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Engineered Immobilised Organocatalysts for the Synthesis of Chiral Amines

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Abstract: The art of tuning functional polymeric materials through the covalent incorporation of organocatalysts lies at the core of creating asymmetric immobilized chiral catalysts that mimic the enzymatic action. Herein, we explore diverse synthetic techniques to immobilize L-proline-derived *N*-carbonyl amides on functional polymeric matrices, transforming them into chiral Lewis bases for facilitating the asymmetric reduction of ketimines with $HSiCl_3$. A comprehensive examination of the design factors, encompassing linker selection, anions, and polymeric support characteristics, enables precise adjustment of steric and electronic features in these immobilized catalysts. This approach establishes structure-performance relationships, ultimately enabling the development of an engineered immobilized organocatalytic system that meets the desired criteria for activity, stability, and selectivity.

Keywords: organocatalysis; imine reduction; immobilized catalyst; continuous flow; asymmetric catalysis

Introduction

Chiral amines hold a pivotal role in organic chemistry as essential building blocks for various synthetic processes.[1] Only in 2022, the US FDA approved 15 small molecule drugs for clinical use, and notably, 11 of them were chiral drugs, from which eight contained chiral amine moieties.[2] An attractive and practical method for synthesizing enantiopure amines is the asymmetric transfer hydrogenation of imines.[3] Trichlorosilane ($HSiCl_3$), an inexpensive bulk chemical that serves as a starting material for the silicon chip industry, is often employed for hydrogen transfer in the organocatalytic reduction of ketimines,[4–5] offering an efficient pathway towards chiral amines.[6] In this context, a broad spectrum of Lewis base organocatalysts has been developed and tested. This is due to their ability to activate trichlorosilane, generating chiral hypervalent hydridosilicates that induce imine reductions with remarkable levels of enantioselectivity.[7]

Most of the catalytic systems described in the literature for ketimine reduction with $HSiCl_3$ involve amino acid-derived formamides for introducing chirality.[6] For instance, in previous work, we systematically designed and optimized a range of *N*-carbamate-amides and bisamides that originate from L-proline as straightforward organocatalysts for the enantioselective reduction of ketimides using $HSiCl_3$.[8] Our results highlighted the persistent influence of the uncatalyzed reaction in this process, underscoring the paramount importance of creating conditions where the rate of the catalysed process significantly surpasses the rate uncatalyzed one to establish an efficient and

enantioselective catalytic system. Careful structural adjustments in the organocatalyst resulted in a 600-fold increase in the reaction rate with respect to the uncatalyzed reaction allowing to conduct the imine reduction with enantiomeric excess as high as 86%.

When aiming at industrial applications, the immobilization of these catalysts onto suitable polymeric support offers several distinct advantages over their homogeneous counterparts.[9–10] This includes simplified workup procedures, the ability to easily separate and recover the supported systems from the reaction mixture, and the added convenience of recycling.[11] These advantages become especially important when dealing with enantioselective organocatalysts, which often require significant catalyst loading to achieve high levels of asymmetric induction. As such, the ability to recover and reuse the chiral component (usually the most costly part of the system) becomes a critical factor in assessing its practical utility. Moreover, the immobilisation of the catalyst can significantly impact various aspects of the catalytic system, including reagent and product diffusion to and from the active sites, as well as the microenvironment.[9,12]

Therefore, careful selection of the polymeric support and the method of catalyst immobilization is essential for developing efficient polymeric-supported asymmetric catalysts. However, the process of immobilizing a specific homogeneous catalyst is not always straightforward. At least four critical elements must be carefully considered: (i) the method of attaching catalytic sites to the support, (ii) the type and length of the spacer between the catalytic sites and the polymeric network, (iii) the density and location of catalytic sites within the polymeric network, and (iv) the physicochemical properties of the polymeric backbone.

In this work, we demonstrate that through a careful evaluation of the impacts of these factors, it is possible to engineer an immobilized organocatalyst with precision, resulting in highly efficient systems in terms of both activity and selectivity. Additionally, the heterogeneous characteristics of the resulting organocatalysts enable the enantioselective reduction of the model imine under continuous flow conditions, leading to an enhancement in asymmetric induction compared to the analogous batch reaction.

