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Asymmetric aldol reaction in a continuous-flow reactor catalyzed by a highly reusable heterogeneous peptide

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ABSTRACT

A solid-supported peptide-catalyzed continuous-flow (CF) process was developed for asymmetric aldol reactions. The catalyst was readily synthesized and immobilized by solid-phase peptide synthesis (SPPS) on a swellable polymer support in one single step. Ignoring the peptide cleavage from the resin means no work-up, no purification, and no product loss. After thorough optimization of the reaction conditions, synthetically useful β-hydroxyketone products were obtained in high yields and stereoselectivities. It was found that the heterogeneous catalytic reaction is diffusion-controlled under the present conditions; thus, elevation of the pressure is necessary to maximize conversion of the flow process. Besides being simple and efficient, the described method is also rapid and promisingly productive, with short residence times on the catalyst bed. The immobilized peptidic catalyst is highly recyclable, while further advantageous features are the ease of product isolation and the possibility of facile scale-up, furnishing sustainable catalytic methodology.

1. Introduction

Asymmetric C–C bond formation has always been a cardinal subject in organic chemistry. Around the turn of the century, proline (Pro) was introduced as a promising new catalyst for reactions involving enamine intermediates [1–3]. In the golden age of asymmetric catalysis, a huge number of Pro-derived organocatalysts were developed that demonstrated enhanced catalytic activity and selectivity [4–14]. Short peptides and peptide-like molecules (as Pro mimetics) proved to be excellent catalysts for asymmetric transformations [15–22]. Small, rigid catalysts offer only a limited number of sites for structural and functional diversity, whereas synthetic peptides have the advantage of designable modularity as they are made up from the same chiral building blocks (amino acid residues) as enzymes [23,24]. The most reactive peptidic organocatalysts developed to date for the aldol [25] and Michael [26,27] reactions were reported by Wennemers et al. These tripeptides contain Pro and carboxylic acid moieties in a specific orientation to each other [28]. It has been shown that both the secondary amine residue and the carboxyl group are crucial for effective catalysis [29,30], while immobilization of the peptide on a solid support does not weaken its effectivity, but ensures excellent ease of use, and catalyst reusability [31,32].

CF technologies have captured attention in modern synthetic chemistry as they offer a massive number of advantages over conventional batch procedures, for example, the efficient mixing of substrates, faster heat and mass transfer, and shorter reaction times [33–39]. The well-regulated CF reactor concept enables reactions to be performed with an unprecedented level of control. The most important reaction parameters (such as flow rate, pressure, and temperature) can be adjusted and monitored quickly and precisely [35,40–43]. The need for the large-scale use of reagents and solvents is eliminated, so that the screening of reaction conditions becomes simple and time- and cost-efficient, which implies even rapid library synthesis and an opportunity for automatization [44–47]. Heterogenizing homogeneous catalysts on a solid support is a trend toward the increase in the efficiency of synthetic techniques [48–51]. Through the incorporation of immobilized catalysts and reagents, the scope of flow chemical processes can be further broadened [52–62]. In consequence of these benefits, the conversion of laboratory-based flow chemistry experiments to the subsequent production scale is straightforward [63,64].

A literature search reveals the thought-provoking finding that aldol reactions in standard batch mode involving the use of peptides or other Pro mimetics as catalysts usually demand many hours or even days if high yields and high stereoselectivities are to be attained (Table S1, see Supporting information). In the last few years, several CF approaches have also been described for organocatalytic aldol reactions; but in most cases, these have a number of

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drawbacks such as (i) long process times [65], (ii) difficulties of product isolation [66], and (iii) lower conversions [67] that limit their practical applicability yet. It must be noted here that, around the final stage of the preparation of this manuscript, Pericas et al. reported a promising CF method for aldol reactions with an immobilized proline derivative as organocatalyst [68].

With the aim of creating a more sustainable and industrially reliable catalytic procedure for stereoselective aldol reactions, we have developed a simple and efficient CF method in which a solid-supported peptide is utilized as chiral organocatalyst. The described technique permits outstanding catalyst reusability, ease of product isolation, and the opportunity of facile scale-up. Reaction condition optimization led to high yields, stereoselectivities, and productivities. Short residence times were utilized on the catalyst bed, this being the fastest CF technique to date to the best of our knowledge.

