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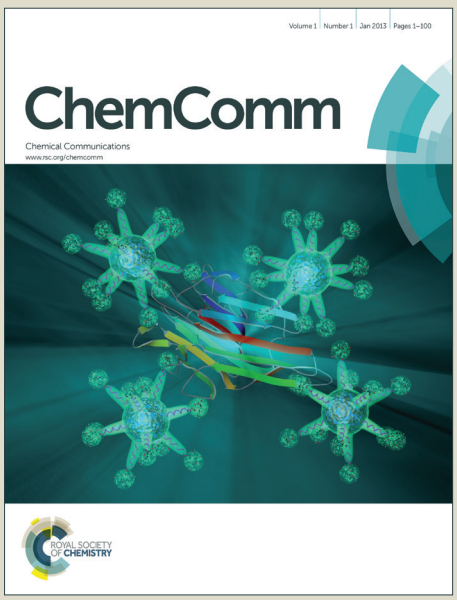

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Expanding the Toolbox of Asymmetric Organocatalysis by Continuous-flow Process

Fernanda Gadini G. Finelli, [a] Leandro S. M. Miranda [b] and Rodrigo O. M. A. de Souza [b]

a- Institute of Natural Products Research, Center of Health Sciences, Federal University of Rio de Janeiro, CEP 21941902

b- Biocatalysis and Organic Synthesis Group, Chemistry Institute, Federal University of Rio de Janeiro, CEP21941909

Corresponding authors:

Keywords: continuous-flow, packed bed reactors, organocatalysis, flow chemistry

Abstract: Despite all organic chemistry reaction methodologies already developed for continuous flow process, asymmetric synthesis is the one who has gained less attention during these years. Since the pioneering work of Barbas and McMillan, organocatalysis has emerged as the third pillar of asymmetric catalysis. In this review, we present a survey of literature regarding the use of organocatalysis under continuous flow conditions.

Introduction

Continuous-flow process has recently emerged for the organic chemistry community as an interesting and alternative method for performing chemical transformations. Despite all advantages of continuous-flow technology, process intensification is a key feature since flow reactors can work at elevated temperatures and pressures expanding the window of reaction conditions for a specific transformation. [1-4]

Another key aspect of continuous flow reactors is compartmentalization. This characteristic allows the combination of different reaction steps, as a multi-step synthesis, working at different temperatures and pressures enabling incompatible reaction conditions to take place on a cascade fashion way. [5-10] This concept is also in agreement with green chemistry principles, avoiding intermediate isolation and consequently, reducing waste production. [11-13]

Despite all organic chemistry reaction methodologies already developed for continuous flow process, asymmetric synthesis is the one who has gained less attention during these years. More specific, organocatalysis, one of the great achievements of organic chemistry in 20th century, has very few contributions over literature. [14] This is probably direct related to the difficulty on recycling the organocatalyst, but immobilization and the use of packed bed reactors can overcome this drawback and bring organocatalysis to the hall of the very important and useful methodologies for continuous flow process. [14-18]

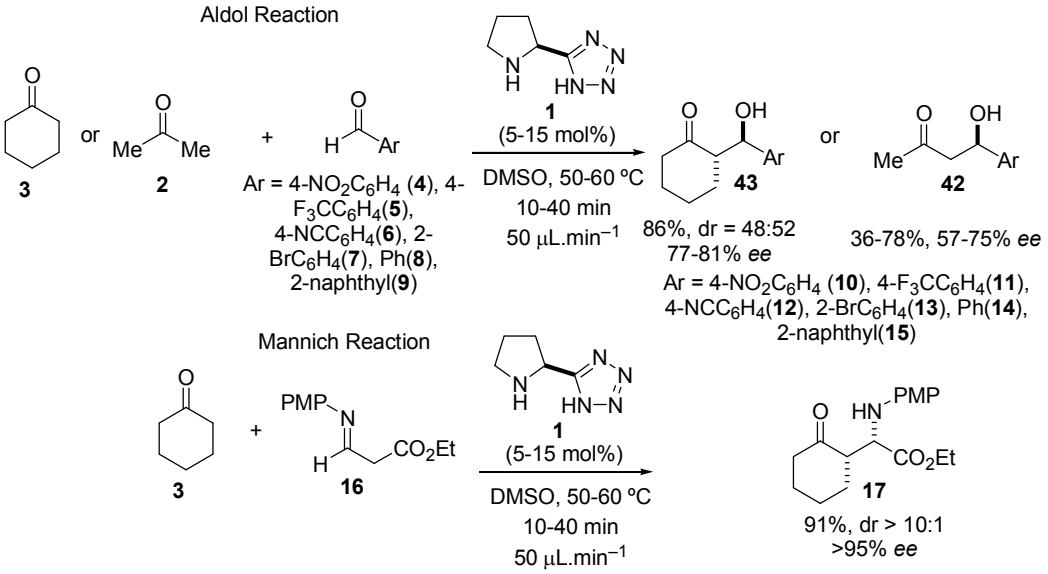
Since the pioneering work of Barbas [19-21] and McMillan [22], organocatalysis has emerged as the third pillar of asymmetric catalysis. In organocatalyzed reactions, products with high enantiomeric excess can be obtained through different modes of activation of the pro-quiral substrate by the organocatalyst such as acid-base or

iminium based activation which leads to application of organocatalysis to many different of reactions The use of organocatalysts has several advantages such as robustness, stability to air and water, low toxicity and ease of handling. However, low turnover and difficulty of organocatalyst recovery represent challenges to be overcome.

In this review, we present a survey of literature regarding the use of organocatalysis under continuous flow conditions. The examples presented here are divided into homogeneous and heterogeneous catalysis and when presented by the author, detailed schemes on the organocatalyst immobilization protocol are shown.

Homogeneous asymmetric organocatalytic reactions under continuous flow conditions:

In 2009, Seeberger and Odedra [23] reported the use of bifunctional activation mode over 5-(pyrrolidin-2-yl)tetrazole **1** organocatalyst, on the asymmetric aldol and Mannich reactions conducted in glass microreactors with volumes of 250 μL and 1.0 mL. The reagents were introduced separately through two inlets using syringe pumps and the fluidic connections were made using Polytetrafluoroethylene (PTFE). Mannich and aldol adducts were prepared in good yields and stereoselectivities, in shorter reaction times and with catalyst loading reduced when compared to batch conditions (Scheme 1).



Scheme 1. Aldol and Mannich reactions catalyzed by 5-(pyrrolidin-2-yl)tetrazole (**1**) under continuous-flow conditions. [23]

Mannich reaction was also subject of interest for Belder and co-workers, [24] who used the Bronsted acid organocatalyzed asymmetric vinilogous Mannich reaction in a microchip using continuous flow technology (Figure 1). In this case, authors used a designed microchip reactor in order to allow integrated analysis of the reaction mixture. For such, a microchip was developed to allow different functionalities *i.e.* a structure for the reaction, a structure for the aqueous dilution of the reaction mixture and a cross section for injection in the mass spectrometer with an integrated nanospray emitter

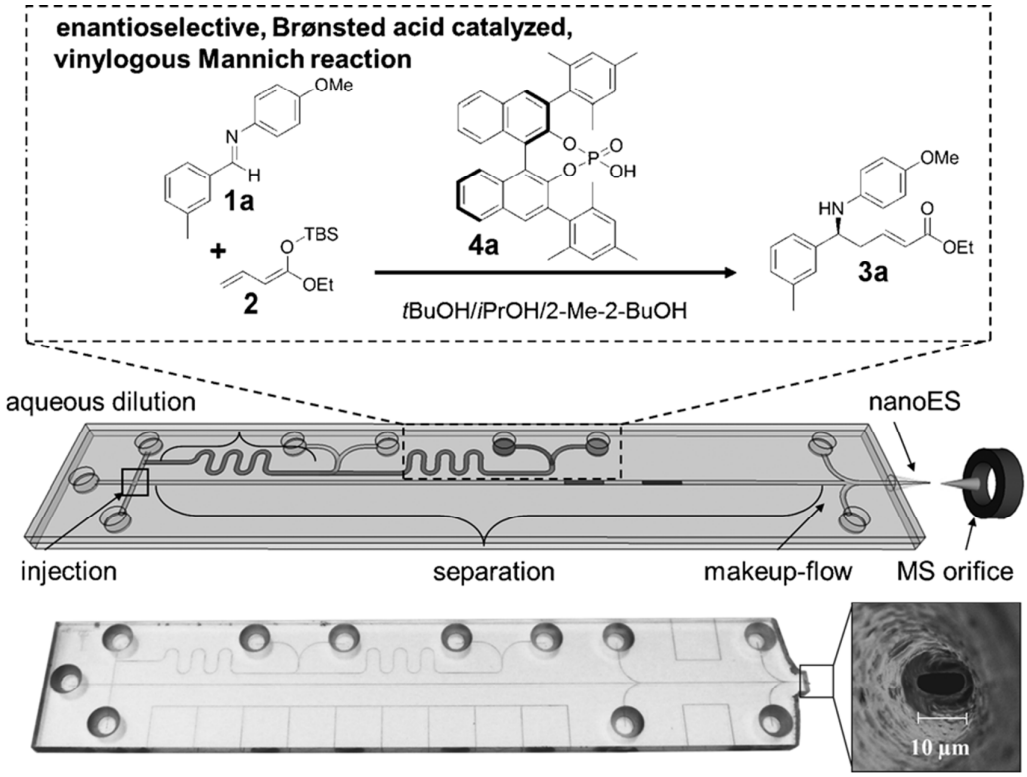
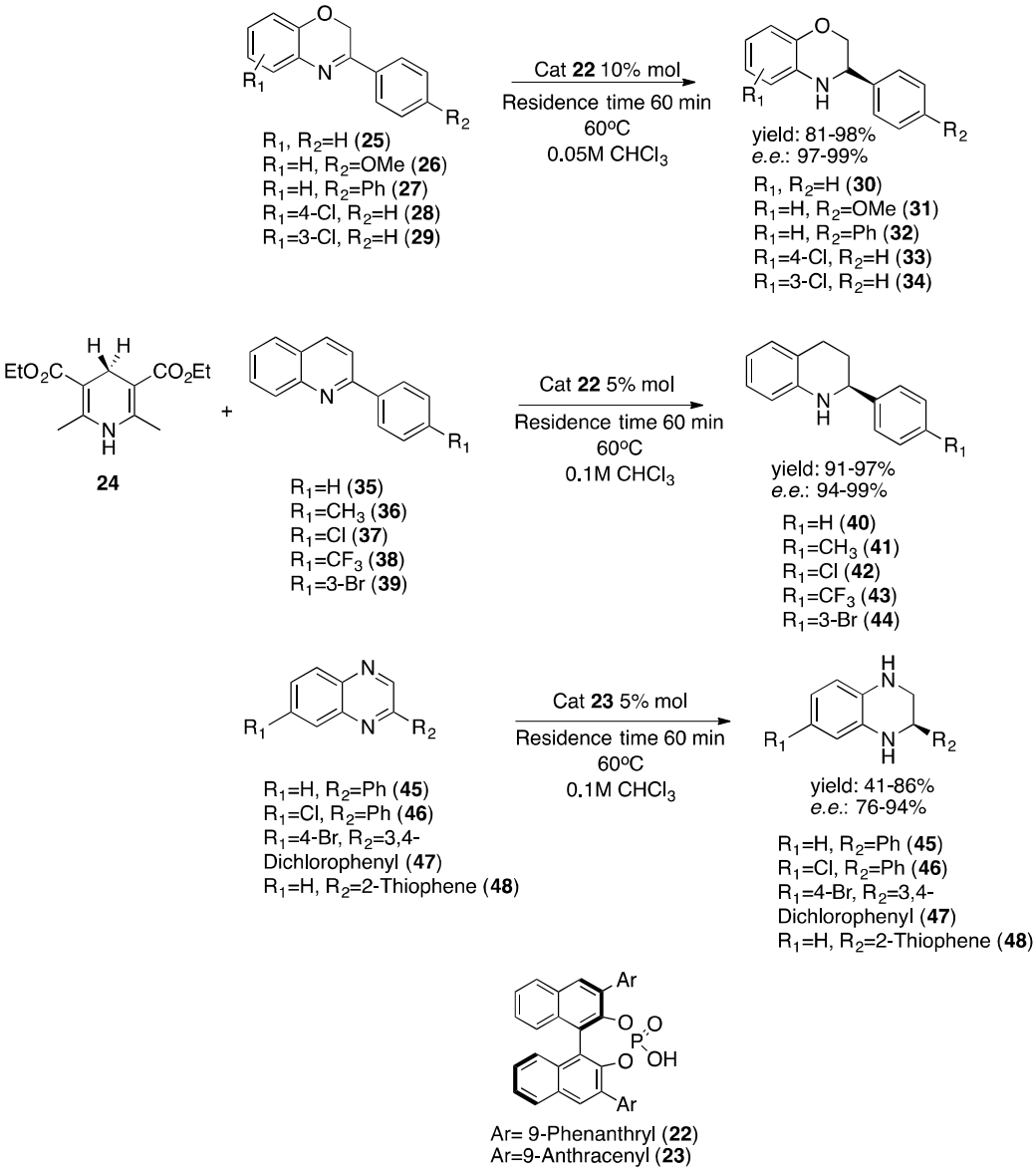


