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Heterogeneous Dipeptide-Catalyzed α-Amination of Aldehydes in a Continuous-Flow Reactor: Effect of Residence Time on Enantioselectivity

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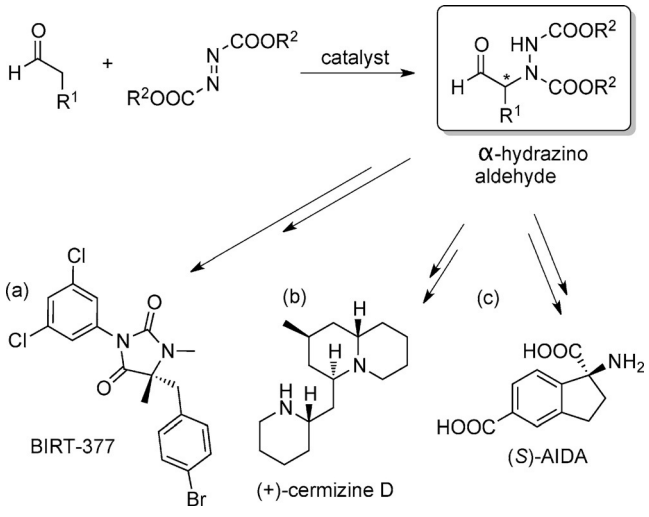
Abstract: A solid-supported dipeptide-catalyzed continuous-flow process was developed for the direct enantioselective α-amination of aldehydes with dibenzyl azodicarboxylate as the electrophilic nitrogen source. With residence time control as an efficient tool for the fine-tuning of the enantioselectivity, synthetically useful α-hydrazino alcohols were achieved with excellent *ee*s. The packed-bed system proved to be highly robust: no decrease in catalyst activity or selectivity was detected throughout 20 h of continuous-flow operation.

Keywords: asymmetric α-amination; continuous-flow reactor; organocatalysis; peptides; supported catalysts

Introduction

The great importance of optically active α-amino acids, α-amino aldehydes and α-amino alcohols has led to intense efforts to develop catalytic asymmetric approaches for the α-amination of carbonyl compounds with azodicarboxylate esters as electrophiles.[1] Up to the end of the 20th century, this field had been completely dominated by chiral transition metal catalysts.[2] In 2002, Jørgensen and List almost simultaneously reported the first metal-free approach for the enantioselective α-amination of aldehydes with azodicarboxylate esters, utilizing L-proline as a readily available organocatalyst.[3] Subsequently, a wide array of proline-derived catalysts have been designed that offer improved catalytic activity and an extended substrate scope, including ketones as well as α-branched and α,β-unsaturated aldehydes.[4] Beneficial features, such as their high stability, availability, non-toxicity and low cost, make the use of such metal-free catalysts extremely attractive as compared with organometallic counterparts,[5] and the organocatalytic α-amination strategy has therefore recently grown into a powerful and promising methodology for the enantioselective synthesis of complex molecules and optically active precursors.[6] Countless applications have emerged for the asymmetric synthesis of natural products,[7] bioactive amino acids[8] and amino acid derivatives,[9] and the strategy has also proved useful for the production of highly functionalized chiral heterocycles (Scheme 1).[10]

The immobilization of organocatalysts on solid supports allows more sustainable chemical synthesis, as such materials can be reused and recycled several times, and the product isolation is greatly simpli-



Scheme 1. Organocatalytic asymmetric α-amination of aldehydes with azodicarboxylate esters, and examples of bioactive products obtained from the corresponding chiral α-hydrazino aldehydes: (a) a cell adhesion inhibitor,[8b] (b) a cernuane-type *Lycopodium* alkaloid,[7a] and (c) a metabotropic glutamate receptor ligand.[8a]

fied.[11] Continuous-flow processes involving the use of supported organocatalysts have attracted considerable attention in recent years,[12] and now comprise a powerful methodology for the synthesis of enantioenriched products.[13] This is not merely due to the ease of use of such heterogeneous materials. In filled reaction columns, the continuous substrate stream interacts with a superstoichiometric amount of catalyst molecules, thereby allowing unprecedented reaction rates;[12] and if catalyst deactivation can be ruled out, the scale of production and the catalyst loading become straight functions of the process time.[14]