2. Experimental

2.1. General information

The materials and reagents used were of the highest commercially available grade and were applied without any further purification steps. Flash column chromatography was performed on Merck silica gel 60, particle size 63–200 μm, and analytical thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} plates. Compounds were visualized by means of UV or $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer, in $CDCl_3$ as solvent, with TMS as internal standard, at 400.1 and 100.6 MHz, respectively. MS analysis was carried out with an Agilent 1100 LC/MSD Trap. HPLC analyzes were performed on an analytical HPLC with a diode array detector from JASCO. An H-Cube® system was utilized as CF reactor.

2.2. Synthesis of catalysts

The peptidic catalysts were synthetized manually by a solid-phase technique, utilizing 9H-fluoren-9-ylmethoxycarbonyl/*tert*-butyl (Fmoc/*t*Bu) chemistry on two solid supports: polyethylene glycol (PEG)–polystyrene (PS) copolymer without any linker (TentaGel, with a loading of 0.27 mmol g^{-1}), and PS resin with a 4-methylbenzhydrylamine linker (PS-MBHA, with a loading of 0.64 mmol g^{-1}) (Fig. 1). When TentaGel resin was utilized, the whole peptide synthesis procedure was carried out in DMF; for PS-MBHA, DMF/CH_2Cl_2 1:1 was used as solvent. Before any synthetic steps, the resin was swollen by agitation for 1 h in the applied solvent. In the case of PS-MBHA, further treatment with 5% *N*,*N*-diisopropylethylamine (DIEA) solution was necessary to liberate the amino function from the HCl salt form. DIEA (6 eq) was added to a solution of Fmoc-protected amino acid (3 eq) and 1-[*bis*-(dimethylamino)methyliumyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridine-3-oxide (HATU, 3 eq). The activated amino acid was then added to the amino-functionalized resin, and the mixture was agitated for 3 h. After coupling, the resin was washed (CH_2Cl_2 3×, MeOH 2×, CH_2Cl_2 3×), and the amino acid incorporation was checked by means of the Kaiser or isatin test [69,70]. Fmoc deprotection was carried out in a solution of 2% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2% piperidine with agitation for 2 × 15 min. After filtration, the resin was washed, and the coupling and deprotection steps were repeated. Finally, the *t*Bu side-chain protecting group was removed from the aspartic acid (Asp) residue in a mixture of trifluoroacetic acid (TFA) and H_2O (9:1 v/v) at room temperature (RT) for 3 h (Scheme 1). After removal of TFA in vacuo, the resin was washed thoroughly (CH_2Cl_2 6×, MeOH 5×, CH_2Cl_2 6×) and was then kept at RT for 6 h to dry. The immobilized catalyst was utilized as TFA salts after the SPPS.

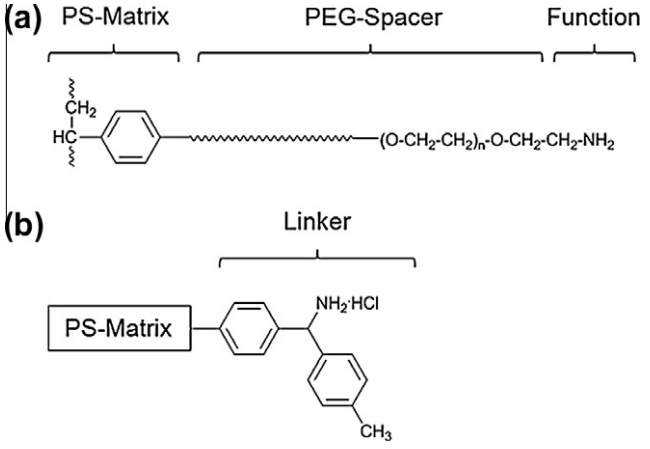


Fig. 1. Solid supports utilized in this study for catalyst immobilization: (a) TentaGel, (b) PS-MBHA.

