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Continuous flow enantioselective processes catalysed by cinchona alkaloid derivatives

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ABSTRACT

Without a doubt, asymmetric catalysis has been significantly enriched by the introduction of cinchona alkaloid derivatives. Moreover, such methods have been further enabled when used in conjunction with continuous flow systems.

Besides being used in flow chemistry as organocatalysts, they also have been used as ligands or modifiers of metal catalysts. This has generally been accomplished via their immobilization on heterogeneous supports and incorporation into catalysis-enabling reactors or similar systems. In this minireview we look at the impact that cinchona-based catalysts and analogues have had on the field of continuous flow-chemistry during the last two decades or so.

1. Introduction

Over the last decade cinchona alkaloids (Fig. 1) have played a prominent role as asymmetry inducers in the field of enantioselective catalysis [1]. These are powerful molecular tools due to their structural features, which, in principle, includes a robust chiral skeleton that is easily functionalized. A key feature, not only that they are biomass derived substances and thus a renewable resource, making them a truly green commodity. For the last 20 years, they have been used as chiral bases, as chiral Lewis bifunctional catalysts, and as quaternized ammonium salts for phase-transfer catalysis. Moreover, due to their intrinsic structural characteristics (potential for functionalization and grafting), they have been very successfully harnessed with continuous-flow systems, proving the chemistry community with a very potent tool. This is the subject of this review.

2. Stereoselective catalytic reactions using cinchona based metal catalysts in continuous flow

Cinchona alkaloid-modified Pt catalysts have been used for the asymmetric hydrogenations of α-ketoesters to the corresponding alcohols as reported by Blaser and colleagues [2]. One route to these targets is through the Orito [3,4] reaction from the late 1970s, which is an early example of the use of such catalytic systems (a Pt/C catalyst with cinchonidine as modifier was used in the hydrogenation of methyl pyruvate at 200–400 °C offering (+)-methyl lactate with an optical yield of 79% ee). Further mechanistic insight into these reactions has been provided by the research groups of Baiker and Garland [5,6].

In addition to these, other workers have used Pt-cinchona chiral catalysts in a continuous-flow fixed-bed reactor (CFBR) system for the enantioselective hydrogenation of ethyl pyruvate to either (*R*)- or (*S*)-lactic acid ethyl ester, depending on the catalytic modifier applied affording yields of up to 90% and enantioselectivities in the range of 90% ee [7]. Operational data offering the best experimental outcome

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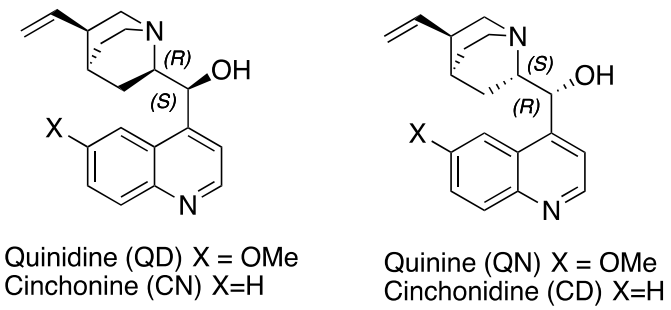


Fig. 1. Structures of cinchona alkaloids derivatives.

was as follows: 80 mg catalyst, toluene/AcOH 9:1 as solvent system, 1 mL/min in flow rate, concentration of modifier 4.4×10^{-3} mM, substrate concentration 45 mM, 80 bar H_2, 283 ± 2 K (+10 °C). The conclusion drawn from this work was that alkaloid modified Pt-catalysts delivered a rate enhancement with Pt-quinine being the fastest (TOF 640 h^{-1}) offering a yield of about 65% and an enantioselectivity of 55% ee (*R*-configuration), whereas Pt-quinidine appeared as the slowest (TOF 430 h^{-1}) with a yield of about 45% and enantioselectivity of 30% ee (*S*-configuration). Unsurprisingly, the results were affected when operating under different experimental conditions: half the catalyst loading (40 mg), temperature 293±2 K, and 40 bar H_2 pressure. The differences observed are ascribed not only to varying experimental methodologies, but also to structural features of the substrate (ethyl pyruvate) when associated with the chiral modifying moiety.

From the same Hungarian group, the reversal of the measured enantiomeric excess in the enantioselective hydrogenation of activated ketones in a continuous-flow fixed-bed reactor (CFBR) system has been studied [8]. From the wealth of data obtained through various multi-factorial studies, a complex picture emerged that in some cases agreed with the previous results, but in other cases were unexpected, such as the variability of the product stereochemistry depending on the solvent and substrate structure. Furthermore, it was postulated that some possible intermediate structures could be accountable for the enantio-differentiation observed. Thus, factors that were considered included: the solvent(s) used, the specific chiral modifier, the structure of the substrate, the eventual addition of a strong acidic component (e.g., trifluoroacetic acid [TFA]), and the reaction conditions. However, also the surface properties of the catalyst itself, i.e., a purely atomic effect expressed by differences in morphology of the solid-state Pt/Al_2O_3 catalyst were also suspected to exert an influence.

In 2007 and 2015, the same group showed that this cinchonidine modified Pt-based catalytic system could be applied specifically to the reduction of ethyl 2-nitro-3-methylphenylpyruvate to (*R*)-3-hydroxy-3,4-dihydro-8-methylquinoline-2(1*H*)-one via the amino-hydroxyester intermediate under flow conditions [9,10]. With two reducible groups – carbonyl and nitro – present in the starting material, the chemistry changed to become a cascade reaction. Thus, thorough investigation of this transformation showed that until the complete conversion of the pyruvate had been achieved the second step was instantaneous leading to the ring-closed quinolone. At low conversions, however, the amino-hydroxy intermediate is accumulated after desorption from the Pt-surface and can only be transformed into the quinolone after re-adsorption. Interestingly, the flow set-up could not compete with the batch-mode operation because, as indicated by available data, a high concentration of the complex between substrate and cinchonidine is possible only in solution. This can then be absorbed on the solid Pd-surface in the presence of a chemical modifier (notably benzylamine) enabling good enantioselectivities.

3. Stereoselective organocatalytic reactions using non-metal containing cinchona catalysts in continuous flow

3.1. Homogeneous systems

Cinchona alkaloid derivatives have had a tremendous impact in the field of asymmetric organocatalysis [11]. Since 2000 several cinchona alkaloid derivatives have emerged, the more promising featuring as organocatalysts, however, belong to the group of cinchona-derived primary amines [12,13] and thioureas [14,15]. Notably, cinchona alkaloid derivatives organocatalyze a wide range of asymmetric reactions, such as Michael Additions, aldol reactions, hydrosilylations, Morita–Baylis–Hillman, Aza-Morita–Baylis–Hillman, Henry, cyanocarbonylation and cyanosilylation, Friedel–Crafts, interrupted Feist–Bénary, Mannich reaction, Aza-Henry, Strecker among others [11].

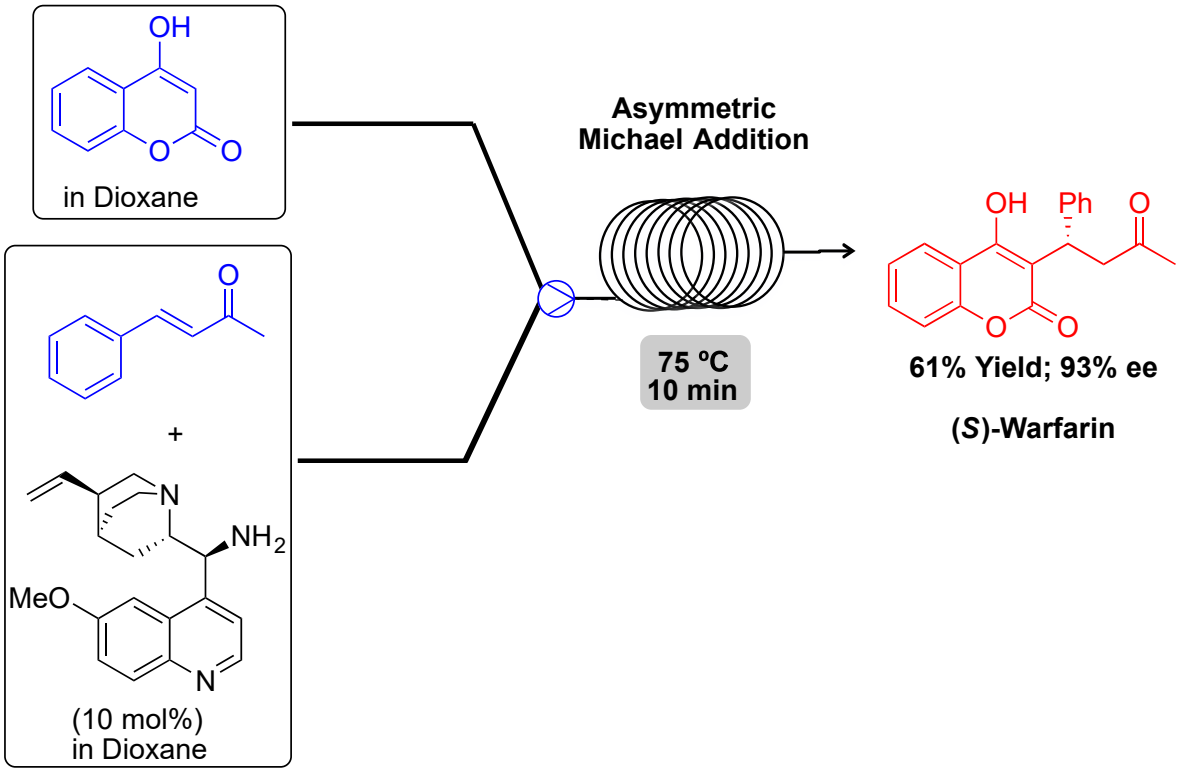
In the case of catalysis under continuous flow conditions, the group of Benaglia has successfully used a quinidine-based organocatalyst for the asymmetric synthesis of (*S*)-warfarin applying a simple organocatalyzed Michael addition as the key step [16,17]. The reaction was carried out using 4-hydroxycoumarin and benzylideneacetone in the presence of the catalyst and trifluoroacetic acid (TFA) as a co-catalyst (Scheme 1). The transformation was very rapid with a 10min residence time using a 10 μL microreactor at 75 °C, and the desired product was obtained in good conversion and excellent enantioselectivity (up to 61% conversion, 93% ee). The researchers also tried scaling-up their continuous flow process using a larger coil, but, unfortunately, the conversion dropped significantly, which was ascribed to mixing issues.

The group of Belder also investigated this Michael addition reaction using a microreactor combined with an integrated 2D-HPLC-MS chip to enable online monitoring of the ee of the product generated [18].

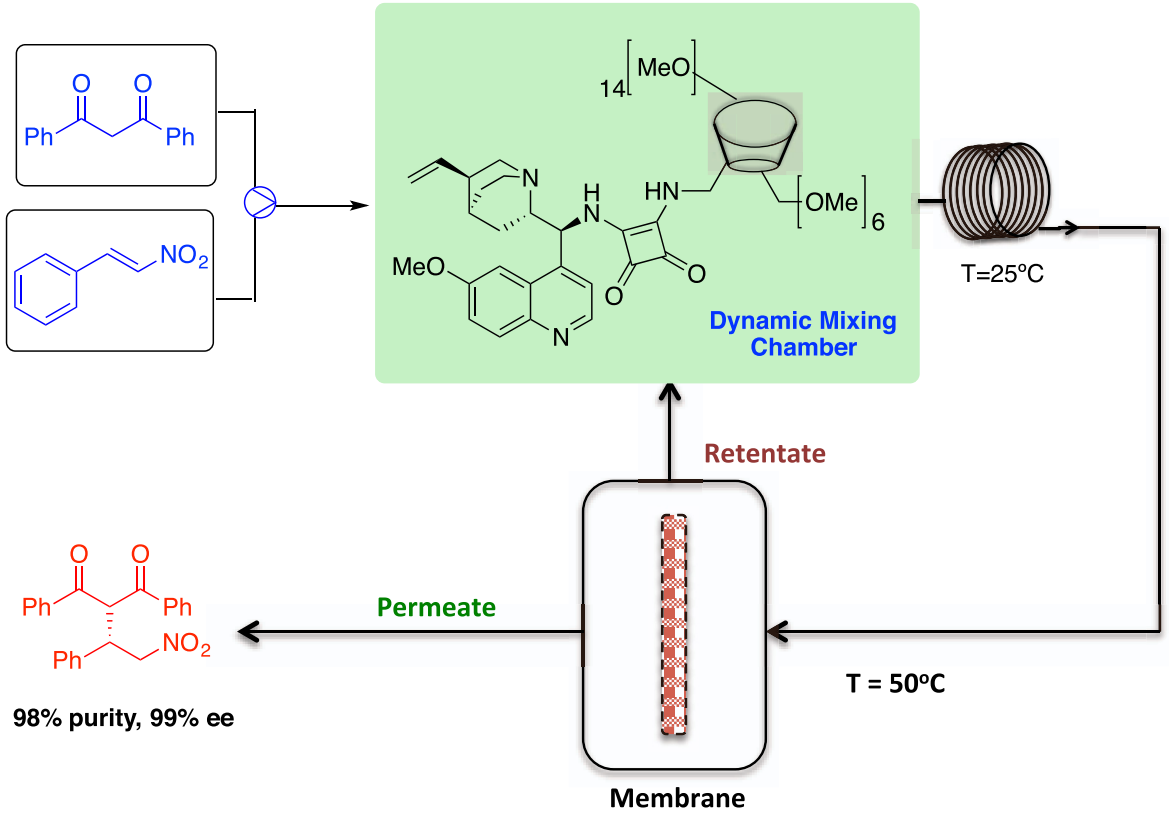
Cinchona-thiourea derivatives are robust and tuneable bifunctional organocatalysts, due to their functionalities they easily adapt to a wide variety of substrates in asymmetric synthesis. These remarkable catalytically active species were independently developed in 2005 by four different groups (see below). Chen and co-workers applied the cinchonine- and cinchonidine-thiourea as organocatalyst in the Michael addition of thiophenol to *N*-cinnamoylbenzamide, furnishing the Michael adduct with low ee (≤17%) [19]. The team of Soós introduced the quinine-quinidine-thiourea organocatalyst and applied it to the asymmetric addition of nitromethane to chalcone, which gave the products with very good yields (up to 93%) and with excellent ee (up to 95%) [20]. Later, simultaneously and independently, Connon's [21] and Dixon's [22] groups, respectively, described the design of similar organocatalysts for application in stereoselective addition reactions of dimethyl malonate to various nitroalkenes (*trans*-β-nitrostyrene and *trans*-2-(2-nitrovinyl)thiophene), furnishing the Michael adducts in high yields (95% and 92%, respectively) and ee values (both 94%).

