line reaction monitoring, also commercial Flow NMR was recently developed. In a flow NMR, the reaction mixture is continuously transferred from a vessel to the NMR magnet into the probe for the (fast) analysis and returned via an insulated line. Due to the popularity of NMR among organic chemists, it is not surprising that, over the past decades, the use of Flow-NMR has been increasingly reported [31]. In-line analysis by NMR spectroscopy is especially attractive for reaction monitoring and mechanistic investigation, since NMR provides sophisticated structural information that is usually distinctive and characteristic, for all species possessing the nuclide under observation and is inherently quantitative in nature. The availability of NMR cryoprobes has greatly enhanced the signal-to-noise ratio, substantially increasing the sensitivity; moreover, significant developments in solvent signal suppression methodology means that non-deuterated solvents can also be used, opening the way to use NMR for reaction monitoring in flow. We expect that Flow-NMR will become an in-line monitoring technique for catalyzed continuous processes in the near future.

In a study conducted by Rueping [32], a ReactIR flow cell was coupled with the microreactor and applied as an inline monitoring device to study the continuous-flow organocatalytic asymmetric transfer hydrogenation of a wide range of cyclic imines. The chiral phosphoric acid **21** was the organocatalyst and Hantzsch dihydropyridine **23** was the hydrogen source. The device allowed studying different reaction conditions and adjusting the reaction parameters until optimum conditions were

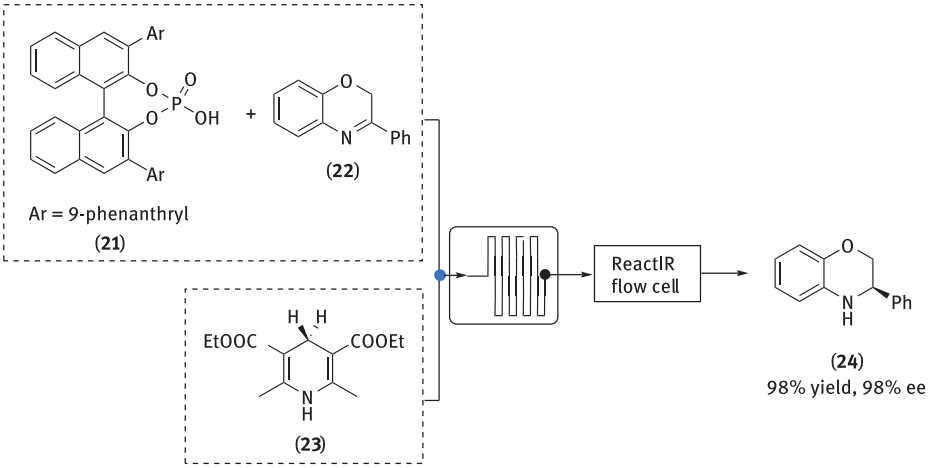

Figure 6: Continuous-flow stereoselective reduction of 3-Ph-benzoxazine promoted by Hantzsch ester in the presence of a chiral phosphoric acid.

found by recording a reaction temperature profile. As an example, hydrogenation of 3-Ph-benzoxazine **22** with 1 h residence time at 60 °C lead to the desired product **24** in 98 % isolated yield and 98 % ee (Figure 6). Noteworthy, the same reaction in batch lead to a noticeable drop in conversion (67 % yield). Better heat transfer in the microreactors compared to the glass flask of batch reactions may be responsible of the observed behavior. The work is a clear demonstration of how flow processes involving microdevices may be coupled with other "enabling technologies", techniques designed to speed up reactions, work up and isolation processes.

As mentioned at the beginning of this section, the use of homogenous organocatalyst in (micro)fluidic devices has the major issue of requiring a separation step of the precious chiral catalyst from the reaction mixture, in order to purify the product and, hopefully, to recycle the catalyst. This is the main reason why continuous-flow processes with an integrated catalyst separation and recovery started to appear in the literature. Integrated catalysis-separation system is a rapidly emerging field; the membrane-assisted recovery of homogeneous catalysts [33] is considered "sustainable" thanks to a low energy consumption. Two other features are the simple scale-up and the possibility to implement the process in continuous-flow quite easily [34]. The choice of the membrane is crucial to have an optimum retention of the catalyst. The other factor that influences the separation efficiency is the molecular weight gap between the catalyst and the other reaction components. In order to improve the separation efficiency, usually the catalyst undergoes a size-enlargement, and this can be done by embedding the catalyst in soluble polymers or conjugating it to dendrimers. A very recent example was reported by Kupai and Szekely: they prepared β-cyclodextrins decorated

with cinchona-thiourea and squaramide catalysts as enlarged organocatalysts for the Michael addition of diketones to β-nitrostyrene [35]. The homogeneous catalysts were first tested in batch and the optimized conditions were used as the starting point for the evaluation of the model reaction in the continuous-flow reactor. The schematic process diagram for the continuous catalysis-separation platform is illustrated in Figure 7. Different membranes with different features were also tested, and the authors chose the most open membrane, that demonstrated 100 % rejection of catalyst **25** and less than 5 % rejection of the other species. This result was possible thanks to the large gap in the size of the catalyst and the reactants. During the integrated synthesis-separation process, the flow reactor outlet stream containing the crude reaction mixture was diverted to a cross-flow membrane cell. The permeate stream consisted of the highly concentrated product **27** (41 g L^{-1}) having a purity of 92 %. The retentate stream in situ recycled 100 % of catalyst **25** and 50 % of the 2-MeTHF solvent. A fresh solution of diketone **26** and *trans*–β–nitrostrene **29** was pumped into a dynamic mixing chamber where it met the recycled stream. The recirculation was defined as the ratio of the retentate flow rate and permeate flow rate. A sensitivity analysis was performed to reveal the effect of recirculation on the productivity, purity and concentrations. It turned out that the illustrated process worked at its best when it was carried out at 50 % recirculation. The temperature played a fundamental role. The membrane unit was thermoregulated at 50 °C to eliminate precipitation of the product. Product **27** crystallized in the collection vessel at room temperature, which allowed the final purity to reach 98 %, with an enantiomeric excess of 99 %. The robustness and

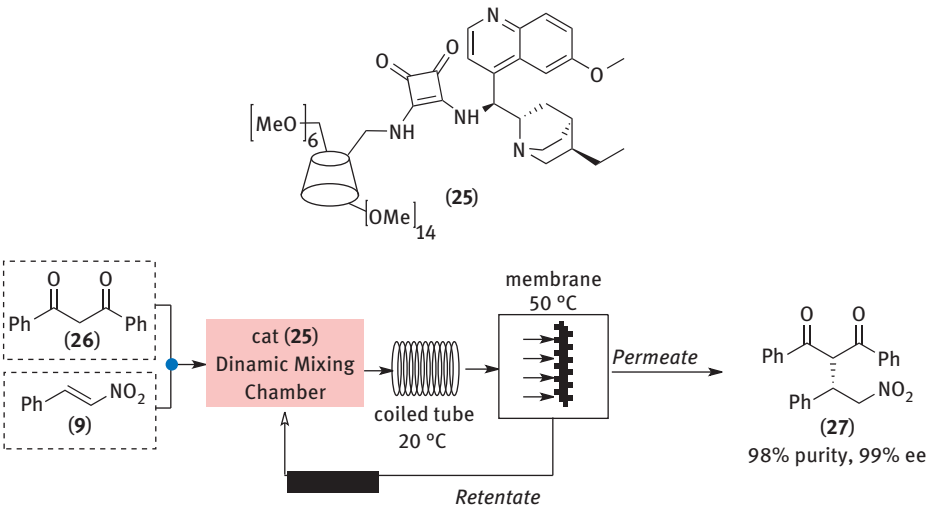

Figure 7: Stereoselective Michael addition with membrane separation.

reusability of catalyst **25** was demonstrated up to 100 °C in the flow reactor, and over 18 days of operation.