One of the most important benefits of packed-bed flow systems is that the contact time of the reactants with the catalyst bed (i.e., the residence time) can readily be fine-tuned through the flow rate, so that optimization of the conversion and throughput becomes simple and easy.[14] Systematic tuning of the residence time affects not only the reaction rate, but also the product selectivity.[15] The importance of making use of the flow conditions to improve the enantioselectivity was realized first in dialkylzinc additions and later in chiral transition metal complex-mediated cyclopropanations.[16] The dependence of *ee* on the residence time was also noted in continuous-flow organocatalytic alkylations and Diels–Alder reactions.[13e,f,k] With regard to the observation that the enantioselectivity of the proline-mediated α-amination of aldehydes is time-dependent due to partial racemization,[3b] heterogeneous catalysis in combination with precise residence time control appears to be a reasonable strategy to overcome racemization and to achieve valuable α-aminated products with high *ee*s.

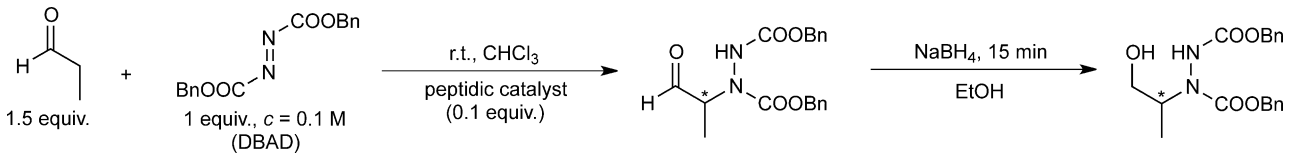
In spite of the obvious benefits, there are very few precedents for heterogeneous organocatalytic asymmetric α-aminations.[13a,p,t,17] As an example, Tanaka et al. employed a heterogeneous tetrapeptide for reactions of aldehydes with azodicarboxylate esters,[17] while Pericàs and co-workers developed a resin-supported diphenylprolinol silyl ether as catalyst for batch and continuous-flow α-aminations.[13p] The main limitation of such reactions is that the possibility of catalyst reuse is strongly limited by the azodicarboxylate component, which can contribute considerably to off-cycle catalyst deactivation.[18] To suppress such a deactivation pathway and to facilitate enamine formation, Pericàs, for example, premixed a large excess of aldehyde and acetic acid as an additive with the resin-bound diphenylprolinol-type catalyst prior to the addition of the azodicarboxylate component.[13p]

Inspired by the above literature findings and limitations, we set out to develop a robust flow chemistry-based approach for the α-amination of aldehydes through use of a highly reusable heterogeneous organocatalyst, and also to investigate the role of residence time control as a tool for the fine-tuning of the enantioselectivity.

Results and Discussion

The use of synthetic peptides as on-demand organocatalysts is highly beneficial in consequence of their modular nature, readily designable structure and inherent chirality.[19] Peptides bearing an N-terminal secondary amine unit and an acidic side-chain can be regarded as mimetics of proline,[20] with the additional benefits of higher structural diversity and simple catalyst immobilization by means of well-established solid-phase peptide synthesis (SPPS).[13n,o] We therefore investigated the catalytic activity of various N-terminal prolyl-peptides in the asymmetric α-amination of aldehydes. At the C-terminus of the peptides, aspartic acid or the homologous glutamic acid served as sources for the carboxylic acid side-chain. The catalysts were prepared by means of SPPS, with Fmoc/*t*-Bu protocols (see the Experimental Section and Scheme S1 in the Supporting Information for details). The solid support in the peptide synthesis also served as a catalyst carrier without the need for further synthetic steps, which eliminated the otherwise laborious peptide work-up and purification steps. The catalysts were initially supported on a polystyrene resin with a 4-methylbenzhydrylamine linker (PS-MBHA, with a loading of 0.59 mmol g^{-1}), and were used as obtained, as salts of trifluoroacetic acid (TFA) after the SPPS.