As discussed above the pioneering cinchona-thiourea catalysts have played a remarkable role on the enantioselective Michael addition reaction of a wide range of substrates, offering high yields and enantioselectivities but overly protracted reaction times (≤192 h) [23]. Nonetheless, considering the high loading of catalyst (20 mol%) inevitably required their application in a continuous flow scenario to overcome the shortcomings with catalyst load and reaction time. In 2019, Kisszekelyi and co-workers [24] described a new continuous process of homogeneous organocatalysis, employing both cinchona-squaramide and -thiourea organocatalysts immobilized on permethyl-β-cyclodextrins in an integrated synthesis-extraction flow reactor.

In the literature, some integrated separation-synthesis flow reactors have appeared; an equipment that enables the identification of the separation efficiency limitations in this type of system [25–34]. The authors improved the separation efficiency by anchoring the organocatalyst to a soluble polymer (β-cyclodextrin), which increased the difference in molecular weight between the organocatalyst and the reagents and, thus improved the retention/recovery of the catalyst by



Scheme 1. Asymmetric continuous flow synthesis of (*S*)-Warfarin as described by Benaglia and co-workers [17].



Scheme 2. The Continuous-Flow Membrane reactor system described by Kisszekelyi and colleagues [24].

the membrane. The researchers successfully immobilized the cinchona squaramide and thiourea organocatalysts to permethyl-β-cyclodextrins and evaluated their catalytic performance in batch and continuous-flow modes using, as their test reaction, the Michael addition of 1,3-diketones to *trans*-β-nitrostyrene. The reaction conditions were optimized in batch mode, and the cinchona-thiourea and –squaramide catalysts furnished excellent yields and enantioselectivities (95/97% and 79/99%, respectively). The continuous-catalyst separation system is depicted in Scheme 2. The best membrane was selected based on its permeability to the products, reagents and solvents, and retention of the organocatalysts. The robustness and reusability of the catalysts were demonstrated over 18 days of operation, being able to tolerate operating temperatures of up to 100 °C in the flow reactor.

The group of Fraile and Alemán, in 2021, reported the asymmetric aza-Michael addition of 2-hydroxybenzophenone imine to wide diversity of nitroolefins (aromatic, aliphatic or heterocyclic derivatives) organocatalyzed by cinchona alkaloid thiourea under batch and flow conditions [35]. They found that the enantioselectivity of this reaction increased with the use of the imine of 2-hydroxybenzophenone, due to the formation of intramolecular hydrogen bonds in the imine portion. After optimization of the reaction conditions, 18 examples were prepared with moderate to excellent yields (up to 98%) and excellent ee values (up to 99%), at rt with reaction times up to 22 h under batch conditions. The aza-Michael reactions under flow conditions were carried out briefly as follows: the starting reagents and the organocatalyst (10 mol%) were dissolved in acetone and flowed through the coil reactor [(V = 18 mL) made of perfluoroalkoxy (PFA) capillary tube (1/8″ OD; 1.60 mm ID, 9 m length)] placed in a cooling bath at 15 °C, by pumping acetone at 0.6 mL/min (Scheme 3). Using these conditions, 5 products were prepared in excellent yields and ee values, up to 92 and 95%, respectively, with residence times up to 1 h. The authors successfully applied this flow setup to the preparation of the bioactive compound, VNI, used to treat Chagas disease. This versatile reaction enables higher yields and shorter reaction times if carried out under flow conditions.

Cinchona-based phase-transfer catalysts also have a major role in the field of asymmetric synthesis and catalysis over the last decades, due to their unique structural features [36]. The development of methodologies using phase transfer catalysts under continuous flow conditions is highly desirable for the chemical industry, due to the combination of its operational simplicity, mild reaction conditions, and reduced reaction time.

Meng [37] and co-workers developed a family of C-2′-modified cinchonine-derived phase-transfer catalysts (Fig. 2), which were successfully applied in the asymmetric photooxygenation of β-dicarbonyl

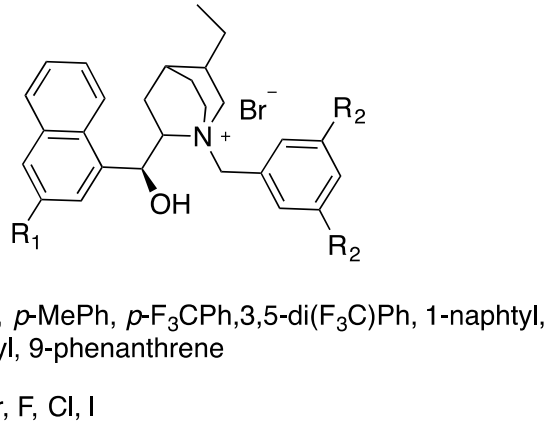
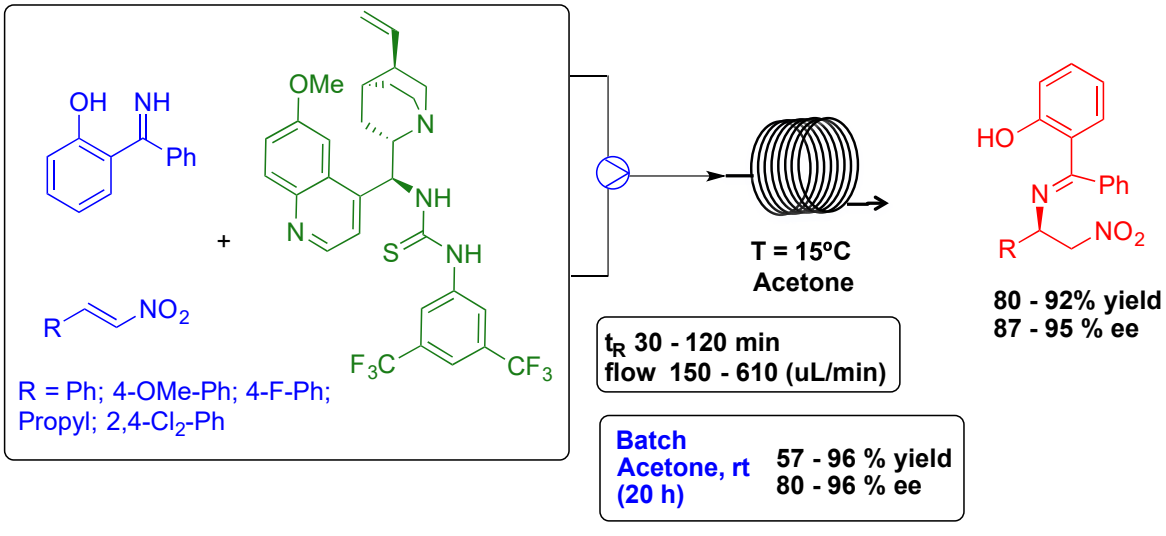


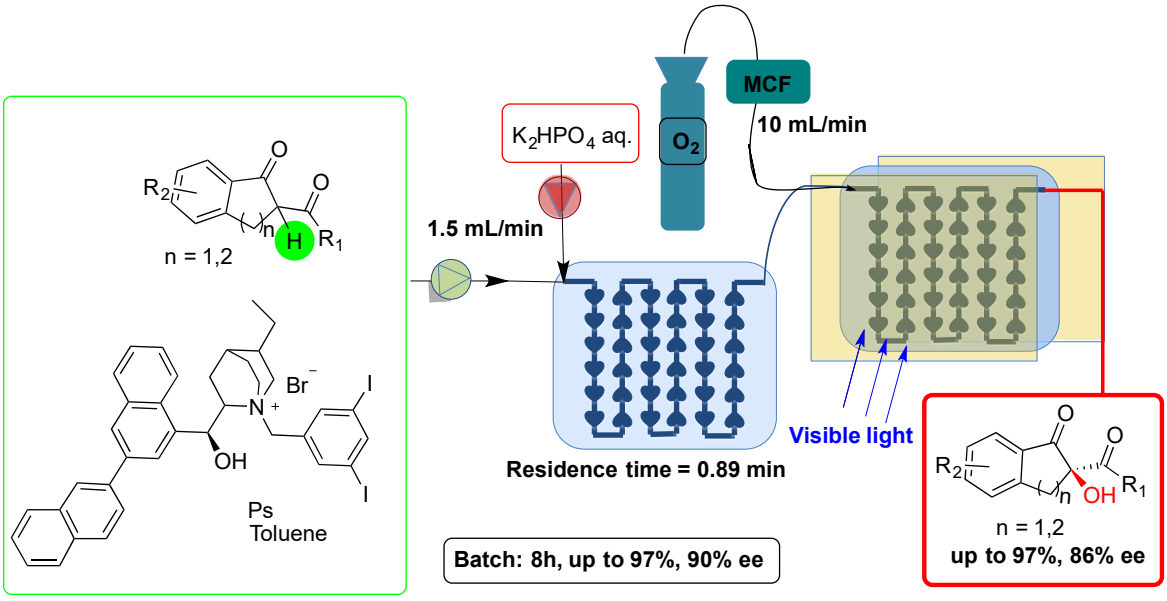
Fig. 2. C-2′-modified cinchonine-derived phase-transfer catalysts.

compounds in batch and in a flow photo-microreactor. The batch reactor furnished yields up to 97% and enantioselectivities up to 90% ee over an 8 h reaction time. However, much better reaction times were obtained in the flow photo-microreactor, offering yields of up to 97% at enantioselectivities ≤86% ee with a residence time of only 0.89min (Scheme 4). Gratifyingly it was possible to scale this up to 1 g, maintaining both yield and enantioselectivity. At the same time, Meng's group reported a closely related work on the asymmetric aerobic oxidation of β-dicarbonyl compounds catalyzed by cinchona-derived phase transfer catalysts under batch and semi-flow conditions [38]. In this case they irradiated the flow photo-microreactor with light blue LEDs instead of visible light, obtaining the desired products in excellent yields (up to 96%) and very good enantioselectivities (up to 90% ee). Once again, the cinchona phase transfer catalysts showed their versatility, acting simultaneously as a chiral catalytic and phase transfer centre, forming a chiral enolate complex with the substrate to act as a photosensitive unit in the reaction. The results obtained for reactions carried out under semi-flow photochemical conditions were very similar to batch conditions but required a shorter reaction time (24 h *vs* 0.89 h).