Results and Discussion

Synthesis and Characterisation of the Supported Organocatalysts

Firstly, the L-proline-derived *N*-carbonyl amide (as Lewis base catalysts for the asymmetric reduction of ketimines) was directly tethered to the support (Figure 1A). This was done through grafting onto commercially available functionalized macroporous PS-DVB (polystyrene-divinylbenzene) resins featuring as linkers benzylic amino groups ($-CH_2NH_2$) in their structure. The existence of these functional groups enables the direct synthesis of *N*-carbonyl amide by reacting the carboxylic acid groups of *N*-protected Cbz-L-proline with the corresponding amino-functionalized polymer. With this approach, the Lewis basic sites found in the organocatalyst -readily for the interaction with $HSiCl_3$ to form a hexacoordinated species able to transfer the H^+/H^- pair to the C=N double bond of the ketimine- are directly bonded to the polymeric backbone without the introduction of any additional spacer. This strengthens any possible elec-

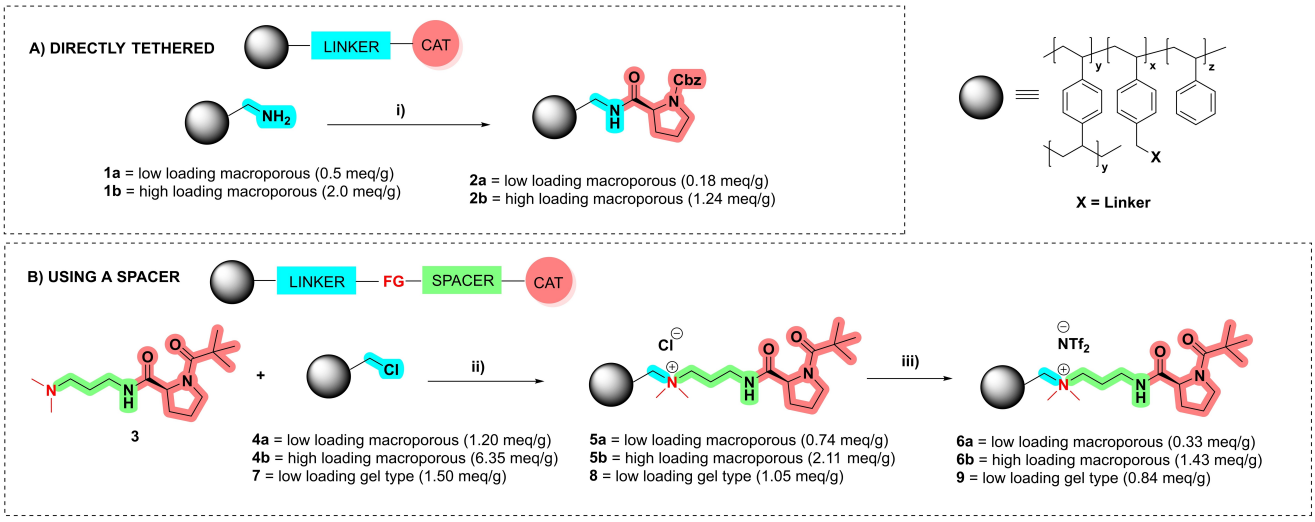


Figure 1. Synthetic strategies used in this study to obtain immobilized organocatalysts. i) Reaction conditions: 1 eq. **1a–b**, 3 eq. Et_3N, 3 eq. ClCOOEt, 3 eq. *N*-Cbz-L-proline, THF, 0 °C to room temperature, N_2 atmosphere, 20 h. ii) Reaction conditions: 1 eq. **4a–b** or **7**, 3 eq. **3**, DMF, 90 °C, 24 h. iii) Reaction conditions: 1 eq. **5a–b** or **8**, 1.1 eq. $LiNTf_2$, MeOH, room temperature, 24 h.

tronic or steric effects induced by the polymeric support.

In this sense, two PS-DVB macroporous resins (**1a–b** in Figure 1a) with different (low and high) degrees of functionalization (amine loadings of 0.5 and 2.0 meq·g^{-1}, respectively) were used as supports. The immobilization of *N*-Cbz-L-proline was carried out in dry THF using ethyl chloroformate as a coupling agent. The immobilised catalysts **2a** and **2b** were found to have loadings of 0.18 meq·g^{-1} and 1.24 meq·g^{-1}, respectively, based on elemental analysis. FTIR spectroscopy confirmed the incorporation of catalytic moieties into the polymeric matrix. For the grafted catalyst **2b**, one can observe a band at 3339 cm^{-1} corresponding to the N–H of the formed amide (Figure S1), along with bands at 1750 cm^{-1} (C=O of the carbamate) and 1689 cm^{-1} (C=O of the amide), which are characteristic of the two new C=O groups integrated into the polymeric matrix.

