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Stereoselective organic reactions promoted by immobilized chiral catalysts in continuous flow systems

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The immobilization of the catalyst on a support with the aim of facilitating the separation of the product from the catalyst, and thus the recovery and recycling of the latter, can be regarded as an important improvement for a catalytic process. However, a system where a catalyst must not be removed from the reaction vessel is even more attractive: in *continuous flow methods* the immobilized catalyst permanently resides in the reactor where it transforms the entering starting materials into the desired products. The retention of the catalytic species inside the reaction vessel can be achieved by different techniques ranging from ultrafiltration through a M_W-selective membrane to immobilization on different supports. In this review we will discuss the most significant examples of *stereoselective reactions promoted by immobilized chiral catalysts and performed under continuous flow conditions*, with particular attention to the more recent contributions of the last few years.

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1. Introduction

Stereoselective catalysis provides a powerful method for the synthesis of chiral molecules that are important ingredients in the pharmaceutical, agrochemical, and fragrance industries.[1] The area has witnessed a tremendous growth in an incessant search for novel synthetic methodologies necessary to face the challenges proposed by the efficient synthesis of new chemical entities of increasing complexity[2] combined with the growing attention towards the development of sustainable processes.[3] Although numerous highly selective chiral catalysts have been developed in recent decades, the practical applications of many homogeneous asymmetric catalysts in industrial processes are still quite limited.[4] Indeed several issues need to be considered: the cost of a chiral catalyst and its general applicability; many of the very selective catalysts have been developed for reactions with selected model substrates but not tested on differently functionalised molecules. In addition, for many

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catalysts little information is available on catalyst selectivity, activity, and productivity; the stability of the catalyst and the possibility of an easy separation and maybe recycling are also important aspects to be considered for an industrial asymmetric catalytic process; in the case of organometallic species difficulties in removing trace amounts of toxic metals from the organic products must also be taken into consideration.

Heterogenization of homogeneous chiral catalysts represents a logical approach to overcome these problems.[5] The heterogenized catalysts can potentially provide easily recyclable and reusable solid catalysts that have uniform and precisely engineered active sites similar to those of their homogeneous counterparts, and therefore combine the advantages of both homogeneous and heterogeneous systems. Many immobilization approaches have been explored, including the attachment of the chiral catalysts to organic polymers, dendrimers, membrane supports, and porous inorganic oxides and *via* biphasic systems.[6] Different types of supports have been used, the most popular being inorganic materials (like silica, zeolites or alumina), soluble organic polymers (PEG, polyethylene glycols, PAA, polyamidoamines, PMHS, polymethylhydrosiloxan, just to name a few) and insoluble polymeric resins. The choice of the support is decisive in determining the experimental set-up for performing the reaction, but also dictates the recovery and the recycle techniques; also the morphology of the material plays a key role in the selection of a suitable field of application of the immobilized catalytic species. It is worth mentioning that in the case of polymeric materials the beads may have either a dense internal structure with no discrete pores (gel resins, also called microporous resins) or a porous, multichannelled structure (macroporous or macroreticular resins). For example in the cross-linked polymers, like DVB-PS (polystyrene cross-linked with divinylbenzene) the voids between the chains of polystyrene are called pores. They are very small and their size is only a few Å. In a macroporous resin a third component—called porogen or phase extender—is incorporated into the reaction mixture, which does not react with the monomers, but only takes up space in the system. Once the polymerisation reaction is finished, the porogen is washed out and leaves voids in the polymer structure, the macropores. These resins are characterized by high effective surface area and give access to the exchange sites for larger ions or molecules; they can be used with almost any solvent, irrespective of whether it is a good solvent for the uncross-linked polymer, and take up the solvent with little or no change in volume. They make more rigid beads, facilitating ease of removal from the reaction system. Microporous resins, since they have no discrete pores, suffer from diffusional limitations on reaction rates, but they offer certain advantages: they are less fragile, requiring less care in handling, react faster in functionalization and applications reactions, and possess higher loading capacities.

The choice of support is of course crucial also for the following point: in the effort to further optimize the catalyst separation and recycling, the setting up of a system where a catalyst must not be removed from the reaction vessel would be particularly attractive. An example comes from continuous flow methods,[7] when the immobilized catalyst permanently resides in the reactor where it transforms the entering starting materials into the exiting products.

For the production of bulk chemicals, dedicated continuous plants have long proved most economical; for a long time the chemical industry has relied on the continuous production of chemicals, usually for commodities.[8] However in the pharmaceutical and agrochemicals business, considering the relatively low volumes and short life-times of most products, multi-purpose plants are generally required, for investment costs reasons. So far, as no flow equipment on the laboratory scale was available until recently, the chemistry developed in the laboratory was based on batch processes. And indeed in the fine chemicals industry, production generally relies on batch or semi-batch processes, where flexibility and versatility are guaranteed. However the possibility to design a multipurpose plant based on continuous technologies could be very intriguing.

Continuous flow technologies[9] have recently attracted attention in modern synthetic chemistry as they offer several advantages over conventional batch procedures, including improved heat and mass transfer, efficient mixing of substrates and shorter reaction times. It should be pointed out that also important safety issues may be addressed by operating under continuous flow conditions, such as the safe and easy handling of hazardous reagents. The well-regulated flow reactor concept enables reactions to be performed with an unprecedented level of control; the most important reaction parameters (such as flow rate, pressure and temperature) can be adjusted and monitored quickly and precisely, leading to uniform reaction conditions throughout the reaction. Furthermore the volume of reagents and solvents is reduced by far, so that the screening of reaction conditions becomes simple, and time- and cost-efficient, which implies even rapid library synthesis and an opportunity for automatization.[10]

In this context it may be useful to distinguish *micro* reactors from *mini* reactors, based on the dimension of the channel

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diameter: if the channel diameter is ranging from 0.05 to 0.5 mm we are talking of micro flow reactors, and if the size is 0.5–2 mm we have a mini flow reactor.[7d] Both types of these miniaturised devices present some positive and negative features. For example the heat transfer capacity is heavily influenced by channel size since this determines the heat transfer area per unit volume. For *mini reactors* the common values are between 100 and 10 000 m^2 m^{-3} (depending on channel size) while for *microreactors* parameters are commonly between 5000 and 50 000 m^2 m^{-3}. Small diameter channels have the advantage of a high heat transfer capacity favoring micro over mini flow reactors. However, the narrow channels can result in high pressure drops, limited flow capacity and a tendency to block. Based on these simple considerations the use of mini reactors for flow processes employing supported catalysts seems more viable.

Of course, the incorporation of immobilized catalysts into a flow system would broaden the general applicability of flow chemical processes and the conversion of laboratory-based flow chemistry experiments to the subsequent production scale would be straightforward.[11] These considerations hold true also in the case of chiral catalysts, employed in the preparation of enantiomerically pure compounds; the potential application of continuous flow technologies as a tool for realizing highly efficient and stereoselective organic synthesis is at present the subject of very active studies by numerous academic and industrial groups.[12]

Considering that chemical synthesis in flow and the use of micro(mini)reactors have been already reviewed extensively, the present work aims to focus specifically on the use of *immobilized chiral catalysts under flow conditions*. The review will cover the more relevant achievements in the area, focusing attention on the pioneer contributions to the field and on the works that have appeared in the last few years, especially after 2008. The chapter does not intend to give a full account of all catalytic systems employed in continuous flow apparatus, but rather it will discuss *chiral catalysts* only, both organometallic and organic; when possible, both the performances of the immobilized catalyst in flow and in batch are discussed; however, it must be said that the comparison is not always straightforward, since reaction conditions and the experimental set-up (stoichiometry, reaction time, concentrations) may be quite different. Since they have been the topic of a recent review,[13] enzymes in flow systems will not be included. Finally a few considerations on the methodologies, the future and the problems related to the use in *organic synthesis of flow processes with supported chiral catalysts* will be also briefly presented.

2. Discussion

The outcome of a stereoselective process is the selective production of different stereoisomers; the control of the reaction, in the attempt to obtain preferentially one stereoisomer over the other ones, requires the use of a "chiral technology".[14] Among the different methodologies (the use of chiral reagents or chiral auxiliaries) the use of chiral catalysts is by far the most desirable.[15] Catalysis is also one of the solutions that the companies are exploring to address the problem of the increasing complexity of the chemical targets. The average number of manipulations required to synthesize an active pharmaceutical ingredient (API) continues to grow and currently amounts to an average of 12 synthetic steps.

However, as already mentioned before, chiral catalysts are often expensive and the possibility to somehow lengthen as long as possible the life of the precious chiral catalytic species is very attractive for obvious economical reasons; supported catalysts may represent a solution also to other issues like an easy separation of the products from the catalyst, or from its possible degradation or leaching byproducts; in the case of organometallic species metal contamination of the compounds for pharmaceutical applications is a crucial factor to be considered. If supported chiral catalysts are used in combination with continuous flow methodologies, the reaction and catalyst separation are performed simultaneously. It must be also considered that in flow no mechanical stirring or agitation is required, thus avoiding the problem of mechanical degradation of the support material that may lead to shortened lifetimes of the immobilized catalyst.

Today it is clear that great opportunities are offered by the use of chiral catalysts under flow conditions; the application of continuous flow methods and microreactors-based technologies are all fields of investigation of potential enormous growth. The retention of the catalyst inside the reaction vessel can be achieved by different techniques ranging from ultrafiltration through a M_W-selective membrane to immobilization on a silica gel column.

According to the method used to incorporate an immobilized catalyst into the microfluidic 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 a solid support, generally an insoluble material (usually silica or a polymeric matrix) that is charged into the reactor. This method has the advantage of being quite straightforward, since it requires the use of classical catalyst immobilization techniques and is very popular among research groups active in catalyst recovery and recycle issues, since the prepared supported catalysts find an immediate application under flow conditions. The main drawback consists in the inhomogeneous packing of the reactor, which 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.[7a] Moreover, if the support is a polymer, the problem can be enhanced by resin swelling properties.

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. The most common method of building a monolithic reactor (as it will be seen in this review) is the copolymerization of different monomers (one containing the catalyst) in the presence of a porogen

inside the reactor. Pressure drops along the reactor are avoided by the high void volume and the large surface area of these materials, making them suitable for flow reactions. Of course, synthesis of a properly modified catalyst appropriate for the polymerization step is required.

Inner wall-functionalized reactors represent a fascinating, still almost unexplored opportunity: the catalyst is covalently attached onto the reactor inner walls. Applications in the development of catalytic mini(micro)reactors to be used in flow processes for promoting stereoselective transformations can be envisaged; however, its use is still very limited due to the complexity of the synthesis.

Recently a few examples of stereoselective catalyzed reactions performed in continuous flow methodology have been reported; the following sections will highlight the more important contributions in this exciting field.

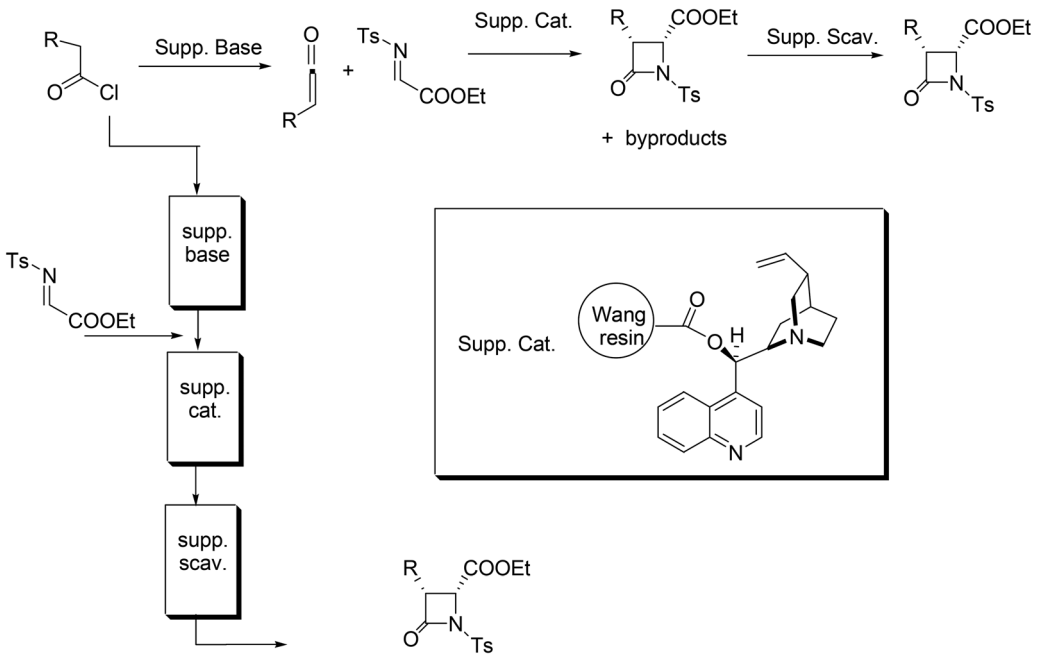
2a. Chiral organic catalysts

The field of catalysis has seen in the last ten years the impetuous advent of an innovative method to activate organic substrates and promote their transformation into the desired product, often with great selectivity: organocatalysis. After scattered reports on this methodology in the 1970s, organic catalysis represents now an established possibility of using an organic molecule of relatively low molecular weight, simple structure, and low cost to promote a given reaction in substoichiometric quantity, in the absence of any metal, and under non-stringent reaction conditions that are typical of organometallic catalysis.[16] The organocatalytic approach fulfils many of the requirements listed in the well known twelve principles of green chemistry.[17] More specifically, organocatalysts may lead to the design of "safer chemicals and products", as expected by modern synthetic chemists, also with the goal to use less hazardous solvents or reaction conditions.