2.3. Analysis of catalysts

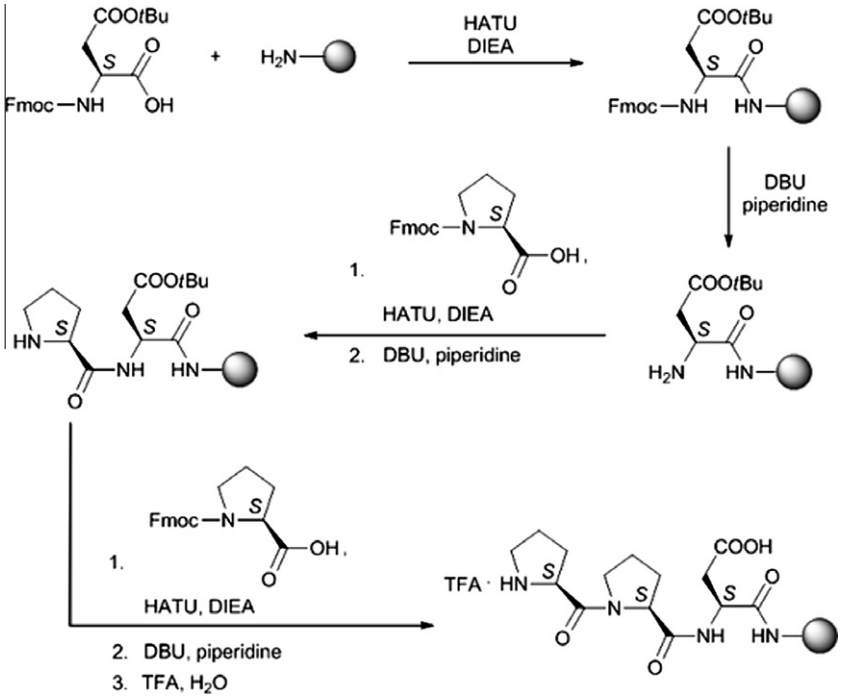
The structure of the TentaGel-immobilized catalysts was checked by means of suspension-phase ^{13}C NMR measurements. In the case of PS-MBHA-immobilized catalysts, the swelling properties of the resin made suspension-phase NMR unfeasible. MS and RP-HPLC investigations were therefore carried out after cleavage from the resin in a mixture of thioanisole, 1,2-ethanedithiol (EDT), TFA, and trifluoromethanesulfonic acid (TFMSA) (2:1:20:2 v/v/v/v) for 0.5 h at −10 °C and then at RT for 1.5 h. The peptide was next precipitated by the addition of cold Et_2O, collected by filtration and dissolved in TFA. After reduction of the TFA volume to 1 mL by evaporation, the peptide was precipitated with Et_2O, collected by filtration, dissolved in 10% AcOH and lyophilized. The detailed analytical data are presented in Supporting information.

2.4. CF methodology

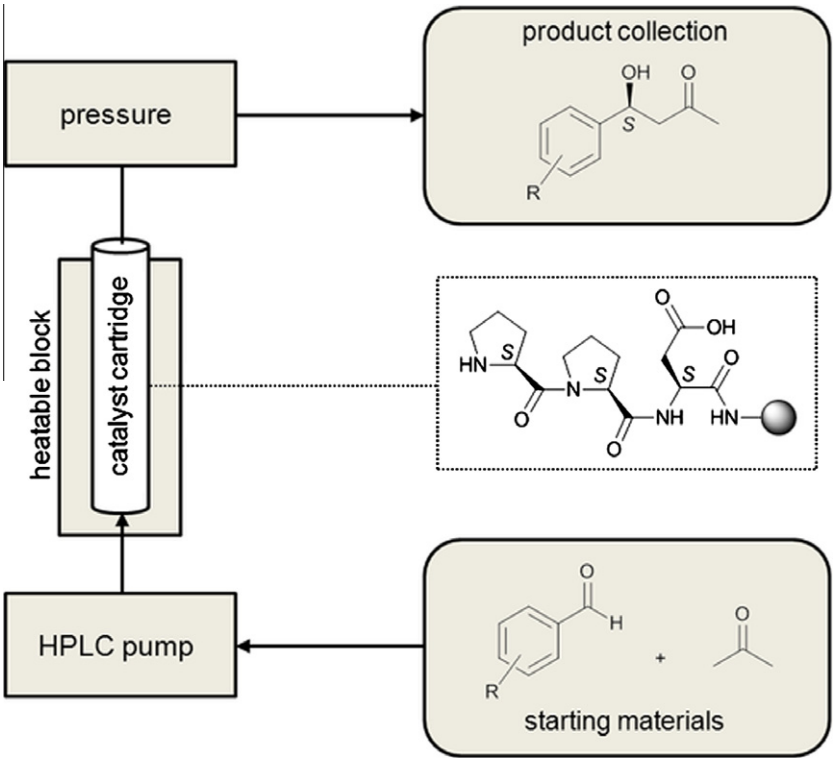
Flow experiments were performed in a dedicated high-pressure CF reactor with a fixed catalyst bed (H-Cube®, operated in "no H_2" mode). For the experiments 300 mg of the solid-supported peptide was incorporated into a replaceable stainless steel cartridge with internal dimensions of 70 × 4 mm. The filled cartridge was placed into a stainless steel block, which contains a Peltier heating system that can be heated to 100 °C. A back pressure valve was built in to ensure constant pressures up to 100 bar. The reaction mixture was pumped through the cartridge by means of an HPLC pump (Knauer WellChrom HPLC-pump K-120) at flow rates of 0.01–1.0 mL min^{-1}. This experimental setup allowed the systematical adjustment of the most important reaction parameters such as catalyst type, pressure, temperature, and flow rate in order to determine the optimal conditions. A brief outline of the CF catalytic system is presented in Scheme 2 [71].