3.1 Continuous-flow organophotoredox transformations

The combination of photocatalysis and flow chemistry has become a well-established procedure for chemical transformations. Performing photochemical transformations under continuous-flow conditions is particularly advantageous since the flow set-up ensures uniform irradiation to the entire reaction solution. The small depth of a microreactor allows maximum penetration of light, and thus irradiation even of relatively concentrated solutions can straightforwardly be achieved. Importantly, the production rate of a photochemical process can easily be adjusted in a microphotoreactor. To change the irradiation time of the photochemical processes it is sufficient to vary the flow rate of the system. As microstructured reactors possess high heat transfer coefficients, cooling that may be required during a photochemical process is achieved efficiently and without greater efforts. Further miniaturization is possible with the use of light-emitting diodes (LEDs) instead of conventional light sources. Moreover, the concept of numbering up by using several microreactors in parallel is regarded to be ideally suited to achieve the industrial production of large amounts of photochemical products. For all these reasons, it is not surprising that, currently, speaking about photocatalytic processes means speaking of flow chemistry.

During the last decade, the concept of dual catalysis of photoredox and organocatalysis emerged. MacMillan et al. [36] first showed that the combination of those two catalytic cycles result in having enantioenriched products with structures that would otherwise be challenging to make. After the initial discoveries of MacMillan, a number of dual organophotoredox catalytic reactions were published, often with high yields and stereoselectivities. Many reviews were published in the last few years, summarizing the findings [37–41].

While there are many reports of non-stereoselective continuous-flow processes involving the combination of microreactors with light-mediated photocatalysis, the use of chiral organocatalysts is still underdeveloped. To our knowledge, up to this day, only two examples exist where research groups developed a successful continuous-flow setup for this dual catalysis methodology, and they will be commented here.

Neumann and Zeitler [42] studied the in-flow reaction between bromo-malonate **29** and octanal **30** in the presence of the second generation MacMillan imidazolidinone (triflate salt) **31**, Eosin Y **28** as photocatalyst and 2,6-lutidine to afford α-alkylated aldehyde **32**. Two different reactor setups were designed, one employing glass micro-reactor technology together with LEDs at 530 nm and the other employing FEP (Fluorinated Ethylene Propylene) HPLC tubing wrapped in coils around the 23 W CFL household bulb which was immersed in a cooling bath, as depicted in Figure 8(a) and Figure 8(b), respectively. FEP is a copolymer of hexafluoropropylene and tetrafluoroethylene, that

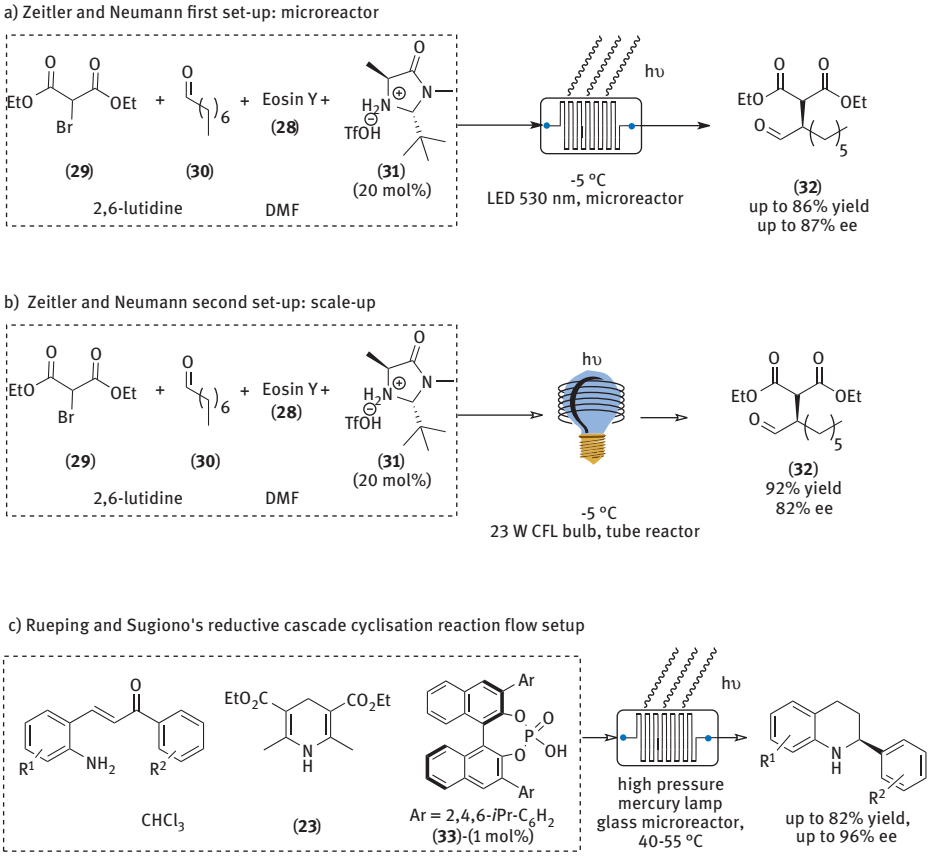

Figure 8: Continuous-flow organophotoredox transformations.

is highly transparent, solvent-resistant, and flexible. The reaction under flow condition still exhibits high enantioselectivity and high yields, leading to product **32** in up to 86 % yield and up to 87 % ee in the microreactor with a residence time of 45 min. The corresponding reaction in batch afforded the products with comparable results but required 18 hours. In the second setup (Figure 8(b)), the authors used a reactor with large reactor volume and length (10.5 mL and 21 m of length) wrapped in two layers around the lamp and they were able to easily scale-up the reaction. It was possible to generate 1.92 mmolPRODUCT/h in 92 % yield and 82 % ee, with a 107-fold increase in productivity with respect to the batch conditions, thanks to the more efficient irradiation.

Rueping and Sugiono reported the organocatalytic photocyclization–transfer hydrogenation cascade reaction starting from 2-amino-chalcones in the presence of the chiral phosphoric acid **33** and Hantzsch ester **23** [43]. For the continuous-flow setup, they used a glass microreactor immersed in a thermostated water bath. Directly next

to it, a high-pressure mercury lamp irradiated the reactor from the side. This methodology allowed to prepare differently substituted isoquinolines in very high yield and ee, starting from readily available 2-aminochalcones (Figure 8(c)). Also in this case, the flow setup showed a significant increase in productivity. Moreover, the continuous removal of the product from the irradiation source avoided over-irradiation that can lead to undesired background reactions.

Those continuous-flow experiments showed a drastic increase of productivity, up to 100-fold, with respect to the batch systems. This is due to the high molar extinction coefficients of organic dyes and metal complexes which prevent most of the internal reactor volume to receive efficient irradiation: under batch conditions, most of the light is absorbed in the first few millimetres of the solution. In continuous flow, the increased surface-to-volume-ratio of the microreactors is exploited to achieve much higher levels of irradiation. The two examples by Zeitler and Rueping well highlight the benefits of performing stereoselective photoredox catalysis under continuous-flow conditions: the more efficient irradiation in the reaction vessel that leads to an easy scalability and the continuous removal of the product from the light source to avoid photodegradation and/or undesired side-reactions.