Figure 1: Designed microreator for integrated analysis used on the bronsted acid organocatalyzed asymmetric vinilogous Mannich reaction. [24]

Also using a microreactor and an acid-base activation strategy Rueping and co-workers [25] developed a continuous-flow process for the organocatalyzed asymmetric transfer hydrogenation. In the presence of a chiral phosphonic acids **22** or **23** as organocatalyst and Hantzsch dihydropyridine **24** as hydride source, authors performed the reduction of benzoxazines **25-29**, quinolines **35-39** and quinoxalines **45-48**.



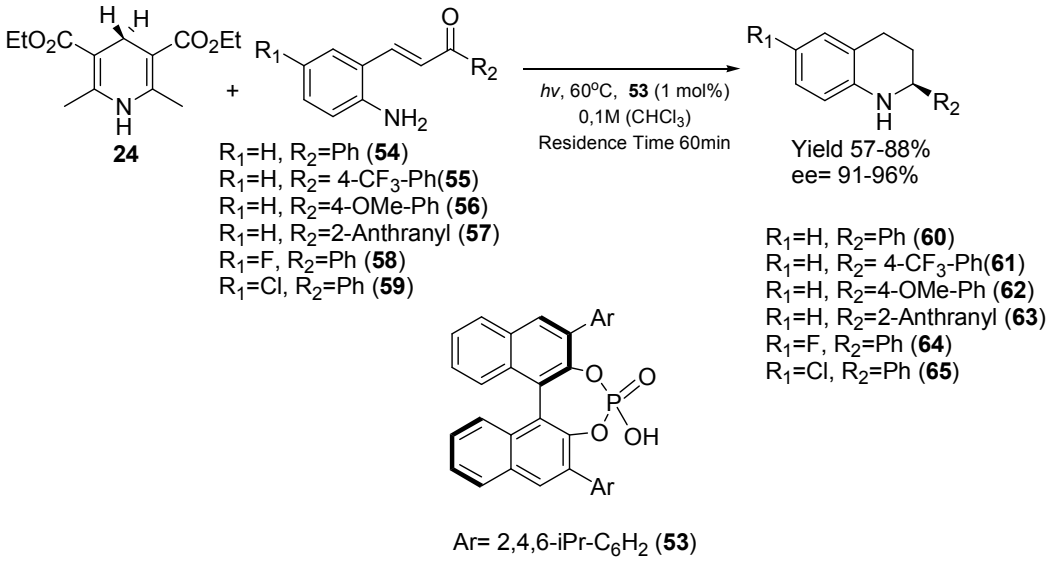
Scheme 2: Continuous-flow microreactor asymmetric transfer hydrogenation. [25]

Reaction time (60 minutes) and temperatures (60°C) were the same for all substrates and good to excellent enantiomeric excess were obtained with moderate to good yields. The amount of catalyst used was in the range between 0.5% and 10%, depending on the characteristics of the substrate (Scheme 2).

Later on, the same group of authors applied the developed methodology shown above, to the synthesis of tetrahydroquinolines under continuos-flow regime using 2-aminochalcones as the starting material in a tandem cyclization reduction

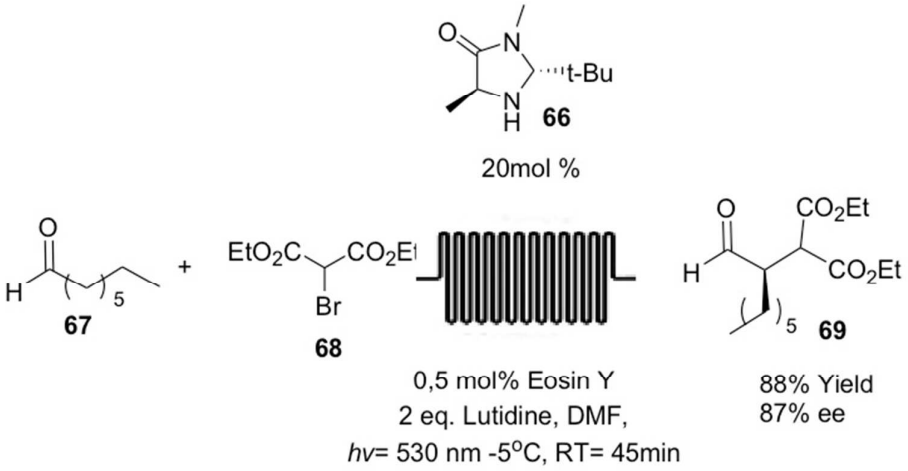
sequence. [26] The authors used a photocatalized cyclization protocol towards the corresponding quinolines, which, in the presence of acid **53** and Hantzsch dihydropyridine **24** led to the optically active tetrahydroquinolines in moderate to good yields and in excellent *e.e*s, as depicted in scheme 3.

It is important to note that in the cases presented on scheme 3, authors observed an inverse dependence of the enantiomeric excess to the residence time. It was speculated that under photochemical conditions, longer residence times could lead to undesired background reaction initiated by photoexcited dihydropyridine.



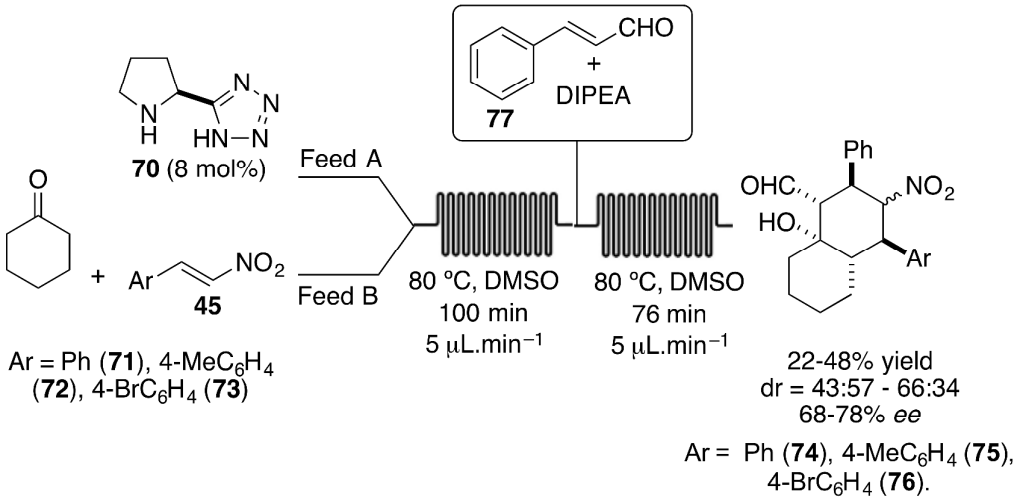
Scheme 3: Synthesis of tetrahydroquinolines under continuos-flow regime. [26]

Zeitler described a similar approach for the synergistic organocatalyzed photoredox α-alkylation of aldehydes using imidazolidinone **66**, in excellent yields and shorter reaction times under continuous flow, scheme 4. [27]



Scheme 4: Organocatalyzed photoredox α-alkylation of aldehydes. [27]

Working on a domino activation process (enamine-iminium), Luisi and coworkers [3] investigated continuous flow domino nitro-Michael-aldol reaction in a chip microreactor, organocatalyzed by a (*S*)-(–)-5-(2-Pyrrolidinyl)-1*H*-tetrazole **70**. Reactions between different β-nitrostyrenes **71-73** and cyclohexanone were conducted in DMSO at 80 ºC with 8 mol% of organocatalyst **70** and a flow rate of 5 $\mu L.min^{-1}$ in a 1.0 mL 2-input glass-microreactor with a Y mixing zone. The desired β-nitroketones were obtained in high yields and connected to a second chip microreactor with a solution of cinnamaldehyde **77** and DIPEA in DMSO at 80 ºC with a flow rate of 5 $\mu L.min^{-1}$. The bicyclo[4.4.0]decane derivatives **74-76** were obtained in moderate yields, low diastereoselectivities and high enantioselectivities, scheme 5.