2.5. General aspects of the preparation of aldol products in CF

For the CF method development, 20 mg (0.13 mmol, 1 eq) *p*-nitrobenzaldehyde (*p*NBA) and 0.9 mg (0.013 mmol, 0.1 eq) imidazole were dissolved in 5 mL acetone. The solution was homogenized by sonication for 3 min and was then pumped through the CF reactor under the appropriate conditions. The completion of the reaction was checked by TLC with a mixture of *n*-hexane/EtOAc as eluent. The crude aldol products were evaporated and then, if necessary, purified by column chromatography with a



Scheme 1. Synthesis of the heterogeneous catalyst H-Pro-Pro-Asp-NH-*resin*.



Scheme 2. A brief outline of the CF organocatalytic procedure.

mixture of *n*-hexane/EtOAc as eluent. The β-hydroxyketones were characterized by NMR spectroscopy and chiral NP-HPLC. The detailed analytical data can be found in Supporting information. Between two reactions in the CF reactor, the catalyst bed was washed for 10 min with acetone at 1 mL min^{-1}.

2.6. Measurement of the residence time on the catalyst bed

The residence time on the catalyst bed was determined by pumping an acetone solution of ink through the system and measuring the time that elapsed between the first contact of the

dye with the resin and the moment when a blue color appeared at the column output.

3. Results and discussion

3.1. Catalyst synthesis and immobilization

Employing a peptide as catalyst was the best possible choice as the catalyst synthesis and the immobilization can easily be combined in SPPS, thereby eliminating the need for further synthetic steps, and it offers the highest structural diversity. After the coupling steps, the deprotection of the carboxyl side chain was carried without cleavage of the peptide, as non-TFA-labile resins were used as support for the SPPS, which served further on as catalyst carrier (Fig. 1 and Scheme 1). This experimental setup is simple and reasonably economical, as there is no need for the time-consuming peptide work-up and purification steps. After thorough washing of the resin, the heterogenized organocatalyst was ready to use in CF. Currently, the most effective peptidic organocatalyst for aldol reactions is the tripeptide H-Pro-Pro-Asp-NH_2 [25], and we therefore chose this catalyst initially for CF method development.

3.2. Optimization of the reaction conditions

For optimization of the initial reaction conditions, the aldol reaction between *p*NBA and acetone was chosen as test reaction, with imidazole as base to prevent the formation of elimination side product. Acetone served not only as reagent, but also as solvent. As concerns the catalyst accessibility, appropriate swelling of the solid support is a crucial factor. In polar solvents, TentaGel resin swells better than PS-MBHA [72]; hence, the H-Pro-Pro-Asp-NH-*resin* catalyst was initially synthetized on TentaGel (catalyst **1**) (Fig. 2). For rapid fine-tuning of the aldehyde concentration in the reaction mixture, an initially high flow rate of 0.5 mL min^{-1}, RT and atmospheric pressure were applied. This quick screening indicated that the lower the amount of aldehyde in the reaction mixture, the higher the conversion (Fig. 3). A concentration of 4 mg mL^{-1} seemed to be a good compromise between conversion and productivity.

There are a number of examples in the literature where elevation of the pressure in organocatalytic procedures led to increased

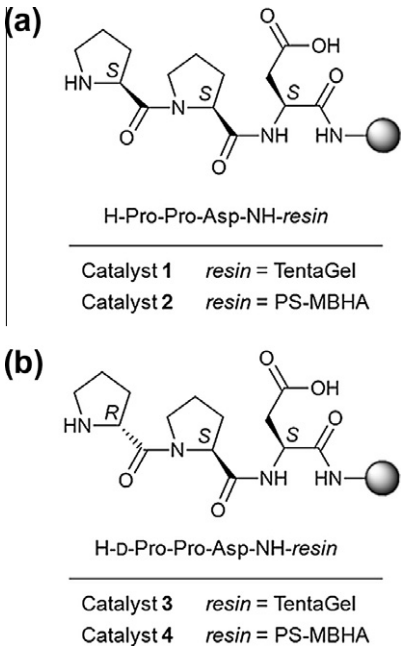


Fig. 2. Heterogeneous peptidic catalysts.