Besides the simplification of the reaction work-up, the recovery and hopefully the recycle of the precious chiral catalyst represent the obvious, more important aspects of the immobilization process of an enantiomerically pure organocatalyst. Immobilization is obviously convenient if the catalyst is expensive, or has been obtained after a complex synthesis, or is employed in a relatively large amount. It should be mentioned that the choice of the support material may be crucial: the synthesis of the supported catalyst should exploit a starting material comparable in cost and synthetic complexity to that of the compound used for the synthesis of the non-supported catalyst.

The great potentiality of supported chiral organic catalysts to be employed in a continuous flow process was recognized already in 2001 by Lectka who pioneered the use of a "series of reaction column".[18] Spectacular results were obtained in a highly stereoselective synthesis of β-lactams, realized through a process that involves the use of different columns in series where solid-phase reagents and catalysts were immobilized.

In Scheme 1 the chemical steps in the catalytic asymmetric synthesis of β-lactams are illustrated, including a ketene generation step (supported base), the β-lactam formation (supported catalyst) and a purification step (supported scavenger). Ketene, generated from the corresponding acid chloride with a polymer supported base (BEMP), was reacted with an imino ester in a reaction catalyzed by the resin-supported metal-free chiral catalyst. In this way, the handling and isolation of reactive ketene intermediates were directly avoided. The catalyst



Scheme 1 Stereoselective synthesis of β-lactams.

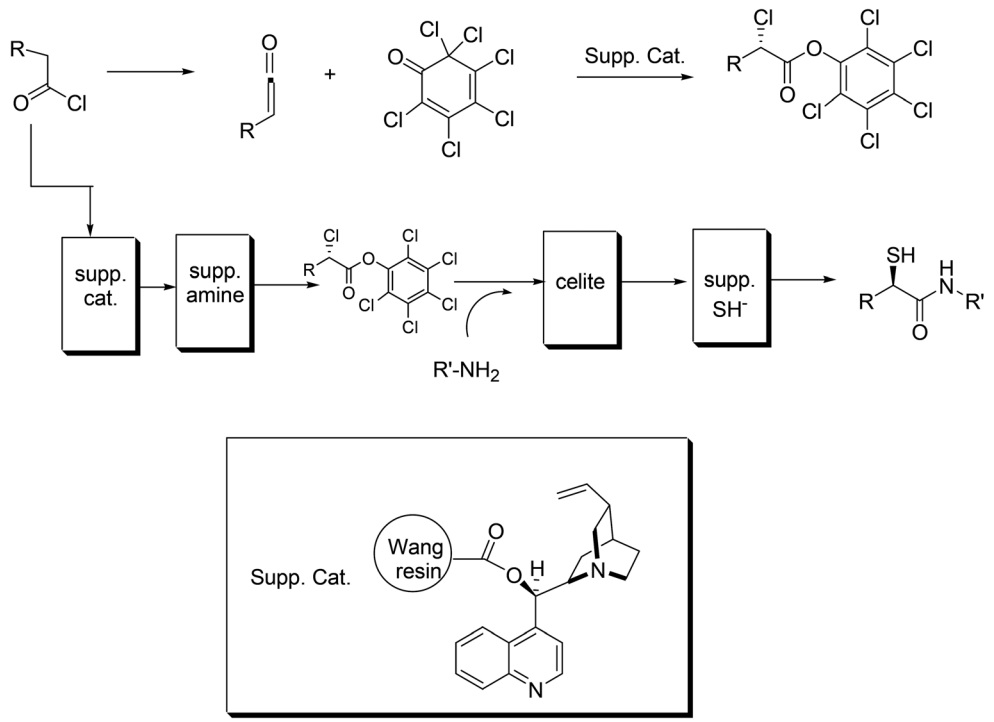
involved is a quinine derivative, anchored to Wang resin through an appropriate spacer, able to afford the products with very high stereoselectivity (>90% ee). Noteworthy, the conduction of chemical reactions on sequential columns led to an easy recovery of the catalyst and reagents, and simplified purification steps that avoid the need for chromatography. And it is important to note that, under continuous flow conditions, product isolation, catalyst recovery and recycling are obtained in a single operation.

This three-step sequence was carried out in a single process using an assembly of jacketed glass columns with gravity driven flow-through over the course of 2 h. The convenience of this approach is demonstrated by the fact that for this system one of the highest recycling numbers for a chiral organic catalyst has been accomplished. Quite interestingly, a few numbers of runs (five to ten) were necessary to obtain a catalyst aged enough to afford consistent results, since quinine "bleeding" from the freshly prepared catalyst was found to occur. A properly aged resin performed with no erosion in yield or selectivity for as many as sixty cycles.

Later the same group has reported the use of the same immobilized organocatalyst for the stereoselective α-chlorination of acid chlorides to afford highly optically active α-chloroesters in high enantiomeric excess, ranging from 88% to 94%, and in good yields (Scheme 2).

It was found that when a solution of a ketene was treated with an equimolar amount of an electrophilic chlorinating agent in the presence of 10 mol% benzoylquinine, α-chloroester was formed in high enantiomeric excess (99% ee) after purification by column chromatography. By employing the resin immobilized cinchona alkaloid derivative it was possible to develop a flow process for that reaction, applying the "catalytic" column previously described (Scheme 2). Since the organocatalysts served the dual purpose of dehydrohalogenation and stereoselective induction the process has been rendered catalytic by an intermittent flush cycle using Hunig's base to deprotonate the beads and remove any hydrochloride salts. Indeed the column was found to be reusable at least up to 100 times, after regeneration each time by flushing with a solution of i-PrNEt$_2$ in THF.[19]

A diastereoselective synthesis of the metalloproteinase inhibitor BMS-275291 was performed using this column-based flow approach, with the α-chlorination reaction as a key step. A combination of individual columns were packed with resin-bound reagents and then linked in sequence and/or in parallel. Substrates were introduced in the mobile phase where they build up chemical complexity by percolating through the linked columns, ultimately eluting as the desired product.[20] Quinine loaded Wang resin-based beads were packed into a jacketed addition funnel, saturated with THF, and then cooled to 0 °C. Acid chloride and a chlorinating agent were then added in sequence to the top of the system and allowed to drip through the column. The reaction mixture then flows into the second column containing a piperazino resin, to remove any remaining acid chloride. Next, the so generated α-chloroester enters into a column filled with Celite, where it is mixed with the peptide. Finally, Cl– is displaced by SH– on the last column of the series. The desired final product was obtained in 34% overall yield and 83% diastereomeric excess. The complete synthesis can be performed in less than 1 day (about



Scheme 2 Stereoselective synthesis of α-chloroesters.

15 h) on the solid-phase system as compared to several days *via* "traditional" reactions. For the sake of comparison it is worth mentioning that the analogous batch method suffered from degradation of the polymer-bound reagents caused by mechanical stirring and consequent loss of activity from batch to batch.

Later in 2006 polystyrene-supported cinchonine and cinchonidine were employed in the Michael addition of indanone to methyl vinyl ketone under flow conditions.[21]

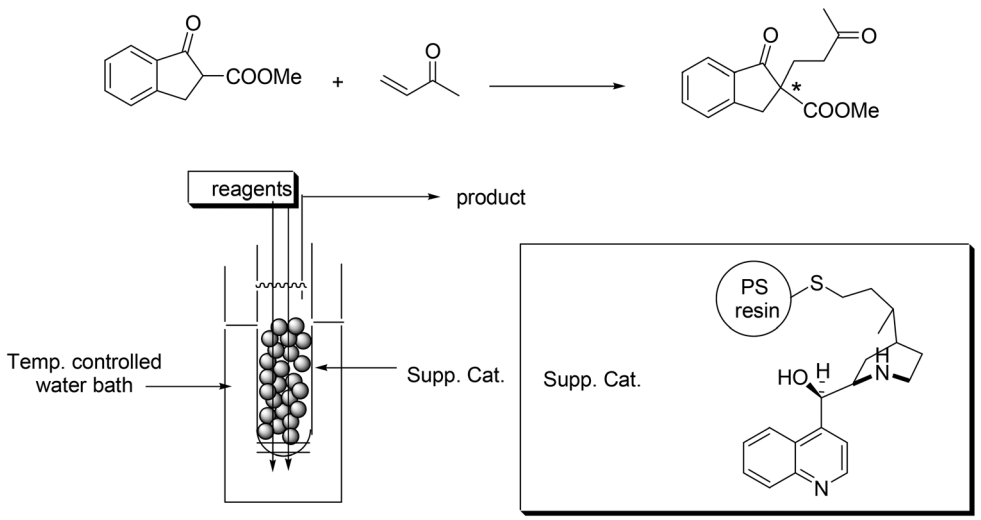
In a glass tube 36 cm long and 14 mm wide (volume 55 ml) with one end closed, a fluid bed reactor was arranged, which allowed for the polymer beads to move around freely. Using peristaltic pumps, solutions of the reagents were pumped, *via* separate long syringe needles, to the bottom of the tube; from there they passed up through the fluid bed of beads affording the product in solution that was taken from the top of the bed by a third syringe needle (Scheme 3). At a flow rate of 5.0 mL h^{-1}, with a residence time of 6 hours, the chiral product was obtained in high yields and an enantiomeric excess of 51%, comparable to the level of stereoselectivity obtained in batch with the free alkaloid derivative.

It should be mentioned that more recently Pini and Mandoli have immobilized dimeric cinchona alkaloid derivatives on polystyrenic supports and have obtained excellent results in the enantioselective catalytic dimerization of ketenes.[22] By taking advantage of a click chemistry approach, the covalent immobilization of a pyridazine derivative bearing two quinidine or hydroquinidine units onto different polymeric matrixes, including Merrifield and ArgoPore™ resins, has been successfully realized. Starting from low cost starting materials and with a simple experimental procedure that did not require any chromatographic purification, a straightforward methodology for the preparation of robust heterogenized systems allowed to synthesize different resins in good yields and with relatively high alkaloid content. More importantly, the supported cinchona alkaloid derivatives promoted the stereoselective dimerization of ketenes in very high enantioselectivity, ranging between 90% and 97% (Scheme 4, ALK = alkaloid residue). The possibility of recycling the immobilized organocatalysts was demonstrated, showing that the polystyrene supported quinine derivative could be recycled up to 20 times with only a marginal decrease of chemical and stereochemical yield.

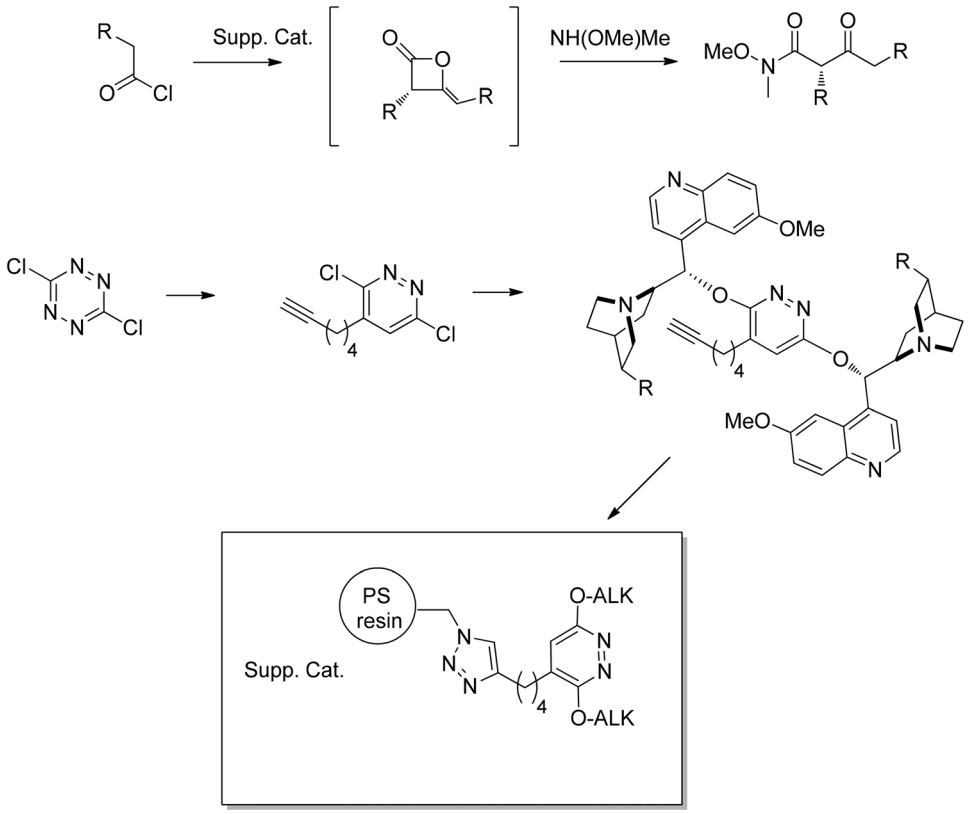
Looking at the performance of the catalyst more in detail, no appreciable loss of activity in the first 13 cycles was observed and, after that, only a minor lowering of ee (from 97% to 90%) was observed. However it is worth mentioning that the recycling of the catalyst allowed to increase its productivity over the non-supported analogous system; indeed, at the same ee level, the number of moles of product per mole of catalyst unit obtained with the supported system is 20 times that obtained with the soluble species.