Scheme 5: Continuous-flow domino nitro-Michael-aldol reaction. [3]

Heterogeneous asymmetric organocatalytic reactions under continuous flow conditions:

Pericas and co-workers have developed several strategies towards the use of immobilized organocatalysts for asymmetric transformations, using most of the time 1,2,3-triazole linkers with polystyrene beads as solid supports for catalyst immobilization (Figure 2). [28-36]

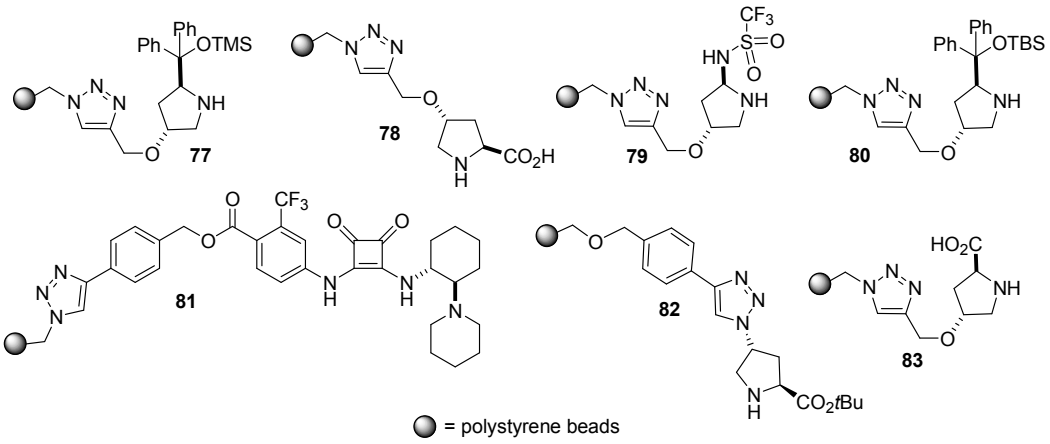
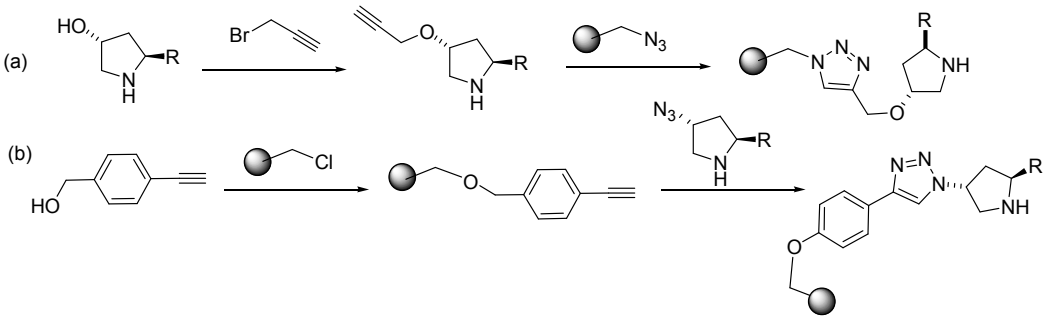


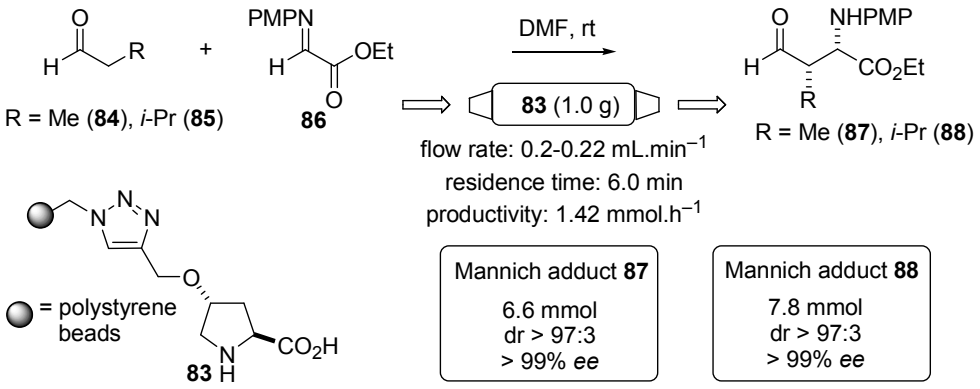
Figure 2: Immobilized organocatalysts developed by Pericas and co-workers. [28-36]

Synthesis of immobilized organocatalysts presented in figure 2 follow two different strategies. For those N-bound to the resin, properly functionalized 3-hydroxyproline or modified catalyst reacts with propargyl bromide under basic conditions in order to have the alkyne moiety necessary for the click reaction with the azide functionalized resin, as depicted in scheme 6a. The other strategy places the alkyne moiety for the click reaction based conjugation on the resin through the use of benzyloxyphenyl acetylene derivatives, which undergoes click reaction towards the azide derivative of the desired organocatalyst , scheme 6b. [35, 36]



Scheme 6: Synthesis of the immobilized organocatalysts developed by Pericas and co-workers.

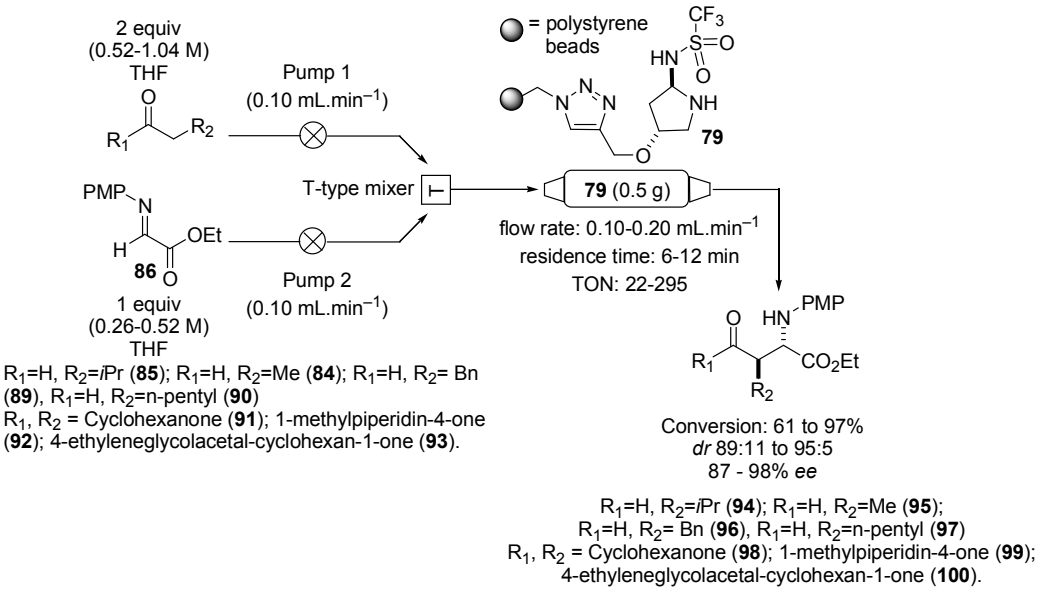
The proof of concept of polystyrene-supported hydroxyproline catalyst **83** was in a Mannich reaction. [35] The catalyst was loaded in a jacketed omnifit column and used in the reaction. Reagents were pumped through a single-piston pump at 0.20 to 0.22 $mL.min^{-1}$ with a solution of propanal **84** or isovaleraldehyde **85** and the preformed *N*-(*p*-methoxyphenyl) (*N*-PMP) ethyl glyoxylate imine **86** in DMF at room temperature (Scheme 7).



Scheme 7: Mannich reaction catalyzed by polystyrene-supported hydroxyproline catalyst **83**, under continuous-flow conditions**.** [35]

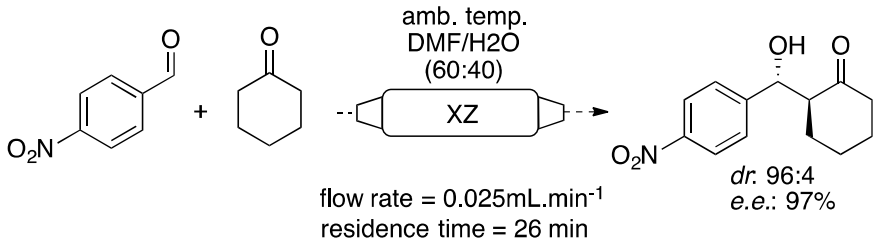
Around 7 to 8 mmol of the enantiomerically and diastereomerically pure Mannich adducts **87** and **88** (*syn*/*anti* > 97:3; *ee* > 99%) were prepared in 5.5 hours employing 1.0g of organocatalyst **83** (functionalization = 0.46 mmol.g^{-1}) and 8,5-9 mmol of the aldehydes under the single-pass operating with 6.0 min of residence time and a productivity of 1.42 mmol.h^{-1} per gram of **1**. According to the batch process described by the authors as reference, the continuous flow process allowed for a significant reduction of the catalyst amount without performance loss.