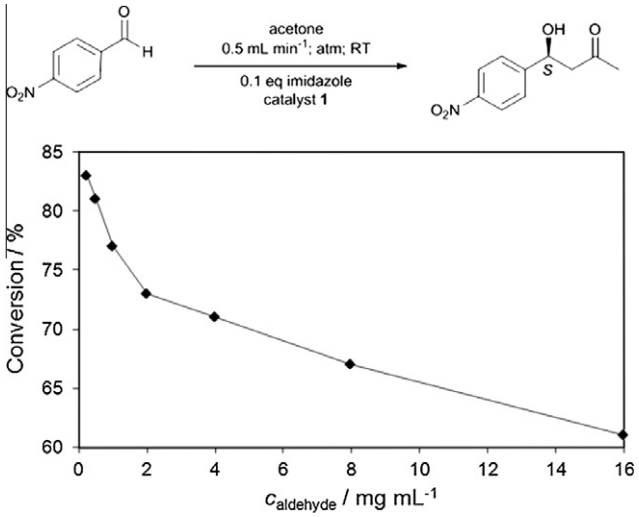


Fig. 3. Fine-tuning of the concentration of *p*NBA in the CF test reaction.

conversion and selectivity [73–76]. Hence, we also investigated the pressure dependence of the aldol reaction. Even at atmospheric pressure ($c_{aldehyde}$ = 4 mg mL^{-1}; flow rate = 0.5 mL min^{-1}; RT), a conversion of >70% and an *ee* of 80% could be achieved, but increase in the pressure resulted in still higher conversions up to an optimal 60 bar (Fig. 4). Further elevation to 100 bar was not beneficial, and the conversion remains steady at around 80%. (It is noteworthy that *ee* was not dependent on the pressure.) This phenomenon raises the question of whether the conversion is dependent on the catalyst activity itself or is influenced by the transport phenomena of the reactants in the matrix of the polymer. To probe the diffusion dependence, the Koros–Nowak test was performed [77,78]. When the catalyst loading in the cartridge was halved by simply using a mixture of 150 mg blank TentaGel resin and 150 mg catalyst **1**, the conversion of the same reaction decreased from 81% to 52%. The fall in the conversion is not proportional to the loading decrease. Consequently, the reaction is diffusion-controlled, and the effect of the elevated pressure is equivalent to an increase in the surface area of the catalyst.

To improve the conversion further, we tried elevating the temperature. It emerged that heating led to higher conversions, but also dramatically lowered *ee*. For example, at 80 °C, 60 bar and a flow rate of 0.5 mL min^{-1}, the conversion was nearly quantitative,

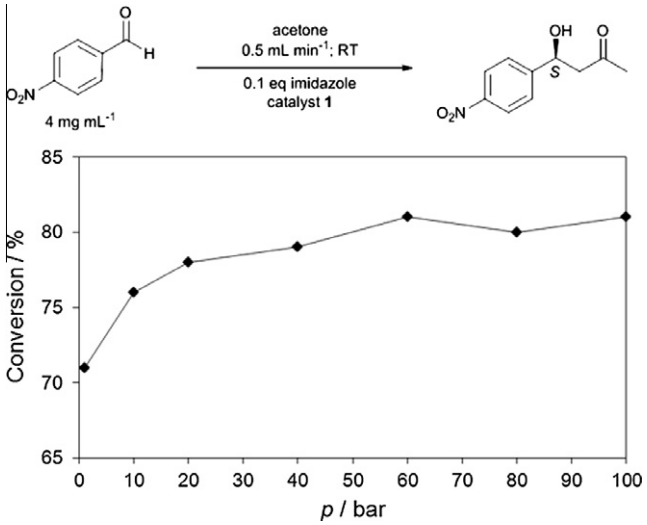


Fig. 4. Investigation of the pressure dependence of the test aldol reaction in CF.