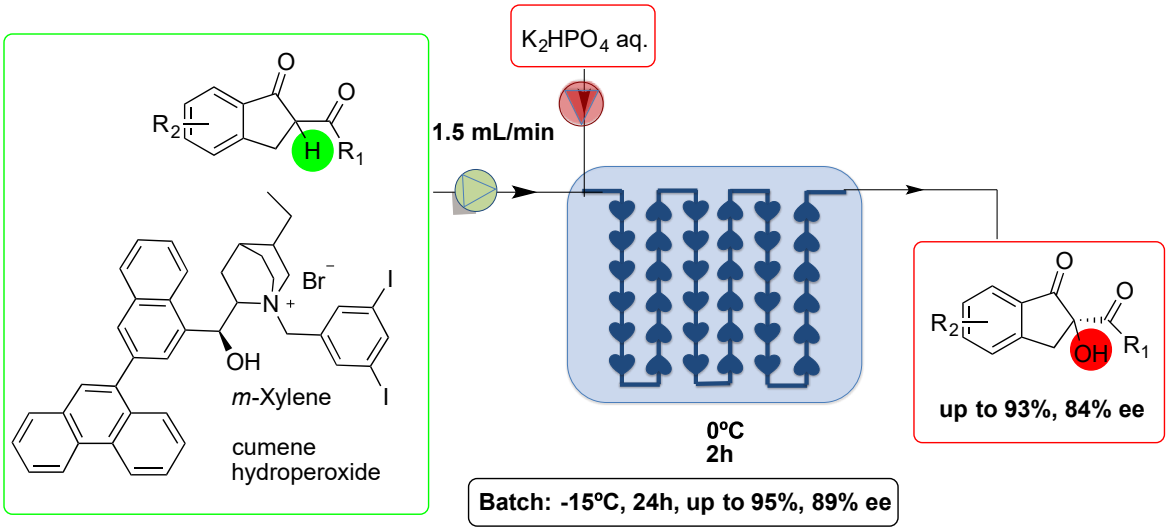
The same group reported the enantioselective α-hydroxylation of β-dicarbonyl compounds catalyzed by C-2′ modified cinchonine-derived phase-transfer catalysts in batch and flow microreactors (Scheme 5) [39]. A main objective of this work was to develop a new method using peroxide as an oxidant to achieve this asymmetric oxidation reaction in these flow microreactors, avoiding the use of the more expensive



Scheme 3. Asymmetric *aza*-Michael addition of 2-hydroxybenzophenone imine to nitroolefins developed by Fraile and Alemán [35].



Scheme 4. Enantioselective photocatalytic oxidation of β-dicarbonyl compounds in a flow photo-microreactor by Meng and co-workers [38].



Scheme 5. Schematic representation of a flow microreactor for asymmetric α-hydroxylation of β-dicarbonyl compounds by Meng and co-workers [39].

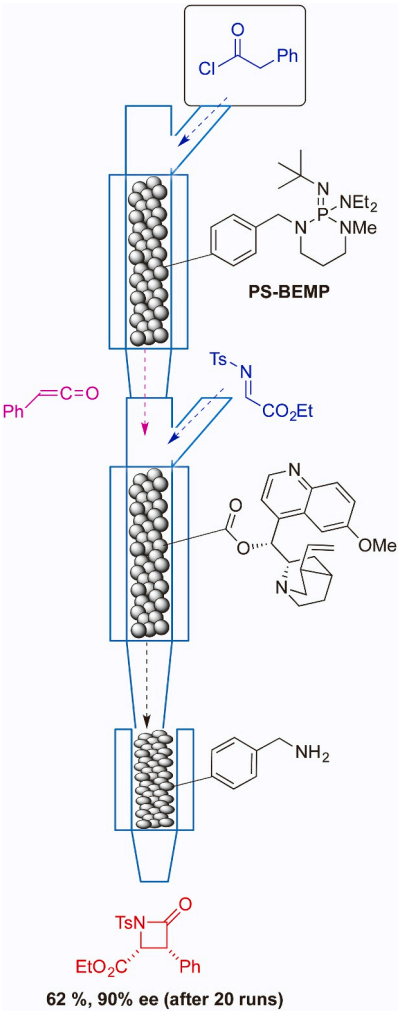
photo-microreactors. The results obtained with this new methodology were very good, affording excellent yields (up to 95%) and high enantioselectivities (up to 89% ee) under batch conditions. When the reaction was carried out in the flow microreactor similar results were obtained (up to 93% yield, 84% ee), but, gratifyingly, the residence time was shortened from 24 h in batch to 2 h in flow. In fact, the results obtained using the flow photo-microreactor (Scheme 4) were very similar to the results obtained in the normal flow microreactor (Scheme 5), but the residence time was shorter.

In general, for reactions catalyzed by cinchona alkaloid derivatives in the homogeneous phase carried out under continuous flow conditions, the yield and enantioselectivities were not affected, but the reaction time decreased significantly in all cases, which is a major advantage when using this technique.

3.2. *Supported-cinchona alkaloid derivatives: heterogeneous systems*

Heterogenization of chiral organocatalysts is well accepted for sustainability, however the use of solid immobilized catalysts in some reactions affects catalyst performance, with concomitant decreases in yield and enantioselectivity. Nonetheless, the inclusion of solid-supported organocatalysts in the catalytic reactor unit of a continuous flow system, brings huge benefits to asymmetric organocatalysis, particularly as regards decreasing the long reaction times generally experienced in batch reactions and even increasing yields and enantioselectivities.

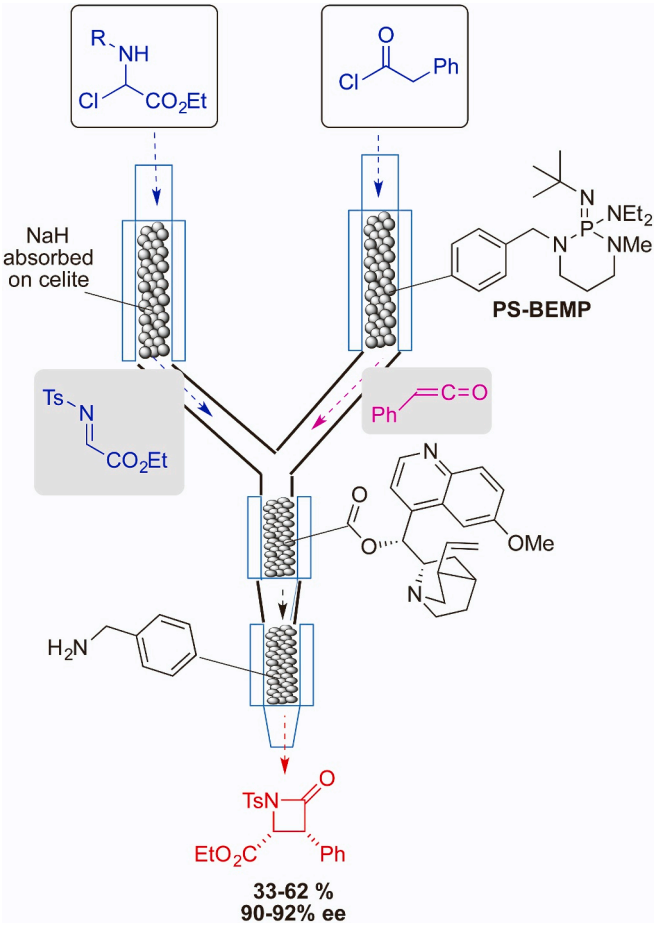
In the early 2000s supported cinchona alkaloid derivatives were applied in continuous-flow systems. For example, Lectka and co-workers carried out some remarkable work on the application of these organocatalysts in continuous-flow settings. The work focused on the enantioselective synthesis of β-lactams using three different reactors in series; (i) the first one contained a polymer-supported base (ii) the next one the immobilized quinidine catalyst and (iii) the last one contained a scavenger resin to prevent the non-reacted material from contaminating the outgoing stream (Scheme 6) [40]. The ketene precursors obtained from acyl chlorides mediated by the polystyrene phosphazene base



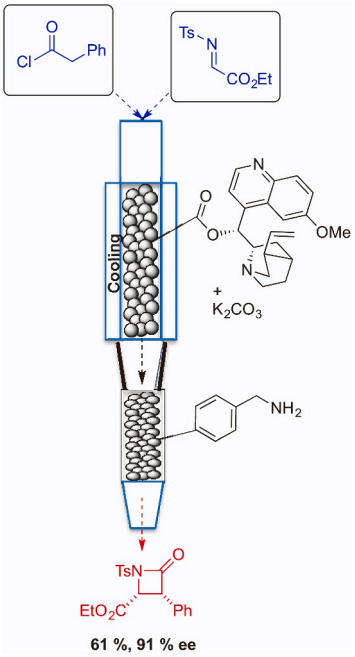
Scheme 6. Preparation of enantioenriched β-lactams in a continuous 3-part flow system described by Lectka and co-workers [40].

(PS-BEMP) (supported) are introduced into the system. Subsequently, in the second reactor these precursors were reacted with the sulfonylimine counterpart in a process catalyzed by the Wang resin supported quinidine. Then, on passing into the third reactor containing benzylamine scavenger resin any unreacted ketene and imine are removed (Scheme 6). Remarkably, using this methodology it was possible to prepare β-lactams with yields of up to 62% and 90% ee after 20 cycles. In fact, this set up was very advantageous for the preparation of enantiopure β-lactams, as it overcame the drawbacks of performing a batch synthesis in flask regime, as the unstable ketene intermediate underwent concomitant reaction once formed, thus minimizing possible side reactions. This set-up was useful in that the BEMP reagent was maintained separated from the ketene and sulfonylimine reagents, preventing their decomposition, or that of the lactam or even epimerization of this product.

Later, Lectka and co-workers designed a new set-up introducing an extra reactor, where the imine intermediates were prepared from α-chloroglycine derivatives using NaH/Celite (6:1) [41]. This column was placed in parallel with the column where the ketene precursors were prepared (see Scheme 7). These two reactors were connected to a third reactor containing the polymer-supported organocatalyst, and the catalytic reaction was the same as that described in the previous arrangement. It is important to emphasize the robustness of both systems particularly regarding the efficiency of the system, the ability to carry out the reaction at least 60 times, maintaining the yields and



Scheme 7. Second Flow set up developed by the Lectka group [41].



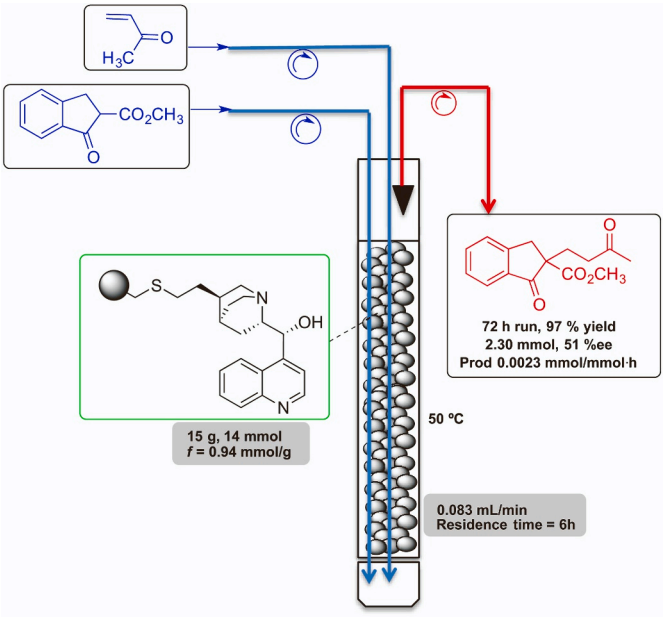
Scheme 8. Schematic flow set-up for the synthesis of β-lactams according to Lectka and colleagues (assembly 3) [42].

enantioselectivities.

In line with this work, Lectka and his team developed an alternative reaction set-up, using only two reactors (Scheme 8), [42]. In this case, the supported-quinine derivative catalyst played a double role, catalyzing both the ketene formation and the β−lactam synthesis. The ketene intermediates were produced from the respective acyl chlorides by reacting them with catalytic amounts of an amine (a dehydrohalogenating agent) and a base (K_2CO_3) in stoichiometric amounts. The generation of the intermediates and the products occurred in a single reactor which was basically a mixture of finely powdered K_2CO_3 and catalyst. The results obtained were not as good as in the previous cases (61% yield, 7:1 dr, 91% ee). However, this methodology has advantages particularly regarding the 2-reactor-assembly system, and due to the fact, that the product could be obtained as a single enantiomer isolated after recrystallization.

In 2004 and 2005, this group reported two other very similar protocols [43,44] for the enantioselective α-chlorination of acyl chlorides mediated by the supported-quinine species, that acted as both a stoichiometric dehydrohalogenating agent and as the enantioselective nucleophilic catalyst for enolate formation from the corresponding acyl chloride. This approach was applied in a "flush-and-flow" system, with the objective to regenerate the supported-quinine after each cycle by washing with a tertiary amine. Using this methodology six compounds were prepared with good yields (up to 61%) and excellent ee values (up to 94%) [45]. Later, the researchers described the use of this reactor system in the preparation of a complex peptide and the multi-step flow synthesis was completely automated [46].