On the other hand the *anti* diastereisomer of Mannich product was presented by Pericas and co-workers in a reaction catalyzed by a polysterene-supported pyrrolidine-based organocatalyst **79**. [29] Solutions of different aldehydes and ketones in THF were pumped to a cartridge containing the immobilized organocatalyst **79** to react with preformed *N*-PMP ethyl glyoxylate imine **86** furnishing the *anti*-Mannich adducts **95-100** at the 0.05-0.1 mol scale in high conversions and stereoselectivities (Scheme 7). Interestingly, the same resin could be used consecutively in experiments of 48 hours, reaching TON values of around 300, a 15-fold improvement when compared with batch conditions (Scheme 8).



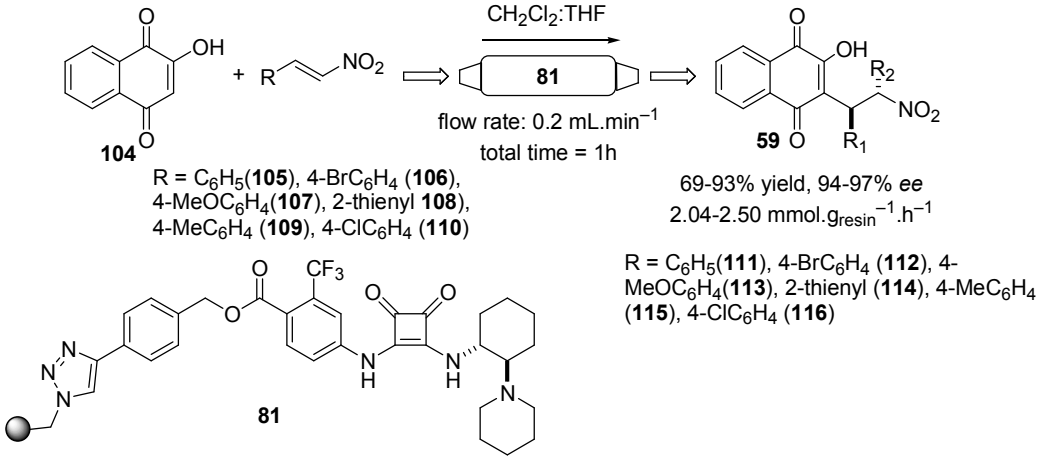
Scheme 8: Diastereocomplementary Mannich reaction catalyzed by polysterene-supported pyrrolidine-based organocatalyst **79** under continuous-flow conditions.

The same strategy was used in a different work where Pericas and co-workers have developed asymmetric aldol reactions under continuous-flow conditions catalyzed by polystyrene immobilized proline derivatives. [32] Reactions were performed by pumping the starting material solution (DMF/H_2O) through the packed bed filled with the immobilized organocatalyst at a flow rate of 0.025mL.min^{-1} and ambient temperature. Good diastereomeric and enantiomeric excess were obtained but after 30h of operation yields start to decrease without compromising the selectivity (Scheme 9).



Scheme 9: Asymmetric Aldol reaction developed by Pericas and co-workers.

Pericàs and coworkers[30] also reported the Michael additions of 2-hydroxy-1,4-naphtoquinone **104** to nitroalkenes **105-110** promoted by a polystyrene supported bifunctional squarimide organocatalyst **81** under continuous flow conditions. The enantioselective reactions were performed by pumping the naphtoquinone **104** and different nitroalkenes, on the same feed, in CH_2Cl_2:THF (10:1) through a low-pressure chromatography column with two adjustable end pieces loaded with the PS-supported organocatalyst **81** using a flow rate of 0.2 mL.min^{-1} These conditions furnishing to the desired adducts **111-116** in good yields, high enantioselectivities and productivities (Scheme 10).

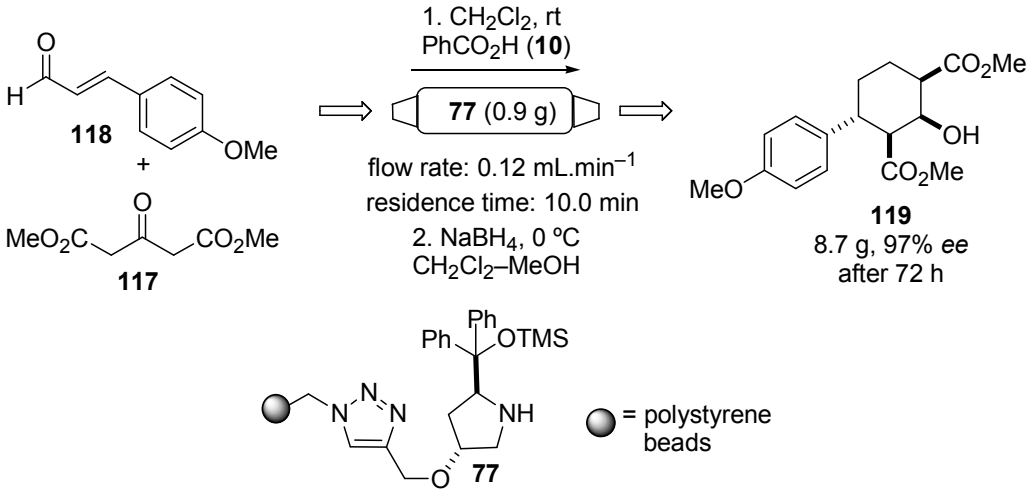


Scheme 10: Michael additions of 2-hydroxy-1,4-naphtoquinone (**56**) to nitroalkenes **105-110** promoted by a polystyrene supported bifunctional squarimide organocatalyst **81** under continuous flow conditions.

A domino Michael-Knoevenagel reaction for the asymmetric synthesis of highly functionalized cyclohexanes have been reported. [34] In the reaction of dimethyl 3-oxoglutarate **117** and 3-substituted acroleins catalyzed by the polystyrene-supported diphenylprolinol trimethylsilyl ether **77** cyclohexane **119** was obtained in high yield

and enantioand diastereoisomeric excess under continuouds flow.

The optimized domino Michael-Knoevenagel batch conditions were adapted to the single-pass continuous flow process allowing the isolation of 27 mmol of pure cyclohexanol **119** with 97% *ee* after 72 hours of operation. This excellent performance was reached pumping a dichloromethane solution of 1 equivalent of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **118** (around 50 mmol), benzoic acid and 1.1 equivalent of 3-oxoglutarate **117** at room temperature over a glass column filled with 900 mg of the organocatalyst **77** at 0.12 mL.min^{-1} flow rate and 10.0 min of residence time, followed by reductive workup with sodium borohydride (Scheme 11).

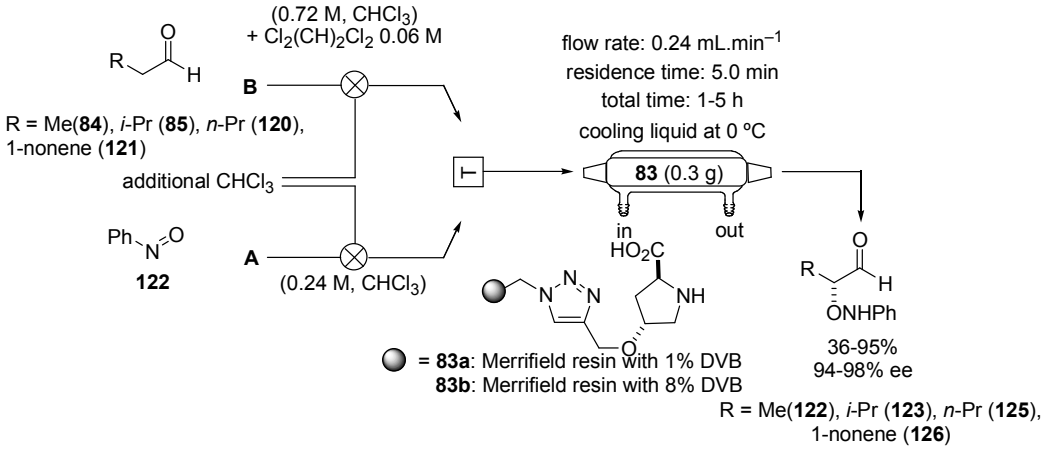


Scheme 11: Michael-Knoevenagel domino reaction catalyzed by organocatalyst **77** under continuous-flow conditions. [34]

α-aminoxylation of aldehydes was also subject of study by Pericàs and coworkers. In order to test the influence of mechanical stability of the resin in organocatalyst performance, the hydroxyproline **83,** scheme 12, was supported in a commercially available Merrifield resin with different proportions of 1,4-divinylbenzene (DVB). [33]

The continuous flow system was setup with flasks containing a supply of pure chloroform, for non-reaction operations such as swelling the resin and washing the tubing before and after the reaction, and chloroform solutions of aldehydes **84,85, 120 and 121** with 1,1,2,2-tetrachloroethane (internal standard) and nitrosobenzene **122** connected to two piston pumps connected through a T-shape connector to a glass chromatography column filled with the immobilized organocatalysts **83a** or **83b,** depending on its load in the DVB resin, connected to a collection flask.

Solutions **A** and **B** were pumped through the column at a rate of 0.12 mL.min^{-1} each at 0 ºC and collected after the reaction at –78 ºC to avoid degradation of the aminoxylated products (Scheme 4). Both immobilized organocatalysts **83a** and **83b** provided the desired products in excellent enantioselectivities and good conversions, however, the resin **83b** exhibited productivities from 3.7 to 16.1 mmol(product).mmol(catalyst)$^{-1}$, while resin **83a** exhibited productivities from 12.6 to 32.7 mmol(product).mmol^{-1}(catalyst). Both **83a** and **83b** showed a moderate stability, with a decrease in the conversion with time and no significant difference in stability related to the degree of cross-linking. Around 30 mmol of product was isolated per mmol of resin **83a** for every flow experiment after 5 hours, a four-fold improvement with respect to the batch process.