4 Solid-supported stereoselective organic catalysts in flow

The preparation of solid-supported catalysts requires a greater synthetic effort if compared to the use of the same catalysts under homogenous conditions. However, in our opinion, the advantages largely overcome the drawbacks. This is particularly evident in the case of continuous-flow processes, in which the catalyst permanently resides in the catalytic reactors [44, 45]. First, as mentioned in the Introduction section, the reaction product is not contaminated by the catalyst at the reactor output, so the separation step is avoided. The product-catalyst separation step is not only time-consuming but also not favorable in terms of solvent using. Second, by choosing the suitable concentrations, during the catalytic process the substrate is continuously exposed to a (super)stoichiometric amount of the catalyst inside the reactor: this may lead to a faster reaction time and a high turnover number (TON). Moreover, side reactions can be suppressed, thus achieving an overall cleaner process. Finally, the confinement of the supported catalyst in the reactor is the most obvious and general way to achieve its continuous recycle. It is not surprising, then, that already back in 1996 Itsuno, one of the pioneers in the use of polymer-supported ligands, reported the preparation of an enantiopure oxazaborolidine supported on an insoluble resin **34**; this system was used to pack a column, in which a solution of cyclopentadiene and methacrolein was slowly percolated [46]. A solution of the chiral Diels-Alder adduct was continuously eluted from the column and collected in a flask. Using 5.7 mmol of the polymeric catalyst **34**, 138 mmol of (*R*)-adduct **35** with 71 % ee were obtained, in what can be considered, in a visionary approach, the precursor of a continuous-flow process (Figure 9).

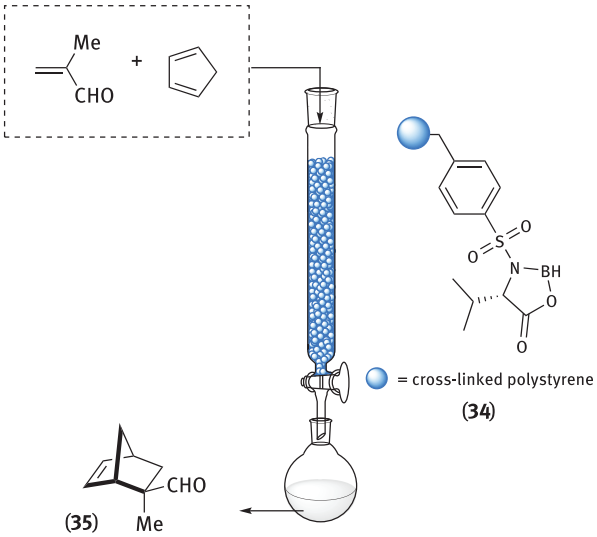

Figure 9: Solid-supported chiral catalyst 34 to promote stereoselective Diels-Alder transformation under fluidic conditions.

The choice of the support is obviously crucial for determining the overall performances of the catalyst and the continuous process. In principle, one can envision to use all the kind of different supports that have been developed and reported in the literature to build the catalytic reactor. In practice, if one looks up in the literature, the choice of the support for performing stereoselective organocatalyis in flow is limited to the classical silica and polymeric organic materials (polystyrenes and polyacrylates), according to the research group's expertise. On the contrary, the preparation and the modification of these materials are well-documented in the literature, so they allow a fast anchoring of the desired catalyst onto the insoluble support.

One exception is represented by textile fibers such as nylon and polyacrilonitrile (see Section 4.1).

4.1 Packed-bed reactors

Packed-bed reactors are the most popular catalytic reactors for flow since they are easily prepared starting from the heterogenized catalyst. The catalyst is immobilized onto an insoluble support (usually silica or a polymeric matrix) and then loaded ("packed") into the reactor. The method for preparing a packed-bed reactor is quite straightforward and requires the use of classical catalyst immobilization techniques. For this reason, packed-bed reactors were developed by those research groups active in the field of catalyst recovery and recycle: in the packed-bed

reactors, the immobilized catalysts found an immediate application in flow. The main drawback consists in the inhomogeneous packing of the reactor: this leads to the formation of stagnation zones and hot spots, resulting in a broad residence time distribution and, in general, in an uncontrolled fluid dynamics. In the presence of an organic polymer as a support, the problem can be enhanced by resin swelling properties, especially with gel-type polymers, that are lightly cross-linked resins. On the contrary, the easy functionalization of inorganic supports like silica gel, zeolites, alumina and carbon, made them popular materials for developing (organo) catalytic continuous processes. However, the low catalyst charge on the inorganic support can be a limiting factor, especially when a high loading is required. Moreover, the high polar nature of these materials can affect the course of the catalyzed reaction, either unfavorably or unexpectedly [47] so a careful study of the influence of the support should be performed.

Already back in 2000, while the term "organocatalysis" was in the process of being coined, Lectka et al. [48] developed what is commonly considered the first example of stereoselective, continuous flow, organocatalytic process. The system consisted in three columns assembled in series: the first containing a polymer-supported base (BEMP), the second a supported organocatalyst (a cinchona derivative), the third a scavenger (a supported aniline), to retain unreacted material. By simply pouring a THF solution of acyl chloride and imine along the system, enantioenriched β-lactams could be prepared in a gravity-driven process. After this pioneering example (and few other examples from the same group), it took some time to assist to the growth of continuous-flow organocatalytic processes that make use of pumps to force the fluid through the system, thus leading to a more accurate control over the flow rate and, consequently, the residence time. Since many specific reviews [44, 45] on this topic [49–51] and a personal account [52] appeared in the last few years, this Section will discuss only selected significant examples.

Fiber materials deserve a special mention in this section. In recent years, the application of fiber materials as supports for immobilization of homogeneous catalysts has become an area of interest in the design and synthesis of heterogenized catalysts [53], and, later on, in the development of continuous processes [54]. List [55] proposed a very uncommon flow setup, consisting of 20 pieces of nylon 6,6 as a solid support for the anchoring of a sulfonamide derivative of cinchona alkaloid. The sulfonamide derivative was UV-irradiated in the presence of penta-erithritol triacrylate (PETA) as a cross-linker to obtain the so-called "organotextile catalyst" **36**, that was tested in the desymmetrization of cyclic anhydrides. As a first study, the authors proved the robustness of the heterogenized catalyst by performing more than 300 batch recycling experiments. The catalyst was then applied to the preparation of a valuable precursor of statin derivatives according to the experimental setup depicted in Figure 10. 20 sheets of nylon-supported sulfonamide **36** were packed into a polypropylene cartridge of a BÜCHI-Flash System and flushed with MTBE before use. A solution of anhydride **37** and MeOH in MTBE was continuously recirculated for 48 h into the reactor, until full

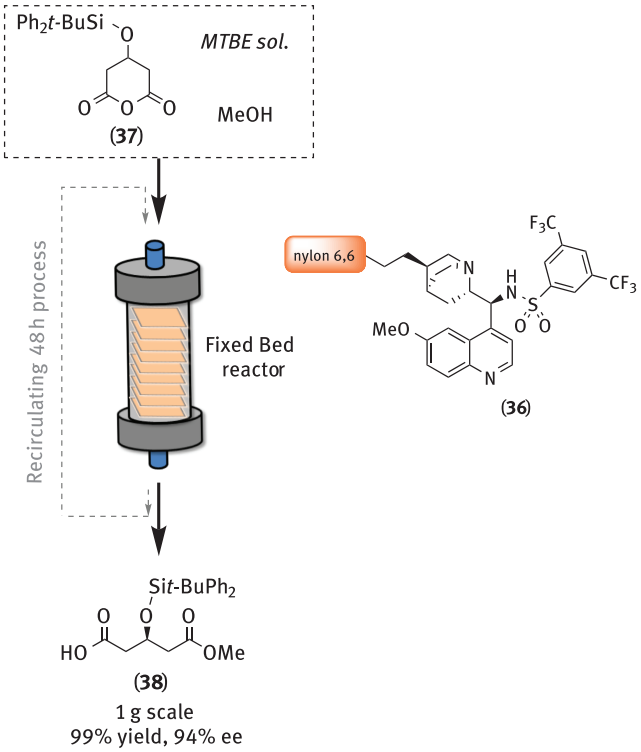

Figure 10: Packed-bed reactor with organocatalyst supported on Nylon fibers.

conversion of the starting material **37** was achieved. After reaction time, it was possible to isolate 1 g of the desired product **38** in 99 % yield and 94 % ee. The column was then washed with MTBE and reused for 10 times with no loss of activity. This system resulted in a multi-gram scale synthesis of product **38** and proved the long-term stability of organocatalyst **36**.