Alternatively, we fine-tuned the separation between the organocatalytic active site and the polymer support using an alkyl linker (Figure 1B). To accomplish this, we employed bisamide **3**, which, in addition to the *N*-carbonyl amide proline moiety, included a dimethyl amino group as a secondary functional group. This amino group is situated at a distance from the organocatalytic active site. In the resulting grafted catalyst, the linker responsible for grafting and the catalytic active site are physically separated thanks to the inclusion of a propylene spacer between them. This approach not only enables the anchoring process but also reduces the risk of steric and electronic hindrance imposed by the polymeric support. Consequently, the active sites exhibit characteristics that are more like those in homogenous catalysts.[9,13,14] Moreover, the use of bisamide **3** provided an additional benefit, as it introduced an *N*-pivaloyl-protected L-proline-derived *N*-carbonyl amide. This group has been proven to enhance catalytic performance by improving both the activity and the enantioselectivity in the reduction of imines with $HSiCl_3$.[7]

The immobilization of **3** (Figure 1B) was carried out using macroporous Merrifield resin with low and high Cl loading (1.20 and 6.35 meq·g^{-1} of polymer, **4a–b**) as an alkylating agent in DMF at 90 °C for 24 hours. The negative NBP (4-(4-Nitrobenzyl)pyridine) colorimetric test (Figure S2) confirmed the complete conversion of all -CH_2Cl groups into corresponding ammonium salts.[16] The FTIR-ATR of the immobilized catalyst **5b** revealed the emergence of two distinct bands at 1668 cm^{-1} and 1607 cm^{-1} analysis (Figure S3), corresponding to the C=O groups of the proline bisamide scaffold. These bands were absent in the initial Merrifield resin. Additionally, the absence of the C–Cl group signal at 1265 cm^{-1} indicated the replacement of all -CH_2Cl groups by the corresponding ammonium salt (–[CH_2-$N^+(CH_3)_2$-R][Cl^-]) on the immobilized system. Furthermore, the elemental analysis provided loadings of 0.74 meq·g^{-1} for **5a** and 2.11 meq·g^{-1} for **5b**, demonstrating the successful incorporation of the catalytic units.

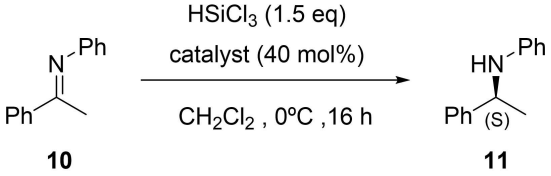
Another essential aspect of immobilised catalyst design is the choice of the ammonium salt counterion (e.g. Cl^-), as it determines the polarity of the resulting supported system.[17] This polarity can be customized via the nature of the anion by simple ion exchange.[18] Consequently, the Cl^- counterion was exchanged with NTf_2^- to create polymeric systems more compatible with nonpolar solvents, like CH_2Cl_2, the designated reaction medium for testing the immobilized catalyst.

The ion exchange was efficiently carried out by immersing polymers **5a–b** in a methanol solution of $LiNTf_2$ salt, yielding catalysts **6a–b** (Figure 1B). Elemental analysis revealed that the organocatalyst loading for the resulting anion-exchanged polymers was 0.33 meq·g^{-1} and 1.43 meq·g^{-1} for compounds **6a** and **6b**, respectively. The success of ion exchange was also confirmed by infrared spectroscopy (Figure S4). This analysis revealed the appearance of three distinct bands at 1183 cm^{-1}, 1135 cm^{-1}, and 1056 cm^{-1}, characteristics of the NTf_2^- anion, conclusively confirming the exchange of Cl^- for NTf_2^-.

Catalytic Evaluation of the Immobilised Catalysts

The organocatalysts prepared were tested for the reduction of ketimine **10** with $HSiCl_3$ at 0 °C using a 40 mol% catalyst loading (Scheme 1). To evaluate the influence of immobilization on catalyst efficiency, we adopted the optimal conditions that were previously established for homogeneous counterparts. Based on prior studies, we selected a ketimine concentration of 0.512 M, CH_2Cl_2 as the solvent, and a catalyst loading of 40 mol% at 0 °C. These experimental parameters were chosen as they have been shown to achieve higher enantioselectivity over a period of 16 hours.[8] The results obtained are summarized in Table 1.