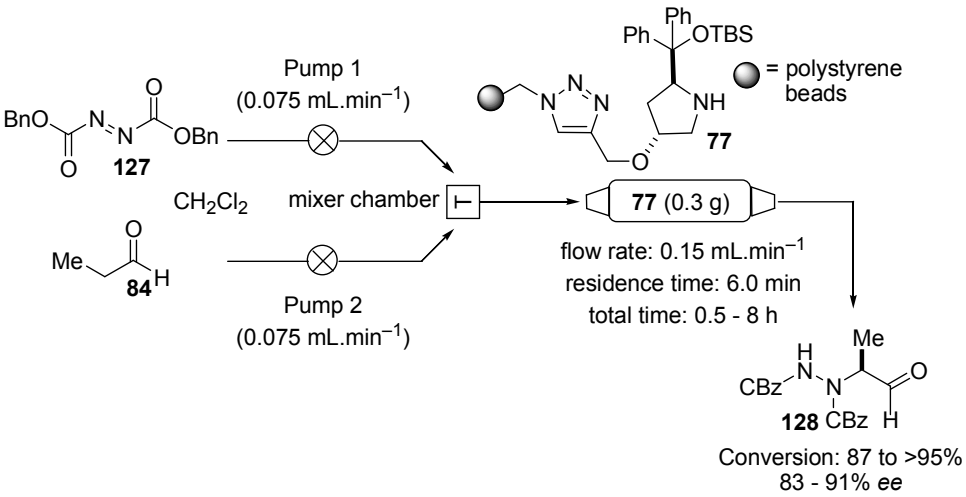


Scheme 12: Continuous-flow α-aminoxylation of aldehydes. [33]

This group also developed another amination reaction where α-amination of propanal (84) with dibenzyl azodicarboxylate (DBAD-**127**) catalyzed by the polystyrene-supported diphenylprolinol *t*-butyldimethylsilyl ether **77** was performed. The aldehyde was used in excess to avoid the deactivation of the organocatalyst by reaction with DBAD. [31]

The mixture of propanal **84** and AcOH in dichloromethane was pumped into the reactor for 60 min at a flow rate of 0.075 mL.min^{-1}, to promote the enamine formation, followed by the addition of DBAD in dichloromethane, using a different pump at the same flow rate. Then, the two streems were mixed in a T-type mixing chamber, before pumping into the reactor.

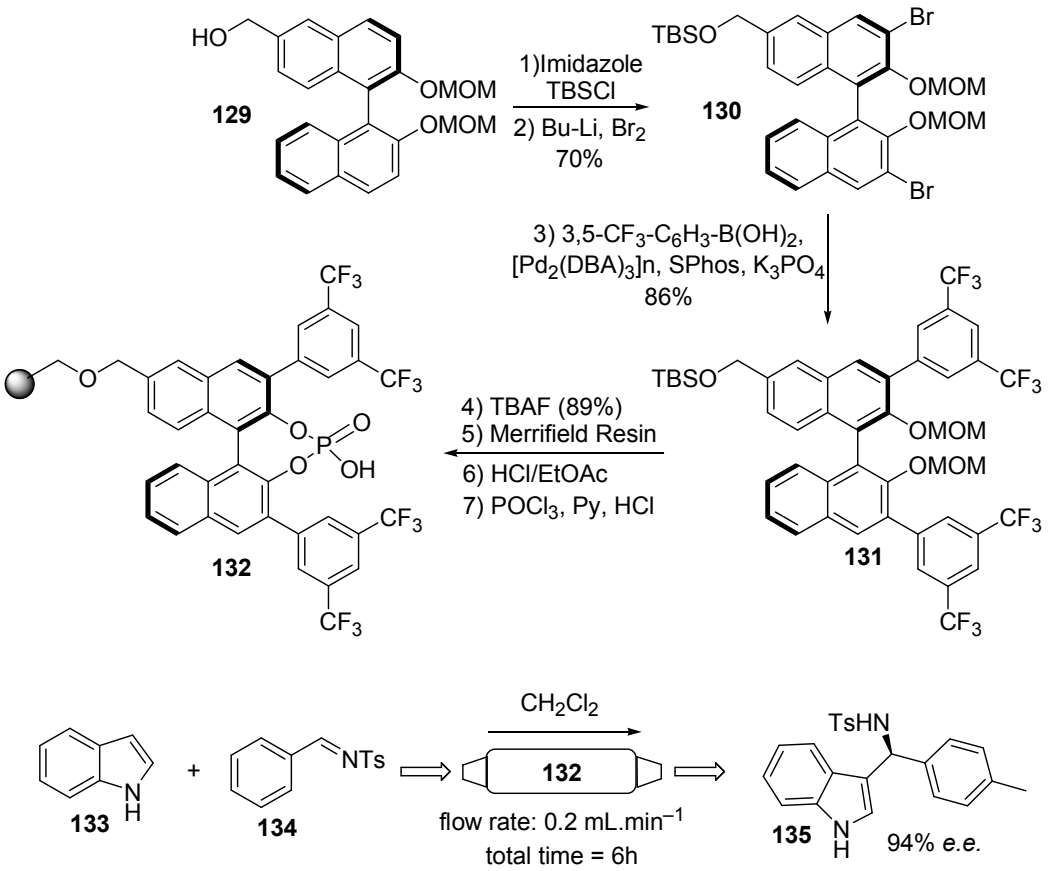
The system was kept operating for 8 hours and the product was collected in a flask at 0 ºC. Full conversion and high enantioselectivities were achieved during the first 6 hours of operation with residence time of 6 min, however, a slight decrease of conversion was observed in the last 2 hours, fursnishing 7.6 mmol of **25** after 8 hours (Scheme 13).



Scheme 13: Continuous-flow α-amination of propanal **84** with dibenzyl

azodicarboxylate (DBAD-**127**) catalyzed by the polystyrene-supported diphenylprolinol *t*-butyldimethylsilyl ether **77.** [31]

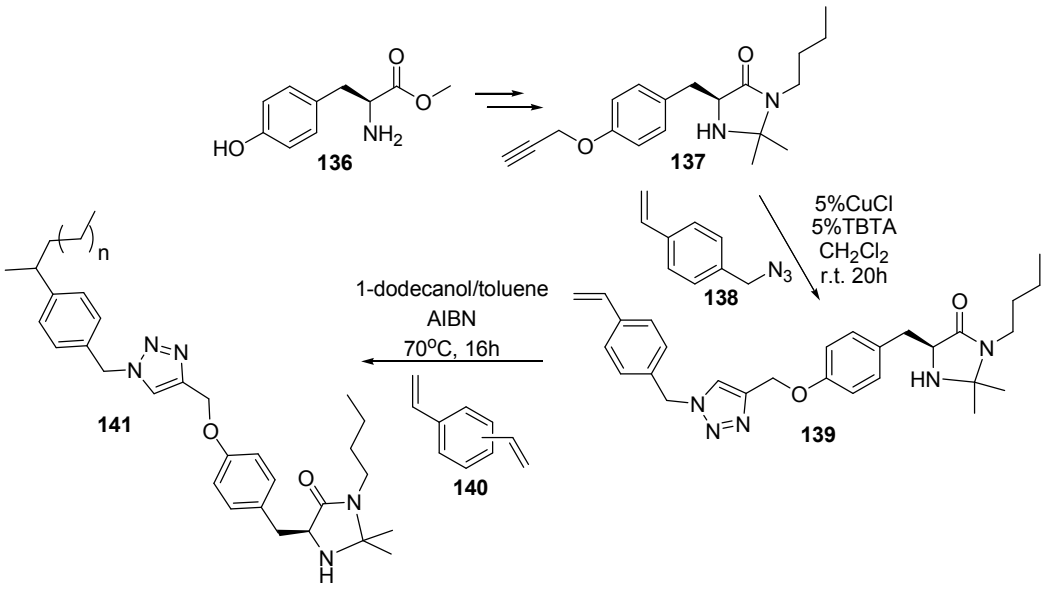
Péricas and co-workers have also immobilized chiral phosphoric acid catalyst in order to perform an enantioselective Friedel–Crafts reaction of indoles and sulfonylimines under continuous-flow conditions using packed bed reactors. [28] The catalyst was immobilized in a polystyrene resin according to scheme 12. With the immobilized catalyst, authors proceeded to the synthesis of a small library of 3-indolylmethanamines under continuous-flow and obtained the 3-Indolylmethanamines in high yield and enantiosselectivity, operating at 0.2 ml.min^{-1} flow rate in dichloromethane for 6h at room temperature (Scheme 14).



Scheme 14: Immobilized chiral phosphoric acid for enantioselective Friedel–Crafts reaction of indoles and sulfonylimines under continuous-flow conditions. [28]

Other polymer types were also used for immobilizing organocatalysts for continuous flow purpose. Chiroli and coworkers [37-39] also reported the development of Friedel-Crafts and cycloadditions reactions in a monolithic reactor loaded with a chiral imidazolidinone organocatalyst.

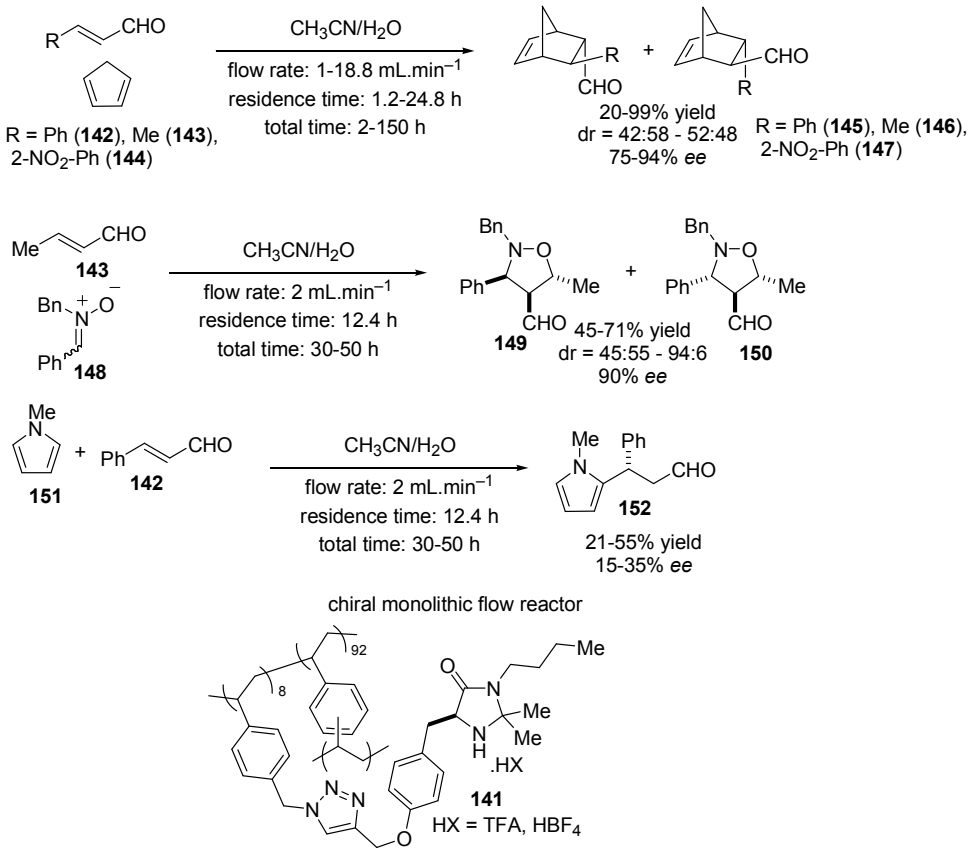
The monolithic organocatalyst was prepared inside a HPLC column through the AIBN initiated copolymerization of divinylbenzene and the tyrosine methyl ester **136** MacMillan imidazolidinone type organocatalyst containing a styrene portion attached to a 1,2,3-triazol linker **139** in 1-dodecanol and toluene, according to Frechét-type conditions (Scheme 15). [38]