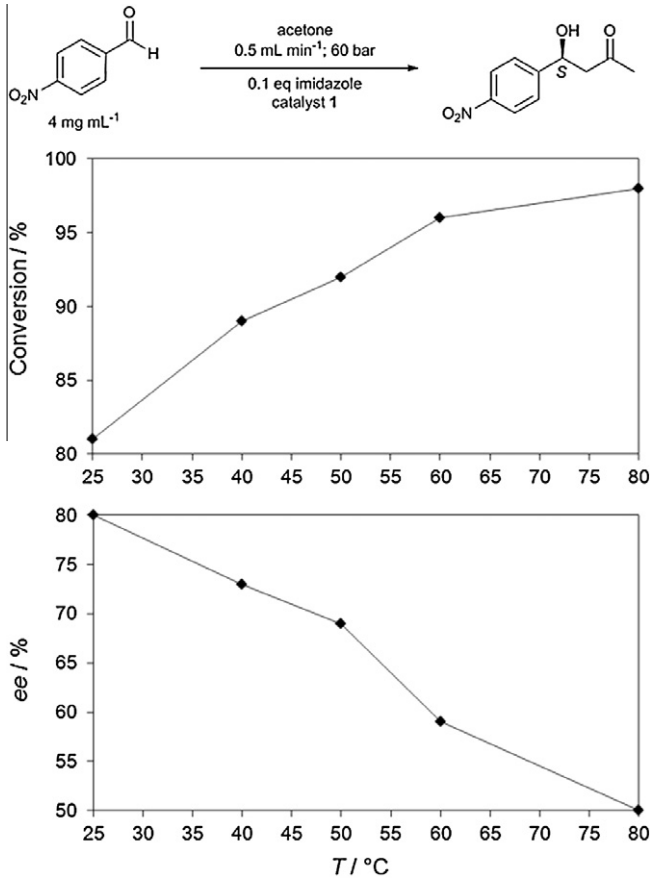


Fig. 5. Investigation of the temperature dependence of the test aldol reaction in CF.

but *ee* fell to 50% (Fig. 5). Thus, RT was regarded as optimal temperature.

In further parameter screening, the aim was to make the procedure efficient while maintaining high conversion and selectivity. Under the previously optimized reaction conditions, the flow rate was also fine-tuned for optimization of the residence time on the catalyst bed; the longer the residence time, the higher the conversion. When the flow rate was reduced to the optimal 0.1 mL min^{-1}, the residence time was long enough to achieve quantitative conversion and 80% *ee*. Even at 1 mL min^{-1}, the conversion was still nearly 60% (Fig. 6). It is worth mentioning that the *ee* was not dependent on the flow rate.

For additional optimization, the peptidic catalyst too was fine-tuned. As a solid support of the H-Pro-Pro-Asp-NH-*resin*, PS-MBHA (catalyst **2**) was tested under the previously optimized conditions. Its poorer swelling properties in acetone resulted in lower conversion and *ee* than with catalyst **1** (Table 1, entry 4). H-D-Pro-Pro-Asp-NH_2 is an effective catalyst for the 1,4-addition of aldehydes to nitroolefins [26]. We were interested in its efficiency in aldol reactions and tested the effect of replacement of the N-terminal L-Pro by D-Pro. H-D-Pro-Pro-Asp-NH-*resin* was synthetized on TentaGel (catalyst **3**) and also on PS-MBHA (catalyst **4**) as solid support, but in both cases, the conversion and *ee* were dramatically less than with catalyst **1** (Table 1, entries 5 and 6). The structures of the utilized catalysts are depicted in Fig. 2.

3.3. Results of the test reaction and comparison with the batch data

Under the overall optimized reaction conditions, with catalyst **1**, the corresponding β-hydroxyketone product of the test reaction was obtained in a yield of >99% with 80% *ee* (Table 1, entry 2).