In 2006, the Hodge group described the application of the polystyrene immobilized cinchona alkaloids through the thiol-ene click reaction [47]. This immobilized cinchonidine was used as a chiral base catalyst for the Michael addition of 1-oxo-indan-2-carboxylate to methyl vinyl ketone (Scheme 9). In this case, the flow system design consisted of a catalytic reactor made of a closed glass tube (360 × 14 mm) filled with the supported catalyst (14.0 mmol, 0.094 mmol/g) and immersed in a hot water bath (50 °C). The starting reagents dissolved in toluene were pumped at the same rate through the catalyst bed under constant flow rate and the crude product were collected and removed by from the system with a peristaltic pump. The experiment was run for 72 h at a flow rate of 0.083 mL/min. The Michael adduct was obtained with high yield 97% and an ee of 51%. This ee value is like that obtained when the



Scheme 9. Schematic representation of flow set-up used by Hodge and collaborators [47].

reaction was carried out under batch conditions (47% ee). In conclusion this flow system is able to reproduce the same yields and ee values than the batch system.

In 2013, the group of Soós described the immobilization of quinine- and quinidine-squaramide organocatalysts for applications in batch and continuous-flow reactions. The supported-quinine-squaramide organocatalyst was evaluated in the Michael addition of 1,3-dicarbonyl compounds to nitrostyrene under continuous-flow conditions [48]. The reactions were kept running for 17 h, afforded 5.3 g of product, with a yield of 89% and enantioselectivity of 97% ee. Gratifyingly the catalytic performance of the catalyst remained constant throughout this period (Scheme 10). These flow reactions were performed with a Syrris Asia setup, constituted by a syringe pump, reagent vessels, injectors, a catalytic reactor, and a backpressure regulator (9 bar). Two different substrates (pentane-2,5-dione and ethyl cyclopentanone-2-carboxylate) were evaluated and furnished the respective Michael adducts with excellent yields (up to 96%), enantioselectivities up to 99% ee and diastereoselectivities up to 96% de.

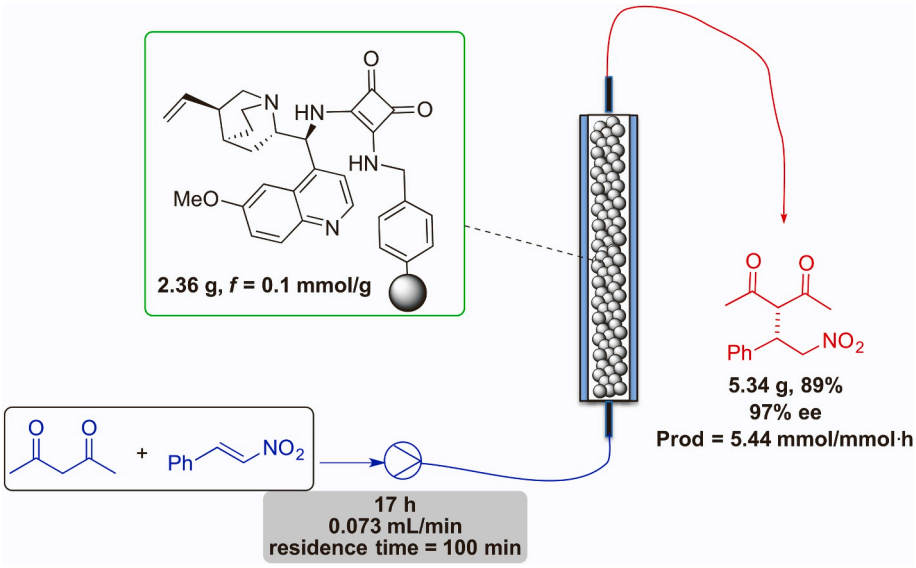
Remarkably, this continuous-flow system was shown to be advantageous in terms of shorter reaction times, easy scale up and automation.

Cinchona primary amine-catalyzed enantioselective reactions have recently appeared as a powerful tool for the synthesis of complex molecules in enantiopure form [49–54]. Due their good catalytic performance, several researchers have reported the immobilization of cinchona-derived primary amines for stereoselective reactions [55,56].

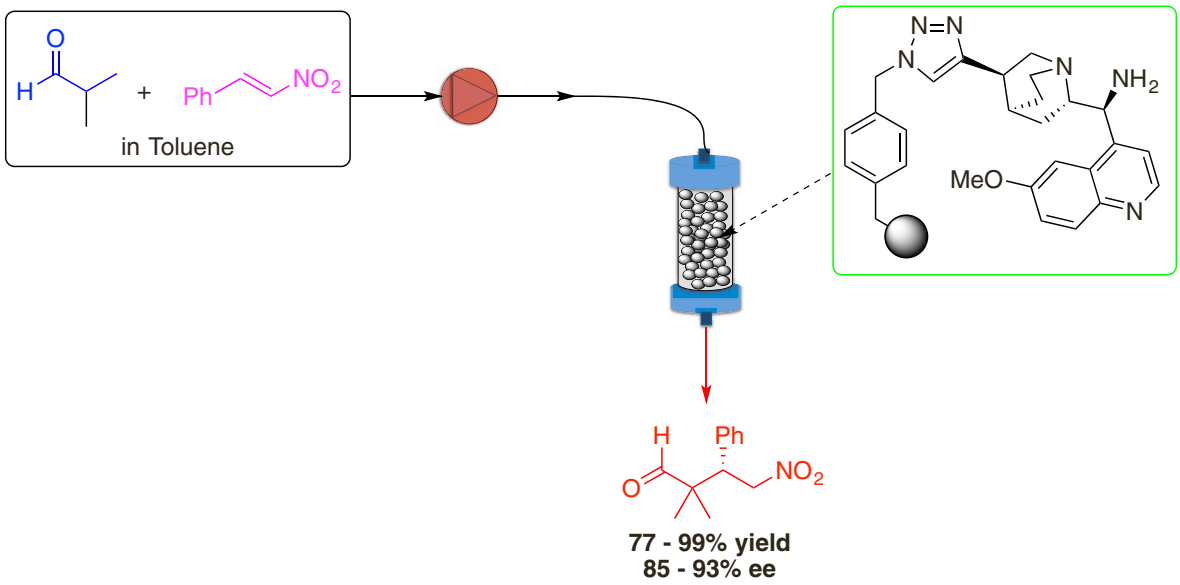
In 2015, almost at the same time and independently, the groups of Benaglia and Pericàs reported the application of supported 9-amino-9-deoxy-*epi*-quinine in stereoselective continuous-flow Michael additions [57,58]. Benaglia's group described the immobilization of a modified 9-amino-*epi*-quinine through a 1,2,3-triazole as a linker with a styrene moiety. The supported catalyst was packed in a stainless-steel column (i.d. 0.4 cm, L 6 cm) where the stereoselective reaction of iso-butyric aldehyde with β-nitrostyrene was carried out under continuous-flow conditions (Scheme 11), using benzoic acid as an additive [57]. After reaction condition optimization, the Michael adduct was obtained with excellent enantioselectivity (up to 93% ee). In addition, the supported organocatalyst was shown to be very versatile, due to the successful application in two different reactions, including an organo-cascade transformation (affording the target compound with an enantiopurity of up to 95% ee). Moreover, using this procedure it was possible to synthesize >1 g of the desired product in high enantiopurity (Scheme 11).

The group of Pericàs reported the enantioselective Michael addition of benzalacetone to ethyl nitroacetate catalyzed by a polystyrene-supported 9-amino-9-deoxy-*epi*-quinine under continuous flow conditions [58]. It is worth noting that the polystyrene used by the Benaglia group was a highly cross-linked and insoluble polymer, whilst the polystyrene used by Pericàs was a swollen resin. In the case of the resin used in the latter example, some care needed to be taken when choosing the reaction solvent, as it could affect the reaction course. The polystyrene-supported organocatalyst was packed into a Teflon tube between two plugs of glass wool. The reaction was carried out by pumping a solution of the two substrates and the benzoic acid co-catalyst in $CHCl_3$ (chosen after solvent screening) at 30 °C with a 40min residence time (Scheme 12). Amazingly, 3.6 g (12.9 mmol) of the desired product was collected during an operating period of 21 h with 97–98% ee and 1:1 dr. Furthermore, a small library of compounds was synthesized by using a combination of four different aromatic enones with three nucleophiles using the same continuous-flow system.

From a pharmaceutical point of view, the preparation of enantiopure amines is in high demand due to the large number of medicinal products that contain the amine functionality [59]. Many of the well-known industrial approaches, such as reductive aminations and hydrogenations of imines or enamines have their associated limitations and hazards that make more sustainable, greener, and safer methods more desirable. One route with these qualities, includes the asymmetric hydrosilylation of



Scheme 10. Michael addition catalyzed by polystyrene supported cinchona-squaramide catalyst as reported by Sóos and co-workers [48].



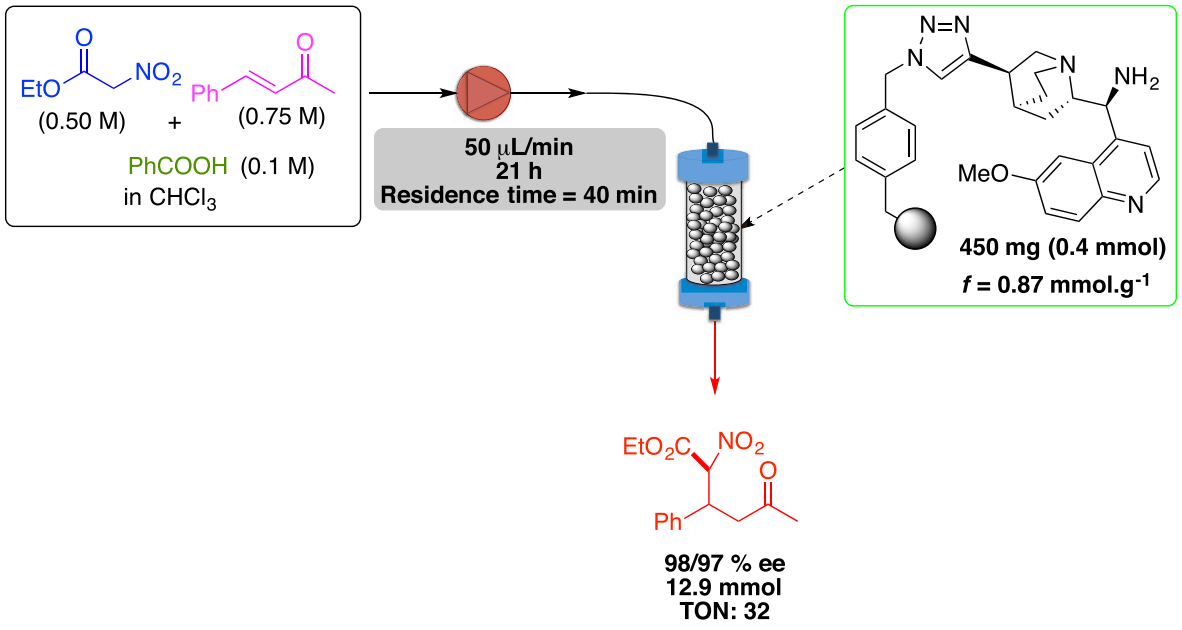
Scheme 11. Asymmetric Michael addition catalyzed by solid supported-organocatalyst under flow conditions [57].

imines using silane reagents. In fact, in 2014, the groups of Burke and Benaglia reported a useful method to afford enantio-enriched chiral amines using an enantioselective reduction of imines with trichlorosilane catalyzed by cinchona picolinamide catalysts [60]. This technology was shown to be appropriate for the synthesis of the active substance rivastigmine, used for the treatment of Alzheimer's disease.