Polyacrylonitrile fiber (PANF), which is well known as "artificial wool", as a synthetic fiber material, offers an ideal starting material for preparing various functionalized catalysts since it contains abundant modifiable cyano groups. Different from the nylon-supported catalyst which was modified by photochemical immobilization with low catalyst loadings, PANF can be modified by chemical immobilization with various functional groups with high catalyst loading in green solvents. Wang and Zhang group reported the design and preparation of chiral pyrrolidine functionalized polyacrylonitrile fiber catalysts, evaluated for their catalytic performance in asymmetric Michael addition of ketones to nitrostyrenes in water. Then the fiber catalysts were further applied to a packed-bed reactor for continuous-flow Michael addition [56].

The family of Cinchona alkaloids gave to organocatalysis some of the most active and stereoselective catalysts of the recent years [57]. 9-amino-9-deoxy-9-*epi*-cinchona

alkaloids gave a boost to the field of asymmetric aminocatalysis since they are easily derived from natural sources and allowed the stereoselective functionalization of a variety of sterically hindered carbonyl compounds, which cannot be functionalized using secondary amines [58]. It is not surprising, then, to learn that there are many examples of supported versions, applied both in batch and in flow processes.

Benaglia research group prepared 9-amino-9-deoxy-9-*epi*-quinine supported on highly cross-linked polystyrene **39a** [59]. Catalyst **39a** was prepared by synthesizing 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 co-monomer, AIBN as a radical initiator, 1-dodecanol and toluene as the porogenic solvents, according to Frechèt procedure [60]. The solid catalyst **39a** was employed in a packed-bed catalytic reactor to perform, for the first time, the enantioselective Michael addition of an aldehyde to *trans*–β–nitrostyrene under continuous-flow conditions. The same catalytic packed-bed reactor was used for the preparation of (*S*)-Warfarin **41** under continuous-flow conditions. A solution of 4-OH-coumarin **42**, benzalacetone **43** and trifluoroacetic acid as a cocatalyst in dioxane was flowed into the reactor containing the polystyrene-supported 9-amino-epi-quinine **39a**. With a residence time of 5 h at 50 °C, the authors were able to isolate the product in up to 90 % yield and up to 87 % ee. (Figure 11) In the same year, the Pericàs group reported the sequential preparation of a small library of enantioenriched Michael adducts in flow mode by using a packed-bed reactor with catalyst **39b** [61]. They used polystyrene with a low degree of cross-linking as the support. The Cinchona-based primary amines require the presence of a Bronsted acid co-catalyst that helps the substrate activation. Ciogli et al. [62] reported the preparation of a silica-based catalyst containing both supported 9-amino-9-deoxy-9-*epi*-quinine and a benzoic acid derivative **40** through radical thiol-ene reaction. The bifunctional material **40** was first tested in batch, showing stereoselectivity comparable to the homogeneous system, and then in flow, in the addition of cyclohexanone to *trans*–β–nitrostyrene. The packed-bed reactor was then used for the preparation of warfarin, affording the desired product in 95 % isolated yield and 78 % ee after 16 h at room temperature (Figure 11).

The revolutionary work of MacMillan in 2000, on the use of chiral imidazolidinones as “organic catalysts” is a milestone in the field of (organo)catalysis, where he reported, for the first time, the reaction of α,β-unsaturated aldehydes through the formation of a transient, chiral iminium ion [63]. In this paper MacMillan used the term “organocatalysis” for the first time. Chiral imidazolidinones proved to be very efficient and versatile catalysts, therefore several authors have become interested in immobilizing these species onto a solid support with the aim of recovery and recycle the precious material [64]. In 2013 Cozzi and Benaglia reported the continuous-flow stereoselective organocatalyzed Diels Alder reactions in a chiral catalytic “homemade” HPLC column [65]; the silica-supported MacMillan imidazolidinone **44** was packed into an empty

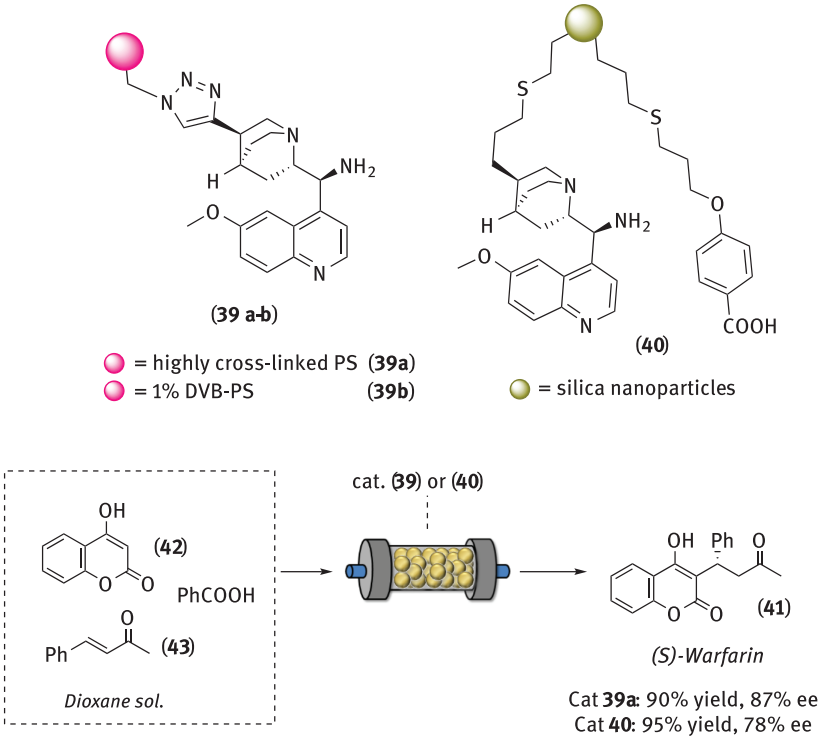

Figure 11: Continuous-flow synthesis of (*S*)-Warfarin by supported quinines.

stainless steel HPLC column and used to efficiently promote stereoselective Diels-Alder reactions on different substrates for more than 150 h of continuous operation [66]. Finelli et al. [67] reported the *in-flow* preparation of the first-generation MacMillan's organocatalyst immobilized onto silica through a carbamate linkage (Figure 12). Their synthesis started from the esterification of *L*-phenylalanine **45** that was carried out at 50 °C in a 3 mL coil (1 hour residence time) in 90% yield, followed by the formation of the corresponding ethanolamide **46** at 60 °C, (3 mL coil, 1 hour residence time, 90% yield). Amide **46** was then reacted with acetone in the presence of *p*-toluensulfonic acid (*p*TsOH) in a 2.4 mL column containing 4 Å molecular sieves (70 °C, 1 hour residence time, 90 % yield) to afford the desired 4-imidazolidinone **47**. The anchoring step was conducted by activating the 4-imidazolidinone **47** with carbodiimide **48** in a 3 mL coil (60 °C, 1.5 hours residence time, 75% yield) followed by pumping intermediate **49** in a 1.2 mL packed-bed reactor containing 3-aminopropyl-functionalized silica together with Et_3N (room temperature, 1.1 hours residence time). The in-flow synthesis of the organocatalyst **50** was accomplished in 4.5 hours and an overall yield of 54 % yield. As a proof of concept, they also evaluated the performance of the organocatalyst **50** in the benchmark reaction: the Diels-Alder between *E*-cinnamaldehyde **51** and