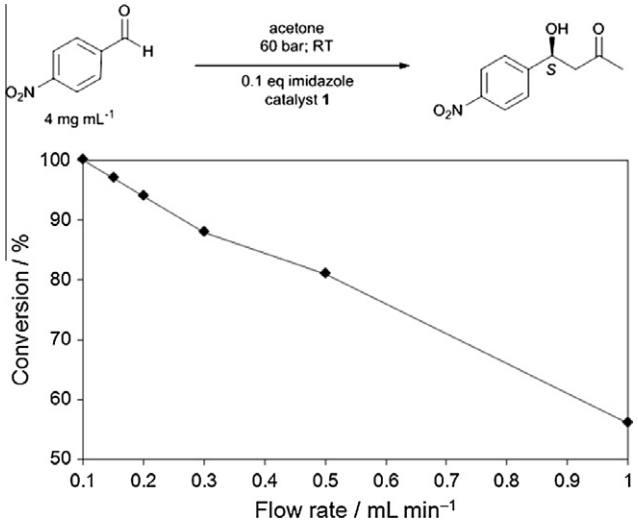


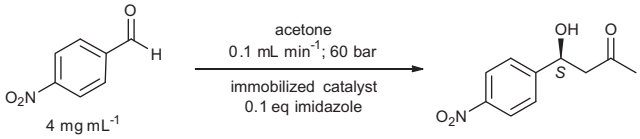
Fig. 6. Fine-tuning of the flow rate in the test CF reaction.

When the reaction was performed at 4 °C instead of RT, *ee* increased to 85%, while the isolated yield was still around 90% (Table 1, entry 3). It is noteworthy that no self-aldol or H_2O-eliminated side product was observed at all. At the optimal flow rate of 0.1 mL min^{-1}, the residence time on the catalyst bed was only 6 min, and it took 50 min to pump through a 5-mL aliquot of the reaction mixture, leading to around 27.5 mg crude product. When the same solid-supported catalyst was used for the aldol reaction between *p*NBA and acetone in a simple flask, a reaction time of 6 h was needed for completion (Table 1, entry 1), and a somewhat lower yield and *ee* were achieved than in CF [32]. When other Pro-derived organocatalysts were employed in batch, the reaction times were even longer (Table S1, entries 1–14). It must be noted here that literature batch reactions were usually carried out in a larger volume than in our small-scale test experiments, but scaling up in CF is straightforward through extension of the reactor size. On collection of the solution of the crude product material, no work-up or purification steps were needed, which further enhances the efficacy of the described method. These promising results are due to the beneficial features of the utilized technique: the application of CF, the swellable polymer-supported peptidic catalyst, and the high local catalyst concentration in the catalyst bed and the high pressure.

3.4. Testing of the catalyst reusability

The efficacy of a reaction mediated by a solid-supported catalyst may be characterized by the degree of reusability of the catalyst. Accordingly, the test aldol reaction between *p*NBA and acetone was repeated under the optimized reaction conditions, the same portion of catalyst **1** loaded in the cartridge being recycled. It was found that after the 20th consecutive experiment, the conversion was still quantitative and *ee* was 80%, just as in the first reaction (Table 2). In each run, a 5-mL aliquot of the reaction mixture was pumped through the system in 50 min, leading to around 27.5 mg crude product without further purification. When all of the test reactions involved in the catalyst recycling study were taken into account, the finding was that, after nearly 17 h of persistent use under optimal flow conditions, the immobilized peptidic catalyst was still as active as initially. The described CF technique is therefore prominently robust. In order to determine the turnover number (TON) of the immobilized catalyst, the experiment was run further after the recycling study, utilizing the same

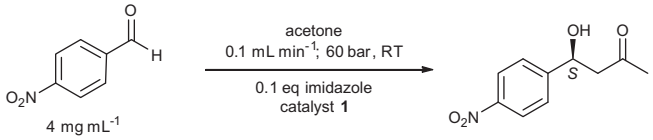
Table 1
Fine-tuning of the catalyst for the aldol reaction between *p*NBA and acetone under the optimized flow conditions, and comparison of the CF results with a batch reference from the literature.



Entry	Process	Catalyst	*T* (°C)	Time (min)[a]	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1[e]	Batch	**1**	RT	360	n.d.	94	78
2	CF	**1**	RT	6	Quant.	>99	80
3	CF	**1**	4	6	90	89	85
4	CF	**2**	RT	6	71	68	62
5	CF	**3**	RT	6	29	27	−26[f]
6	CF	**4**	RT	6	19	16	−18[f]

[a] Reaction time of the batch experiment, residence time of the CF reactions.
[b] Determined by ^{1}H NMR spectroscopic analysis of the crude material.
[c] Yield of isolated product.
[d] Determined by chiral-phase HPLC analysis.
[e] Batch reference from the literature [32].
[f] Absolute configuration of the resulting β-hydroxyketone inverted to *R*.

Table 2
Testing of the reusability of catalyst **1** in CF under optimal conditions.