Of the two covalent immobilization strategies selected, the one utilizing linkers and *N*-alkylated scaffolds (catalysts **5a–b** and **6a–b**) yielded better results compared to the linker-free approach, as bisamide Cbz-L-proline systems **2a–b** yield to racemic amines (Entry 1–2, Table 1). Ionic groups in the



Scheme 1. Benchmark asymmetric reduction of ketimine **10** is used to develop the organocatalysts in this work.

Table 1. Enantioselective reduction of ketimine **10** catalyzed by 40 mol% of organocatalysts **2a–b**, **5a–b** and **6a–b**.[a]

Entry	Catalyst	Conv. (%)[b]	Yield (%)[b]	*e.e.* (%)[c]
1	**2a**	47	33	8
2	**2b**	84	74	0
3	**5a**	100	100	0
4	**5b**	98	98	0
5	**6a**	98	98	32
6	**6b**	50	49	18

[a] Reaction conditions: Concentration **10** = 0.512 M, 1.5 eq. $HSiCl_3$, CH_2Cl_2, 0 °C, 16 h.
[b] Conversions and yields determined by ^{1}H-NMR on the crude reaction mixture.
[c] Enantiomeric excess determined by chiral HPLC (*S* configuration for the major enantiomer).

polymer structure, particularly NTf_2^-, exhibited asymmetric induction in the reduction reaction. Notably, catalysts **6a** and **6b** with NTf_2^- showed improved enantioselectivity, achieving 32% *e.e.* and 18% *e.e.* of the amine product, respectively, whereas **5a** and **5b** with chloride as a counterion produced the amine product in its racemic form (Entries 3–6, Table 1).

It is essential to highlight that in this process, the uncatalyzed reaction always plays a role, and achieving a situation where the catalyzed rate significantly exceeds the uncatalyzed rate is crucial for developing an efficient and enantioselective catalytic system.[8] This becomes even more critical when dealing with immobilization into macroporous polymers, as the availability of active sites and the effective diffusion of reagents to these sites are pivotal for achieving enantioselectivity. If the immobilized catalysts do not have good compatibility with the reagents, i. e. hindering diffusion, non-enantioselective reductions occur in the reaction solution, far from the chiral catalytic sites within the polymer pores of the microporous resin.

Therefore, while the enantioselectivity values are modest, the increase from 0% to 32% in enantioselectivity can offer valuable evidence to guide us in enhancing the catalyst's performance. It is evident that the presence of ammonium salts can create a specific microenvironment within the catalyst. This particular microenvironment can boost the reaction rate, favouring a more stereoselective process.[9,13,14] Furthermore, the more hydrophobic nature of the NTf_2^- counterion can enhance the compatibility between the support and the reaction medium, promoting better diffusion. This observation is further substantiated by the fact that polymers with lower loading displayed slightly higher enantiomeric excess. This once again underscores the significance of creating a specific microenvironment to attain an active and selective process.

Enhancing the Catalyst Efficiency by Varying the Polymer Nature

If the diffusion of reagents to the active sites is identified as a primary factor that can impede asymmetric induction, alternative types of polymers, as opposed to highly crosslinked macroporous supports, can be employed to mitigate such effects.[19] It is well-established that PS-DVB microporous resins, also known as gel-type resins, in the presence of a suitable solvent, cause a significant expansion in volume (swelling) and expose most of their active sites. This characteristic minimizes issues associated with mass transfer, addressing the challenge of achieving a supported catalyst not limited by diffusion. Hence, catalysts with a structure like that of compound **6a** but supported on a gel-type PS-DVB resin could potentially enhance the catalytic efficiency of the immobilized system, providing that diffusion represents one of the limiting factors.

To test this hypothesis, a gel-type Merrifield resin with a low degree of crosslinking (1% DVB), like polymer **6a**, was synthesized and characterized. For this, a polymer with a low degree of functionalization was chosen, as these systems had previously exhibited superior asymmetric induction. Consequently, resin **8** was produced by alkylating this polymer with compound **3**, followed by ion exchange to replace Cl^- with $LiNTf_2$, resulting in polymer **9**. These supported systems present loading of 1.05 meq·g^{-1} and 0.84 meq·g^{-1} for catalysts **8** and **9**, respectively. The FTIR-ATR spectroscopy confirms the intended structure of the catalysts. Both systems were found to be active in the reduction reaction, although the one with the chloride anion **8** did not exhibit significant asymmetric induction, resulting in the corresponding amine being obtained in a nearly racemic form (Entry 1, Table 2). However, as postulated, the gel-type polymer **9** with NTf_2^- as the counterion notably enhanced the enantioselectivity of the process, achieving an enantiomeric excess of 70% *e.e.* (Entry 2, Table 2). This clearly demonstrates the significant