The stability of the immobilized catalytic systems, the demonstrated recyclability and its excellent performance in the enantioselective dimerization of ketenes make the systems a good candidate for further developments and for its application in continuous-flow systems; indeed preliminary experiments showed some very promising results.[23]

Another class of organocatalysts of enormous success is proline derivatives; proline represents a paradigmatic example of a chiral organic catalyst, with several positive features like low molecular weight, simple structure, high stability, non-toxicity, and extremely low cost, which make the use of organocatalysts extremely attractive compared to organometallic species. Even if the utility and the relevance of supporting a catalyst as cheap as proline is questionable, nevertheless, its immobilization may help to overcome some limitations: high catalyst loading, low activity and stereoselectivity for some substrates and reactions, and limited solubility profile.[24] It is also worth mentioning that some of the recently developed prolinamides contain chiral, expensive diamine or aminoalcohol scaffolds, which contribute to improving the



Scheme 3 Stereoselective Michael addition.



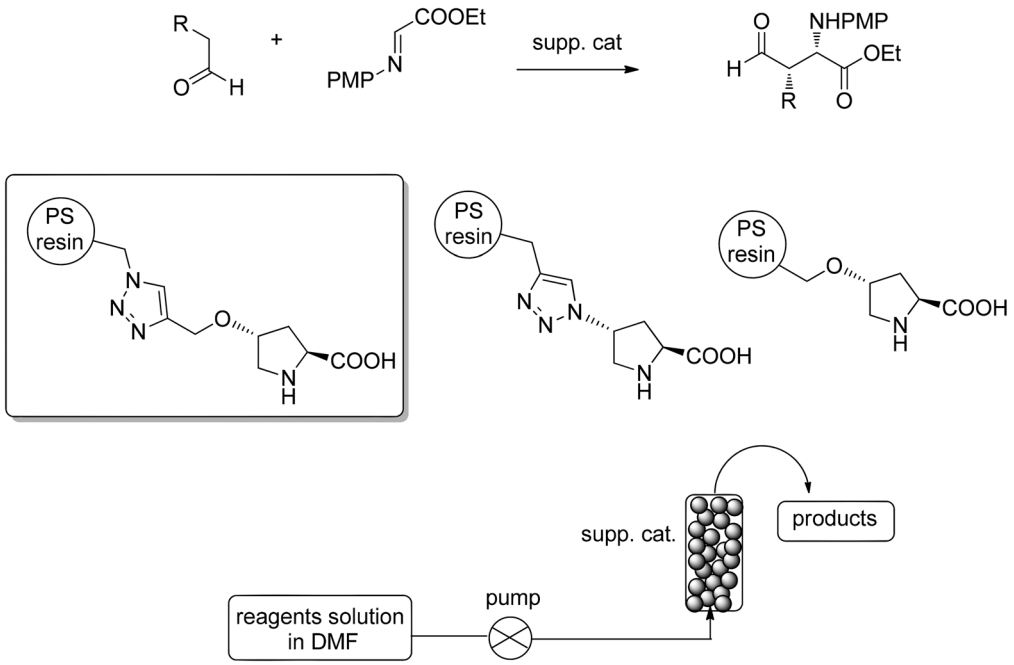
Scheme 4 Stereoselective dimerization of ketenes.

stereochemical efficiency of the newly designed catalysts, but also make them more expensive; the possibility to recycle such aminoacid-based catalytic systems is very appealing. Pericas, following his long standing studies on supported proline derivatives for aldol reactions,[25] reported for the first time the successful development of a resin-supported proline derivative used in a continuous flow, single-pass system for promoting highly stereoselective Mannich reactions.[26]

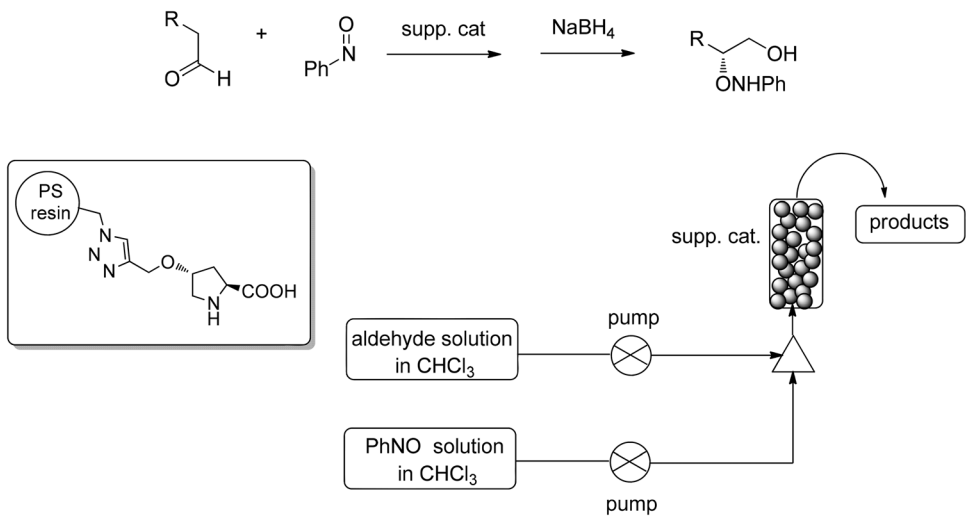
trans-4-Hydroxyproline was connected to polystyrene beads through different linkers and the catalytic performances of the supported systems were investigated in the addition of aldehydes and ketones to *N*-(4-methoxyphenyl)ethyl glyoxylate imine in DMF (*N*,*N*-dimethylformamide). The catalyst of choice showed to be extremely robust, as demonstrated by the recyclability of the supported organocatalyst, which was reused three times with no appreciable loss of activity and stereochemical efficiency. Based on the short reaction time when aldehydes were employed as donors (only a few hours were necessary for a complete conversion, while longer times were required for the reaction with ketones) the possibility to perform the reaction under continuous flow conditions was envisaged (Scheme 5).

The polystyrene supported proline derivative was loaded in a jacketed omnifit column and connected to a single-piston pump used to feed the reactor with a solution of both reagents in DMF. Using 1.0 g of resin (loading of 0.46 mmol g^{-1}) isovaleraldehyde was reacted with the glyoxylate imine, with a flow-rate of 0.20 mL min^{-1}, affording the products with comparable stereoselectivity of the batch process. After 5.5 h all the reagents (8.65 mmol of imine and 17.31 mmol of aldehyde) were consumed. The methodology had 6.0 min residence time and a productivity of 1.42 mmol h^{-1} per gram of resin; compared to the batch process, the continuous-flow process allowed for a four-fold reduction of the catalyst amount without any deterioration in its performance. It is worth mentioning that always in 2009 it was reported a continuous flow process for aldol and Mannich reactions performed in a microfluidic device.[27] However, in that work, mixtures of reagents and catalysts were pumped into the microreactor and longer residence times and elevated temperatures were necessary; additionally, in that case the proposed system could not take advantage of the use of an immobilized support, which has the peculiarity to greatly facilitate the work-up and purification of the product. It should be mentioned also that Mannich adducts are highly polar and rather labile substances, which may suffer important degradation in their diastereoisomerical and even chemical composition during chromatography. Once again, a flow process employing an immobilized catalyst could help in improving the isolation yield of a pure final product, without the need for further purification.

The same catalytic system was reported by Pericas and coworkers as an efficient organocatalyst in the α-aminoxylation of aldehydes (Scheme 6).[28]



Scheme 5 Stereoselective Mannich reaction.



Scheme 6 Stereoselective α-aminoxylation reaction.

The preparation of the immobilized catalyst was easily achieved by using as a key step the copper catalyzed 1,3-dipolar cycloaddition between azidomethylpolystyrene, prepared from a Merrifield resin, and propargyloxyproline derivative, which was readily obtained in two steps from commercially available (2*S*,4*R*)-*N*-Boc-4-hydroxyproline.

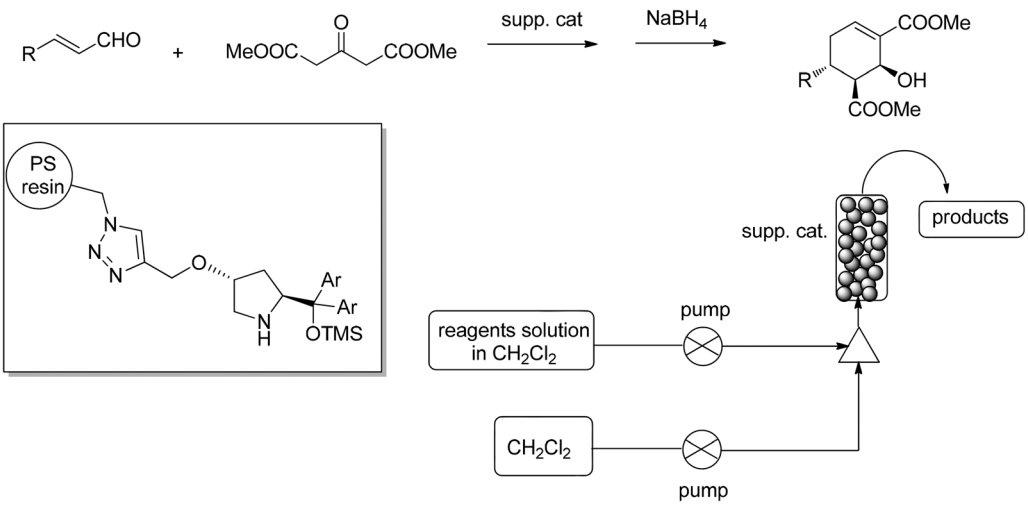
The two reagents were separately pumped at a rate of 0.12 mL min^{-1} into the reactor through a T-shaped connector, which acted as a mixing chamber; the packed-bed reactor that consisted of a glass chromatography column (10 mm pore size and up to a maximal 70 mm of adjustable bed height) was filled with 0.3 g of swollen resin (*ca*. 17 mm bed height). The conversion at any given moment was determined from the ^{1}H-NMR spectra of samples periodically collected from the reactor output. At the end of the experiment the product was collected in a cold bath (−78 °C) to prevent product degradation and then reduced with sodium borohydride to afford the corresponding more stable alcohol derivative. By employing different aldehydes the product was obtained always with high enantioselectivity (higher than 90% ee). About 30 mmol of the product was produced per mmol of resin for every flow experiment (5 h), thus showing a four-fold improvement with respect to the batch process. However the supported catalyst suffered from a moderate stability, a slow decrease in the conversion being observed with time, possibly due to the formation of an oxazolidinone between proline and the aldehyde,

rather than a physical denaturation of the polymer, as proposed by the authors.

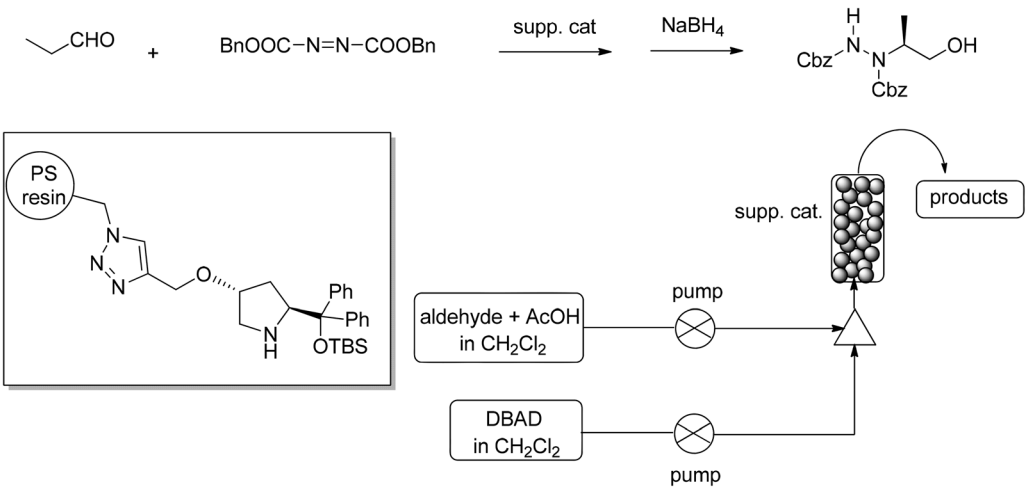
It is worth mentioning that the same stereoselective transformation was recently reported to be catalyzed by simple proline in a continuous flow process.[29] The system relies on a multistep sequence in which an aldehyde and thiourea additive are passed through a packed-bed column of solid (*S*)-proline, presumably forming a soluble oxazolidinone intermediate. This transports a catalytic amount of proline from the packed-bed into the reactor coil for subsequent combination with a solution of nitrosobenzene, affording the desired optically active α-aminooxy alcohol after reduction. The methodology proposes a strategy to achieve generation of a soluble catalytic system starting from a solid material, but it must be noted that leaching of the chiral catalyst into solution leads, as the final output of the reaction, to a mixture of products and catalyst that needs to be separated and eventually recovered with standard techniques, without all the advantages intrinsic to a hetereogenized species.