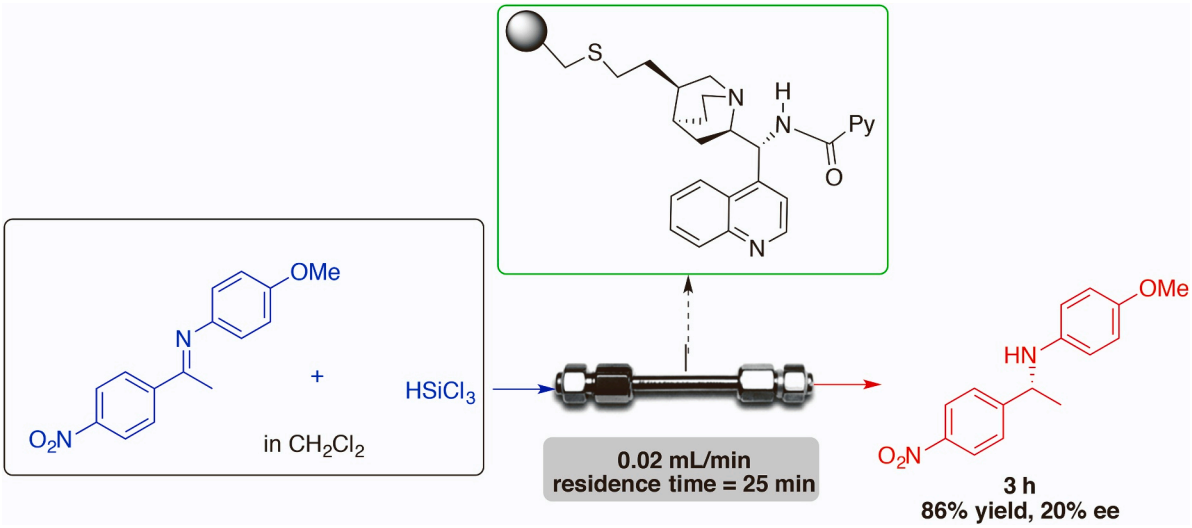
In 2016, the same groups reported the preparation of five immobilized cinchona-based picolinamides which were evaluated in the asymmetric hydrosilylation of imines. Furthermore, this was the first application of these polymer-immobilized organocatalysts for the stereoselective reduction of imines with trichlorosilane under continuous flow conditions. The researchers investigated two different solid supports; silica and polystyrene, the latter offering higher enantioselectivities. The chiral compound *N*-4-methoxy-*N*-(1-(4-nitrophenyl)ethyl) aniline was obtained in very high yields from imine *N*-(4-methoxyphenyl)-1-(4-nitrophenyl)ethan-1-imine catalyzed by the polystyrene-supported supported picolinamide cinchona catalyst with a 3 h retention time under continuous flow, unfortunately at quite low enantioselectivities (20–47%) (Scheme 13) [61]. The reason for the poor outcome, can probably be related to the decomposition of the catalyst inside the reactor.

In a similar fashion, Cinchona amide hybrids I-III (Fig. 3), which are bifunctional organocatalysts, were shown by Huang et al. to catalyze the asymmetric allylsilylation and crotylsilylation of aldehydes with high yields and enantioselectivities [62]. In 2022, the group of Ng [63] reported the immobilization of cinchona alkaloid amide I (R═H) to a polystyrene-support and their evaluation in the asymmetric allylation of several aldehydes using allyltrichlorosilane under both batch and continuous-flow conditions (Scheme 14). High yields and enantioselectivities were obtained for the allylation of aliphatic aldehydes in batch, and the catalyst could be reused for more than 10 runs while maintaining its effectiveness. This supported organocatalyst was successfully used in a packed bed flow catalytic reactor furnishing similar results.

Continuous flow conditions were optimized with respect to temperature and flow rate to achieve high yields and enantioselectivities,



Scheme 12. Continuous flow Michael addition system designed by Pericàs and co-workers [58].



Scheme 13. Continuous-flow system used for asymmetric hydrosilylation of imines, adapted from the work of Burke and Benaglia and their teams [61].

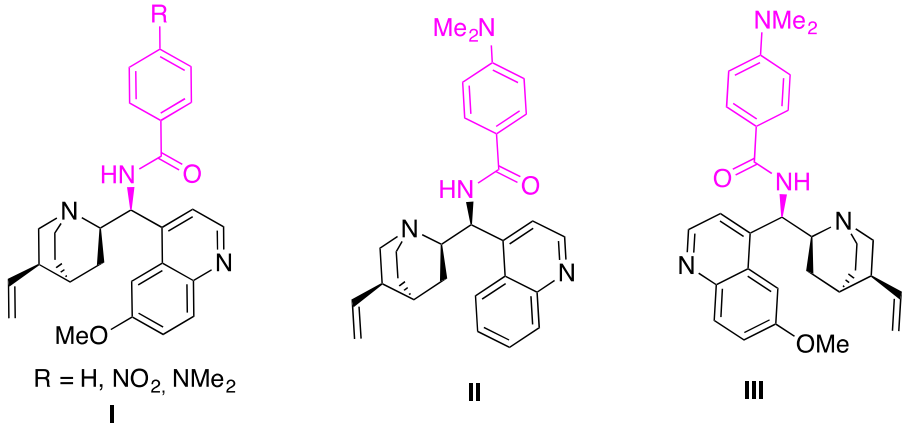
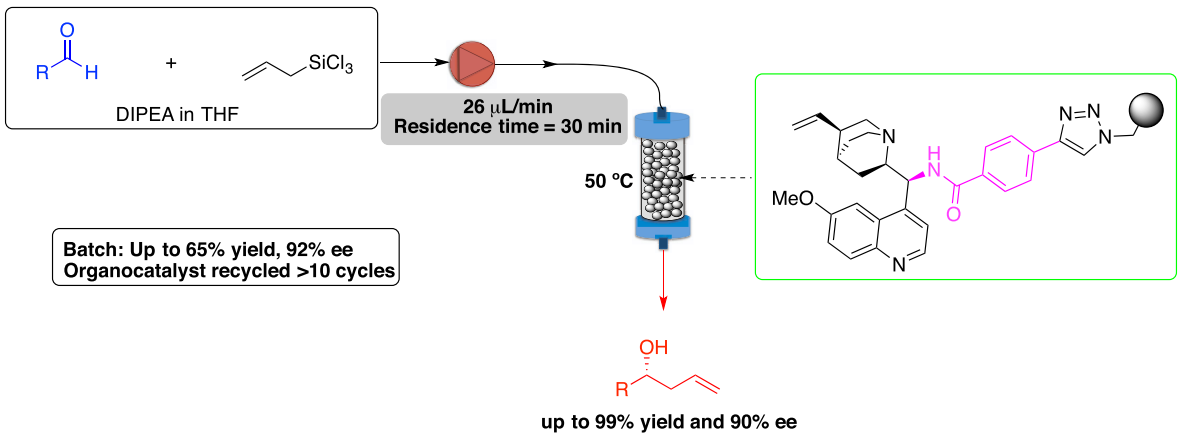


Fig. 3. Cinchona amides hybrids I-III developed by Huang and colleagues [62].



Scheme 14. Asymmetric allylation in continuous flow following the procedure designed by Ng and team [63].

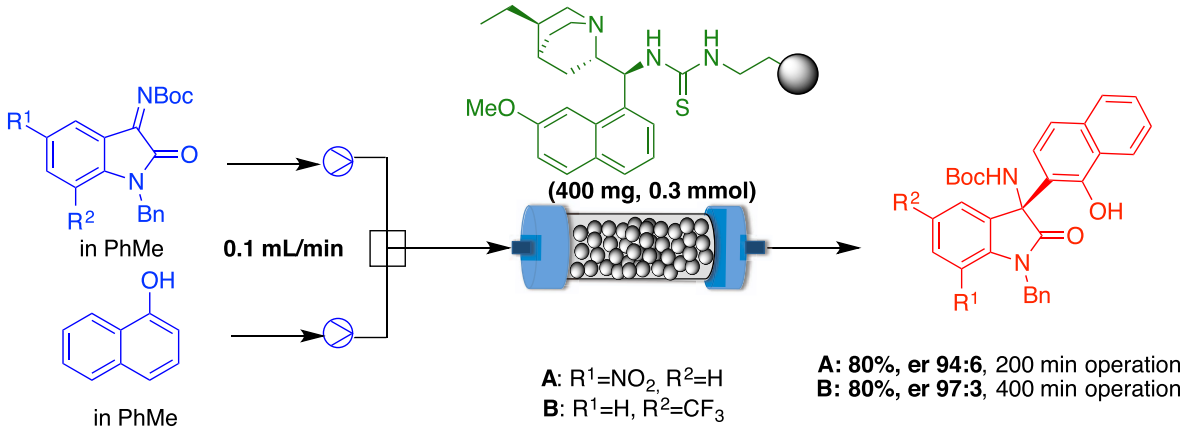
the best conditions were found to be 50 °C at a flow rate of 26 μL/min with a residence time of 30min. These conditions were used for the enantioselective allylation of aliphatic citronellal and naphthaldehyde, furnishing the respective products with very good yields and ee values. The newly developed organocatalyst and its immobilization made a notable contribution to the preparation of enantiopure homoallylic alcohols. This heterogeneous catalyst performed very well in both batch and continuous flow synthesis; however, continuous flow synthesis can significantly reduce the residence time.

In 2020, the groups of André and Pedrosa described the immobilization of cinchona-thiourea derivatives onto polystyrene resin and evaluated their catalytic performance in the asymmetric aza-Friedel-Crafts reaction of naphthol derivatives with a diversity of *N*-Boc ketimines derived from isatin [64]. After optimization of the reaction conditions, 17 examples are reported in moderate to excellent yields (up to 99%) and enantiomeric ratio, er, up to 98:2 under batch conditions. The asymmetric aza-Friedel-Crafts reaction of naphthols with *N*-Boc ketimines derived from isatin were carried out under flow conditions (multigram scale) operated in a Teflon column (6.6 mm ID) filled with the supported catalyst and two different solutions of imines (20 or 40 mL, respectively, 0.14 M in toluene) and 1-naphthol (20 or 40 mL, 0.20 M in toluene) were separately injected via a syringe pump (0.1 mL/min) at room temperature. The products were collected in a flask cooled to 15 °C to avoid further side reaction of the unreacted reagents (Scheme 15). The desired products were obtained in very good yields (80%) and excellent er:s (up to 97:3), with only 10.3min of residence time. The productivity of the reactions was 2.2 mmol $_{cat}^{-1}$ h^{-1}. Thus, comparing the continuous flow mode with the batch mode, the significant reduction in reaction time from 3 h to 10.3min is noteworthy.

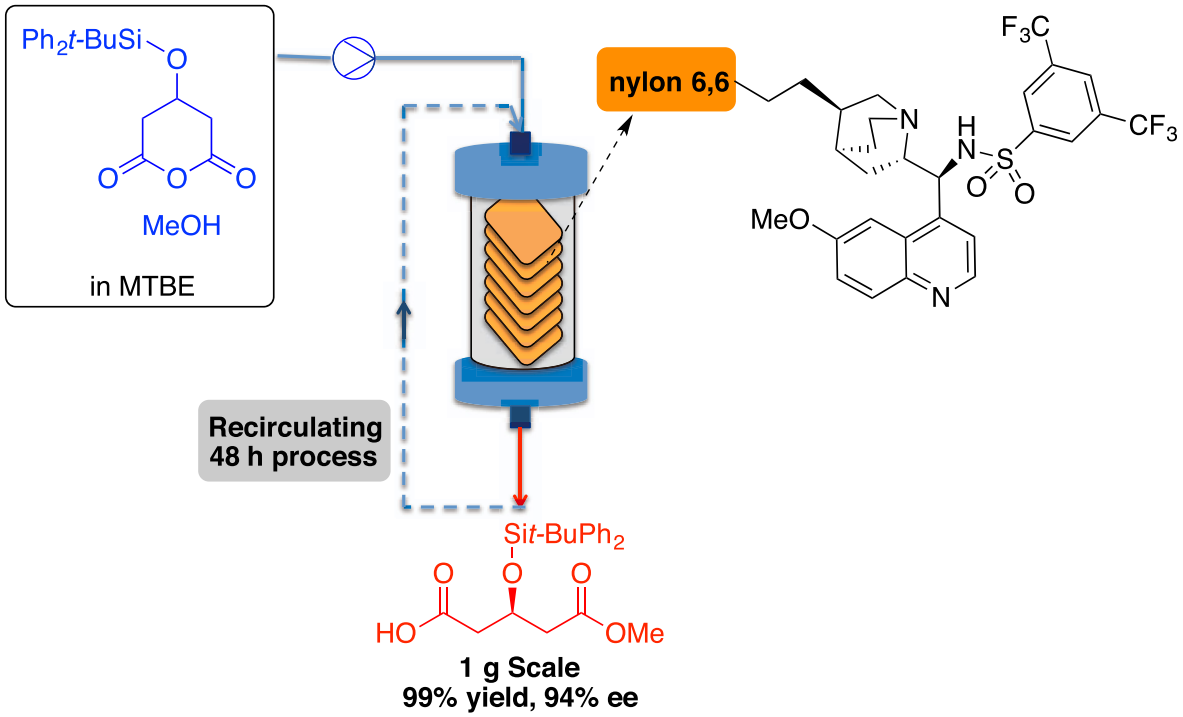
In 2013, the List group reported the uncommon immobilization of cinchona-sulfonamide catalysts on nylon-6,6, through UV irradiation using penta-erythritol triacrylate (PETA) as a cross-linker. The supported catalyst was called "organotextile catalyst" (Scheme 16), which was packed in a fixed-bed reactor (as 20 sheets of the catalyst) and tested in the desymmetrization of cyclic anhydrides under continuous-flow [65]. Amazingly, the authors proved the robustness of the heterogenized catalyst by performing more than 300 batch-recycling experiments, in which some experimental conditions were varied (catalyst, and MeOH load, as well as concentration of the substrate). As a logical consequence, the catalyst was applied in the continuous flow synthesis of statin derivatives (cholesterol-lowering agents) at a multigram scale using a continuous circulatory reactor packed with sheets of the immobilized catalyst (Scheme 16).