The immobilized peptidic catalysts were screened under conventional batch conditions, the electrophilic α-amination of propanal with dibenzyl azodicarboxylate (DBAD) serving as a model reaction. The mixture for each reaction contained 1 equivalent of DBAD, 1.5 equivalents of aldehyde and 0.1 equivalent of the corresponding catalyst, in $CHCl_3$ as solvent (Scheme 2), and was stirred at ambient temperature



Scheme 2. Solid-supported peptide-catalyzed α-amination of propanal with DBAD as electrophilic nitrogen source, and reduction of the resulting α-hydrazino aldehyde to the corresponding alcohol.

until the yellow color of the azodicarboxylate had disappeared (or for 24 h at most). As the resulting α-hydrazino aldehydes are prone to racemization, the corresponding stereochemically stable alcohols were isolated after reduction with $NaBH_4$.[21]

Tripeptides with the general formula H-L/D-Pro-Pro-Xaa-NH_2, where Xaa is aspartic or glutamic acid, were recently reported to be effective organocatalysts for asymmetric reactions of aldehydes involving enamine intermediates in batch and in continuous-flow systems.[13n,o,20] We therefore tested H-Pro-Pro-Asp-NH-PS-MBHA, H-D-Pro-Pro-Asp-NH-PS-MBHA, H-Pro-Pro-Glu-NH-PS-MBHA and H-D-Pro-Pro-Glu-NH-PS-MBHA (catalysts **1**–**4**) as heterogeneous organocatalysts for the α-amination of propanal (Figure 1a). Although most of these peptides proved highly active in the model reactions (conversion 86–100% after 19–24 h), only low or moderate enantioselectivities were observed (*ee* 6–59%, Table 1, entries 1–4). The effects of *N*-methylmorpholine (NMM) base were next investigated, to liberate the catalysts from their TFA salt form and to check the efficacy of the desalted peptides. It emerged that, following addition of the base, the rates of the reactions increased significantly (complete conversion was obtained with each peptide in shorter reaction times), but at the same time the enantioselectivity decreased dramatically (Table 1, entries 5–8), presumably because of base-promoted racemization.

Catalyst **2** performed best among the tripeptides, leading to a conversion of 86% and an *ee* of 59% without NMM (Table 1, entry 2). However, as these results were far below optimal, we next focused on the role of the central proline unit. Heterogeneous dipeptides were prepared consisting of a C-terminal aspartic or glutamic acid and an N-terminal proline moiety (Figure 1b). After the omission of the central proline residue, the resulting dipeptides proved more suitable for asymmetric catalysis. Besides high activities, most of the novel catalysts exhibited improved enantioselectivities (*ee* 52–76%, with quantitative conversion in each case after 20–22 h) as compared with the corresponding tripeptides (Table 1, entries 9–12 *vs.* entries 1–4). H-Pro-Asp-NH-PS-MBHA (catalyst **5a**) was found to be most promising, yielding quantitative conversion after 22 h, a productivity of 0.46 mmol product × mmol catalyst^{-1} × h^{-1} and a satisfactory *ee* of 76%, with the (*R*)-hydrazino alcohol as the major product (Table 1, entry 9). The absolute configuration of the product was predominantly controlled by the N-terminus of the catalyst. Peptides with an N-terminal D-proline residue (catalysts **2**, **4**, **6** and **8**) gave the (*S*)-alcohol.