Entry	Cycle	Conv. (%)[a]	Yield (%)[b]	*ee* (%)[c]
1	1–5	98-quant.	97–>99	79–80
2	6–10	Quant.	97–>99	78–81
3	11–15	Quant.	>99	79–80
4	16–20	99-quant.	98–>99	79–80

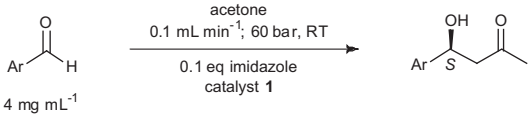
[a] Determined by ^{1}H NMR spectroscopic analysis of the crude material.
[b] Yield of isolated product.
[c] Determined by chiral-phase HPLC analysis.

portion of resin and the optimized CF conditions, with continuous pumping-through of a 4 mg mL^{-1} solution of *p*NBA and 0.1 eq imidazole in acetone [79]. The CF conditions resulted in a TON of 710 [80], whereas the TON calculated from the batch data was 472 [32].

3.5. Investigation of the scope and applicability of the method

In order to verify the scope and applicability of the described CF method, a number of further aldol reactions between various aromatic aldehydes and acetone were carried out under the optimized conditions with catalyst **1**. The data in Table 3 (entries 1–8) demonstrate that, for aldehydes with an electron-withdrawing group on the aromatic ring, good or excellent yields (68–>99%) and high *ee* (75–80%) were obtained. When the conversion was quantitative, no further work-up or purification steps were needed (Table 3, entries 1–4). The yield increased with the electron-withdrawing capability of the substituting residue and was dependent on the position of the electron-withdrawing group: in the aldol reaction between *o*-chlorobenzaldehyde and acetone, the yield was >99%, but for *m*- and *p*-chlorobenzaldehyde, it was lower. Aldehydes bearing an electron-donating substituent on the aromatic ring or no substituent at all proved to be weaker reaction partners in the aldol reaction with acetone. Lower yields (27–59%), but still high

Table 3
Investigation of the scope and applicability of the CF organocatalytic procedure under the overall optimized reaction conditions.



Entry	Ar[a]	Productivity[b]	Conv. (%)[c]	Yield (%)[d]	*ee* (%)[e]
1	*p*-$NO_2C_6H_4$	1.96	Quant.	>99	80
2	*o*-$NO_2C_6H_4$	1.96	Quant.	>99	79
3	*p*-NCC_6H_4	2.26	Quant.	>99	74
4	*o*-ClC_6H_4	2.11	Quant.	>99	79
5	*m*-ClC_6H_4	1.50	78	71 (5)[f]	76
6	*p*-ClC_6H_4	1.48	80	70 (7)[f]	78
7	*p*-BrC_6H_4	1.09	76	68 (6)[f]	80
8	*p*-FC_6H_4	2.05	Quant.	86 (13)[f]	79
9	*o*-$MeOC_6H_4$	0.81	39	37	76
10	C_6H_5	1.65	76	59 (13)[f]	70
11	2-Naphthyl	0.57	37	30 (5)[f]	75
12	1-Naphthyl	0.51	35	27 (4)[f]	71

[a] A 5-mL aliquot of the solution of the starting material was pumped through in 50 min.
[b] In mmol of pure isolated product (mmol$^{-1}_{resin}$ h^{-1}).
[c] Determined by ^{1}H NMR spectroscopic analysis of the crude material.
[d] Yield of isolated product.
[e] Determined by chiral-phase HPLC analysis.
[f] Yield of the corresponding dehydration product.

ee (70–76%), were obtained. No side reaction of self-aldol product formation occurred, but in several cases, H_2O elimination from the resulting β-hydroxyketone was observed. These yield and *ee* values are competitive with those of the standard batch procedures (for comparison, a number of batch references are listed in Table S1), and the productivities were excellent in almost all cases (Table 3).

4. Conclusions

We have developed a heterogeneous catalytic CF method for asymmetric aldol reactions utilizing a solid-supported peptide as organocatalyst. The peptide was synthetized by SPPS and immobilized in the same step. The lack of peptide cleavage has the results

that no work-up and no purification are necessary, and there is no product loss. After optimization of the reaction conditions and the peptidic catalyst, β-hydroxyketone products were obtained in high yields and stereoselectivities comparable with literature batch results. The residence time on the catalyst bed was as low as 6 min and, due to further beneficial features of the technique, promisingly high productivities were achieved. The peptidic catalyst is highly recyclable, so that the procedure is exceedingly robust, while the ease of product isolation and the possibility of facile scale-up further enhance the efficacy of the described method. Heterogeneous catalysis is therefore a useful tool for broadening the scope of flow chemistry.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2012.08.006.

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