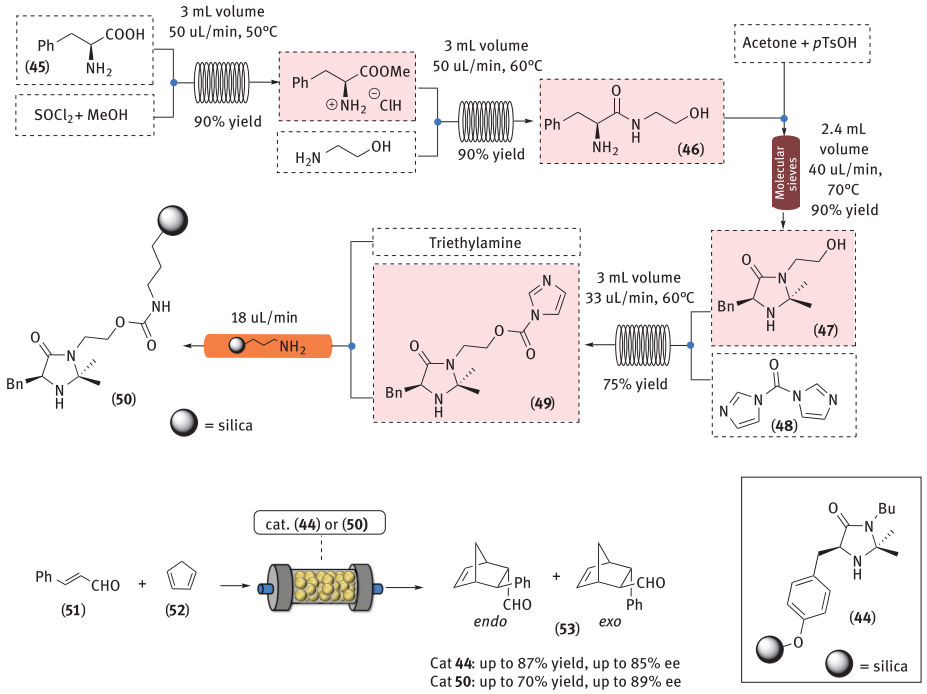

Figure 12: In-flow preparation of MacMillan's organocatalyst 50 immobilized onto silica and its use in the Diels-Alder reaction between *E*-cinnamaldehyde and cyclopentadiene.

cyclopentadiene **52**. The in-flow prepared catalyst **50** needed a long conditioning time (10 hours). After this time, adduct **53** was produced with yield from 60 % to 70 % and enantioselectivity from 84 % to 89 % for around 10 hours. However, a drastic drop in yields and enantioselectivity was observed after this time, with no possibility to regenerate the catalyst.

Hayashi–Jørgensen catalyst is a chiral catalyst belonging to the class of diarylprolinol silyl ethers. This organocatalyst was independently reported in 2005 by the groups of Jørgensen and Hayashi [68–70], and its popularity increased during the time since it is able to promote reactions both via the enamine and iminium ion activation modes, thus opening the possibility to use a variety of different substrates. It also proved to be excellent promoter of tandem processes. The Pericàs group was very active in the support and application of this catalyst and its modifications [71, 72]. In 2016 they reported a more challenging transformation, the asymmetric cyclopropanation promoted by catalyst **54** [73]. The authors prepared different types of supported catalysts, with different solid supports, having different swelling properties (microporous *vs* macroporous polystyrene) and the presence or absence of a triazole moiety as a linker/spacer. After extensive studies, catalyst **54** was selected for the continuous-flow cyclopropanation reaction between α,β-unsaturated aldehydes and bromo methyl

malonate in the presence of *N*-methylimidazole as a base, as illustrated in Figure 13. To improve the process, at the end of the column the authors quenched with acid and introduced a liquid-liquid separator, in order to perform an in-line work-up. After evaporation, the desired products were purified by chromatography.

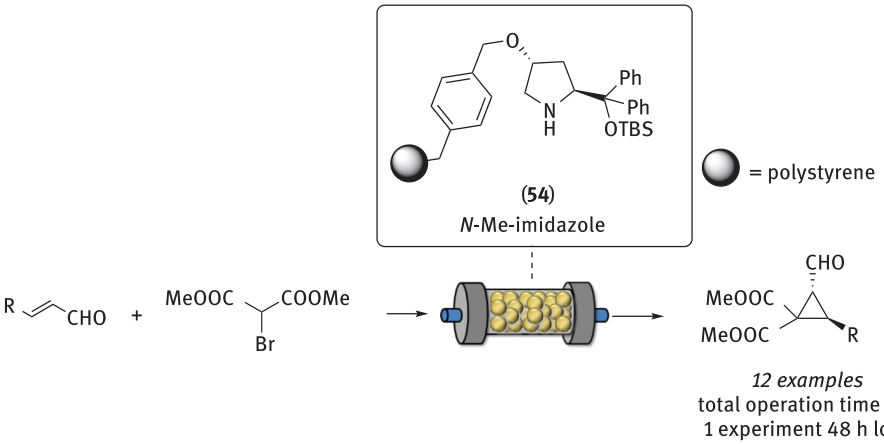

Figure 13: Stereoselective cyclopropanation with supported catalyst 54.

The Szczesniak group reported the preparation of a Wang resin-supported Hayashi–Jørgensen catalyst as optimal catalyst for the Micheal addition of aldehydes to *trans*–β–nitrostyrene [75]. Synthetic elaboration of the produced adducts lead to functionalized products, such as cyclic nitrones and pyrrolidines. The authors envisaged that also the *trans*-3,4-disubstituted piperidine ring systems of (+)-Paroxetine and (+)-Femoxetine could be built using the same methodology [74]. (–)-Paroxetine and (–)-Femoxetine are two selective serotonin reuptake inhibitors, widely used for the treatment of depression, anxiety, and panic disorders. For their investigations, they studied the Wang resin-supported Hayashi–Jørgensen catalyst **55**, in a simple home-made flow setup, consisting of feeding stream connected to a syringe pump and column packed with immobilized catalyst. (Figure 14(a)) Aldehyde **56** reacted with **57** to afford (+)-Paroxetine precursor **58** in 100 % conversion after 4 hours with 81:19 *syn: anti* ratio and with 93 % ee for the *syn* isomer. The synthetic modifications of **58** to (+)-Paroxetine were then conducted in batch mode. Almost simultaneously, Ötvös, Pericàs and Kappe reported a similar strategy for the preparation of a key intermediate of (-)-Paroxetine: the enantioselective asymmetric conjugate addition between 4-fluorocinnamaldehyde **59** and dimethyl malonate **60** to yield chiral aldehyde **61** [74]. As the chiral catalyst, they selected a polystyrene-supported *cis*-4-hydroxydiphenylprolinol TBS ether **62** developed as a modified version of the classical *trans* analogue. The authors performed extensive reaction parameters screening in flow, using a

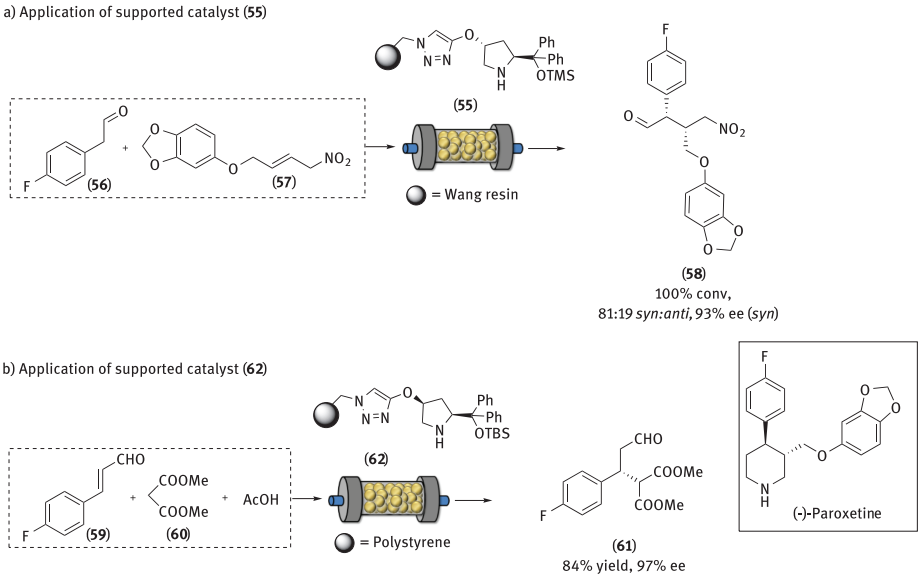

Figure 14: Continuous-flow synthesis of (+)- and (-)-Paroxetine precursors 58 and 61.