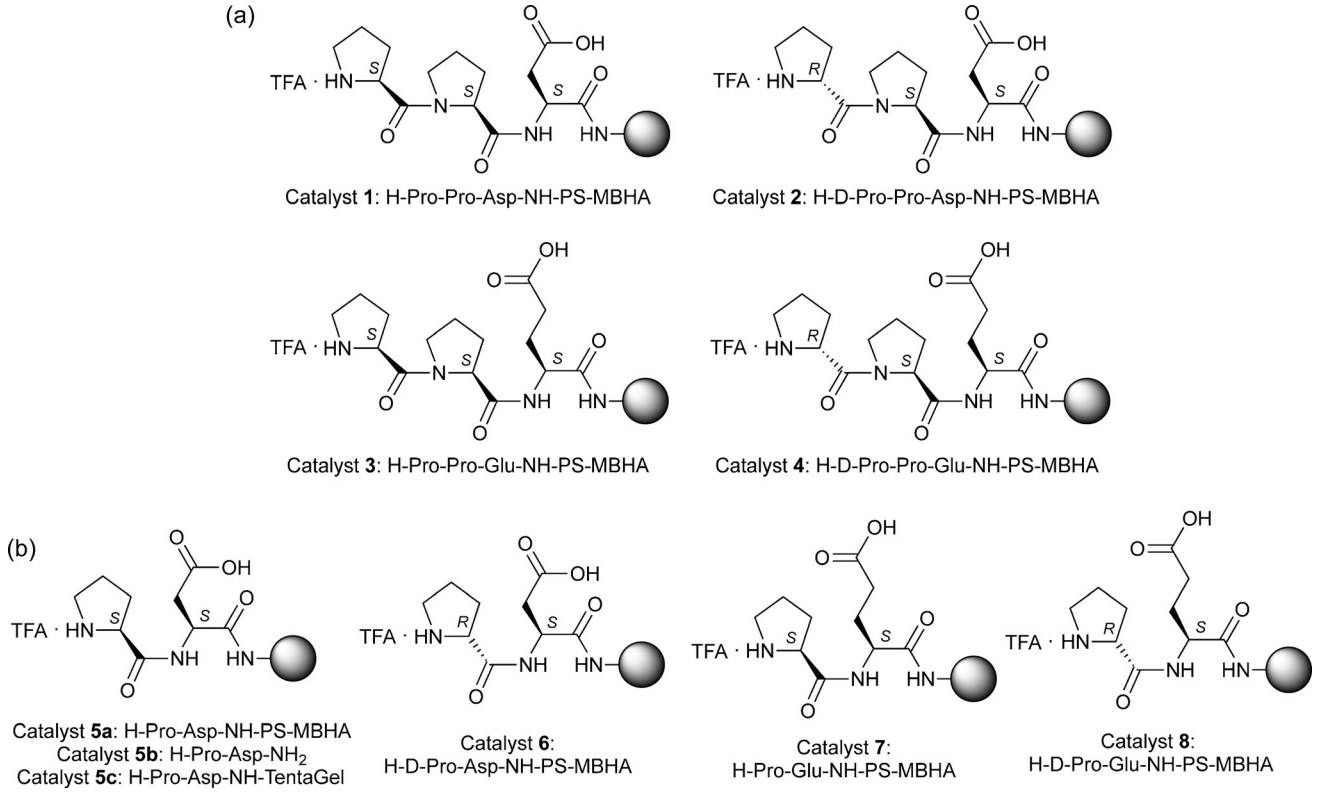


Figure 1. Immobilized peptides utilized as catalysts for the α-amination reactions: (a) tripeptides known from previous studies,[13n,o,20] and (b) novel dipeptides.

Table 1. Screening of solid-supported peptidic catalysts in the batch reaction of propanal with DBAD (see Scheme 2 for the reaction conditions).

Entry	Catalyst	Reaction time [h]	Conv. [%][a]	*ee* [%][b]	Abs. config.
1	**1**	19	97	24	*R*
2	**2**	24	86	59	*S*
3	**3**	23	100	31	*R*
4	**4**	22	100	6	*S*
5[c]	**1**	2	100	18	*R*
6[c]	**2**	2	100	17	*S*
7[c]	**3**	3	100	26	*R*
8[c]	**4**	3.5	100	*rac.*	–
9[d]	**5a**	22	100	76	*R*
10	**6**	22	100	53	*S*
11	**7**	22	100	66	*R*
12	**8**	20	100	52	*S*
13[e,f]	**5b**	20	100	79	*R*
14[d]	**5c**	22	100	75	*R*

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude material.
[b] Determined by chiral-phase HPLC analysis after reduction with $NaBH_4$.
[c] 0.1 equivalent of NMM was used as basic additive.
[d] Productivity was 0.46 mmol product × mmol catalyst^{-1} × h^{-1}.
[e] Productivity was 0.5 mmol product × mmol catalyst^{-1} × h^{-1}.
[f] $CHCl_3$:*i*-PrOH 9:1 was used as solvent.