In 2011, the use of polystyrene-supported diarylprolinol silyl ethers in a stereoselective domino Michael–Knovenagel reaction was reported. Silyl protected diarylprolinols have recently established themselves as very efficient general catalysts.[30] The so-called Hayashi–Jorgensen type catalyst showed its synthetic usefulness, efficiency, selectivity, and robustness in the activation of aldehydes in various reactions. In addition to the enamine-mediated activations, α,β-unsaturated aldehydes can also be efficiently functionalized by applying the diarylprolinol silyl ether system *via* conjugate addition through iminium-ion-mediated processes, that is, LUMO activation. The ability of the catalysts to participate in various enamine- and iminium-ion mediated processes also makes them ideal for the sequential addition of nucleophiles and electrophiles in a cascade manner, leading to products having at least two stereocenters. In this context the development of an immobilized version of a catalyst of such a general interest is really attractive; following a precedent wok on the preparation of a resin-supported diphenylprolinol trimethylsilyl ether for Michael reactions.[31] Pericas has studied the catalytic batch and continuous flow process for the preparation of enantiomerically enriched cyclohexane derivatives, through a domino reaction of dimethyl 3-oxoglutaric ester and substituted acroleins (Scheme 7).[32]

Two distinct catalysts were immobilized *via* the well established methodology of the click chemistry, employing a tris(triazolyl)methanol copper complex as an effective catalyst for the 1,3-dipolar cycloaddition, due to its compatibility with free amino groups in the substrate. In the model reaction between cinnamaldehyde and 3-oxoglutarate the catalyst bearing two phenyl groups behaved better than the derivative substituted with 3,5-bis(trifluoromethyl)phenyl residues. The use of benzoic acid (10% mol) as an additive was found to have a positive effect on the chemical yield, and it allowed the product to be obtained by using 5% mol of supported catalyst in 72% yield and 98% ee after 4 hours at room temperature; the immobilized catalyst favourably compares with the homogeneous soluble counterpart, leading to a basically enantiomerically pure product with four stereocenters. Polystyrene-supported diphenylprolinol OTMS was recycled six times, with no loss of enantioselectivity but a decrease in the chemical yield after three runs. In light of the high catalytic activity a continuous flow process was developed. By employing a similar apparatus as shown above, a solution of the two reagents was pumped into the column containing the functionalized beads. A 0.12 mL min^{-1} flow was applied to the column filled with 0.9 g of the resin with the attached catalyst (10 minutes residence time); in the flow system it was necessary to increase the amount of benzoic acid from 10% to stoichiometric amounts, but under the present conditions, the flow process afforded the product in high enantioselectivity. After 72 hours 8.7 g of product was isolated with 97% ee, with a tenfold increase of performance compared to the in batch process.



Scheme 7 Stereoselective domino Michael–Knovenagel reaction.



Scheme 8 Stereoselective α-amination of aldehydes.

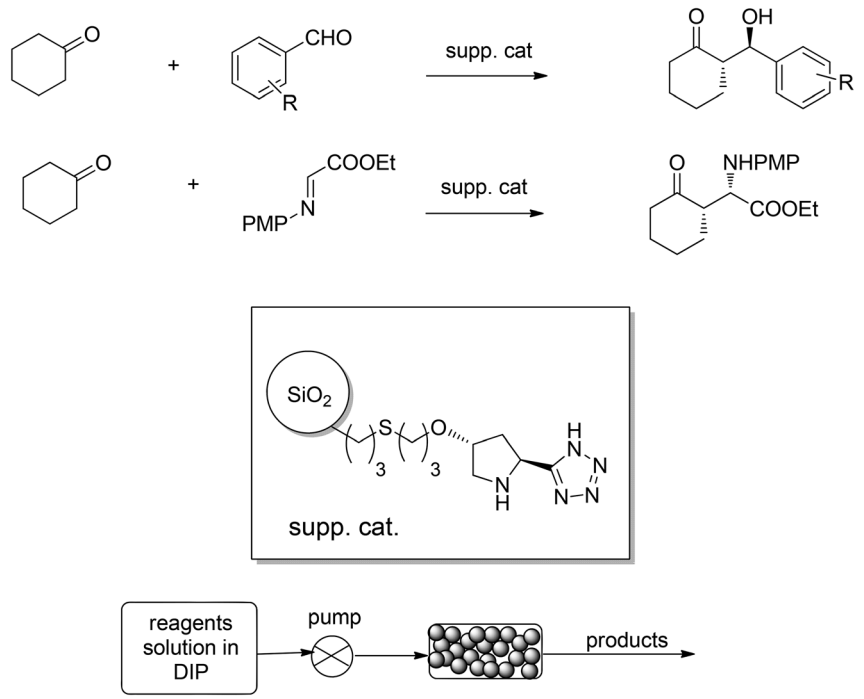
Various diphenylprolinol silyl ether derivatives were supported on polystyrene resins and investigated also in the stereoselective α-amination of aldehydes.[33] In order to avoid silyl group loss from the catalyst during the reaction, TES, TBS and TIPS protecting groups were used instead of the more labile TMS (trimethylsilyl). α-Amination in acetonitrile of propanal with DBAD (dibenzyl azodicarboxylate) was selected as the model reaction, but the solvent proved to be not the best choice. The use of benzoic acid as an additive and the use of DCM, a better resin-swelling solvent, afforded better results (Scheme 8). Thus, the combination of 2 mol% of supported catalyst and 10 mol% of acetic acid led to complete conversion in 45 min, and afforded the product with 93% ee. Noteworthy, while the method showed general applicability to linear aldehydes, no reaction was detected when α-branched or β-branched aldehydes were used in the reaction.

When the recycling was studied, low conversion (37%) in the second cycle was observed, indicating that the catalyst was partially deactivated during the reaction. Further studies evidenced that neither propanal nor AcOH nor the reaction product had a significant negative effect on the catalyst, while premixing the catalyst with DBAD made the catalyzed reaction much slower. In the attempt to develop a practical solution to the catalyst deactivation, a slow addition of DBAD in DCM to a DCM solution of propanal, AcOH and catalyst was performed. Finally, in a recycling test using 5 equiv. of propanal, a sample of 2 mol% of supported catalyst could be reused 10 times, affording the product in an overall 96% yield with 88% ee (TON of 480).

In order to realize a continuous flow process, 0.3 g of resin-bound catalyst were swollen with DCM and loaded into a packed-bed reactor. After pumping a mixture of propanal (1.25 M) and AcOH (0.125 M) in DCM into the reactor for 60 min at a flow rate of 0.075 mL min^{-1} to promote enamine formation, a DBAD solution in DCM (0.25 M) was circulated at the same flow rate, the two flows being combined in a mixing chamber before entering the reactor. A full conversion was achieved during the first 6 h of operation with a residence time of 6 min, with no appreciable erosion of the enantioselectivity, while a slight decrease in conversion was observed in the last 2 h of operation, still remaining higher than 87%.

Finally, in the area of supported proline derivatives it should be mentioned that in 2012 the use of silica-supported 5-(pyrrolidin-2-yl)tetrazole was reported.[34] Different heterogeneous derivatives were investigated, namely prolinamide, a sulfonamide and pyrrolidinyl tetrazole, as suitable candidates to act as promoters which are not prone to the deactivation pathway; therefore they are expected to provide organocatalytic packed-bed microreactors with improved stability and, eventually, better reaction profiles. The catalysts were anchored to silica *via* thermal/photoinduced thiol–ene coupling (TEC), chosen as the covalent immobilization strategy that employed silica functionalized with an alkyl thiol chain. The tetrazole derivative reported in Scheme 9 proved to be the catalyst of choice in the model aldol reaction between cyclohexanone and aromatic aldehydes (modest *anti* selectivity but high enantioselectivity, often higher than 90%). The supported catalyst was also tested in other reactions affording very good results in the Mannich reaction with the imine derived from ethyl glyoxylate and in the α-amination with diethyl azodicarboxylate (up to 95% ee).

The tetrazole catalyst was then employed in the continuous-flow aldol reaction of cyclohexanone with 4-nitro benzaldehyde. A micro-HPLC was suitably adapted for this study with minimized extra-columns volumes. The packed-bed microreactor was prepared by filling (packing by gravity) a stainless steel column (diameter 2.1 mm × length 50 mm) with a silica-supported tetrazole proline derivative. Morphological analysis showed the particles to have a pore size of 60 Å, particle size of 50 μm, superficial area of 500 m^2 g^{-1}, and a loading of 0.76 mmol g^{-1}. By using 3 mol eq. of cyclohexanone for 1 mol eq. of aldehydes, and by pumping a 0.03 M solution of the aldehyde in DIP (diisopropyl ether) at 5 μL min^{-1}, with a residence time of 25 min, the level of enantioselectivity of the



Scheme 9 Stereoselective Mannich reaction.

batch process was reached (95% ee) and maintained constant for all the process in flow. The increasing of the reaction temperature up to 50 °C led to a complete conversion of the starting material to the aldol product, without compromising the stereoselectivity of the process. The packed-bed microreactor was employed to verify the general applicability of the system to the reaction with other aldehydes and showed to work affording consistent results for an overall time of 80 hours. A progressive decrease of catalytic activity was observed after 120 hours at 50 °C.

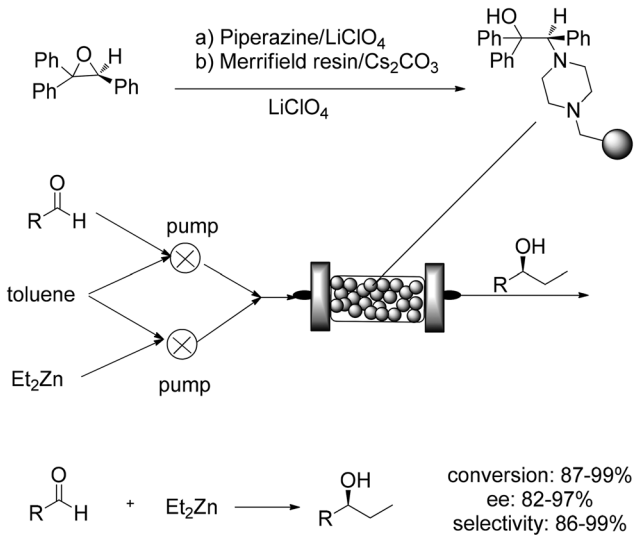
2b. Chiral organometallic catalysts

Chiral metal catalysis is generally performed using a chiral ligand able to coordinate the metal ion. With the aim of developing a supported version of a chiral metal complex, in most cases the catalyst is grafted by the formation of a covalent bond between the chiral ligand and the solid support, in the attempt to minimize catalyst leaching. The obvious evolution of a supported catalyst is its application in stereoselective reactions under flow conditions; concerning chiral metal complex-catalyzed continuous flow reactions, several issues should be addressed in order to perform an efficient catalysis. A serious problem is the leaching of metal, which may be not only precious and expensive, but somehow toxic; the contamination of the products by a toxic metal is not acceptable, especially in pharmaceuticals, and, if not properly addressed, it could prevent the use of supported metal complexes in industrial applications.

In 2008 Pericas and co-workers published the application of a polymer-supported amino alcohol ligand for the fast and enantioselective production of 1-aryl-1-propanols. The ligand was easily prepared from enantiopure triphenylene oxide through a ring-opening strategy, supported on Merrifield resin and used for the ligand-accelerated addition of diethyl zinc to aromatic aldehydes.[35] The ligand was first investigated in the ethylation of benzaldehyde and differently substituted benzaldehydes with diethyl zinc under stirred batch conditions, using 6 mol% of the ligand in toluene at 10 °C for 4 h. The resulted alcohols were obtained with conversions ranging from 71% to >99% and high enantiomeric excesses (78–93%); selectivities were also very high (76 to >99%) and the only detected byproduct was the corresponding benzyl alcohol.

The continuous flow system consisted of a vertical, fritted and jacketed Omniglass column (10 mm × 70 mm) containing the supported catalyst. Addition of diethyl zinc to benzaldehyde in toluene was used as a model reaction to determine the best operation conditions for the single-pass, continuous ethylation of the aldehyde; (*S*)-1-phenyl-1-propanol was obtained with essentially complete conversion (98%) and 93% enantioselectivity using a residence time of the reagents in the column of only 9.8 min. The methodology was then extended to differently substituted activated aromatic aldehydes, and in the case of highly reactive 4-cyanobenzaldehyde the residence time was reduced to 2.8 min, leading to the production of enantioenriched alcohol of 13 mmol h^{-1} per gram of resin.

The authors investigated also the possibility of using the column for the consecutive alkylation of different substrates; after the production of the desired amount of 1-aryl-1-propanol, the column was washed with toluene and a different aldehyde was passed through. Three different alcohols could be prepared with complete selectivity and a high level of



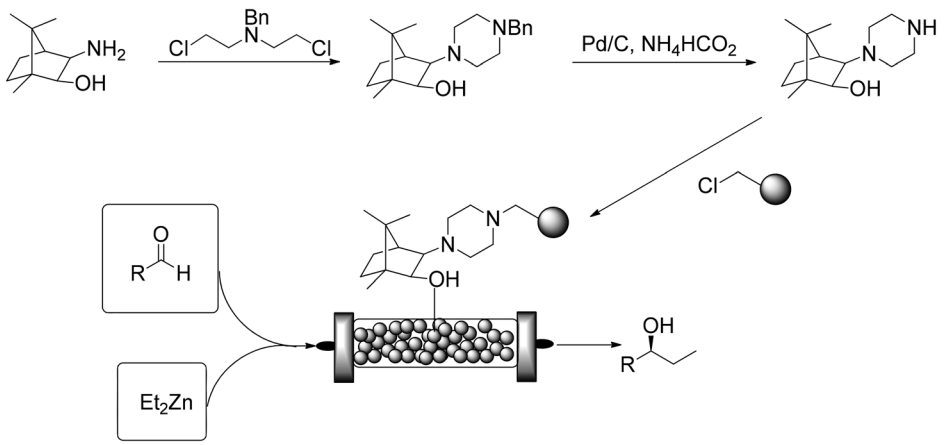
Scheme 10 Resin-supported chiral aminoalcohol for the addition of Et_2Zn to aldehydes.

enantiomeric excess. This is an example of a packed-bed reactor in which the reaction rate is very fast (Scheme 10).