packed-bed Omnifit glass column as a flow reactor. They found that heating at 60 °C was beneficial for enhancing the reaction rate without erosion of the enantioselectivity; moreover, running the reaction under solvent-free conditions allowed them to reduce the waste and to speed-up the product isolation. They also assessed the robustness of the catalyst and the preparative capability of their system by running a scale-out experiment. A mixture of aldehyde **59**, dimethyl malonate **60** (eq. (2)) and acetic acid as an additive was pumped into the flow reactor containing 1 g of the supported catalyst **62** maintained at 60 °C, with a flow rate of 70 µL/min in order to have 20 min residence time. (Figure 14(b)) After 7 h long continuous-flow experiment, they isolated more than 17 g of the chiral aldehyde **61** by simply removing unreacted components by evaporation (84 % isolated yield, 97 % ee). The large-scale synthesis offered a productivity of 2.47 g/h of the chiral aldehyde. Notably, adduct **61** was processed further via a telescoped reductive amination-lactamization-amide/ester reduction sequence to afford the chiral key intermediate of (-)-Paroxetine. These two last examples highlight the great potentiality of flow chemistry in the preparation of APIs or APIs precursors [13, 19, 21].

The Dixon group recently developed a new class of bifunctional catalysts [76], the chiral iminophosphorane (BIMP) organosuperbase catalysts, carrying a thiourea and a powerful Bronsted base, as an alternative to bifunctional tertiary amine/H-bond donor organocatalysts in Michael addition reactions. The authors developed a polystyrene-supported version of this new class of catalysts [77] that proved very active and that were, later on, applied to the continuous flow, stereoselective Michael

additions of low-reactive pro-nucleophiles [78]. Polystyrene-supported catalyst **63** was tested in the reaction between **64** and *trans*–β–nitrostyrene **9** under flow chemistry conditions (Figure 15). The authors demonstrated the continuous-flow production of 8.6 g of **65** over the course of 13 h, in 79:21 dr and 78 % ee, with a productivity of 7.14 $mmol_{product}\ h^{-1}\ mmol_{catalyst}^{-1}$ (or 7.20 $mmol_{product}\ h^{-1}\ g_{catalyst}^{-1}$) with an effective catalyst loading of 0.8 mol %.

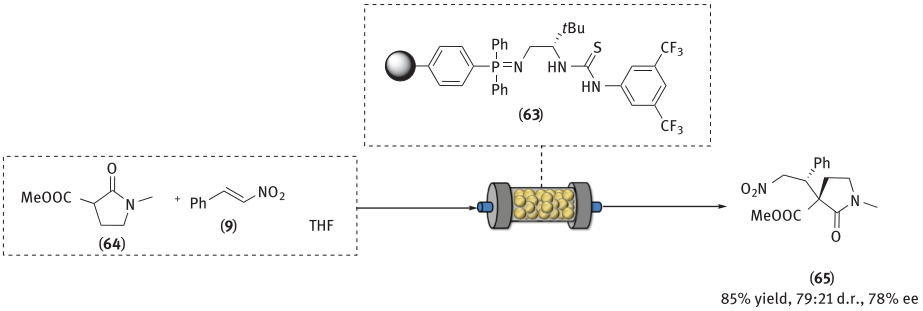

Figure 15: Polystyrene-supported iminophosphorane bifunctional catalyst 63 in stereoselective Michael additions under flow conditions.

As discussed this far, it should be clear that, to prepare a packed-bed reactors, a certain amount of the solid material, containing the catalytic supported species, is inserted in a reactor, typically an empty stainless steel or glass column, and used in a continuous process. Therefore, most of the packed-bed devices reported so far belong to the class of meso-reactors. Only recently, the "lab-on-a-chip" approach was also introduced to study heterogenized stereoselective catalysts at the microscale by the group of Massi and Belder [79]. The authors developed a lab-on-a-chip platform integrating a nanoliter-sized packed bed reactor which was seamlessly interfaced with a HPLC functionality using a chiral stationary phase for in-situ separation of enantiomeric products in the reactor effluent. The chip device, that was engineered based on the authors' expertise in designing glass chips incorporating HPLC columns, included two packed microcolumns, one for catalysis in flow and the other for direct downstream HPLC enantioseparation. The amount of supported catalyst packed in the microcolumn was in the ng scale, a massive reduced amount with respect to the classic packed bed reactor. For their studies, they used two different organocatalysts supported onto silica, a proline tetrazole derivative and the Hayashi-Jørgensen diaryl prolinol silylether. The novel approach, integrating immobilized heterogeneous organocatalysis with HPLC-MS on a single microfluidic device, enabled the rapid analysis of minute amounts of reactor output, by using little quantities of precious catalysts. Notably, it was possible to reuse a single chip over a time period of a couple months and the determined diastereo- and enantioselectivities were in good agreement with

batch or up-scaled flow experiments. Given the possibility to easily change both stationary phases, namely the chiral catalyst and selector, we can expect that, in the future, this sort of device may serve as a useful screening tool.

4.2 Monolithic reactors

In a monolithic reactor, the catalyst occupies the space of the reactor in the form of a "monolith", a structured material possessing a regular or irregular network of channels, that is generally synthesized inside the reactor. The material has two types of pores: large flow-through pores, that allow the flow of the solution through the reactor, and smaller pores (meso- or micropores) that provide large surface area (typically $> 100\ m^2$) and allow the diffusion of reactants to the catalytic sites. Different types of monolithic materials were developed for applications in chromatography: because of their porous nature, they guarantee a great tolerance to high flow rates and an efficient mass transfer through their pores. The use of monolithic reactors for catalytic purposes offers several advantages over conventional packed beds: the greater tolerance to high flow rates allow higher back pressure and higher productivity.

Typically, a monolithic reactor is built by the copolymerization of different monomers, one containing the catalyst, and a large excess of cross-linking agent, in the presence of porogens inside the reactor. After the removal of the porogens, the resulting materials possess high void volume and large surface area that prevent pressure drops along the reactor, making them suitable for flow reactions. Moreover, due to the high cross-linking degree and the rigidity of the macromolecular network, these materials swell to a limited extent and are more resistant to mechanical stress. Of course, the synthesis of a properly modified catalyst appropriate for the polymerization step is required. Drawbacks of the monolithic reactors include pore clogging and non-uniformity of radial permeability. Moreover, the reduced accessibility of the catalytic sites buried deeply inside the micropores of the monolith lead to a "loss" of potentially active stereoselective sites. There are several reliable methods in the literature for the preparation of monoliths by radical addition polymerization of vinyl monomers and most of them are reported by Fréchet et al. [60].

These methods are often slightly modified to allow the convenient direct incorporation of the chiral catalyst into the polymer. However, when a different combination of monomers is attempted, some efforts can be required to obtain the desired polymeric structure. For this reason, also post-functionalization of the monolith is possible, where the monolith is prepared according to well-established standard procedures, based on polymerization of chloromethylstyrene/divinylbenzene [80], methacrylates [81] or norbornene-type monomers [82].

While there are different examples of metal-based monolithic catalytic reactors [44, 83] the application of monolithic reactors for stereoselective organocatalysis is still limited.