It is noteworthy that the performance of the optimized heterogeneous peptide (catalyst **5a**) was comparable to that observed with its non-supported counterpart. Thus, the peptide H-Pro-Asp-NH_2 (catalyst **5b**) afforded an *ee* of 79% and a marginally improved reaction rate, which involved a reaction time of 20 h for completion and a slightly better productivity of 0.5 mmol product × mmol catalyst^{-1} × h^{-1} (Table 1, entry 9 *vs.* 13).

With an optimized catalyst in hand, we turned our attention to continuous-flow operation. The catalyst carrier was changed from PS-MBHA to the polystyrene-polyethylene glycol grafted copolymer TentaGel (with a loading of 0.48 mmol g^{-1}), which is a more robust and pressure stable resin, ideally suited for flow chemistry-based applications.[13o] It was verified that the exchange of the solid support had no effects on the catalytic activity or selectivity, as the peptide H-Pro-Asp-NH-TentaGel (catalyst **5c**) performed comparably to its PS-MBHA-bound counterpart (catalyst **5a**) in the batch model reaction between propanal and DBAD (Table 1, entry 9 *vs.* 14). A simple and cheap instrument was assembled for the flow reactions (Figure 2). 200 mg of catalyst **5c** were encompassed in a cylindrical PEEK column (with internal dimensions of 100 × 4 mm), through which a continuous stream of the reactants was passed by a single HPLC pump. The α-hydrazino aldehydes obtained in the continuous-flow reactions were immediately reduced to the corresponding alcohols with $NaBH_4$ in order to avoid racemization.

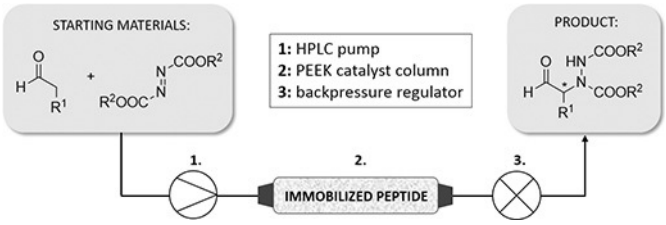


Figure 2. Experimental set-up for continuous-flow α-amination reactions. The resulting α-hydrazino aldehyde was reduced to the corresponding alcohol with $NaBH_4$.

The effects of the aldehyde excess were first investigated under flow conditions utilizing the propanal–DBAD model reaction (Figure 3). It emerged that high aldehyde amounts pushed the reaction to com-

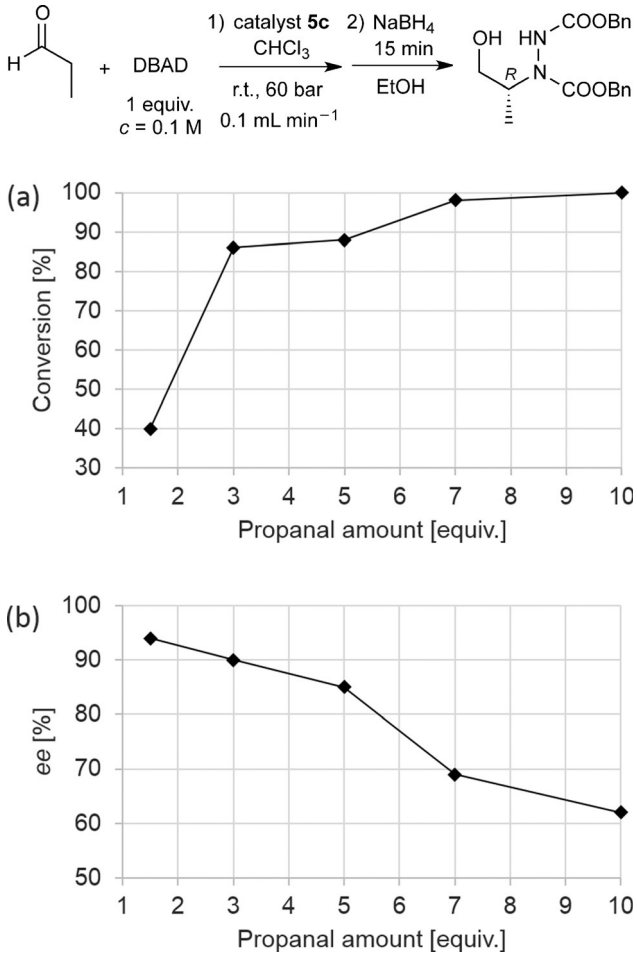


Figure 3. Investigation of the dependence of (a) the conversion and (b) *ee* on the aldehyde excess in the continuous-flow α-amination of propanal with DBAD. An aldehyde amount of 3 equivalents was chosen as optimum.