The same supported catalyst was used later for the synthesis of diaryl methanols in the presence of the mixed species ArZnEt, readily prepared from triarylboroxines.[36] The resin was tested in enantioselective phenylation of *p*-tolualdehyde using triphenylboroxin under batch conditions to determine the minimal ratio between triphenylboroxin and diethylzinc able to suppress competing ethyl transfer processes, and the minimal amount of arylating species allowing to obtain complete conversion of the aldehyde. Under the best conditions (0.4 equiv. of triphenylboroxin and 2.5 equiv. of diethylzinc) the product was obtained in 73% yield and 89% ee, data comparable to those obtained using the homogeneous catalyst. For the continuous flow process, a system similar to those depicted in Scheme 10 was used. Under optimized conditions (*S*)-phenyl(4-tolyl)methanol was obtained with complete conversion and 83% enantiomeric excess. The authors pointed out that, working under these conditions, the system could be operative for several hours without any significant degradation of the catalytic bed: for example, it could be possible to prepare 3.2 g of (*S*)-phenyl(4-tolyl)methanol with 81% ee in 4 h. Also in this case the methodology was extended to differently substituted aldehydes.

As previously stated, the necessity of having a robust and stable supported catalyst is crucial in order to develop an efficient and really applicable system under continuous flow conditions. The above discussed supported catalyst showed a lifetime not sufficient to allow a prolonged use in the flow system, since it suffered from base-catalyzed fragmentation of the C–C bond in the β-aminoalcohol moiety that led to extensive catalyst degradation. In 2012 the same group reported an improvement of the system using a more stable immobilized catalyst. 3-*exo*-Piperidinoisoborneol was then chosen as an alternative ligand to be supported on Merrifield resin as the analog of 3-*exo*-morpholinoisoborneol, which is known to efficiently promote dialkylzinc addition to aldehydes.[37]

Synthesis of the new ligand started from (2*S*)-(−)-3-*exo*-aminoisoborneol which was reacted with benzyl-protected bis-(2-chloroethyl)amine to build the piperazine ring, followed by hydrogenolysis of the benzyl group and anchoring on the Merrifield resin. The resin was extensively studied under batch reaction conditions showing a high catalytic efficiency: for example, benzaldehyde was completely converted into the enantiopure alcohol in 6 h using 10 mol% of supported catalyst and 2 equiv. of diethylzinc at 0 °C. These batch conditions also suited well for differently substituted benzaldehydes (both with electron-donating and -withdrawing groups) leading to the corresponding alcohols with yields ranging between 50 and 92%, selectivities 76 and >99% and enantiomeric excesses between 92 and 99%. The supported catalyst was also recovered and recycled for 5 cycles without any loss of stereochemical activity or chemical yield. The obvious evolution of this very efficient system was the single-pass, continuous flow process for enantioselective ethylation of benzaldehyde using the experimental setup previously reported and depicted in Scheme 11. The system could sustain at least



Scheme 11 Merrifield resin-supported 3-*exo*-piperidinoisoborneol and application to the enantioselective addition of Et_2Zn to aldehydes in continuous flow.

20 h of continuous flow operation before observing a small drop in conversion but no deterioration in the enantioselectivity. This new supported ligand notably extended the lifetime of its predecessor (Scheme 10) by 1 order of magnitude and has a higher TON, affording 13.0 g of enantiopure alcohol in a single continuous flow operation (the reported productivity is 6.4 mmol h^{-1} per gram of resin). It is worth pointing out that under batch conditions the time required to obtain full conversion at the same temperature was 6 h (98% conversion, 98% ee), while in the described flow system the residence time was 6 min.

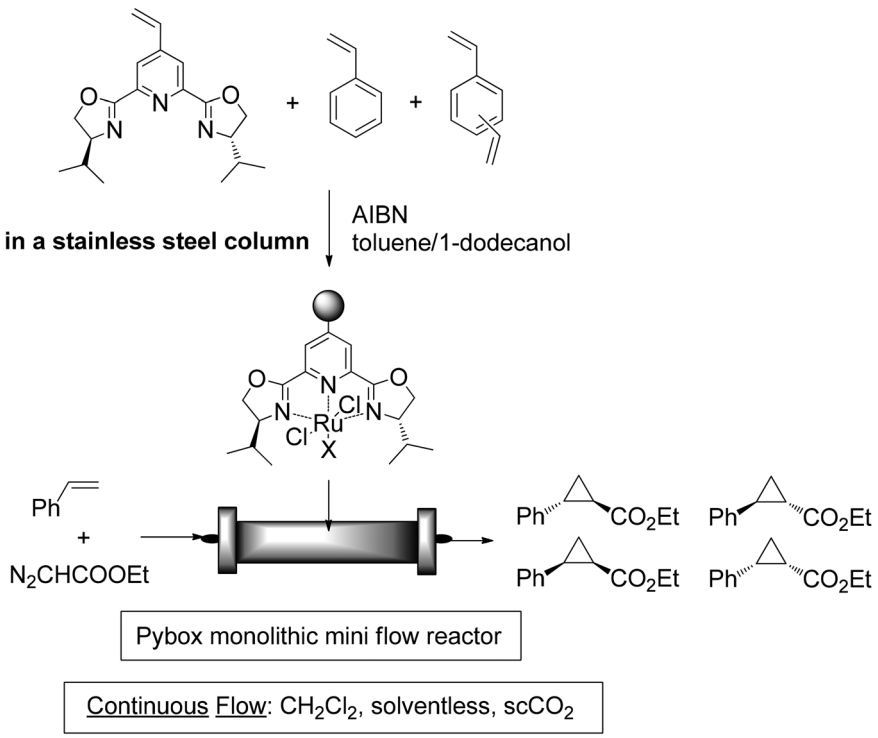
Chiral oxazoline–metal complexes, in all derivative forms – bis-oxazolines (Box), pyridinebisoxazolines (PyBox), aza-bisoxazolines (aza-Box) and phosphinooxazolines (Phox) – are among the most popular catalysts for stereoselective synthesis because of their versatility and because they are easily obtained from cheap amino alcohols.[38] After a period of great interest dealing with the immobilization of this kind of catalysts on many different types of supports (polymer, inorganic, mesoporous silica)[6] there is a renewed research interest in the application of the supported catalysts in a flow reaction. It is not surprising that in recent years quite a number of publications concerning the use of oxazoline–metal complexes in continuous flow systems have appeared. We report here a few recent examples of supported chiral oxazoline–metal complexes used in flow reactions.

In 2007 Luis and coworkers reported the synthesis of a heterogenized chiral pybox by polymerization of 4-vinyl-pybox in the presence of styrene and divinylbenzene to generate a macroporous monolithic miniflow reactor.[39]

The polymerization step is made into a stainless steel column (i.d. 1/4 in. × 15 cm) in the presence of AIBN as the radical initiator and toluene/1-dodecanol as the porogenic precipitating mixture. The ruthenium/pybox complex was prepared by treatment of the monolithic reactor with an excess of solution of dichlororuthenium(II) (*p*-cymene), allowing a dichloromethane solution of the metal to pass through the column at a low flow rate for 24 h using a recirculation system. The ruthenium/pybox complex was evaluated in the cyclopropanation reaction between styrene and ethyldiazoacetate under flow conditions in dichloromethane as a solvent in order to assess the optimum flow rate (Scheme 12). Complete conversion of ethyldiazoacetate was achieved although with moderate yields in cyclopropanes (about 50%, 80/20 *trans*/*cis*) and 77% ee for the *trans* isomer (48% ee for the *cis*). These data are consistent with those obtained in the homogeneous reaction performed in batch.

In the search for more environmentally friendly protocols, the authors demonstrated that the system performed well also in the absence of a solvent: solventless conditions were achieved by pumping a mixture of pure reagents into the monolithic column and afforded results comparable to those obtained in dichloromethane. The same system performed well also using supercritical-CO_2 as a vehicle.

A slightly modified monolithic mini-flow reactor containing a supported *box (bisoxazoline*) instead of a *pybox* (*pyridyl bisoxazoline*) was prepared and the corresponding $Cu(OTf)_2$ complex was used in the same cyclopropanation reaction. Also in this case the flow reaction could be performed in dichloromethane, solventless and in $scCO_2$; the latter, in particular,



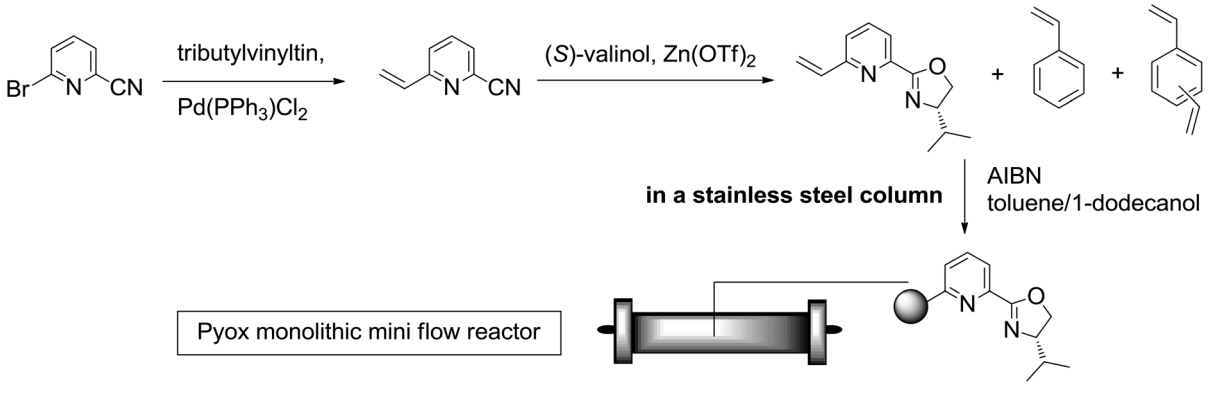
Scheme 12 Pybox monolithic miniflow reactor for cyclopropanation reaction.

allowed to considerably increase the productivity of the system (from 11 g of products per g of Cu^{2+} in dichloromethane, to 33 g of products per g of Cu^{2+} solventless to 55 g of products per g of Cu^{2+} in $scCO_2$). The level of enantioselectivity reached up to 71% ee for the *trans*-isomer and 55% ee for the *cis*-isomer.[40]

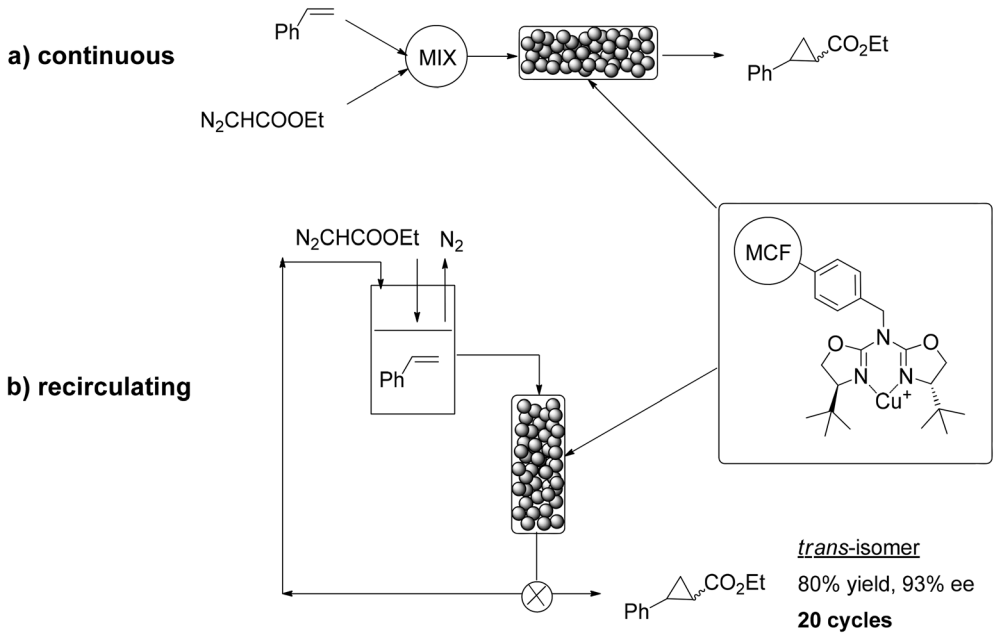
Recently the same group reported the continuous flow cyclopropanation reaction between styrene and ethyldiazoacetate promoted by a new supported catalyst with improved efficiency. Contrary to the general approach, in which the polymer backbone should be kept as far as possible from the catalytic site, the catalyst was specifically designed so that the polymer backbone was in close proximity to the catalytic active site, thus playing an active role in the catalytic cycle.[41]