Scheme 15: Preparation of chiral imidazolidinone organocatalyst **141**. [38]

They performed a comprehensive study of optimization by varying the flow parameters using the Diels-Alder reaction between cyclopentadiene and cinnamaldehyde as model, achieving excellent yields and stereoselectivities as well as

a higher productivity compared to batch conditions. Moreover, the flow system was adjusted to sequentially promote the Diels-Alder reaction, the 1,3 dipolar cycloaddition and the Friedel-Crafts reaction using the same column, furnishing excellent results with 310 hours on stream (Scheme 16).

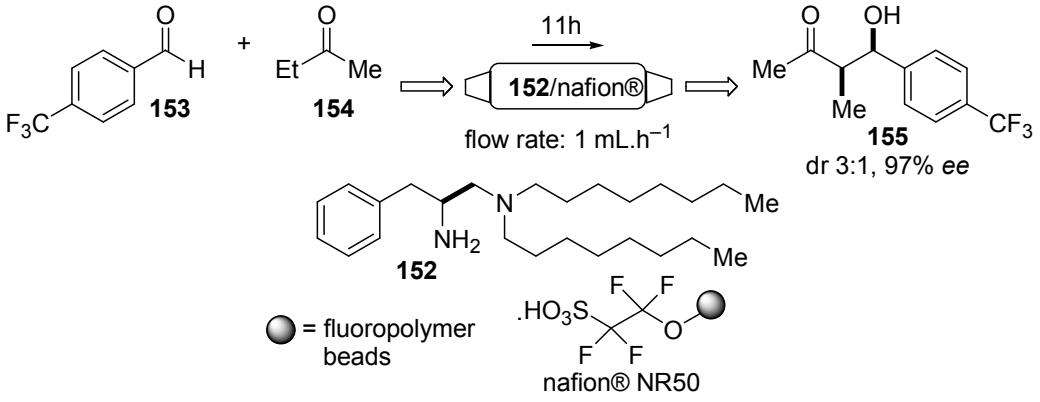


Scheme 16: Friedel-Crafts and cycloadditions reactions in a monolithic reactor loaded with a chiral imidazolidinone organocatalyst.

In another example, Sels and coworkers [40] developed a direct asymmetric aldol reactions of linear ketones in a continuous-flow system activated by a non-covalent immobilized chiral primary amino acid-derived diamine **152**, supported on sulfonated fluoropolymer nafion® NR50.

The fixed bed was filled with the heterogeneous catalyst prepared *in situ* by mixing 1.2 equivalents of organocatalyst **152** and 1 equivalent of the solid acid was

continuously fed at 1 $mL.h^{-1}$ with the preheated solution of 4-(trifluoromethyl)benzaldehyde **153** at 45 ºC in 2-butanone **154** (Scheme 17). The immobilized catalyst showed good cumulative activity and improved diastereo- and enantioselectivity of the aldol reaction after 11 hours of operation under continuous conditions, with dr = 3:1 and 97% *ee* for the major *syn*-isomer **155** compared to dr = 2.5:1 and 94% *ee* under batch conditions.



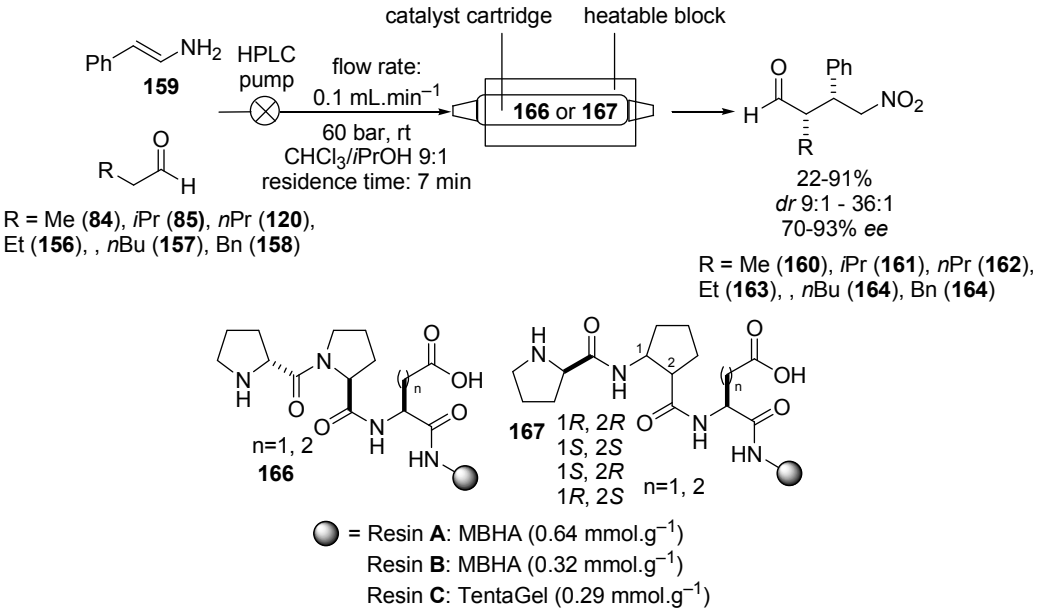
Scheme 17: Nafion supported organocatalyst for asymmetric aldol reactions under continuous-flow conditions. [40]

A different approach was proposed by Fueloep and coworkers in two different works, [41, 42] where a polymer-supported tripeptide-containing proline and carboxylic acid moieties was used for an asymmetric conjugate addition of aldehydes to nitroolefins and asymmetric aldol reactions under continuous flow conditions.

The peptide catalysts were synthesized by classical peptide coupling steps followed by removal of the side-chain protecting groups using Fmoc/*t*Bu protocols on polyethylene glycol-polystyrene copolymers (TentaGel) and polystyrene resins with 4-methylbenzhydrylamine (MBHA).

The conjugate addition of aldehydes to nitroolefins reactions were performed in an H-Cube (Thalesnano) system with a cartridge-like stainless steel tube filled with the organocatalyst covered by a Peltier heating system connected to a HPLC pump. [41]

The addition of the aldehydes **84, 85, 120, 156-158** to *E*-β-nitrostyrene **159** was carried out under the optimized reaction condition, employing the organocatalyst H-D-Pro-Pro-Asp-NH-resin A **166** in chloroform/isopropanol (9:1) at room temperature, pressure of 60 bar, flow rate of 0.1 mL.min^{-1} and residence time of 7 minutes. The γ-nitroaldehydes **160-164** were obtained in moderate to good yields (60 to 90%), enantiomeric excess higher than 90% and diastereoselectivities between 11:1 to 36:1. Addition of more hindered aldehydes led to γ-nitroaldehydes in lower yields (20%, **161** R = *i*Pr) or no conversion (Scheme 19).



Scheme 19: Tripeptide-containing proline for an asymmetric conjugate addition of aldehydes to nitroolefins and asymmetric aldol reactions under continuous-flow regime.

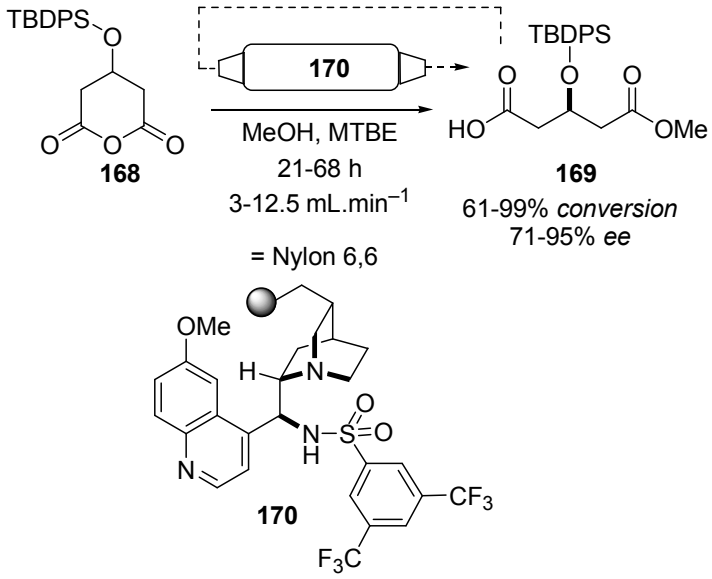
Further studies showed that the longer the residence time, the higher the yield; however, the longer the residence time, the lower the diastereoselectivity, due to an epimerization promoted by the catalyst. Increasing the pressure from atmospheric to 60 bar led to higher yields, further elevation proved to be not beneficial. Increase of temperature provided higher yields, but lowered diastereo- and enantioselectivities.

The results were comparable to the batch procedure, allowing the preparation of synthetic useful γ-nitroaldehydes in shortened reaction times (24h to 7 min), good yields and stereoselectivities, using organocatalysts synthesized and immobilized in one single step.

The same catalyst was used on the asymmetric aldol reaction [42] between substituted aromatic aldehydes and acetone. It is important to point out the short residence time optimized by the authors with good yields and selectivities in just 6 minutes of residence time. The recyclability of the catalyst bed was also tested and after 20 experiments (50 minutes each), yields and selectivities remains the same.