pletion, but also dramatically decreased the enantioselectivity. With 1.5 equivalents of propanal, for example, a conversion of only 40% was achieved, whereas the *ee* was as high as 94%. In contrast, the use of 10 equivalents of aldehyde led to complete conversion, but at the expense of a significant fall in *ee* to 62%. Thus, 3 equivalents of aldehyde were found to be optimal, affording a high conversion and an excellent *ee* at the same time.

To investigate the role of the residence time on the catalyst bed, the dependence of the α-amination on the flow rate was next tested. At 0.05 mL min^{-1} a conversion of 89% was achieved, and at 0.1 mL min^{-1} only a slight conversion decrease to 86% was observed (Figure 4a). However, it turned out that the reaction is very sensitive to further reduction of the residence time, as any higher flow rate resulted in a significant fall in the conversion (at 0.2 mL min^{-1}, for example, the conversion was only 44%). Importantly, the residence time proved to influence not only the conversion, but also the enantioselectivity of the flow process (Figure 4b). This phenomenon can be explained by the secondary amine moiety of the organocatalyst, which is able not only to aid asymmetric C–N bond formation through an enamine-based catalytic cycle, but also to promote the enolization and hence the racemization of the resulting chiral α-hydrazino aldehyde in an undesired off-cycle pathway.[3b,13n] Accordingly, it was found that enhancement of the flow rate led to an increase in *ee*. At 0.05 mL min^{-1}, for example, the *ee* was 85%, whereas at 0.5 mL min^{-1}, the *ee* improved to 97%. A flow rate of 0.1 mL min^{-1}, which corresponded to a residence time on the catalyst bed of 8 min, offered the best compromise between the conversion (86%) and the enantioselectivity (90%), and was thus selected as an optimum value.

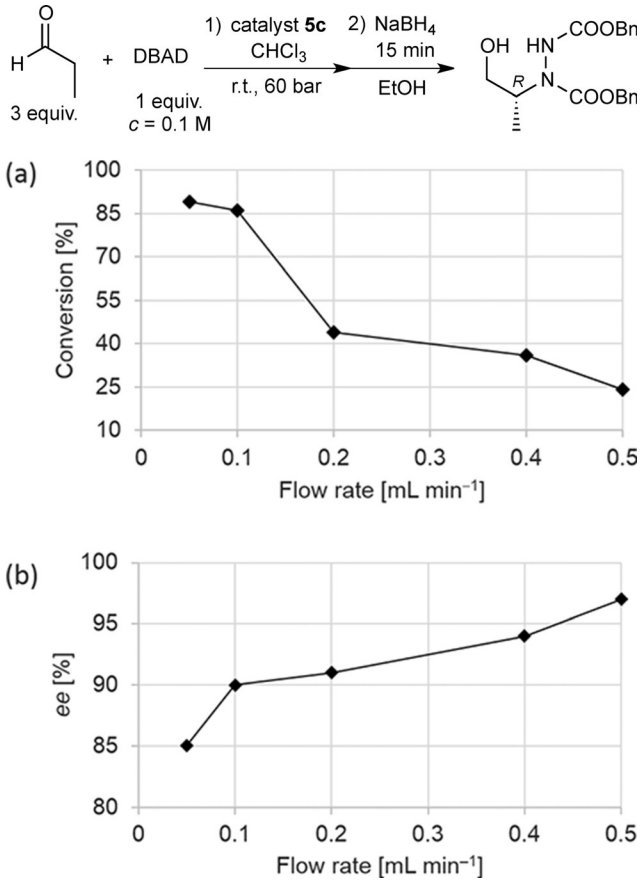


Figure 4. Investigation of the dependence of (a) conversion and (b) *ee* on the flow rate in the continuous-flow α-amination of propanal with DBAD. A flow rate of 0.1 mL min^{-1} was chosen as optimum, which corresponds to a residence time on the catalyst bed of 8 min.