The aim of the authors was to maximize the influence of the steric hindrance and the electronic effect of the polymer backbone on the catalytic site. The catalyst of choice was pyridineoxazoline(*pyox*)–copper complex, known to have low activity in the homogeneous enantioselective cyclopropanation reaction. The synthesis of the ligand was improved and optimized with respect to those previously reported in the literature, reducing the number of steps and simplifying the purification of the product. The monolithic mini-flow reactor was prepared by co-polymerization of 6-vinyl-pyox, styrene and divinylbenzene in a column in the presence of AIBN, toluene and 1-dodecanol (Scheme 13). The continuous flow reaction run in the monolithic catalyst afforded better results than the homogeneous counterpart, proving the beneficial effects of the polymer backbone, and results comparable with those obtained with the heterogenized catalyst. In particular, the monolithic catalyst allowed higher yields (around 50%), chemoselectivities (around 70%) and enantioselectivities of the cyclopropanes (around 40% ee for the *cis*-isomer and around 44% ee for the *trans*-isomer) to be obtained with respect to the homogeneous catalyst; moreover, the flow process showed higher productivity than the batch process. The system stability was demonstrated for up to 14 h operation, during which the *cis*/*trans* ratio and the enantioselectivities remained constant; after that time a slight decrease in the yield was observed, probably because of the leaching of copper during the stream. Interestingly, when copper triflate was replenished, the catalyst activity was restored. As previously shown, the flow process could also be run using $scCO_2$ as a vehicle.[41]

In 2008 Ying and co-workers reported the immobilization of chiral aza(bisoxazoline) on siliceous mesocellular foam (MCF). This is a mesoporous silica with an ultralarge 3-dimensional pore structure (>10 nm) allowing a more effective diffusion of the substrates. The authors prepared spherical MCF microparticles (about 5 μm) to obtain a more effective packed-bed and to reduce the back pressure in the reaction at high flow rate.[42] The chiral azabox bearing a trimethoxysilane group was prepared and anchored by post-grafting to MCF. A variety of silica catalysts were prepared differing in support capping (with TMS group in order to study the influence of free silanols on the silica surface), catalyst linker group, catalyst loading and support postcapping; optimization of the reaction conditions was conducted in the stereoselective cyclopropanation of styrene promoted by MCF-supported azabox–Cu(I) complex in the presence of ethyldiazoacetate. The most active catalyst afforded the cyclopropanes in 82% yield (*trans*/*cis* 72/28) after 75 minutes reaction, with 94% ee for the *trans* isomer and 90% ee for the *cis* isomer; these results were comparable to those obtained by using the homogeneous counterpart. Moreover, the catalyst could be recovered and recycled 6 times without any loss of stereochemical activity (*trans*/*cis* 72/28, 94% ee for the *trans* isomer and 90% ee for the *cis* isomer in the 7^{th} run) and a slight decrease in the chemical yield (54% yield in the 7^{th} run after 15 minutes). Given the high productivity and excellent recyclability, the optimal catalyst was initially applied to a continuous flow reactor consisting of a small HPLC column (i.d. 4.6 mm × 50 mm) packed with the heterogenized catalyst using a commercial slurry packer. A low flow rate was used to obtain full conversion at the initial reaction time, but this led to a steady decrease of both conversion and stereoselectivity (Scheme 14). According to the authors, the large amount of nitrogen gas produced during the reaction remained trapped in the reactor and damaged the catalytic system. To overcome this problem, the reactor was modified with a recirculating system which allowed to use a high flow rate and guarantee the quick



Scheme 13 Pyox monolithic miniflow reactor.



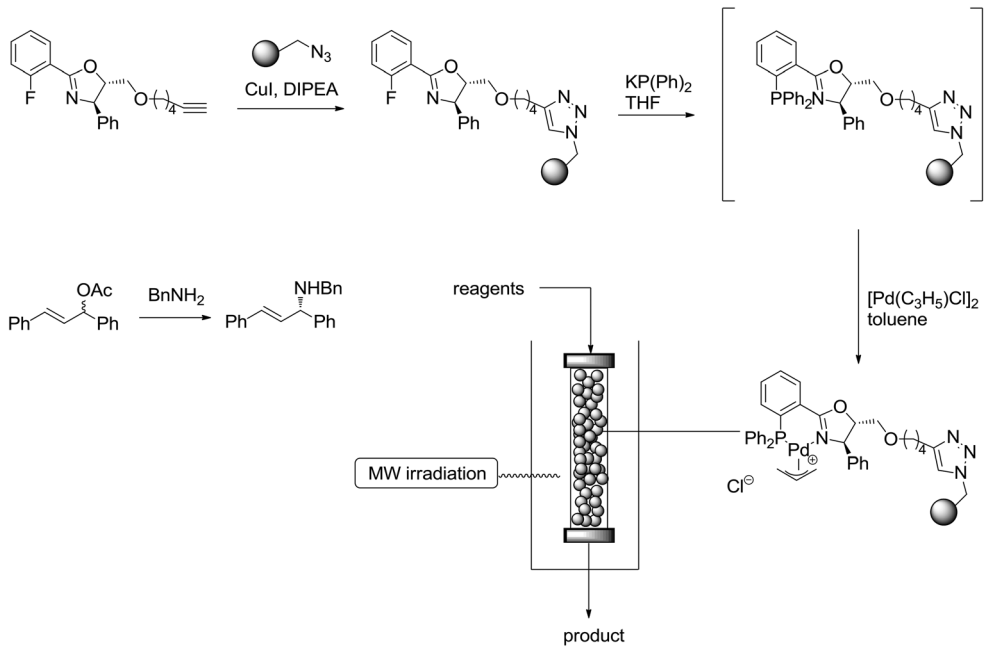
Scheme 14 Continuous and recirculating flow cyclopropanation promoted by MCF-azabox.

removal of nitrogen gas from the reactor. This second system showed better performances, affording the cyclopropanes in 80% yield and 93% enantiomeric excess (for the *trans*-isomer) during 20 cycles. Although the circulation of the mixture into the reactor is a drawback because it can be seen as a limitation for the flow, this system not only afforded the product in a shorter reaction time than in batch but had a TOF higher than other similar catalytic reactors and worked with higher stereoselectivity.

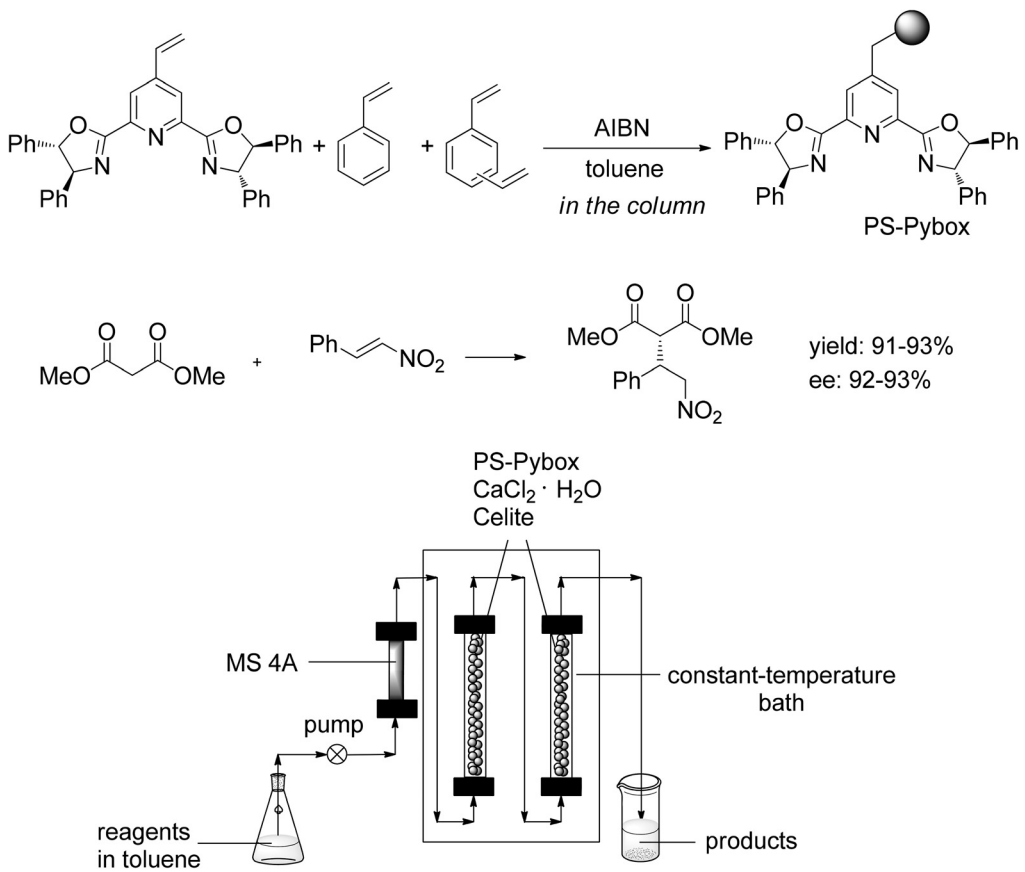
In 2009, the Pericas group reported the synthesis of polymer-supported enantiopure diphenylphosphinooxazolines (PHOX) to be used as ligands for Pd in the enantioselective allylic amination.[43] The strategy involved the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition between the PHOX bearing a terminal alkyne and Merrifield resin-supported azide, followed by the formation of the Pd π-allyl complex. The complex was first studied under batch conditions in the reaction between (*rac*)-(*E*)-3-acetoxy-1,3-diphenyl-prop-1-ene and benzylamine to determine the best conditions. It was found that microwave irradiation led to high activity and good enantiomeric excess (99% yield, 91% ee in 2 h); these results were comparable to those obtained with the non-supported (homogeneous) catalyst. The optimized catalyst was then used in continuous flow: the flow set-up consisted of a vertical teflon tube (i.d. 1/4 in.) in which the supported catalyst was packed. The reactor was placed in the cavity of a microwave oven in order to perform the reaction under microwave irradiation, since it proved beneficial to obtain complete conversion of the substrate in a short reaction time. In the experiment, the resin was first swollen by pumping dichloromethane, then low-power microwave irradiation started (1 W) and a dichloromethane solution of the reagents (*rac*-(*E*)-3-acetoxy-1,3-diphenyl-prop-1-ene, benzylamine and *N*,*O*-bis(trimethylsilyl)-acetamide as additives) was pumped into the system for 3 h. The conversion decreased from the initial 85% to 54% but the enantiomeric excess remained at a high level (81–86%) with a residence time of 8.5 min (Scheme 15).

Recently, Kobayashi and coworkers reported the asymmetric 1,4-addition of dimethylmalonate to nitrostyrene in continuous flow using a polymer-supported pyridinebisoxazoline (PS-Pybox). Vinyl-pybox was prepared and co-polymerized with styrene and divinylbenzene to afford PS-Pybox.[44] The prepared supported catalyst was tested in a batch reaction between dimethyl malonate and nitrostyrene in the presence of $CaCl_2$ as metal species and triethylamine affording the product in 92% yield and 94% enantiomeric excess after 24 h at −20 °C.

It is interesting to note the use of $CaCl_2$ which is rarely seen in organic synthesis but is a non-toxic, cheap and easy-to-handle reagent. The use of $CaCl_2$ allows one to obtain a very stable Ca–Pybox complex that can be easily handled in air; moreover, due to its peculiarities, calcium is particularly suitable for pharmaceuticals production in flow synthesis, since it avoids toxic metal product contamination. The packed-bed flow system consisted of a pre-column (i.d. 0.5 cm × 5.0 cm) containing activated 4 Å molecular sieves to dry the substrate solution followed by two glass columns (i.d. 1.0 cm × 10 cm) filled with a mixed catalyst powder (PS-Pybox, $CaCl_2$ hydrate and Celite). The feeding solution containing the substrates (dimethyl malonate and nitrostyrene) and triethylamine in toluene was passed through the system in different flow and temperature conditions. Working at 0 °C and with a flow rate of 6 mL h^{-1}, after 12 h stabilization of the system, the product was obtained in high yields (92% average of 12 fractions collected in 61 h) and high enantiomeric excess (average 93%). The authors further prolonged the reaction time and observed no deactivation of the catalyst after 216 h flow, proving that



Scheme 15 Allylic amination under flow conditions and microwave irradiation.



Scheme 16 PS-Pybox in flow reaction.

the prepared polymer was robust and efficient (Scheme 16). They also extended the scope of the flow reaction to several substituted nitroalkenes, aliphatic, heteroaromatic and aromatic, bearing both electron-withdrawing and electron-

donating groups, obtaining in all cases very good yields and enantioselectivities (only for aliphatic nitroalkene yield and ee were lower).