The Zhao group reported the immobilization of quinine-squaramide organocatalyst onto porous carbon nanosheets (PCNs) for application in enantioselective Friedel-Crafts addition of pyrazolones to isatin ketimines under both batch and continuous-flow conditions [66]. The researchers also enhanced the structural features of the PCN supports, such as the macroporous (interconnected macropores) and hydrophobicity, which did not affect the catalytic performance in the heterogeneous phase, furnishing the products with high yields (up to 90%) and with high ee values (up to 99%). Gratifyingly these results were very similar to the homogeneous catalyst.

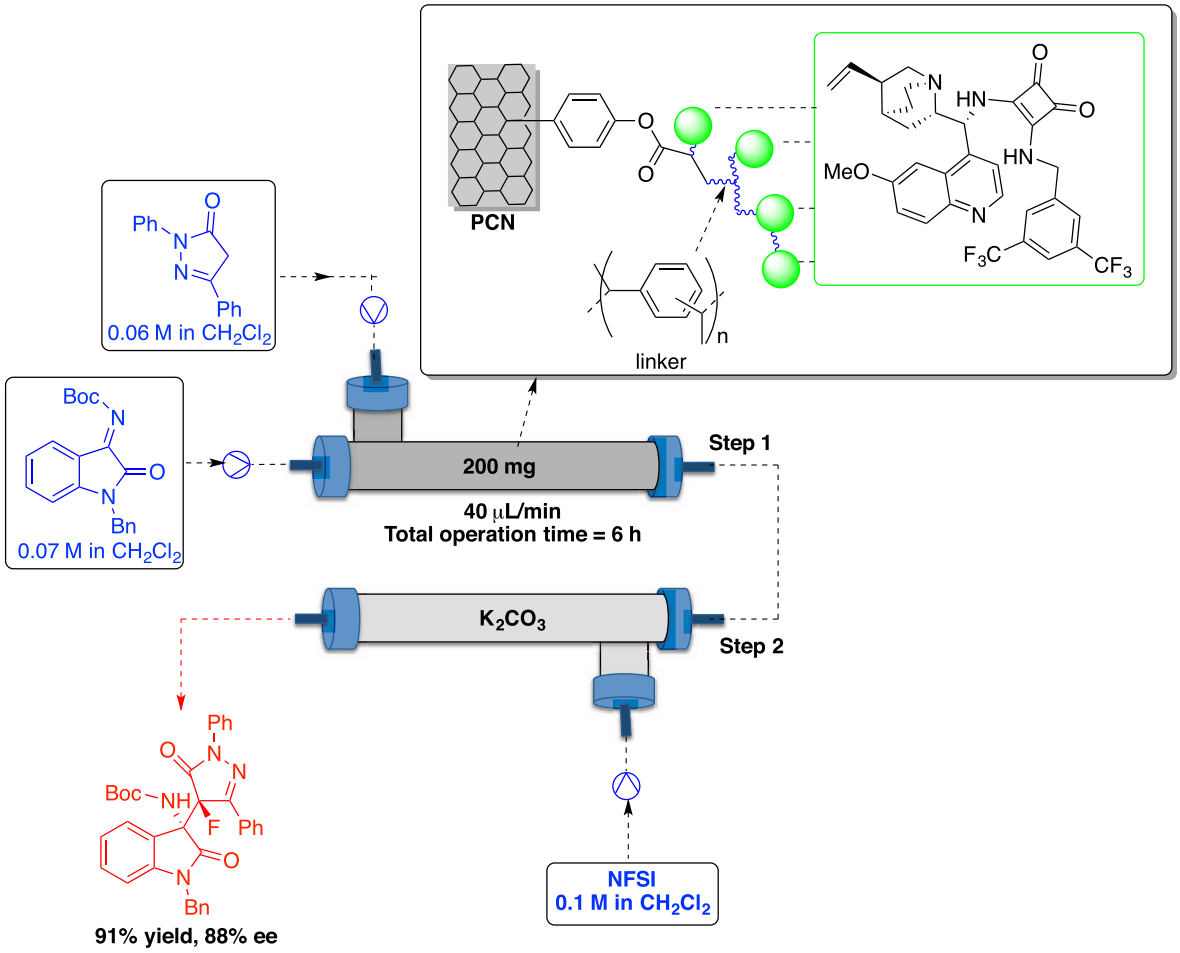
The heterogeneous catalyst, which consisted of the quinine-squaramide grafted onto a porous carbon nanosheet, was applied in a continuous flow system (Scheme 17). The experimental setup consisted of a two-pump system with two packed bed catalytic reactors. The first reactor contained the supported catalyst to which the pyrazolones and



Scheme 15. Schematic representation of flow set-up experiment reported by Andrés' and Pedrosa's groups [64].



Scheme 16. Continuous flow anhydride desymmetrization as described by List and co-workers [65].



Scheme 17. Asymmetric Friedel-Crafts addition/fluorination sequence under continuous-flow conditions by Zhao and co-workers [66].

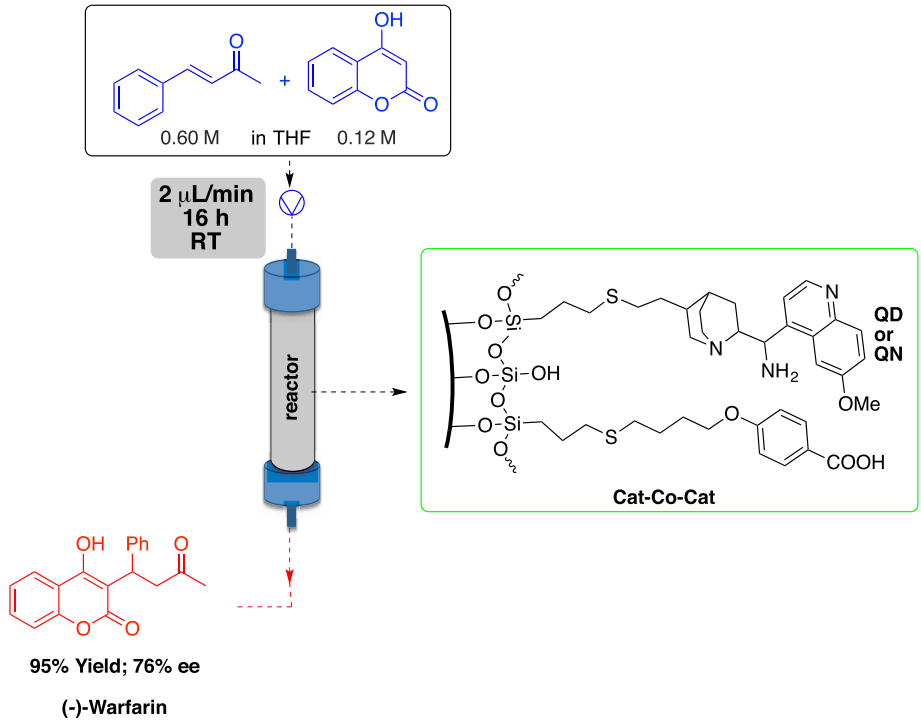
isatin ketimine substrates were fed. This reactor was connected to the second reactor filled with K_2CO_3 into which *N*-fluorobenzenesulfonimide (NFSI), an electrophilic fluorination reagent was pumped, giving the desired product, with excellent yield (91%) and very good ee (88%). The catalyst supported on a PCN could be reused up to five times, both in batch reactions and in a continuous-flow process. In this case, the ee values had a slight decrease when compared with results obtained in batch reaction. Furthermore, the supported catalyst can be reused in 5 runs (in both processes) without losing its catalytic efficiency.

The group of Ciogli have described the immobilization of 9-amino-9-deoxy-*epi*-quinine (or quinidine) and benzoic acid derivative onto the same silica support [67]. These organocatalysts were also immobilized on a polymeric support and applied in a Michael addition reaction under continuous flow conditions, showing very good to excellent yields and ee:s. Firstly, the researchers evaluated the supported catalyst and co-catalyst for the asymmetric Michael addition of ketones to *trans*-β-nitrostyrene, furnishing the Michael adduct with diastereo- and enantioselectivities like those obtained in the homogeneous reaction (dr≤90:10 and 90% ee). Furthermore, the supported catalyst and co-catalyst could be recycled and reused for up to 4 cycles while maintaining its catalytic performance. The supported catalyst was then applied in Michael reactions under continuous-flow conditions. The optimal residence time with the highest level of stereoselectivity (83% ee) was found to be 2 μL/min for the reaction between cyclohexanone and *trans*-β-nitrostyrene. Additionally, using this continuous flow reactor it was possible to prepare the anti-coagulant drug substance (−)-warfarin (for comparison, see above the report by Benaglia; Scheme 1, in which no catalytic reactor was used, and the temperature was 70 °C) in excellent yield (95%) and high enantioselectivity (78% ee) over 16 h at room temperature (Scheme 18).

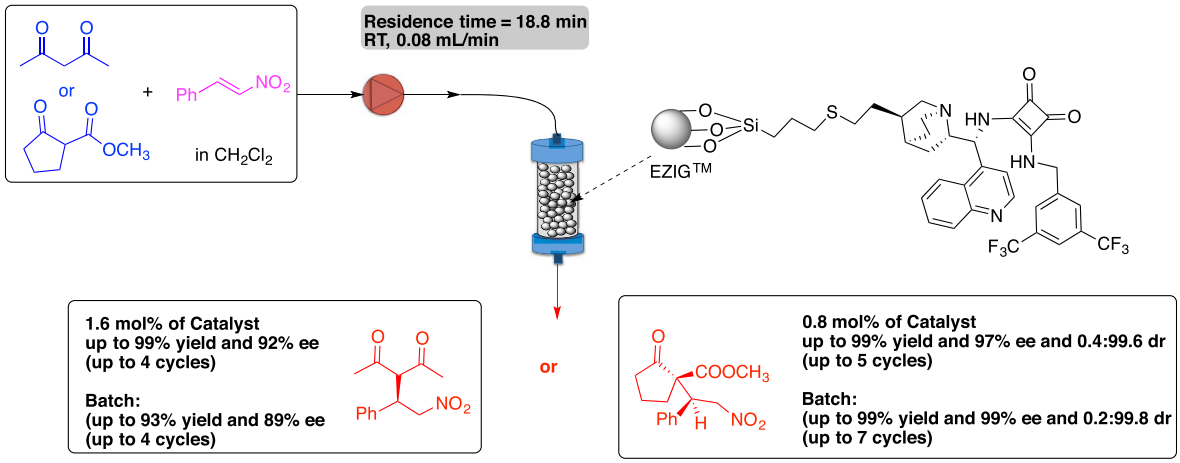
Recently, teams at the University of Evora and the contract company Chiratecnics reported the first immobilization of cinchona-squaramide organocatalysts onto three types of porous glass beads EziG™ (specified as controlled pore glass with three surface modifications; (i) an organic polymer leading to hydrophobic (Amber), (*ii*) semi-hydrophobic (Coral), or (*iii*) hydrophilic (Opal) resins commercialized by EnginZyme, Stockholm, Sweden), supports that only previously were used to immobilize enzymes [68,69]. These novel catalysts have been evaluated in asymmetric Michael reactions under both batch and continuous-flow conditions. Curiously, the best heterogeneous organocatalyst for the batch conditions was Opal-cinchonine-squaramide, whereas in the case of the continuous-flow system the best support was found to be Coral [70]. Gratifyingly the reactions proceeded with high efficiencies using catalyst loads of only 0.8 and 1.6 mol% under batch conditions. These immobilized catalysts were then evaluated under continuous flow using a packed-bed flow reactor (Scheme 19), and excellent results could be achieved (up to 99% yield and 97% ee, with dr = 0.4:99.6). Furthermore, the immobilized catalysts could be recycled 5-times (without losing their catalytic performance). The yields and ee:s obtained for the continuous flow system were very similar to the values obtained under batch conditions, but the reaction times were considerably shorter.

Furthermore, in 2023, the same team demonstrated, for the first time, successful organocatalysis in deep eutectic solvents based on betaine (DES) [71]. Thus, it was shown that asymmetric Michael additions could be performed in good to excellent chemical yields (≤99%) and stereoselectivities (≤98%) even under conditions where the catalyst was recycled up to 9 times at a catalyst loading of 1 mol-% (5 times at 0.5 mol-% catalyst). These promising, quasi-immobilized systems, show a great potential for conducting a broad range of chemical transformations in an efficient and sustainable manner.