Table 2. Enantioselective reduction of ketimine **10** catalyzed by 40 mol% of organocatalysts **8** and **9**.[a]

Entry	Catalyst	Conv. (%)[b]	Yield (%)[b]	*e.e.* (%)[c]
1	**8**	100	100	6
2	**9**	95	95	70

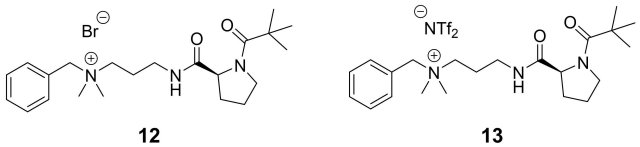
[a] Reaction conditions: Concentration **10** = 0.512 M, 1.5 eq. $HSiCl_3$, CH_2Cl_2, 0 °C, 16 h.
[b] Conversions and yields determined by ^{1}H-NMR on the crude reaction mixture.
[c] Enantiomeric excess determined by chiral HPLC (*S* configuration for the major enantiomer).

influence of the polymer's nature on the efficiency of the supported catalytic system.

P. Kočovský and colleagues have observed a similar effect regarding the immobilization of *N*-methylvaline-based organocatalysts for the enantioselective reduction of imines.[20–21] While the immobilization on solid-supported catalysts resulted in lower enantioselectivity compared to their soluble counterparts,[20] this can be attributed to a significant background non-enantioselective reaction, which is more pronounced due to diffusion problems in heterogeneous systems. In contrast, catalysts immobilized onto soluble dendrimeric supports do not exhibit such a decline in enantioselectivity.[21] This highlights the impact of the mass transfer limitations on the efficiency of the catalytic process, particularly in terms of enantioselectivity.

Hence, it appears that organocatalysts immobilized on macroporous polymeric supports may encounter diffusion issues for reagents to reach the catalyst's active sites within the polymeric matrix, thus limiting the attainment of higher enantioselectivity values. In contrast, the use of microporous resins helps mitigate these diffusion problems by enhancing access to the active centers. In fact, when conducting a swelling study of the two gel-type resins utilizing CH_2Cl_2, the solvent for the reduction reaction, it was observed that resin **8** (with Cl^- as anion) exhibited 49% swelling (Figure S5), whereas its equivalent with NTf_2^- (**9**) reached 90% swelling (Figure S6), approaching the nearly 100% swelling observed for the starting Merrifield resin. Swelling serves as a measure of the exposure of the functional groups, and this value is higher when the functional groups are more exposed. Therefore, the results obtained can be attributed to the greater swelling, and consequently, enhanced exposure observed for resin **9**.

In order to understand experimental outcomes linked with the matrix's nature, we conducted a detailed evaluation of a homogeneous counterpart **12** and **13** (Scheme 2) that replicates the structural characteristics of immobilized systems **8** and **9**, including necessary anchoring groups. The enantioselective reduction of ketimine **10** was performed with **12** and **13** under identical experimental conditions than for the heterogeneous systems. The results were revealing. Compound **12**, corresponding to the immobilized system **8**, achieved a 90% yield with a 5% *e.e.*, while compound 13, analogous to system 9, resulted in a 97% yield with 66% *e.e.* The partial solubility of compound **12** in CH_2Cl_2 might be a contributing factor to its lower enantioselectivity.



12 13

Scheme 2. Homogeneous organocatalysts used in this study.

Both the homogeneous and immobilized systems exhibited comparable levels of enantioinduction. This observation suggests that the differences in catalytic efficiency may be primarily due to the accessibility of the catalytic sites. Notably, when the gel-type polymer is adequately swollen by the solvents, the performance of both systems appears to converge. This outcome underscores the crucial role of the accessibility of active sites within the polymer matrix in determining the efficiency of the catalytic process, highlighting the intricate interplay between the physical structure of the polymer and the efficacy of the catalysis.

From Batch to Continuous Flow Systems

After confirming the enantioselective activity of polymer **9** in the reduction of the model imine, the feasibility of conducting this reaction in a continuous flow mode was investigated. Apart from the advantages inherent in a continuous flow system, such as enhanced safety, reproducibility, and efficient interaction between reagents and catalyst, it is theoretically possible to recover and reuse the catalyst multiple times. Therefore, continuous flow systems offer a straightforward setup for assessing the stability of a supported catalyst.