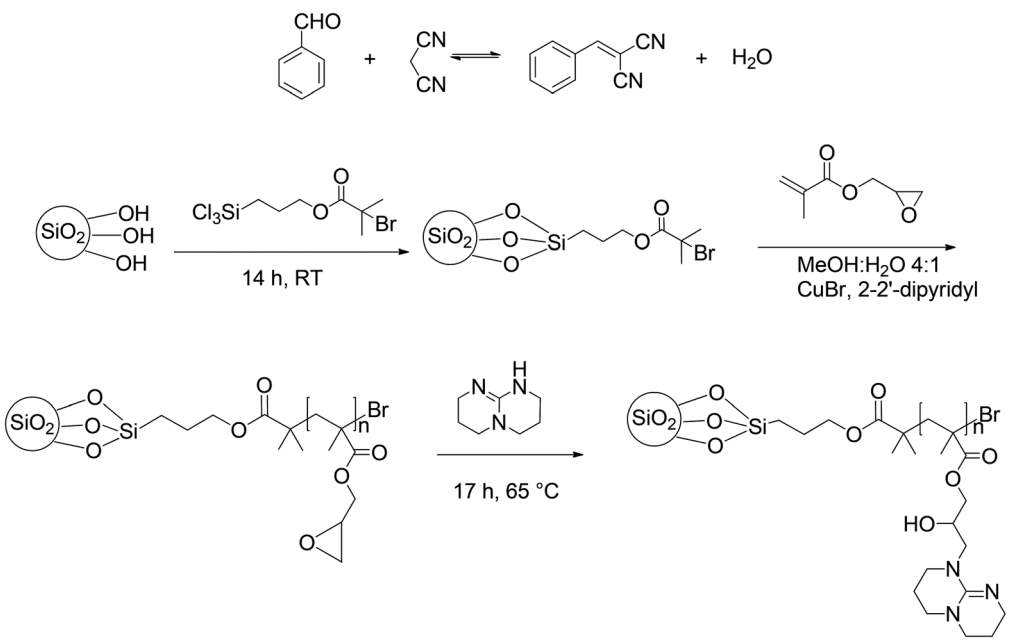
3. Outlook and perspectives

In the examples described in the previous sections we have discussed stereoselective reactions performed under flow conditions, speaking generally of flow reactors. However the last decade has witnessed a tremendous acceleration, specifically in the miniaturization of flow processes, thus making available bench sized microstructured devices in the laboratory. Numerous positive features are offered by microreactor technology: precise control of reaction variables, enhanced mixing quality, improved operational safety, reduced reagent consumption, ready scale-up of chemical processes, high thermal rate and high portability of substrates due to the high surface area-to-volume ratios. The development of micro and mini reactors has been demonstrated by the exponential growth of publications in the field.[8]

Indeed chemistry in flow can be coupled with packed-beds or purification concepts using solid phase scavengers, immobilized reagents and catalysts; the combination of flow reactors with an immobilized catalyst is an ideal set-up that opens up enormous possibilities. And several immobilized achiral catalytic species have been already employed under flow conditions.[45] As we have shown in the previously discussed examples, several solid supports are suited for heterogeneous catalysis or for heterogenization of homogeneous catalysts.[46] However in the field of flow processes much less work has been done with chiral catalysts; only in the last few years, reports on stereoselective transformations promoted under flow conditions by chiral catalysts, immobilized on different materials, have appeared. Independently from the type of support, three approaches may be undertaken in developing flow processes with heterogenized catalysts, as discussed in the Introduction. Among those three strategies, the use of packed-bed reactors has been widely exploited, both with chiral organometallic and organic catalysts. The preparation of monolithic catalytic systems has been less frequently realized. Even if a few examples of monolithic chiral organometallic catalysts able to promote reactions in flow reactors have been reported (and presented in section 2b), it must be noted that no analogous studies with chiral organocatalysts have been published so far. Our group and many others are actively pursuing the goal and probably many significant advances in the field will be reported in the near future.

Finally the third approach is almost completely unexplored: the growth, on the microreactor inner walls, of an insoluble polymer film and its use for the immobilization of the chiral catalytic species is very attractive in view of its use in minireactors, but no work with chiral catalysts has ever been reported, as far as we know. In these microfluidic devices the catalytic system may be immobilized onto the system walls coated with "brush-type" polymers. In this context only one example of achiral organocatalyst has been published.

In 2009, a work where an achiral organic catalyst was anchored onto the microchannel walls was reported.[47] The epoxy groups of a polymeric nanostructure of polyglycidylmethacrylate (PGMA) polymer brushes anchored to the inner wall of a silicon-glass microreactor were used to covalently attach an organic catalyst, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), *via* nucleophilic attack. According to the procedure summarized in Scheme 17, the inner walls of several microreactors (100 μm width and depth, 103 cm length) were coated



Scheme 17 Synthesis of PGMA–TBD coated devices.

with PGMA polymer brushes by filling the channel with a solution of glycidyl methacrylate (GMA) monomer in MeOH–H_2O 4 : 1 in the presence of CuBr and 2,2′-dipyridyl and leaving the solution inside for 20–120 min. Afterwards, a 0.1 M solution of TBD in EtOH was flowed through the channel at 65 °C for 17 h. By varying the polymerization time and consequently the nanostructure thickness of the polymer brushes, the amount of catalyst could be easily tuned, starting from a monolayer of TBD containing 0.7 μg of catalyst measured by X-ray photoelectron spectroscopy (XPS). An acid–base titration procedure, applied to estimate the number of TBD units in the polymer, allowed to determine that 2, 4 and 9 μg of TBD were contained for the devices with thicknesses of 50, 150 and 400 nm, respectively.

The Knoevenagel reaction between benzaldehyde and malononitrile to give 2-benzylidene malononitrile 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 (Scheme 17). The formation of the condensation product was monitored in real time by in-line UV-vis detection and the reaction times were varied by changing the flow rates from 20 to 0.2 μL min^{-1}. The polymeric coating turned out to be highly effective in the catalysis and all the experiments carried out with 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 of the catalytic activity or leaching after being used 25 times. The catalytic device, stored under nitrogen, was able to reproduce the same results of the experiments also after 30 days.

Polymer brushes (PBs) represent general and versatile molecular constructions to shape surface properties for applications in domains such as synthesis, electronics, and biology. A detailed examination of catalytic PBs, under the growth and modification point of view, and the impact of different thicknesses on catalytic activity was performed in 2012 by Olivier Riant.[48]

The reported systems were prepared by complexation of $Pd(OAc)_2$ to pendant dipyridylamine (dpa) ligands incorporated onto poly(2-hydroxyethyl methacrylate) (PHEMA) PBs of various thicknesses and evaluated in a model reaction based on the palladium(0)-mediated deprotection of alloc-coumarin. A series of catalytic samples of various thicknesses, architectures and associated palladium loadings were obtained by adjusting the conditions (*e.g.*, solvent, concentration, reaction time) of the surface-initiated atom-transfer radical polymerization. ICP-MS revealed in particular a near-linear relationship between the thickness of the polymer brush and palladium content and related catalytic activity.

The functionalization of glass walls of micro(mini)reactors is a hot topic of the moment and studies in the field relate not only to chiral and achiral catalysts but also to other species like photosensitizers. Advantages of microfluidics for photochemical are shorter path lengths for light penetration and small reaction volumes, improving safety in handling hazardous reactants and only small volumes of solvent oxygenated at any one time.

Immobilization of photosensitizers as porphyrins on solid silica, silica gel and polymer matrices has been investigated to achieve better separation of photosensitizers from products and remaining reactants, reducing the need for complicated work-up procedures; there has also been some research into glass-supported photosensitizers, but mostly on micrometer-scale glass beads. Research has also been reported in microphotochemistry, in which the photosensitizer is in solution with the reaction mixture, while solid supported reagents have been shown to be useful in total product synthesis.

In 2012 Boyle examined the effect of the immobilized porphyrin based photosensitizer on the glass walls of a microfluidic device for conducting the photooxidation mediated by singlet molecular oxygens of three model substrates, cholesterol, α-terpinene and citronellol, under flow conditions, and the results were compared with similar batch reactions.[49]

The porphyrin was immobilized by the reaction of the isothiocyanate group with an amino group introduced by silanization with (3-aminopropyl)-triethoxysilane (APTES), used for the silanization on the glass of the microfluidic device. The chip was designed with parallel channels originating from three inlets for gas and solutions and one outlet, in order to make it possible to introduce reagents and oxygen gas directly into the chip and collect the product from the outlet.

The reactions performed under flow condition were compared with equivalent batch reactions and also flowing the porphyrin and the substrates together in solution through the same chip. The results showed that the immobilized porphyrin was more effective at photooxidizing than a comparable flow experiment with the porphyrin in solution. A possible explanation for these results is that the lifetime of $^1O_2$ is short and it is likely that diffusion is low even when the photosensitizer is in solution. In any case, neither of the flow reactions was capable of producing yields of oxidized cholesterol close to those obtained in the batch reaction. However, the batch reaction was conducted for 60 min, in comparison with a residence time of approximately 30 s for the flow reaction on-chip.

Although the overall yields for these reactions under flow conditions were modest, the improved efficiency and purity could be of use in identifying new products in the area of natural products where sample sizes are often limited.

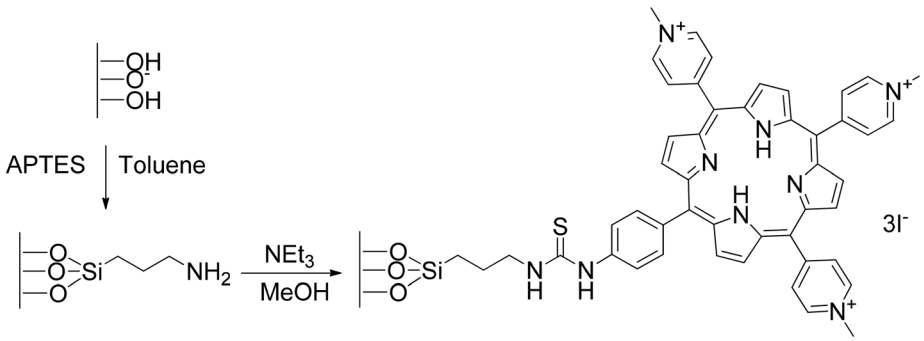
In addition to the already mentioned positive characteristics, the flow process may offer the opportunity to take advantage of some technological innovations; an example comes from the incorporation of inline analytical devices for

the monitoring of the progress of reactions that can allow fast reaction screening and optimization.

In a very recent work by Rueping, 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 reaction conditions with different substrates and catalysts (Scheme 19).[50]

The microreactor system for the experiment was set up either with a single reactor or with multiple reactors when a prolonged residence time was needed. The reagents were introduced separately, by using a syringe pump, through two inlets connected to Y-shaped connectors and the internal reaction temperature was monitored with an internal thermal sensor. The ReactIR 45m microflow cell equipped with a DiComp ATR (diamond-composite attenuated total reflection) probe was attached to the microreactor at the end of the reaction stream. The IR spectra were recorded at predefined intervals and the raw data were analyzed with iC-IR analysis software.

As the first reaction, carried out at 0.1 mL min^{-1} flow rate, the asymmetric organocatalytic transfer hydrogenation of 3-Ph-benzoxazine in the presence of Hantzsch dihydropyridine as a hydrogen source and a catalytic amount of chiral Brønsted acid was examined (Scheme 18). Fig. 1b and 1c show real-time IR spectra of the reaction mixtures after the subtraction of the solvent in the spectral region of 1440 and 1530 cm^{-1} and the signals at 1479 cm^{-1} and 1495 cm^{-1} could be assigned to 3-Ph-



Scheme 18 Immobilization of porphyrin onto glass channel walls.

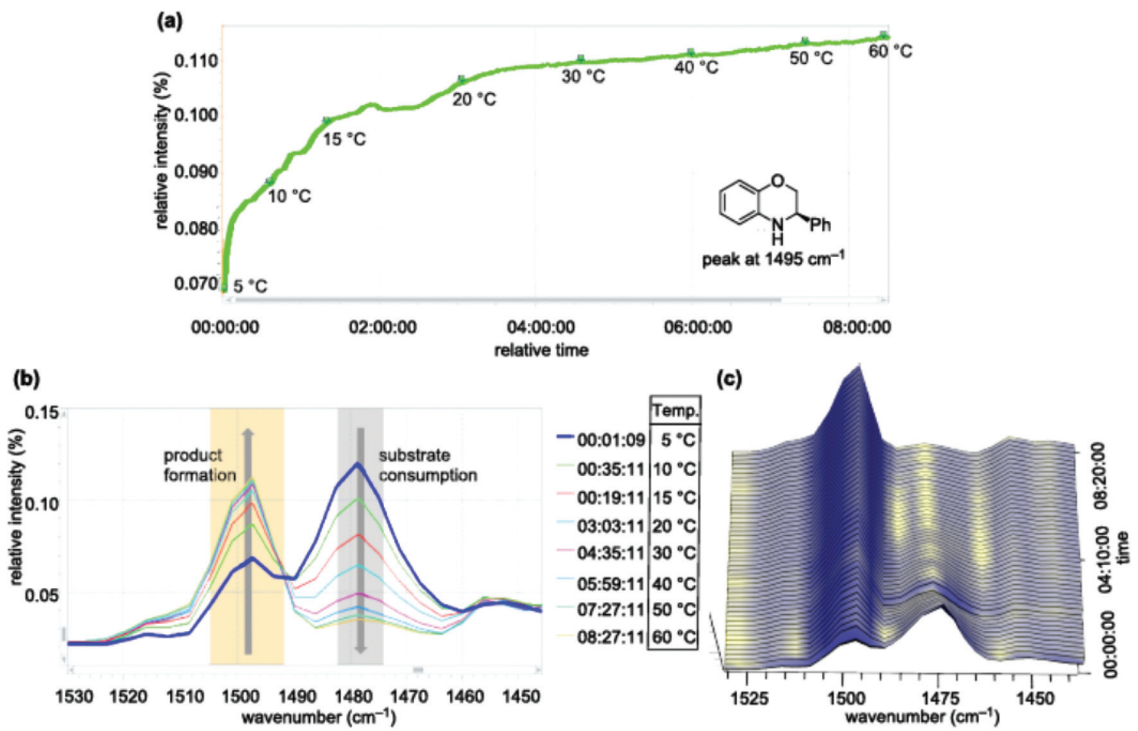


Fig. 1 *In situ* ReactIR monitoring. (a) Trend curve of product formation at different temperatures. (b) Reaction spectra showing the consumption of the substrate and the formation of product at difference temperatures. (c) Three-dimensional time-resolved spectral data. (Reproduced from open source *Beilstein J. Org. Chem.*, ref. 50.)

benzoxazine and 3-Ph-dihydrobenzoxazine. Thus, in continuous flow the substrate consumption and product formation could readily be determined.