In summary, heterogeneous reactions catalyzed by cinchona alkaloid derivatives under continuous flow conditions showed some advantages in terms of efficiency and sustainability. However, in the case of some reactions, a slight decrease in enantioselectivity was observed, which is probably due to the lack of access to the stereogenic centres due to the packing of the supported catalysts in the column. The choice of the catalyst is crucial, and the catalyst should be stable under the flow conditions chosen. Metal-based catalysts on the other hand tend to undergo redox processes as well as being vulnerable to water and oxygen, which is not the case for organocatalysts.



Scheme 18. Schematic representation of the continuous-flow system developed by Ciogli and co-workers [67].



Scheme 19. Process outline of a continuous-flow system used for the asymmetric Michael addition [70].

4. General conclusions

In this review we have shown the significant progress has been made over the last two decades in the field of enantioselective catalysis under continuous flow conditions utilising cinchona alkaloid organocatalysts. The catalysts can either be used in their original form under homogeneous conditions or can be grafted onto a polymer support to serve in a heterogeneous set-up. The catalytic systems are typically very robust and durable, delivering high yields and excellent enantioselectivities. Continuous flow systems are in many cases superior over batch mode as reaction times can be shortened, sensitive intermediates can be handled well, processes can be scaled in most cases and run under automated conditions. Multiple reactor systems allow for the handling of more complex reactions with integrated purification steps. Michael additions have been well studied with cinchona catalysts under continuous flow conditions. Very good examples have been reported for hydrosilylations, allylations or Friedel-Crafts reactions. Even an unusual immobilization of cinchona catalysts onto porous glass beads has been successfully carried out. That said, many challenges remain, for example, reducing catalyst loadings and maintaining high selectivities and turnover numbers in flow processes. Some flow processes are not easily scalable, that poses some risks and difficulties for larger scale reactions and industrial use. There is also the question of catalyst deactivation, but this can be resolved through the choice of reaction conditions, solvent, temperature, retention time, additive etc. Also, in the case of catalytic reactors the choice of support is crucial, to reduce disadvantageous side effects, and enhance catalyst stability, etc. Generally larger pore supports are better. The linker length can have an effect, generally the longer the better, but this is not always the case. Returning to the point on the reaction conditions, one needs to consider three possible modes of action: covalent intermediate formation (enamine) or hydrogen -bonding, or ion-ion interactions (in the case of PTC). In the case of the former the conditions should promote the formation of an enamine (right choice of solvent, maybe an additive like benzoic acid etc), in the case of the latter two, avoid a protic or a charged solvent that will compete with the catalyst.

As regards how to select a more suitable continuous flow reactor, one that provides good catalytic efficiency, and product selectivity, which is a significant challenge to those working in the field and particularly novices. There are many very comprehensive reviews published on this topic including one outstanding example by Gilmore and Seeberger [72]. Also, the proverbial process of trial and error has an important part to play in this.

We trust that organocatalysis employing cinchona catalysts in continuous flow systems will gain more importance as soon as a more sustainable way to carry out chemical reactions selectively and in high yields is obtained. A further step towards expanding the capabilities of organocatalysis has recently been reported [73], where the opportunities for a fruitful connection with the field of biocatalysis is highlighted as "a synergistic approach to catalysis" opening an avenue for application of designer-organocatalysts as co-factors working in concert with enzymes. This is an attractive and promising path towards further improvement of stereo-, chemo-, and regioselectivities under mild and sustainable conditions, and we look forward to seeing more developments in this area in the future.

Declaration of competing interest

All authors contributing to this paper submitted to Tetrahedron Green Chemistry declare that they hold no competing financial interest nor any personal relationships that have affected the work reported herein.

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References

[1] M. Li, W. He, S.-Y. Zhang, The use of cinchona alkaloid derivatives as chiral ligands and organocatalysts in asymmetric catalysis, Mini-Reviews Org. Chem. 19 (2022) 146–165, https://doi.org/10.2174/1570193X18666210428133120.
[2] H.-U. Blaser, M. Müller, Enantioselective catalysis by chiral solids: approaches and results, Stud. Surf. Sci. Catal. 59 (1991) 73–92, https://doi.org/10.1016/S0167-2991(08)61108-8.
[3] Y. Orito, S. Imai, S. Niwa, Asymmetric hydrogenation of methyl pyruvate using a platinum-carbon catalyst modified with cinchonidine, J. Chem. Soc. Jpn. (8) (1979) 1118–1120, https://doi.org/10.1002/chin.197949149 (in Japanese).
[4] Y. Orito, S. Imai, S. Niwa, G.-H. Nguyen, J. Synth. Org. Chem., Jpn. 37 (1979) 173–174, https://doi.org/10.5059/yukigoseikyokaishi.37.173.
[5] D.M. Meier, D. Ferri, T. Mallat, A. Baiker, Molecular insight into the dynamics of chiral modification of Pt/alumina, J. Catal. 248 (2007) 68–76, https://doi.org/10.1016/j.jcat.2007.03.011.
[6] F. Gao, L. Chen, M. Garland, A new origin for stereo-differentiation in the Orito reaction: residual chiral induction and enantiomeric excess reversal during piecewise continuous experiments using a chiral fixed-bed reactor, J. Catal. 238 (2006) 402–411, https://doi.org/10.1016/j.jcat.2005.12.018.
[7] G. Szöllősi, S. Cserényi, K. Balázsik, F. Fülöp, M. Bartók, New data in the enantioselective hydrogenation of ethyl pyruvate on Pt-cinchona chiral catalyst using continuous-flow fixed-bed reactor system: the origin of rate enhancement, J. Mol. Catal. Chem. 305 (2009) 155–160, https://doi.org/10.1016/j.molcata.2009.01.030.

[8] S. Cserényi, G. Szőllősi, K. Szőri, F. Fülöp, M. Bartók, Reversal of the ee in enantioselective hydrogenation of activated ketones in continuous-flow fixed-bed reactor system, Catal. Commun. 12 (2010) 14–19, https://doi.org/10.1016/j.catcom.2010.08.008.

[9] L. Kovács, G. Szöllösi, F. Fülöp, Pt-cinchonidine catalyzed asymmetric catalytic cascade reaction of 2-nitrophenylpyruvates in flow system, J. Flow Chem. 5 (2015) 210–215, https://doi.org/10.1556/1846.2015.00012.

[10] B. Hermán, G. Szőllősi, F. Fülöp, M. Bartók, Enantioselective hydrogenation of α,β-unsaturated carboxylic acids in fixed-bed reactor, Appl. Catal., A 331 (2007) 39–43, https://doi.org/10.1016/j.apcata.2007.07.022.

[11] T. Marcelli, H. Hiemstra, and citations therein, Cinchona Alkaloids in Asymmetric Organocatalysis, Synthesis (8) (2010) 1229–1279, https://doi.org/10.1055/s-0029-1218699.

[12] Y.-C. Chen, The development of asymmetric primary amine catalysts based on cinchona alkaloids, Synlett (13) (2008) 1919–1930, https://doi.org/10.1055/s-2008-1078524.

[13] G. Bartoli, P. Melchiorre, A novel organocatalytic tool for the iminium activation of α,β-unsaturated ketones, Synlett (12) (2008) 1759–1772, https://doi.org/10.1055/S-2008-1078503.

[14] S.J. Connon, The design of novel, synthetically useful (Thio)urea-Based organocatalysts, Synlett (3) (2009) 354–376, https://doi.org/10.1055/s-0028-1087557.

[15] S.J. Connon, Asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea organocatalysts, Chem. Commun. (2008) 2499–2510, https://doi.org/10.1039/B719249E.

[16] S. Rossi, M. Benaglia, A. Puglisi, C.C. De Filippo, M. Maggini, Continuous flow stereoselective synthesis in microreactors: nucleophilic additions to nitrostyrenes organocatalyzed by a chiral bifunctional catalyst, J. Flow Chem. 5 (2015) 17–21, https://doi.org/10.1556/JFC-D-14-00030.

[17] R. Porta, M. Benaglia, F. Coccia, S. Rossi, A. Puglisi, Enantioselective organocatalysis in microreactors: continuous flow synthesis of a (S)-Pregabalin precursor and (S)-Warfarin, Symmetry 7 (2015) 1395–1409, https://doi.org/10.3390/sym7031395.

[18] C. Lotter, E. Poehler, J.J. Heiland, L. Mauritz, D. Belder, Enantioselective reaction monitoring utilizing two-dimensional heart-cut liquid chromatography on an integrated microfluidic chip, Lab Chip 16 (2016) 4648–4652, https://doi.org/10.1039/c6lc01138a.

[19] B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, Asymmetric Michael addition of arylthiols to α,β-unsaturated carbonyl compounds catalyzed by bifunctional organocatalysts, Synlett (4) (2005) 603–606, https://doi.org/10.1055/s-2005-863710.

[20] B. Vakulya, S. Varga, A. Csámpai, T. Soós, Highly enantioselective conjugate addition of nitromethane to chalcones using bifunctional cinchona organocatalysts, Org. Lett. 7 (2005) 1967–1969, https://doi.org/10.1021/ol050431s.

[21] S.H. McCooey, S.J. Connon, Urea- and thiourea-substituted cinchona alkaloid derivatives as highly efficient bifunctional organocatalysts for the asymmetric addition of malonate to nitroalkenes: inversion of configuration at C9 dramatically improves catalyst performance, Angew. Chem. Int. Ed. 44 (2005) 6367–6370, https://doi.org/10.1002/anie.200501721.

[22] J. Ye, D.J. Dixon, P.S. Hynes, Enantioselective organocatalytic Michael addition of malonate esters to nitroolefins using bifunctional cinchonine derivatives, Chem. Commun. (2005) 4481–4483, https://doi.org/10.1039/B508833J.

[23] B. Vakulya, S. Varga, T. Soós, Epi-cinchona based thiourea organocatalyst family as an efficient asymmetric Michael addition promoter: enantioselective conjugate addition of nitroalkanes to chalcones and α,β-unsaturated N-acylpyrroles, J. Org. Chem. 73 (2008) 3475–3480, https://doi.org/10.1021/jo702692a.

[24] P. Kisszekelyi, A. Alammar, J. Kupai, P. Huszthy, J. Barabas, T. Holtzl, L. Szente, C. Bawn, R. Adams, G. Szekely, Asymmetric synthesis with cinchona-decorated cyclodextrin in a continuous-flow membrane reactor, J. Catal. 371 (2019) 255–261, https://doi.org/10.1016/j.jcat.2019.01.041.

[25] U. Kragl, C. Dreisbach, Continuous asymmetric synthesis in a membrane reactor, Angew. Chem. Int. Ed. 35 (1996) 642–644, https://doi.org/10.1002/anie.199606421.

[26] G. Giffels, J. Beliczey, M. Felder, U. Kragl, Polymer enlarged oxazaborolidines in a membrane reactor: enhancing effectivity by retention of the homogeneous catalyst, Tetrahedron: Asymmetry 9 (1998) 691–696, https://doi.org/10.1016/S0957-4166(98)00011-1.

[27] S. Rissom, J. Beliczey, G. Giffels, U. Kragl, C. Wandrey, Asymmetric reduction of acetophenone in membrane reactors: comparison of oxazaborolidine and alcohol dehydrogenase catalysed processes, Tetrahedron: Asymmetry 10 (1999) 923–928, https://doi.org/10.1016/S0957-4166(99)00050-6.

[28] J. Wöltinger, A.S. Bommarius, K. Drauz, C. Wandrey, The chemzyme membrane reactor in the fine chemicals industry, org, Process Res. Dev. 5 (2001) 241–248, https://doi.org/10.1021/op000111i.

[29] S.B. Tsogoeva, J. Wöltinger, C. Jost, D. Reichert, A. Kühnle, H.-P. Krimmer, K. Drauz, Juliá-colonna asymmetric epoxidation in a continuously operated chemzyme membrane reactor, Synlett (5) (2002) 707–710, https://doi.org/10.1055/s-2002-25352.

[30] J. Wöltinger, H.-P. Krimmer, K. Drauz, The potential of membrane reactors in the asymmetric opening of meso-anhydrides, Tetrahedron Lett. 43 (2002) 8531–8533, https://doi.org/10.1016/S0040-4039(02)02075-0.

[31] S.A. Chavan, W. Maes, L.E. Gevers, J. Wahlen, I.F. Vankelecom, P.A. Jacobs, W. Dehaen, D.E. De Vos, Porphyrin-functionalized dendrimers: synthesis and application as recyclable photocatalysts in a nanofiltration membrane reactor, Chem. Eur J. 11 (2005) 6754–6762, https://doi.org/10.1002/chem.200500251.

[32] W.E. Siew, C. Ates, A. Merschaert, A.G. Livingston, Efficient and productive asymmetric Michael addition: development of a highly enantioselective quinidine-based organocatalyst for homogeneous recycling via nanofiltration, Green Chem. 15 (2013) 663–674, https://doi.org/10.1039/C2GC36407G.