In general, it is recognized that the actual instantaneous catalyst/substrate ratios within the fixed-bed reactor, operating under flow conditions, are significantly higher than those under batch conditions. This can promote an increase in both the activity and enantioselectivity of the process, especially when the reaction can proceed in the absence of a catalyst.[9]

For the continuous flow reduction of the model imine using catalyst **9**, a system with two syringe pumps was employed (Figure S7). These pumps delivered the model imine and the reducing agent, both separately dissolved in dichloromethane. The fixed-bed reactor was established by loading the Omnifit glass column with dry catalyst **9**, filling it to half of its volume, using 1.169 g of polymer. Following this, dichloromethane was introduced to initiate a "swelling" process, causing the gel-like polymer to expand to nearly double its initial volume. This resulted in a final fixed-bed reactor with a volume of 3.34 mL. Under these conditions, the system was sealed and connected to the previously described setup to carry out the imine reduction using the same experimental conditions as in the case of homogeneous catalysts. A total constant flow rate of 7 $\mu L \cdot min^{1}$ was achieved by combining the flow rates of the imine solution, to ensure a high conversion of the ketamine. Although catalyst deactivation occurs over time, possibly due to

the hydrolysis of $HSiCl_3$ (Figure S8), which can obstruct active sites, the results obtained with this continuous flow catalytic setup outperform the same catalyst in a batch system (see Table 3).

The performance of catalyst **9** under flow conditions achieves an enantiomeric excess of 84%, which is higher than the 66% *ee* obtained with the structurally analogous homogeneous catalyst **13**. This observation is particularly significant as it suggests that the immobilized catalyst (catalyst 9) can outperform its homogeneous counterpart in terms of enantioselectivity, challenging the common perception that homogeneous catalysts are generally more efficient. Moreover, the enhanced enantioselectivity observed under flow conditions, surpassing the results in batch processes, is another critical aspect of our findings. While the batch process yields a 70% *ee*, the flow conditions facilitate an increase to 84% *ee*.

It should be noted that Benaglia and coworkers successfully demonstrated the feasibility of conducting the stereoselective reduction of imines with trichlorosilane under continuous flow conditions catalysed by different immobilized organocatalysts with levels of asymmetric induction like the ones obtained by our systems.[22] Their findings also highlight a decrease in asymmetric induction encountered in transitioning from batch to continuous flow processes. Thus, for instance, for the use of a catalytic reactor with a polymer-immobilized chiral picolinamide, a significant drop in enantiomeric excess was noted when shifting from batch processes (90% *ee*) to flow processes (47% *ee*).[23] Similarly, even in highly efficient catalytic systems that utilize immobilized imidazolidinone-based picolinamides with L-tyrosine as a chiral scaffold, a noticeable decline in catalyst efficiency is observed when transitioning from batch to continuous flow processes. Here, the enantiomeric excess decreases from 97% in the batch process to a range of 85–73% under continuous operation in flow conditions.[22]

Contrary to these findings our system demonstrates an increase in enantiomeric excess when the reaction is conducted under flow conditions.

Kinetic tests conducted under batch conditions for related homogeneous catalysts,[8] reveal that the concentration of the catalyst and the ratio of catalyst to substrate are critical factors influencing both the activity and enantioselectivity of the reaction. An interesting observation from these tests is that maintaining a high molar concentration of the catalyst, along with a high catalyst-to-substrate ratio, resulted in considerable efficiency even at low molar loadings. This efficiency is attributed to the creation of conditions where the rate of the catalyzed reaction significantly exceeds that of the uncatalyzed reaction. Such an environment optimizes the selectivity and overall effectiveness of the catalytic process, demonstrating the importance of these parameters in catalytic reactions.[8] The enhanced performance observed in the system when transitioning from batch to flow chemistry can indeed be attributed to specific operational conditions. Firstly, the use of higher concentrations of both the ketimine and the catalyst in our experiments (0.512 M compared to 0.05 M used in the systems reported above) plays a crucial role. This higher concentration likely facilitates more efficient and effective catalytic reactions, leading to improved outcomes. Secondly, the substantial catalyst/substrate ratios within the fixed bed reactor in the flow system are significantly higher than those in the batch process. This increase in the catalyst/substrate ratio can enhance the reaction efficiency by providing more catalyst sites for the substrate to interact with, thus increasing the likelihood of the desired reaction occurring. This setup in the flow system can be particularly effective in minimizing the impact of any competing uncatalyzed reactions, thereby improving the overall enantioselectivity and yield of the desired product.