In order to find the optimal temperature for the asymmetric continuous-flow reduction, a temperature profile was recorded starting from 5 °C to 60 °C over a period of 8 h, while the conversion was monitored by inline IR-spectroscopy. Fig. 1a shows the real-time plot of the peak intensity *versus* reaction time for the 1495 cm^{-1} absorption band at different temperatures and the trend-curve analysis by peak-height integration of this absorption band shows increased product formation with increasing temperature providing an optimal temperature of 60 °C for this reaction.

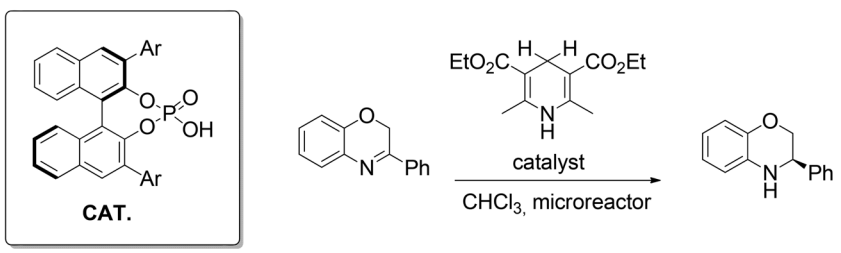
By using the optimized reaction temperature and flow rate of 0.1 mL min^{-1}, further experiments were conducted to examine the influence of the residence time on the conversion; with optimized residence times of 60 min, the product was isolated in 98% yields with 94% enantiomeric excess. Having found the optimum reaction conditions, the asymmetric organocatalytic transfer hydrogenation of 2-substituted quinolones, quinoxalines and 3*H*-indoles, the presence of Hantzsch dihydropyridine as a hydrogen source and a catalytic amount of chiral Brønsted acid was investigated (Scheme 19). All the desired reduction products were isolated in good to high yields and with excellent enantioselectivities.

Although continuous-flow reactions provide many advantages, in certain cases it can be beneficial to conduct reactions under classical batch conditions; therefore a direct comparison was carried out. Transferring the reaction conditions of the reduction of 3-Ph-benzoxazine from continuous-flow to the batch showed a noticeable drop in conversion and the product was isolated only in 67% yield. This observation was general, and typically lower reactivities were obtained. This can be explained by the better heat transfer in the microreactors as compared to the glass flask typically used in a batch reaction.

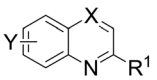
The work is a clear demonstration of how flow processes involving microdevices may be coupled with other "enabling technologies", techniques designed to speed up reactions, work up and isolation processes.[51] Not only the design of continuous flow reactors and the use of supported catalysts (or reagents) are part of these new technologies but also the study of new heating devices or of alternative liquid systems; the combined use of all these innovative technologies may offers a truly new perspective and unprecedented opportunities to the modern synthetic chemist. Examples come in particular from the use of $scCO_2$ as a green solvent alternative or microwave, as the heating method, or a membrane as a different approach to the development of immobilized catalysts employed under flow conditions. Recently in this context, Muller and Vogt reported the use of Polyhedral Oligomeric Silsesquioxanes (POSS) as a molecular weight enlarger of triphenylphosphine in order to facilitate the recovery of the homogeneous catalyst using nanofiltration in a continuous flow process.[52]

Triphenylphosphine was functionalized with three sterically hindered POSS residues as illustrated in Scheme 20 and used as Rh ligand in the test hydroformylation reaction of 1-octene in batch, showing a turnover frequency (TOF) of 1350 h^{-1}. It was then applied in a continuous flow nanofiltration reactor consisting of two loops (a gas saturation/reaction loop and a membrane filtration loop) continuously filled with a substrate solution by a HPLC pump, while the product-containing mixture is continuously collected at the backside of the membrane module. The ceramic membrane had a molecular weight cut-off of 450 Da and separated the product from the catalyst.

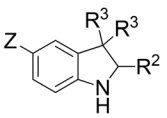
The system showed the highest conversion (99%) after 17 h and worked at this level for two weeks (the linear/branched ratio was 2.5, identical to that of unsupported PPh_3) with an accumulated turnover number of 120 000 Rh-1 after 13 days, proving the high stability and robustness of the POSS-enlarged



Asymmetric catalytic transfer hydrogenation products

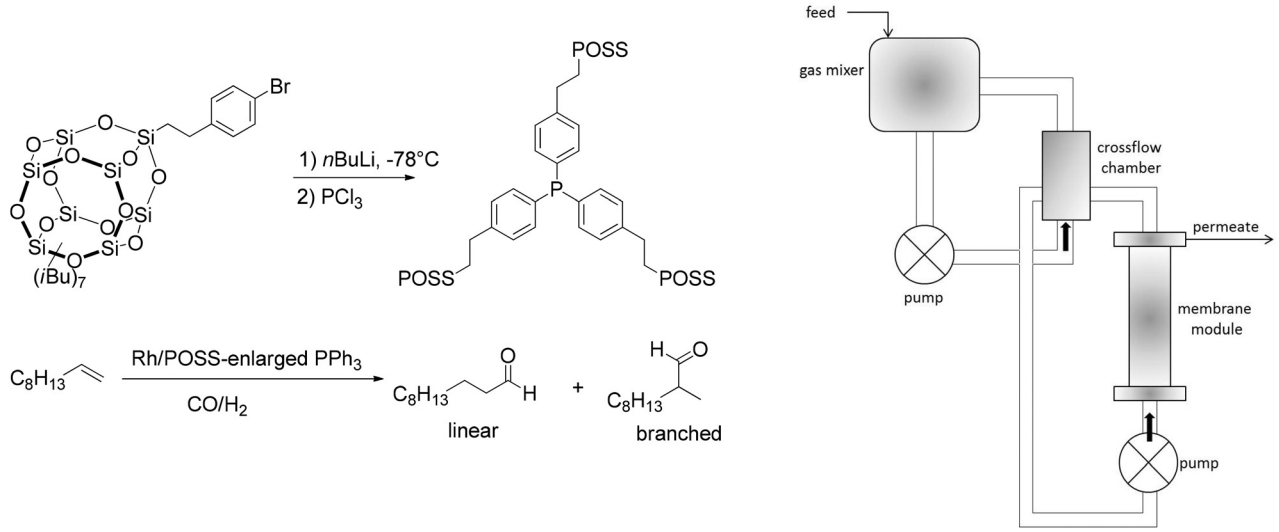


X = O,C,N
Y = H, Cl, Br
R^1 = Ph, 4-OMePh, 4-PhPh, 4-MePh, 4-ClPh, 4-CF_3Ph, 3-BrPh, 3,4-ClPh, 4-Thiophenyl-2-yl



Z = H, OMe
R^2 = Ph, 4-FPh, 4-BrPh, 4-CF_3Ph
R^3 = Me, -$(CH_2)_5$-

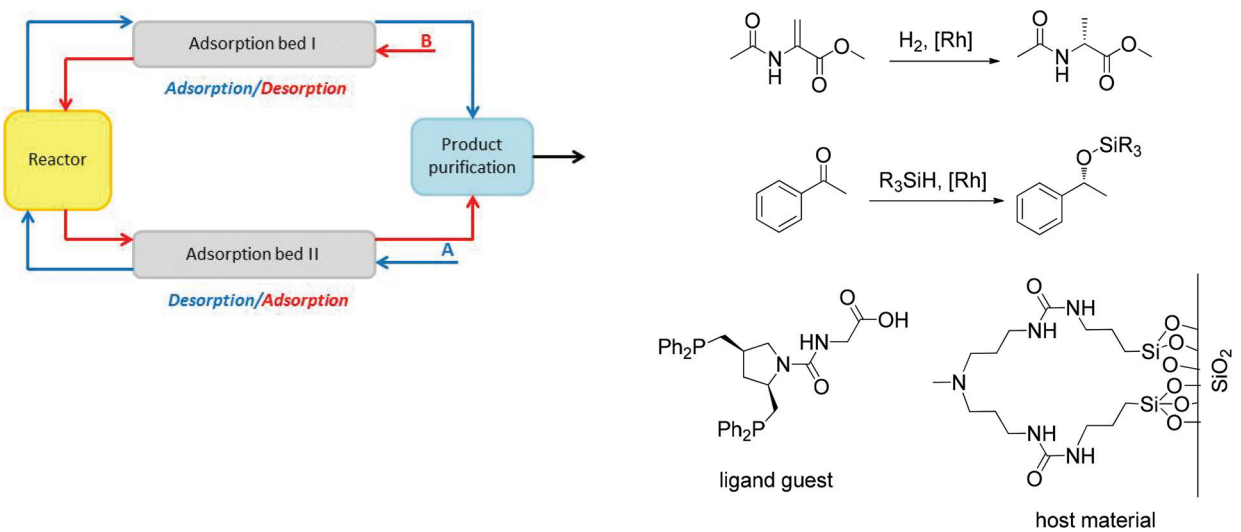
Scheme 19 Stereoselective organocatalytic transfer hydrogenation.



Scheme 20 Synthesis of POSS-enlarged PPh_3 and application to a continuous flow nanofiltration reactor.

PPh_3/Rh catalyst. Further studies demonstrated that 99.96% of the Rh was effectively retained by the membrane, facilitating the recovery and recycle of the metal.

A similar approach was reported by Reek and van Leeuwen, who showed the application of RFA (reverse-flow adsorption) to a continuous-flow reactor.[53] In a RFA approach, the homogeneous catalyst promotes the reaction and is then adsorbed on one of the adsorption beds from the product flow that leaves the reactor; simultaneously it is desorbed into the reactor from the other adsorption bed by the substrate flow feeding the reactor (Scheme 21). The novelty introduced by the authors is the one-step adsorption of the complex, both the metal and the ligand, thus avoiding the potential decomposition of the complex. The system was applied to the enantioselective hydrogenation of methyl acetamidoacrylate and enantioselective hydrosilylation of acetophenone. The catalyst of choice was a bis-phosphine/Rh complex while a silica-supported bis-amide was used as the host material. In a typical RFA experiment, the reaction mixture is pumped from the reactor to the first adsorption bed and the metal complex adsorbed. Simultaneously, two solutions, one containing the metal complex and the other containing the substrate, are added to the reactor. After a part of the reactor solution is collected outside of the first adsorption bed, the direction of the flow is reversed. A substrate solution is pumped into the reactor and passes through the first adsorption bed, desorbing the metal complex into the reactor. At the same time, the reaction mixture is pumped from the reactor through the second adsorption bed. The flow direction is changed regularly. Although conversions and enantiomeric excesses are not very



Scheme 21 Reverse-flow adsorption (RFA).

high (but are comparable to those obtained in batch), the RFA system is an alternative method to recover and recycle a homogeneous catalyst. Moreover, several parameters, including structural modifications and solvent polarity, can be tuned in order to optimize the binding strength between the host and the guest, thus improving the adsorption/desorption cycle.

Recent progress in flow chemistry techniques using mini and micro flow reactors have opened up a new era in chemical synthesis; particularly, the combination of flow reactors with heterogenized catalysts as well as new heating techniques and/or new solvents (*e.g.* ionic liquids) creates ideal technical devices for the rapid continuous production of chemicals with minimum purification. In the case of flow chemistry with chiral catalysts it is evident that the field is still in its infancy and it holds a lot of promise. It should be noted that a process based on a catalytic methodology is already "green" by definition, since it is clearly stated that "catalysts are preferable to stoichiometric reagents" because they minimize waste and increase energy efficiency; a catalyst often allows to run a reaction in milder experimental conditions, once again improving the efficiency of a process from the economic and energetic point of view. Furthermore the possibility of using catalytic amounts of an organic compound of relatively simple structure to promote reactions that previously required costly and possibly toxic transition metals-based catalysts can be regarded as a significant step toward the development of a truly green chemistry. Specifically the use of chiral catalysts under flow conditions may lead to the design of "safer chemicals and products", as expected by modern synthetic chemists, also with the goal to use less hazardous solvents or reaction conditions, to minimize the amount of solvent and to further optimize the efficiency of the process.

The synthesis of fine chemicals in flow also presents new and exciting challenges and opportunities for both homogeneous and heterogeneous transformations. Multistep reaction sequences can be conducted in a completely different fashion in flow compared to batch processes. By employing several microfluidic devices a continuous multistep process can be designed, for example, by setting a linear arrangement of flow reactors. Reagents can be introduced into the stream of reactants anywhere in the flow system with a great control on some parameters (addition time, addition rate, order of addition) that may be extremely convenient for the reaction success.[54]

However it must be said that this "technological switch" from batch to flow is not without problems.[55] Flow chemistry does not represent the panacea for all possible difficulties in synthesis either on lab or on large scale. There are principal differences between batch and flow processes with respect to production time and yield. It is not our aim to discuss this topic that has been the subject of a recent very meaningful review where the authors have provided chemists and engineers with all the information necessary to decide whether it might be appropriate to perform a given reaction in batch or in flow reactors. Our goal in this review was to present all the recent progress made in the field of supported chiral catalysts used under flow conditions. Our aim was to highlight how in the last few years new exciting achievements have been published, including the first examples of immobilized chiral organocatalysts used in continuous flow systems. It may be expected that many other new developments will appear in the future, in an area that is in great expansion, open to the interdisciplinary contributions of organic, material chemists and engineers. It is a really multifaceted and stimulating chemistry where creativity, fantasy and courage are all qualities required by the modern chemist who wishes to successfully work in this field.

Note added in proof

For a very recent report on an extraordinary stable and long-lasting polymer-supported organocatalyst for Michael addition, see ref. 56. See also ref. 57.

Acknowledgements

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