[33] T. Fahrenwaldt, J. Großeheilmann, F. Erben, U. Kragl, Organic solvent nanofiltration as a tool for separation of quinine-based organocatalysts, Org. Process Res. Dev. 17 (2013) 1131–1136, https://doi.org/10.1021/op400037h.

[34] J. Großeheilmann, H. Büttner, C. Kohrt, U. Kragl, T. Werner, Recycling of phosphorus-based organocatalysts by organic solvent nanofiltration, ACS Sustainable Chem. Eng. 3 (2015) 2817–2822, https://doi.org/10.1021/acssuschemeng.5b00734.

[35] A. Guerrero-Corella, M.A. Valle-Amores, A. Fraile, J. Alemán, Enantioselective organocatalyzed aza-michael addition reaction of 2-hydroxybenzophenone imines to nitroolefins under batch and flow conditions, Adv. Synth. Catal. 363 (2021) 3845–3851, https://doi.org/10.1002/adsc.202100635.

[36] S.-S. Jew, H.-G. Park, Cinchona-based phase-transfer catalysts for asymmetric synthesis, Chem. Commun. (2009) 7090–7103, https://doi.org/10.1039/B914028J.

[37] X.F. Tang, J.N. Zhao, Y.F. Wu, Z.H. Zheng, S.H. Feng, Z.Y. Yu, et al., Enantioselective photooxygenation of β-dicarbonyl compounds in batch and flow photomicroreactors, Org. Biomol. Chem. 17 (2019) 7938–7942, https://doi.org/10.1039/C9OB01379B.

[38] X.-F. Tang, J.-N. Zhao, Y.-F. Wu, S.-H. Feng, F. Yang, Z.-Y. Yu, Q.-W. Meng, Visible-light-driven enantioselective aerobic oxidation of β-dicarbonyl compounds catalyzed by cinchona-derived phase transfer catalysts in batch and semi-flow, Adv. Synth. Catal. 361 (2019) 5245–5252, https://doi.org/10.1002/adsc.201900777.

[39] X.-F. Tang, J.-N. Zhao, Y.-F. Wu, Z.-H. Zheng, C.F. Ma, Z.-Y. Yu, L. Yun, G.-Z. Liu, Q.-W. Meng, Asymmetric α-hydroxylation of β-dicarbonyl compounds by C-2′ modified cinchonine-derived phase-transfer catalysts in batch and flow microreactors, Synth. Commun. 50 (2020) 2478–2487, https://doi.org/10.1080/00397911.2020.1781183.

[40] A.M. Hafez, A.E. Taggi, H. Wack, W.J. Drury, T. Lectka, Column asymmetric catalysis for β-lactam synthesis, Org. Lett. 2 (2000) 3963–3965, https://doi.org/10.1021/ol006659r.

[41] A.M. Hafez, A.E. Taggi, T. Dudding, T. Lectka, Asymmetric catalysis on sequentially-linked columns, J. Am. Chem. Soc. 123 (2001) 10853–10859, https://doi.org/10.1021/ja016556j.

[42] A.M. Hafez, A.E. Taggi, H. Wack, J. Esterbrook, T. Lectka, Reactive ketenes through a carbonate/amine shuttle deprotonation strategy: catalytic, enantioselective α-bromination of acid chlorides, Org. Lett. 3 (2001) 2049–2051, https://doi.org/10.1021/ol0160147.

[43] S. France, H. Wack, A.E. Taggi, A.M. Hafez, T.R. Wagerle, M.H. Shah, C.L. Dusich, T. Lectka, Catalytic, asymmetric α-chlorination of acid halides, J. Am. Chem. Soc. 126 (2004) 4245–4255, https://doi.org/10.1021/ja039046t.

[44] H. Wack, A.E. Taggi, A.M. Hafez, W.J. Drury, T. Lectka, Catalytic, asymmetric α-halogenation, J. Am. Chem. Soc. 123 (2001) 1531–1532, https://doi.org/10.1021/ja005791j.

[45] D. Bernstein, S. France, J. Wolfer, T. Lectka, A column-based 'flush and flow' system for the asymmetric α-chlorination of acid halides, Tetrahedron: Asymmetry 16 (2005) 3481–3483, https://doi.org/10.1016/j.tetasy.2005.09.014.

[46] S. France, D. Bernstein, A. Weatherwax, T. Lectka, Performing the synthesis of a complex molecule on sequentially linked columns: toward the development of a "synthesis machine", Org. Lett. 7 (2005) 3009–3012, https://doi.org/10.1021/ol050980y.

[47] F. Bonfils, I. Cazaux, P. Hodge, C. Caze, Michael reactions carried out using a bench-top flow system, Org. Biomol. Chem. 4 (2006) 493–497, https://doi.org/10.1039/B515241K.

[48] G. Kardos, T. Soós, Tether-free immobilized bifunctional squaramide organocatalysts for batch and flow reactions, Eur. J. Org. Chem. (2013) 4490–4494, https://doi.org/10.1002/ejoc.201300626.

[49] J. Duan, P. Li, Asymmetric organocatalysis mediated by primary amines derived from cinchona alkaloids: recent advances, Catal. Sci. Technol. 4 (2014) 311–320, https://doi.org/10.1039/C3CY00739A.

[50] O. Lifchits, M. Mahlau, C.M. Reisinger, A. Lee, C. Farès, I. Polyak, G. Gopakumar, W. Thiel, B. List, The cinchona primary amine-catalyzed asymmetric epoxidation and hydroperoxidation of α,β-unsaturated carbonyl compounds with hydrogen peroxide, J. Am. Chem. Soc. 135 (2013) 6677–6693, https://doi.org/10.1021/ja402058v.

[51] Y-h. Lam, K.N. Houk, Origins of stereoselectivity in intramolecular aldol reactions catalyzed by cinchona amines, J. Am. Chem. Soc. 137 (2015) 2116–2127, https://doi.org/10.1021/ja513096x.

[52] P. Melchiorre, Cinchona-based primary amine catalysis in the asymmetric functionalization of carbonyl compounds, Angew. Chem., Int. Ed. 51 (2012) 9748–9770, https://doi.org/10.1002/anie.201109036.

[53] C.E. Song, Cinchona Alkaloids in Synthesis and Catalysis: Ligands, Immobilization and Organocatalysis, Wiley-VCH, Weinheim, 2009. ISBN: 978-3-527-62818-6.

[54] W. Liu, D. Mei, W. Wang, D. Duan, Highly enantioselective conjugate addition of nitroalkanes to enones catalyzed by cinchona alkaloid derived primary amine, Tetrahedron Lett. 54 (2013) 3791–3793, https://doi.org/10.1016/j.tetlet.2013.05.019.

[55] J. Zhou, J. Wan, X. Ma, W. Wang, Copolymer-supported heterogeneous organocatalyst for asymmetric aldol addition in aqueous medium, Org. Biomol. Chem. 10 (2012) 4179–4185, https://doi.org/10.1039/C2OB25106J.

[56] W. Wang, X. Ma, J. Wan, J. Cao, Q. Tang, Preparation and confinement effect of a heterogeneous 9-amino-9-deoxy-epi-cinchonidine organocatalyst for asymmetric

aldol addition in aqueous medium, 5715-5126, Dalton Trans. 41 (2012), https://doi.org/10.1039/C2DT12390H.
[57] R. Porta, M. Benaglia, F. Coccia, F. Cozzi, A. Puglisi, Solid supported 9-Amino-9-deoxy-epi-quinine as efficient organocatalyst for stereoselective reactions in batch and under continuous flow conditions, Adv. Synth. Catal. 357 (2015) 377–383, https://doi.org/10.1002/adsc.201400821.
[58] J. Izquierdo, C. Ayats, A.H. Henseler, M.A. Pericàs, A polystyrene-supported 9-amino(9-deoxy)epi quinine derivative for continuous flow asymmetric Michael reactions, Org. Biomol. Chem. 13 (2015) 4204–4209, https://doi.org/10.1039/C5OB00325C.
[59] Chiral Amine Synthesis, in: T.C. Nugent (Ed.), Methods, Developments and Applications, first ed., Wiley-VCH, 2010 https://doi.org/10.1002/9783527629541.
[60] P.C. Barrulas, A. Genoni, M. Benaglia, A.J. Burke, Cinchona-derived picolinamides: effective organocatalysts for stereoselective imine hydrosilylation, Eur. J. Org. Chem. (2014) 7339–7342, https://doi.org/10.1002/ejoc.201403180.
[61] S.D. Fernandes, R. Porta, P.C. Barrulas, A. Puglisi, A.J. Burke, M. Benaglia, Stereoselective reduction of imines with trichlorosilane using solid-supported chiral picolinamides, Molecules 21 (2016) 1182, https://doi.org/10.3390/molecules21091182.
[62] Y. Huang, L. Yang, P. Shao, Y. Zhao, Practical, highly stereoselective allyl- and crotylsilylation of aldehydes catalyzed by readily available Cinchona alkaloid amide, Chem. Sci. 4 (2013) 3275–3281, https://doi.org/10.1039/C3SC50973G.
[63] X.Q. Ng, M.H. Kang, R.W. Toh, V. Isoni, J. Wu, Y. Zhao, A green access to supported cinchona alkaloid amide catalysts for heterogeneous enantioselective allylsilylation of aldehydes and process intensity evaluation in batch and flow, Green Synth. Catal. 3 (2022) 272–277, https://doi.org/10.1016/j.gresc.2022.07.004.
[64] M. Rodríguez-Rodríguez, A. Maestro, J.M. Andrés, R. Pedrosa, Supported bifunctional chiral thioureas as catalysts in the synthesis of 3-amino-2-oxindoles through enantioselective aza-friedel-crafts reaction: application in continuous flow processes, Adv. Synth. Catal. 362 (2020) 2744–2754, https://doi.org/10.1002/adsc.202000238.
[65] J.-W. Lee, T. Mayer-Gall, K. Opwis, C.E. Song, J.S. Gutmann, B. List, Organotextile Catalysis, Science 341 (2013) 1225–1229, https://doi.org/10.1126/science.1242196.
[66] L. Zhao, X. Bao, Q. Hu, B. Wang, A.-H. Lu, Porous carbon nanosheet-supported chiral squaramide for highly enantioselective friedel–crafts reaction, ChemCatChem 10 (2018) 1248–1252, https://doi.org/10.1002/cctc.201701897.
[67] A. Ciogli, D. Capitani, N. Di Iorio, S. Crotti, G. Bencivenni, M.P. Donzello, C. Villani, Eur. J. Org. Chem. (2019) 2020–2028, https://doi.org/10.1002/ejoc.201900148.
[68] K. Engelmark Cassimjee, M. Kadow, Y. Wikmark, M. Svedendahl Humble, M. L. Rothstein, D.M. Rothstein, J.-E. Bäckvall, A general protein purification and immobilization method on controlled porosity glass: biocatalytic applications, Chem. Commun. 50 (2014) 9134–9137, https://doi.org/10.1039/C4CC02605E.
[69] K. Engelmark Cassimjee, H.-J. Federsel, EziG: a universal platfrom for enzyme immobilization, in: G. deGonzalo, P. Dominguez de Maria (Eds.), Biocatalysis: an Industrial Perspective, RSC Catalysis Series No.29, The Royal Society of Chemistry, London, 2018, pp. 345–362, https://doi.org/10.1039/9781782629993-00345 (Chapter 13).
[70] A.C. Amorim, D.P. Fonseca, E.P. Carreiro, G.J. Hermann, H.-J. Federsel, A.J. Burke, Immobilization of functionalized epi-cinchonine organocatalysts on controlled porous glass-beads: application in batch and continuous flow, Synlett (33) (2022) 1756–1762, https://doi.org/10.1055/a-1916-4858.
[71] D.P. Fonseca, A.C. Amorim, E.P. Carreiro, J.P. Prates Ramalho, G.J. Hermann, H.-J. Federsel, A.R.C. Duarte, A.J. Burke, Sustainable OrganoCatalyzed enantioselective catalytic Michael additions in betaine derived deep eutectic solvents, SynOpen 7 (2023), https://doi.org/10.1055/a-2117-9971.
[72] For an excellent review covering basic principles and fundamentals of flow chemistry, see: M.B. Plutschack, B. Pieber, K. Gilmore, P.H. Seeberger, The hitchhiker's guide to flow chemistry Chem. Rev. 117 (2017) 11796–11893, https://doi.org/10.1021/acs.chemrev.7b00183.
[73] J. Murray, D.R.W. Hodgson, A.M.C. O'Donoghue, Going full circle with organocatalysis and biocatalysis: the latent potential of cofactor mimics in asymmetric synthesis, J. Org. Chem. 88 (2023) 7619–7629, https://doi.org/10.1021/acs.joc.2c02747.