These factors combined – higher concentration of reactants and favourable catalyst/substrate ratios – are key to understanding the superior performance of the flow system compared to traditional batch processes. This improvement underlines the potential benefits of flow chemistry, not only in terms of operational efficiency but also in potentially enhancing the catalytic performance. This insight is valuable for the field of asymmetric catalysis, indicating directions for optimizing catalytic processes.

Table 3. The catalytic efficiency of **9** for the enantioselective reduction of imine **10** using immobilized catalyst **9** under batch and continuous flow conditions.[a]

Entry	System	Conv.[c] (%)	Yield[c] (%)	*e.e.*[d] (%)
1	Batch[a]	95	95	70
2	Flow[b]	99	91	84

[a] Reaction conditions: Concentration **10** = 0.512 M, 1.5 eq. $HSiCl_3$, 40 mol% **9** (0.2447 g), CH_2Cl_2, 0 °C, 16 h, $V_{reactor}$ 1 mL. Productivity: 0.124 mmol of **11** $g^{-1}h^{-1}$.

[b] Reaction conditions: Concentration **10** = 0.512 M, 1.5 eq. $HSiCl_3$, CH_2Cl_2, 0 °C, $V_{reactor}$ 3.338 mL, 1.169 g catalyst **9**, residence time: 7.9 h, Productivity: 0.167 mmol of **11** $g^{-1}h^{-1}$.

[c] Conversions and yields determined by ^{1}H-NMR on the crude reaction mixture.

[d] Enantiomeric excess determined by chiral HPLC (*S* configuration for the major enantiomer).

Conclusion

This work demonstrates that the assessment of various design factors associated with the immobilization

strategy provides the ability to precisely adjust the steric and electronic characteristics of the catalysts. By engineering these factors, it is possible to create a tailored immobilized organocatalytic system that meets the desired criteria for activity, stability, and selectivity. Polymer-supported systems can prove to be equally efficient as their homogeneous counterparts, even in terms of enantioselectivity, given that the right parameters are optimized. The design of a fixed-bed reactor using the best-immobilized catalyst **9** has enabled the enantioselective reduction of imines in a continuous flow system achieving 91% yield and 84% *ee.* of the (S)-enantiomer of the amine product, which is higher than the 66% *ee* obtained with the structurally analogous homogeneous catalyst **13**. This observation is particularly significant as it suggests that the immobilized catalyst under flow conditions can outperform its homogeneous counterpart in terms of enantioselectivity, challenging the common perception that homogeneous catalysts are generally more efficient, showcasing the benefits of combined use of immobilized catalyst and flow chemistry. This accumulated knowledge will pave the way for a systematic approach to developing polymer-supported chiral catalysts in the future.

Experimental Section

General Procedure for the Asymmetric Reduction with $HSiCl_3$

To a stirred solution of imine **10** (0.1 g, 0.512 mmol) and the corresponding catalyst (40 mol%) in dry CH_2Cl_2 (1 mL) at 0 °C and under nitrogen atmosphere, trichlorosilane (77 µL, 0.768 mmol) was added. The reaction mixture was stirred at 0 °C for 16 h. Then, a saturated $NaHCO_3$ solution was added to the reaction mixture and the product was extracted with CH_2Cl_2 (3×10 mL). The organic phase was washed with brine (1×10 mL), dried over anhydrous $MgSO_4$, and the solvent was removed by distillation at reduced pressure. Conversion and yield were determined using the crude product by ^{1}H-NMR, and enantiomeric excess by HPLC (in all reactions of this work (*S*)-enantiomer was the one obtained in excess).

General Procedure for the Asymmetric Reduction with $HSiCl_3$ for the Flow Process