In the first example, Benaglia and Mandoli reported an *ad hoc* designed MacMillan type catalyst bearing a triazole spacer and a styrene moiety (compound **66**, Figure 16), easily synthesized starting from (*S*)-tyrosine methyl ester [84]. Compound **66** was used as a monomer in a copolymerization reaction inside an empty HPLC column at 70 °C in the presence of divinylbenzene (DVB) as a co-monomer, AIBN as a radical initiator, 1-dodecanol and toluene as the porogenic solvents (3: 1 v/v, approx. 60 vol % of the feed mixture). All the chiral monomer **66** 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 **51** and cyclopentadiene **52** as a model reaction. The first flow device was activated by trifluoroacetic acid and tested under different flow rates. After a conditioning time of 4–6 hours, 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 non-supported catalyst, product **53** 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 µL/min the product was isolated in 77 % yield that was further incremented to 91 %, by operating

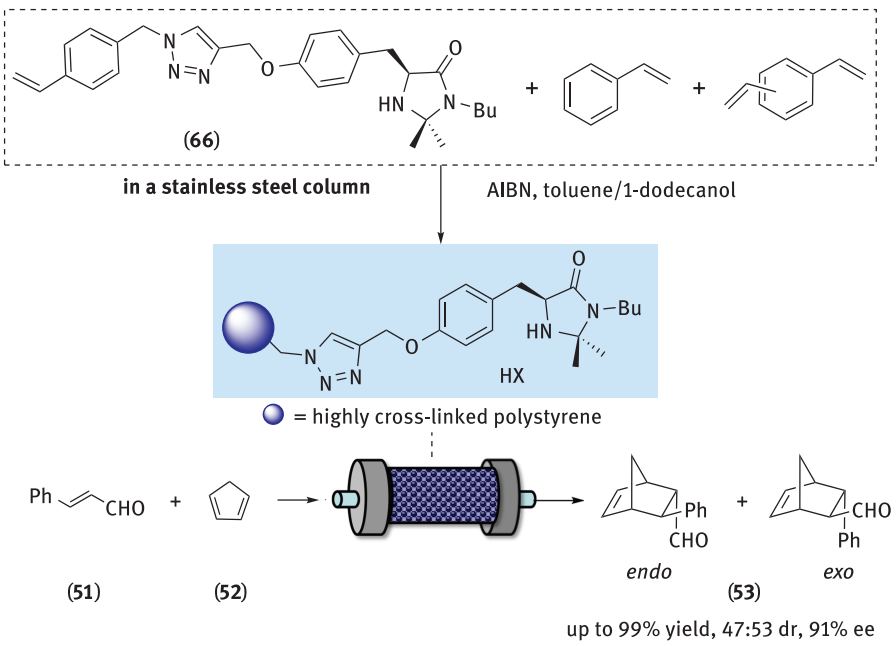

Figure 16: Preparation of a chiral monolithic flow reactor and its use in stereoselective Diels-Alder cycloaddition of *trans*-cinnamaldehyde with cyclopentadiene.

at 1 μL/min. This reactor was used to catalyze two additional organocatalytic reactions: the 1,3-dipolar cycloaddition between *N*-benzyl-*C*-phenyl nitrone and crotonic aldehyde, and the Friedel–Crafts alkylation of *N*-methyl pyrrole with cynnamaldehyde. A second flow device was activated by tetrafluoroboric acid and used for performing the reaction *in continuo* between cyclopentadiene and three different aldehydes. 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 enantioselectivity up to 85 % ee. Finally, in order to verify the activity of the system after a prolonged TOS the reactor was washed once more and used to promote again the initial reaction between cyclopentadiene and cinnamic aldehyde. Indeed, after 150 working hours of the catalytic reactor, the product was isolated in yield and stereoselectivity totally comparable to those of the first 24 hours of activity. Despite the low flow rates necessary to reach satisfactory conversions, the authors demonstrated that the tetrafluoborate 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. The monolithic reactor outperformed the corresponding packed-bed reactor with a 3-fold increase in productivity.

In a similar approach, Massi et al. [85] prepared a polystyrene monolithic pyrrolidinyl-tetrazole reactor to promote the aldol reactions of various cyclic and acyclic ketones with differently substituted aromatic aldehydes. Interestingly, integration of an analytical platform for monitoring the reaction progress in the flow regime was an important objective of this study. The polymerization mixture containing monomer **67** (Figure 17) was transferred into the stainless steel column, which was heated at 70 °C for24 h in a standard convection oven. After cooling, the resulting monolithic microreactor was connected to a HPLC instrument and then washed with THF to remove the porogens and residual non-polymeric material. The *N*-Boc deprotection step was next performed by sequentially flowing TFA/THF and Et_3N/THF solutions through the column. The authors observed nearly no swelling in water–ethanol (1: 1) solvent. The outflow of the microreactor was redirected to a 6-port 2-position switching valve, connected to a second pump for dilution and a HPLC. This set-up allowed to easily monitor the reaction course and to speed up the optimization conditions. The scope of the reaction was extended to 16 aldol products that were easily isolated in ee comparable to the ee reported in the literature for the non-supported catalyst in batch. The authors also assessed the remarkable long-term stability of the catalytic bed (ca. five days on stream).

In Section 4.1 it was already reported the work by Pericàs and Rodrìguez-Escrich, who developed different reactors with supported Jørgensen-Hayashi diarylprolinol for the continuous preparation of enantioenriched cyclopropanes [73]. In this same work, they also prepared the monolithic version of catalyst **54** (see Figure 13). Catalyst preparation was achieved under the classic Frechèt-type polymerization conditions of the proper monomer in the presence of styrene and divinylbenzene as the co-monomers.

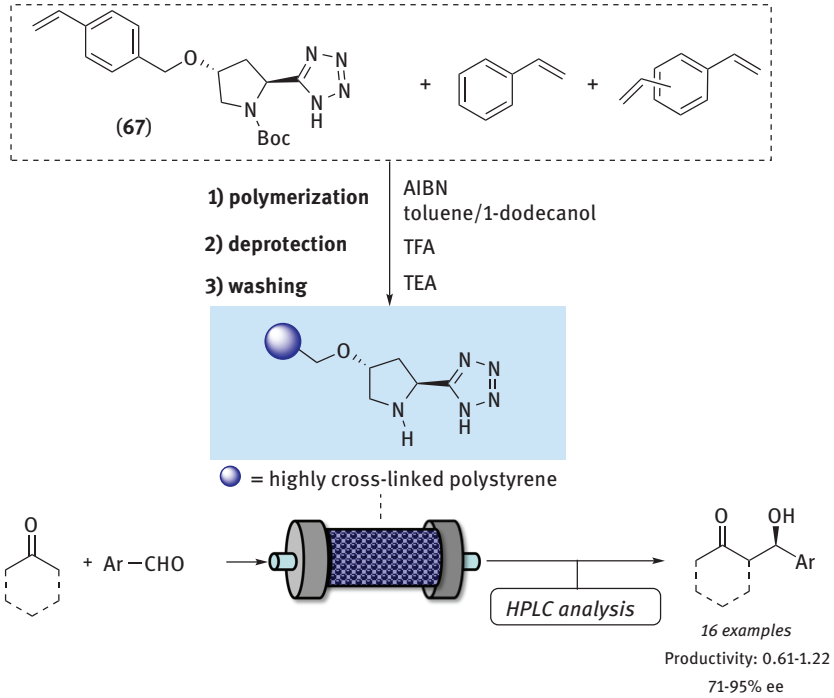

Figure 17: Preparation of a chiral polystyrene monolithic pyrrolidinyl-tetrazole flow reactor and itsuse in stereoselective Aldol reactions.

The authors prepared three different monomers, exploiting different anchoring sites and the presence of a spacer (a triazole moiety). As mentioned, they also synthesized the analogue resins for comparison purpose and tested the 6 supported catalysts in the cyclopropanation reaction between α,β-unsaturated aldehydes and bromomalonate with *N*-methylimidazole as a base. They found out that the resin (microporous polymer) was more performing that the monolith (macroporous polymer), that showed a sharp drop in catalytic activity after 24 h operation, probably due to mechanical collapse of the system under the operating pressure.