List and co-workers [43] have used functionalized Nylon for a continuous flow alcoholytic desymmetrization of cyclic anhydride. The photochemical immobilization of the bifunctional organocatalyst occurred through irradiation (ultraviolet light) of Nylon 6,6 wetted with acetonitrile solution of the *cinchona*-sulfonamide organocatalyst and the crosslinker PETA (penta-erythritol triacrylate).

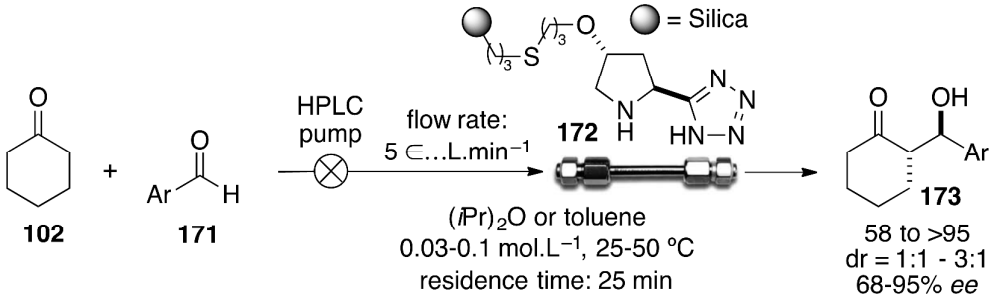
The desymmetrization was performed in a continuous circulatory reactor by pumping 2.5-5.5 mmol of anhydride **168** and MeOH in MTBE (methyl *t*-butyl ether) through the catalyst **170** packed in a polypropylene cartridge with a flow rate of 3-25 $mL.min^{-1}$ leading to the enantioenriched hemiester **169** in conversions of 61-99% and 71-95% *ee* (Scheme 20).



Scheme 20: Continuous flow alcoholytic desymmetrization of cyclic anhydride. [43]

Different groups have chosen silica as support for organocatalyst immobilization. Bortolini and coworkers [44, 45] presented in 2012 the continuous flow aldol reactions activated by 5-(Pyrrolidin-2-yl)tetrazole functionalized silica **172,** prepared by photoinduced thiol–ene coupling.

A micro-HPLC was adapted for this study with a short stainless steel column filled with the immobilized organocatalyst **172** and fed with a solution of cyclohexanone **102** and the Benzaldehyde **171** in diisopropyl ether or toluene**.** The reaction was maintained at 25-50 ºC for 4 h at 5 μL.min^{-1} flow rate leading to the *anti-syn* aldol adducts **173** in productivities from 50 to 256 mmol(product).h^{-1}.mmol(catalyst)$^{-1}$ and good diastereo- and enantioselectivities. It is noteworthy that the packed-bed microreactor showed long-term stability after 80 hours of operation at 50 ºC with high catalytic activity and reproducibility (Scheme 21).

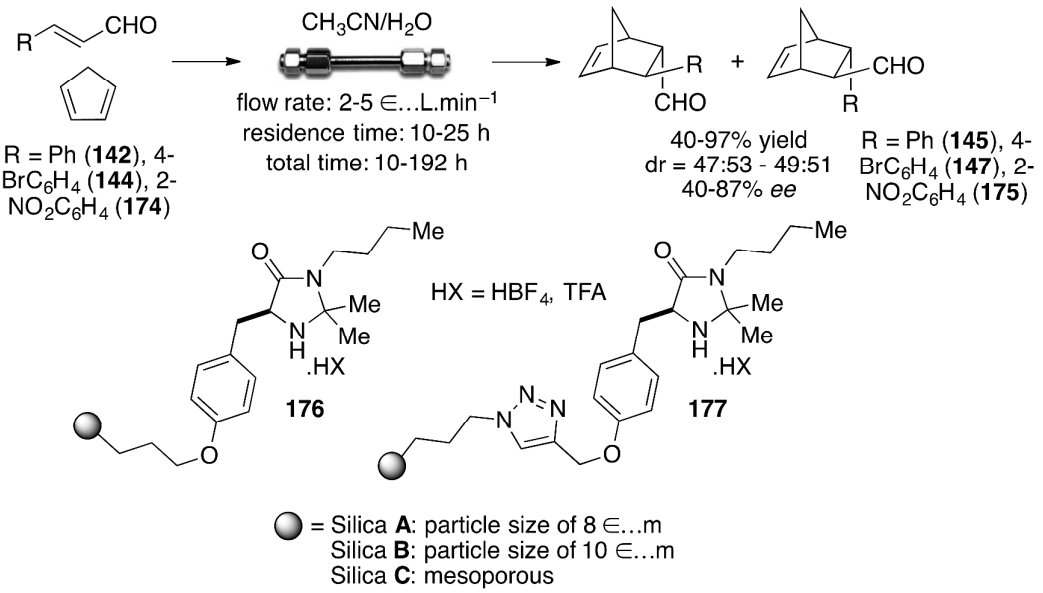


Scheme 21: Continuous flow aldol reactions activated by 5-(Pyrrolidin-2-yl)tetrazole functionalized silica **172.** [44, 45]

Silica support catalyst was also used by Benaglia and coworkers on their work on continuous flow Diels-Alder reactions organocatalyzed by imidazolidinones supported in silica nanoparticles of different morphological properties. [37-39]

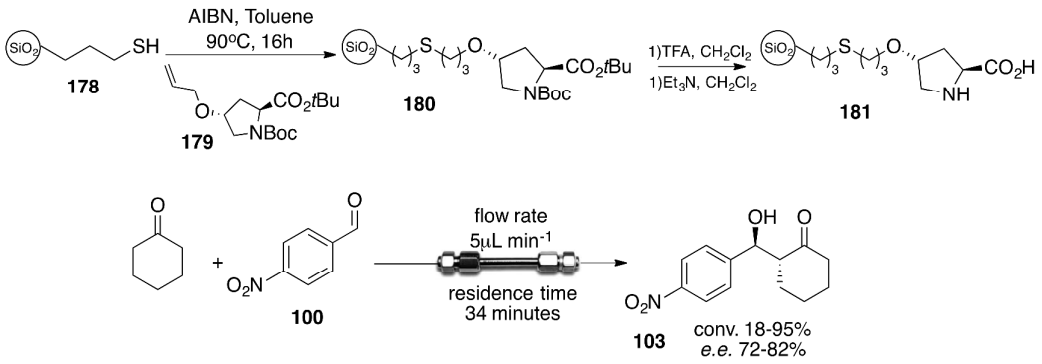
The tyrosine derived MacMillan-type organocatalyst **176** and **177** were immobilized through reaction with allyl bromide followed by platinum-catalyzed hydrosilylation with trimethoxysilane to furnish the organocatalyst **176** and through reaction with propargyl bromide followed by CuAAC reaction with the azide-functionalized silica to furnish the organocatalyst **177**.

The Diels-Alder cycloadditions were performed into stainless-steel columns loaded with the tetrafluoroborate and trifluoroacetate salts of the supported imidazolidinones at room temperature, flow rate from 2 to 5 □L.min^{-1}, residence time from 10 to 25 hours and reaction times from 10 to 192 hours were applied to give the cycloadducts in good yields, *endo*/*exo* ratio around 1:1 and good enantioselectivities. However, 18 hours of conditioning time are necessary to reach good chemical and stereochemical activities in this process (Scheme 22).



Scheme 22: Tyrosine derived MacMillan-type organocatalyst **176** and **177** were immobilized for asymmetric Diels-Alder cycloadditions.

Massi & Cavazzani and co-workers, [44, 46] in to different works, also used proline immobilized on silica support for studying the aldol reaction. Kinetic and thermodynamic behavior of continuous flow heterogeneous asymmetric aldol reaction was analyzed by reaction progress kinetic analysis (RPKA) and thermodynamic information from nonlinear chromatographic measurements leading to important information regarding the dependence of reaction order on feed composition and saturation capacity of the catalytic bed (Scheme 23).

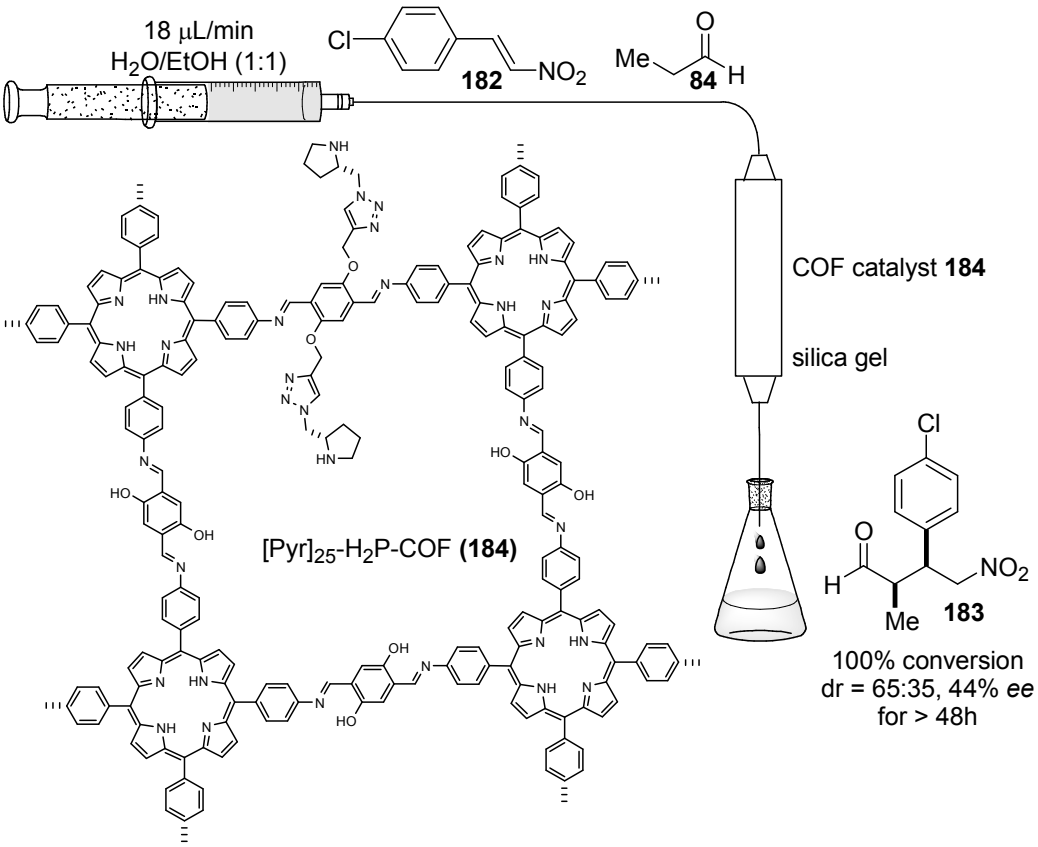


Scheme 23: Proline immobilized on silica for asymmetric aldol reactions under continuous-flow conditions. [44, 46]

Covalent organic frameworks (COFs) were also used as support for organocatalyst immobilization, as reported by Jiang and coworkers for the continuous-flow asymmetric Michael additions. [47]

COF catalyst **184** was synthesized by a three-component reaction with 5,10,15,20-tetrakis(4'-tetraphenylamino) porphyrin as the vertices and a mixture of 2,5-bis(2-propynyloxy)terephthalaldehyde (BPTA) and 2,5-dihydroxytere-phthalaldehyde (DHTA) at 25 mol% ([BPTA]/([BPTA]+[DHTA]) x 100 = 25) as the edge units, followed by click reaction of the ethynyl units with the pyrrolidine azide to anchor the chiral organocatalyst.