Two lines were connected to an Omnifit reactor loaded with 1.169 g of polymer **9** (length reactor: 8.5 cm, internal diameter: 1 cm). The reactor was stabilized by a flow rate of 50 µL·min^{-1} of dichloromethane to optimize the correct swelling of the polymer and then was cooled at −10 °C by using a jacketed reactor and cryocool. In the first line, a solution of 0.70 M imine **10** in dry CH_2Cl_2 under a nitrogen atmosphere was pumped (with a syringe pump) into the reactor with a flow rate of 5 µL·min^{-1}. In the second line, a solution of 2.63 M $HSiCl_3$ in dry CH_2Cl_2 under a nitrogen atmosphere was pumped (with a syringe pump) with a flow rate of 2 µL·min^{-1}. The reaction fractions were collected on a saturated $NaHCO_3$ solution using an automatic fraction collector to halt the reaction through hydrolysis of any unreacted $HSiCl_3$. Each fraction was extracted with CH_2Cl_2 (5 mL), washed with brine (5 mL), dried over $MgSO_4$ anhydrous, and the solvent was removed by distillation at reduced pressure. Conversion and yield were determined using the crude product by ^{1}H-NMR, and enantiomeric excess by HPLC (in all reactions of this work (*S*)-enantiomer was the one obtained in excess).

Synthesis and Characterisation of the Immobilised Catalysts

All synthetic procedures and the full characterisation details are included in the supporting information.

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References

[1] T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753–819.
[2] T. D. Benedetto, L. Bagnoli, O. Rosati, F. Marini, C. Santi, L. Sancineto, *Pharmaceutica* **2022**, *14*, 2538.
[3] L. Deng, X. Liu, S. Song, *Org. Chem. Front.* **2022**, *9*, 874–889.
[4] R. A. Benkeser, D. Snyder, *J. Organomet. Chem.* **1982**, *225*, 107–115.
[5] K. K. Popov, J. L. P. Campbell, O. Kysilka, J. Hošek, C. D. Davies, M. Pour, P. Kočovský, *J. Org. Chem.* **2022**, *87*, 920–943.
[6] W. Chen, C.-H. Tan, H. Wang, X. Ye, *Eur. J. Org. Chem.* **2021**, *2021*, 3091.
[7] S. Guizzetti, M. Benaglia, *Eur. J. Org. Chem.* **2010**, 5529–5541.
[8] M. Maciá, R. Porcar, V. Martí-Centelles, E. García-Verdugo, M. I. Burguete, S. V. Luis, *Molecules* **2021**, *26*, 6963.
[9] B. Altava, M. I. Burguete, E. Garcia-Verdugo, S. V. Luis, *Chem. Soc. Rev.* **2018**, *47*, 2722–2771.
[10] C. Rodríguez-Escrich, M. A. Pericàs, Asymmetric Organocatalysis: New Strategies, Catalysts, and Opportunities: Volume 1–2, **2022**, *1–2*, 349–391.
[11] P. A. Jacobs, D. E. Devos, I. F. J. Vankelecom, Chiral Catalyst Immobilization and Recycling; VCH Publishers: Weinheim, **2000**.
[12] A. Bastero, D. Font, M. A. Pericàs, *J. Org. Chem.* **2007**, *72*, 2460–2468.

[13] D. Font, S. Sayalero, A. Bastero, C. Jimeno, M. A. Pericas, *Org. Lett.* **2008**, *10*, 337–340.
[14] E. Alza, X. C. Cambeiro, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 3717–3720.
[15] J. M. Andres, N. de La Cruz, M. Valle, R. Pedrosa, *ChemPlusChem* **2016**, *81*, 86–92.
[16] F. Galindo, B. Altava, M. I. Burguete, R. Gavara, S. V. Luis, *J. Comb. Chem.* **2004**, *6*, 859–861.
[17] V. Sans, N. Karbass, M. I. Burguete, V. Compañ, E. García-Verdugo, S. V. Luis, M. Pawlak, *Chem. Eur. J.* **2011**, *17*, 1894–1906.
[18] N. Karbass, V. Sans, E. García-Verdugo, M. I. Burguete, S. V. Luis, *Chem. Commun.* **2006**, 3095–3097.
[19] D. C. Sherrington, *Chem. Commun.* **1998**, 2275–2286.
[20] A. V. Malkov, M. Figlus, P. Kočovský, *J. Org. Chem.* **2008**, *73*, 3985–3995.
[21] M. Figlus, S. T. Caldwell, D. Walas, G. Yesilbag, G. Cooke, P. Kočovský, A. V. Malkov, A. Sanyal, *Org. Biomol. Chem.* **2010**, *8*, 137–141.
[22] R. Porta, M. Benaglia, R. Annunziata, A. Puglisi, G. Celentano, *Adv. Synth. Catal.* **2017**, *359*, 2375–2382.
[23] R. Porta, M. Benaglia, R. Annunziata, A. Puglisi, G. Celentano, *Adv. Synth. Catal.* **2017**, *359*, 2375–2382.