4.3 Inner wall-functionalized reactors

One of the major drawbacks of the flow devices of the smallest section is their strong propensity to clog, especially if the narrow channels are packed with a powdered catalyst or filled for a significant volume fraction (e. g 30–40 %) by a monolithic porous material. From the fluid-dynamic point of view, a better solution would be the catalyst deposited onto the channels' inner walls to leave a free central bore for unhindered flow. On the contrary, given the confinement of the

catalyst in a seemingly small fraction of the overall channels volume, this choice might look less than optimal in view of the reduced amount of active species which can be immobilized onto the continuous-flow reactor walls and the limited contact between the reactants and the catalyst sites.

Inner wall-functionalized, also called "wall-coated" reactors, represent a fascinating, still almost unexplored opportunity in which the catalyst is covalently attached onto the reactor inner walls. The fabrication of this type of catalytic reactor can simply involve a deposition of the catalyst onto the bare reactor walls. The word "deposition" can be immediately associated with metals: and indeed, most of the reported examples involve the use of metal or metal oxides catalysts confined inside borosilicate glass or metal capillaries [83].

Regarding organocatalysis, the only reported example belong to Verboom group, who developed a method to covalently immobilize poly(glycidyl methacrylate) (PGMA) polymer brushes on the interior of a microreactor to get a brush film [86]. The oxirane groups of the PGMA brushes were used for the anchoring of an achiral catalytic base, namely, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) **68**. The authors observed that the catalytic brush film thickness linearly increased on increasing the polymerization time; this lead to an enhanced catalytic loading on the microchannel walls. The preparation procedure is summarized in Figure 18: several microreactors (100 µm width and depth, 103 cm length) were filled with a solution of glycidyl methacrylate (GMA) monomer **69** in MeOH:H_2O 4:1 in the presence of CuBr and 2,2′-dipyridyl. The solution was left inside the channels for 20–120 min. Afterward, a 0.1 M solution of TBD **68** in EtOH was flowed through the channel at 65 °C for 17 h, leaving the inner walls coated with PGMA polymer brushes. By varying the polymerization time, it was possible to tune the thickness of the polymer brushes and the amount of catalyst. The amount of catalyst in the brushes was measured by X-ray photoelectron spectroscopy (XPS). An acid-base titration procedure

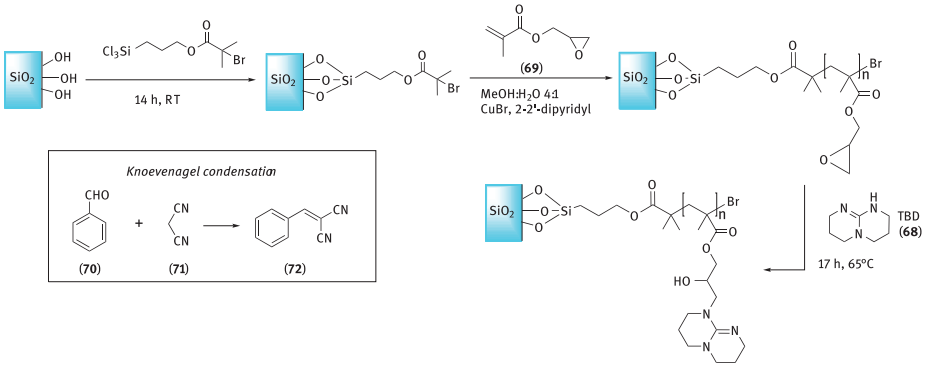

Figure 18: Preparation of inner-wall functionalized microreactor and application in Knoevenagel condensation.

allowed to estimate the number of TBD units in the polymer and to correlate this number to the brushes thicknesses. The Knoevenagel reaction between benzaldehyde **70** and malononitrile **71** to give 2-benzylidene malononitrile **72** was selected as a model reaction to study the performance of these catalytic microreactors and was carried out in acetonitrile at 65 °C, in continuous flow (Figure 18). The formation of the condensation product was monitored in real time by in-line ultraviolet–visible (UV–vis) detection and the reaction times were varied by changing the flow rates from 20 to 0.2 μL/min. The polymeric coating turned out to be highly effective in the catalysis and all the experiments carried out with the microreactors bearing coatings with different thicknesses, measured by high-resolution scanning electron microscopy (HR-SEM), showed a linear dependence with the catalytic activity. According to the authors, the whole nanostructure was involved in the catalysis and the reaction did not occur only at the interface, but the reagents diffused throughout the coating to reach all catalytic units driven by the complete swelling of the PGMA polymer brushes in acetonitrile. After each experiment, the catalytic system was regenerated by flushing a 0.1 M solution of triethylamine through the microchannel. The PGMA-TBD coated devices showed no decreasing in the catalytic activity or leaching after being used for 25 times. The catalytic device, stored under nitrogen, was able to reproduce the same results of the experiments also after 30 days.

Later, the same group reported the hydrolysis of 4-nitrophenyl acetate catalyzed by a lipase supported on poly(methacrylic acid) polymer brushes [87].

Applications of the polymer-brushes methodology in the development of catalytic mini or microreactors to be used in flow processes for promoting stereoselective transformations can be easily envisaged; however, the use is still unreported at the moment.

5 Outlook and perspectives

In the last 10 years, we assisted to a blossoming of organocatalytic processes in flow. In one sense, the use of flow chemistry for organocatalytic reactions helped to overcome the main problem associated with organocatalysis, the high catalyst loading. Although some of the studies discussed in this chapter reported that grams of relatively complex organic products could be obtained at a reasonable productivity rate with mini- and-micro-continuous-flow reactors developed by academic research groups, there is still the need of improving the productivity of these systems. Some issues have to be overcome if we want to develop a reliable organocatalytic flow process, for example activation, efficiency, lifetime, degradation of the catalysts and possible reactivation of supported chiral catalysts. Improvements can be achieved by either (i) improving the catalyst efficiency or (ii) improving the support stability in order to obtain long-lasting continuous process in case of supported catalysts.

Regarding the organocatalysts, by going through the data one may have the impression that the relevance of much of the work published so far is essentially limited to the proof-of-concept stage. This is true if we consider that most of the new devices are tested for benchmark reactions; the transformation of compounds of practical interest often turns out to be more challenging than with the model substrates. However, we have demonstrated, with selected examples, that useful intermediates or precursors of interesting molecules can be easily prepared in useful amounts by exploiting chiral organocatalysts in flow. The potential for discovery of these organocatalytic systems is still not fully exploited.

The use of supported (chiral) organocatalysts is undoubtedly more appealing: at the cost of an *ad hoc* designed and prepared catalyst, the organic chemist has the opportunity to develop a more efficient and convenient reaction, in which the product is recovered almost pure. Regarding the possible supports, the choices appear almost unlimited; however, it is basically the expertise of the users, together with the final application (reaction, solvent, etc.) that will drive the decision towards one material or another. We showed that, at the moment, only few materials are usually employed.

Another big issue to consider is the robustness of the catalysts. Although some systems proved to be more robust than others, the problem of catalyst's degradation and/or deactivation is a huge limit for the application of organocatalysts in industry. We expect that, in the near future, some of the most promising catalytic systems will undergo studies for their deactivation pathways, in order to bring deeper knowledge and thus leading to improved protocols for extending the lifespan of the catalyst.

We assisted to a great improvement of organocatalytic processes, that now can bear the competitions with metal-based systems. Chiral catalyst immobilization emerged as a step toward the solution of the longstanding problem of homogeneous catalysis: recovery and reuse. The subsequent application of organocatalytic systems in continuous-flow reactions contributed to opening the way towards industrial applications. We expect that the combination of organocatalysis with flow chemistry and other enabling technologies will greatly implement the arsenal of the synthetic organic chemists towards the development of sustainable and efficient processes.

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