The asymmetric Michael addition was performed in a column loaded with silica gel at the bottom, as a plug to prevent COF from flowing out, and $[Pyr]_{25}$-H_2P-COF **184** (10 mg, 10 mm bed height) atop the silica gel coupled to a syringe pump used to feed the system at 18 μL.min^{-1} with a solution of propanal **84** and *trans*-chloro-β-nitrostyrene **182** in H_2O/EtOH, furnishing the desired product **183** with 100% conversion, dr = 65:35 and 44% *ee* for more than 48 hours under flow conditions (Scheme 24).



Scheme 24: Covalent organic frameworks (COFs) as support for organocatalyst immobilization and asymmetric Michael addition under continuous-flow conditions.[47]

Conclusion

The development of continuous flow protocols for asymmetric organocatalysis is under construction and until now the results are impressive since the recycle of catalyst is enhanced easily enabling development of cascade process for multistep organocatalyzed protocols. Improvement must be made on the characterization of the immobilized organocatalyst in order to provide more information to understand the outcome of the reactions under continuous flow conditions.

Acknowledgment

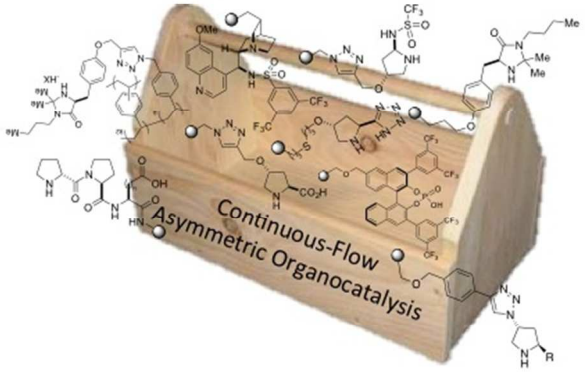
Authors thanks CNPq, CAPES and FAPERJ for financial support in Brazil.

References

1. J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev*, 2013, **42**, 8849-8869.
2. V. Hessel, D. Kralisch, N. Kockmann, T. Noel and Q. Wang, *Chemsuschem*, 2013, **6**, 746-789.
3. L. Carroccia, B. Musio, L. Degennaro, G. Romanazzi and R. Luisi, *J. Flow Chem.*, 2013, **3**, 29-33.
4. J. Wegner, S. Ceylan and A. Kirschning, *Adv. Synth. Catal.*, 2012, **354**, 17-57.
5. Y. Su, N. J. W. Straathof, V. Hessel and T. Noel, *Chem. Eur. J.*, 2014, **20**, 10562-10589.
6. E. M. Schuster and P. Wipf, *Israel J. Chem.*, 2014, **54**, 361-370.
7. Z. J. Garlets, J. D. Nguyen and C. R. J. Stephenson, *Isr. J. Chem.*, 2014, **54**, 351-360.
8. I. R. Baxendale, L. Brocken and C. J. Mallia, *Green Proc. Synth.*, 2013, **2**, 211-230.
9. I. R. Baxendale, *J. Chem. Technol. Biotech.*, 2013, **88**, 519-552.
10. J. P. Knowles, L. D. Elliott and K. I. Booker-Milburn, *Beilst. J. Org. Chem.*, 2012, **8**, 2025-2052.
11. L. Vaccaro, D. Lanari, A. Marrocchi and G. Strappaveccia, *Green Chemistry*, 2014, **16**, 3680-3704.
12. S. G. Newman and K. F. Jensen, *Green Chem.*, 2013, **15**, 1456-1472.
13. S. V. Ley, *Chemical Record*, 2012, **12**, 378-390.
14. D. Kampen, C. M. Reisinger and B. List, in *Asymm. Organocatal.* ed. B. List, 2009, pp. 395-456.
15. S. Bertelsen and K. A. Jorgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178-2189.
16. S. G. Ouellet, A. M. Walji and D. W. C. Macmillan, *Acc. Chem. Res.*, 2007, **40**, 1327-1339.
17. S. Bertelsen, M. Marigo, S. Brandes, P. Diner and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2006, **128**, 12973-12980.
18. J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719-724.
19. R. Thayumanavan, F. Tanaka and C. F. Barbas, *Org. Lett.*, 2004, **6**, 3541-3544.
20. W. Notz, F. Tanaka and C. F. Barbas, *Acc. Chem. Res.*, 2004, **37**, 580-591.

21. D. B. Ramachary, N. S. Chowdari and C. F. Barbas, *Tetrahedron Lett.*, 2002, **43**, 6743-6746.
22. I. K. Mangion, A. B. Northrup and D. W. C. MacMillan, *Angew. Chem. Int. Ed.*, 2004, **43**, 6722-6724.
23. A. Odedra and P. H. Seeberger, *Angew. Chem. Int. Ed.*, 2009, **48**, 2699-2702.
24. S. Fritzsche, S. Ohla, P. Glaser, D. S. Giera, M. Sickert, C. Schneider and D. Belder, *Angew. Chem. Int. Ed.*, 2011, **50**, 9467-9470.
25. M. Rueping, T. Bootwicha and E. Sugiono, *Beilstein J Org Chem*, 2012, **8**, 300-307.
26. E. Sugiono and M. Rueping, *Beilstein J. Org. Chem.*, 2013, **9**, 2457-2462.
27. M. Neumann and K. Zeitler, *Org. Lett.*, 2012, **14**, 2658-2661.
28. L. Osorio-Planes, C. Rodriguez-Escrich and M. A. Pericas, *Chem. Eur. J.*, 2014, **20**, 2367-2372.
29. R. Martin-Rapun, S. Sayalero and M. A. Pericas, *Green Chem.*, 2013, **15**, 3295-3301.
30. P. Kasaplar, C. Rodriguez-Escrich and M. A. Pericas, *Org Lett*, 2013, **15**, 3498-3501.
31. X. Fan, S. Sayalero and M. A. Pericas, *Adv. Synth. Catal.* 2012, **354**, 2971-2976.
32. C. Ayats, A. H. Henseler and M. A. Pericas, *Chemsuschem*, 2012, **5**, 320-325.
33. X. C. Cambeiro, R. Martin-Rapun, P. O. Miranda, S. Sayalero, E. Alza, P. Llanes and M. A. Pericas, *Beilstein J Org Chem*, 2011, **7**, 1486-1493.
34. E. Alza, S. Sayalero, X. C. Cambeiro, R. Martin-Rapun, P. O. Miranda and M. A. Pericas, *Synlett*, 2011, 464-468.
35. E. Alza, C. Rodriguez-Escrich, S. Sayalero, A. Bastero and M. A. Pericas, *Chem. Eur. J.*, 2009, **15**, 10167-10172.
36. D. Font, C. Jimeno and M. A. Pericàs, *Org. Lett.*, 2006, **8**, 4653-4655.
37. R. Porta, M. Benaglia, V. Chiroli, F. Coccia and A. Puglisi, *Isr. J. Chem.,* 2014, **54**, 381-394.
38. V. Chiroli, M. Benaglia, A. Puglisi, R. Porta, R. P. Jumde and A. Mandoli, *Green Chem.*, 2014, **16**, 2798-2806.
39. V. Chiroli, M. Benaglia, F. Cozzi, A. Puglisi, R. Annunziata and G. Celentano, *Org. Lett.*, 2013, **15**, 3590-3593.

40. A. L. W. Demuynck, L. Peng, F. de Clippel, J. Vanderleyden, P. A. Jacobs and B. F. Sels, *Adv. Synth. Catal.*, 2011, **353**, 725-732.
41. S. B. Oetvoes, I. M. Mandity and F. Fueloep, *Chemsuschem*, 2012, **5**, 266-269.
42. S. B. Oetvoes, I. M. Mandity and F. Fueloep, *J. Catal.* 2012, **295**, 179-185.
43. J.-W. Lee, T. Mayer-Gall, K. Opwis, C. E. Song, J. S. Gutmann and B. List, *Science*, 2013, **341**, 1225-1229.
44. O. Bortolini, A. Cavazzini, P. P. Giovannini, R. Greco, N. Marchetti, A. Massi and L. Pasti, *Chem. Eur. J.*, 2013, **19**, 7802-7808.
45. O. Bortolini, L. Caciolli, A. Cavazzini, V. Costa, R. Greco, A. Massi and L. Pasti, *Green Chem.*, 2012, **14**, 992-1000.
46. A. Massi, A. Cavazzini, L. Del Zoppo, O. Pandoli, V. Costa, L. Pasti and P. P. Giovannini, *Tetrahedron Lett.*, 2011, **52**, 619-622.
47. H. Xu, X. Chen, J. Gao, J. Lin, M. Addicoat, S. Irle and D. Jiang, *Chem. Comm.*, 2014, **50**, 1292-1294.



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