Conventional batch-based operations do not allow such easy and precise control over the reaction time. In batch reactions with the same heterogeneous dipeptide (catalyst **5c**) or with its non-supported derivative (catalyst **5b**), much lower *ee*s of 75% and 79% were found after reaction times of 22 and 20 h, respectively, in spite of the lower propanal excess utilized (Table 1, entries 13 and 14). We believe that this significant contrast results from the fundamental differences between a classical batch experiment and a packed-bed flow system. The well-defined short contact time of the starting materials with the high local catalyst concentration in the packed bed ensures efficient enamine catalysis, but can reduce enolization upon strict residence time control. Whereas in batch, there is a broad reaction window where both processes can occur more or less simultaneously. These results highlight the importance of strategic residence time control, and illustrate the feasibility of continuous-flow processing for asymmetric syntheses involving configurationally labile products.

Study of the pressure dependence of the continuous-flow reaction demonstrated that enhancement of the pressure from atmospheric to 60 bar significantly improved the rate of the reaction, but further elevation was not beneficial, possibly because of erosion of the resin (Figure 5). The enantioselectivity did not change in response to pressurizing: the *ee* was in the interval 89–91% in all cases. It was established earlier that, when swellable resins are used as heterogeneous catalyst carrier, the continuous reactions are diffusion-controlled, and the role of pressure is to aid the diffusion of the reactants into the swollen polymer matrix toward the active catalyst sites.[13n,o,22]

Since catalyst deactivation is an important limit of heterogeneous catalytic approaches toward α-aminated products,[13p,17] the reaction of propanal with DBAD was scaled up in order to investigate the stability and preparative capability of the immobilized catalyst. The large-scale experiment was run under the previously optimized conditions (0.1 mL min^{-1} flow rate and 60 bar), with a fresh portion of catalyst **5c** packed into the catalyst bed. The concentration

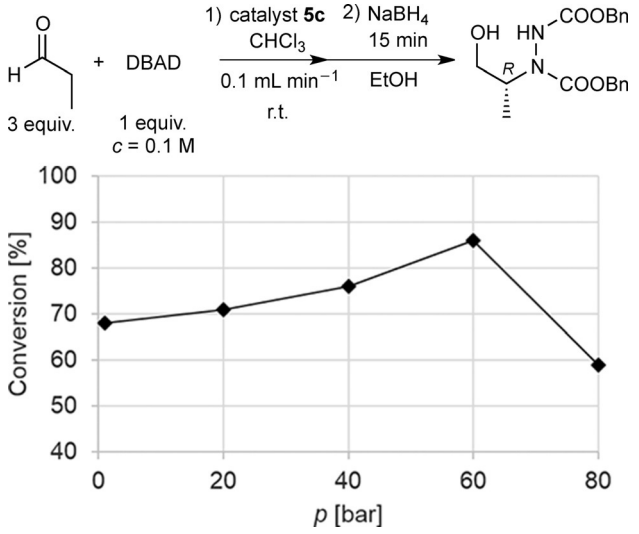
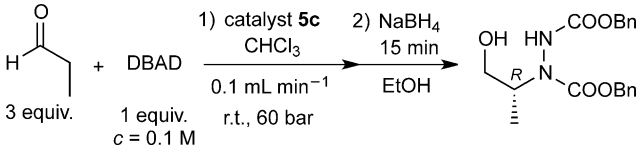


Figure 5. Pressure dependence of the α-amination of propanal with DBAD in continuous-flow mode. 60 bar was found optimal. The enantioselectivity was independent of the pressure: *ee* was in the interval 89–91% in all cases.

and ratio of the starting materials were not changed for the scaling-up, and the eluting product solution was collected for 20 h in 2 h fractions, the conversion and *ee* being determined for each fraction separately. We were delighted to find that the packed-bed flow system proved highly robust, as no decrease in catalyst activity or selectivity was detected in the monitored reaction window. The conversion and *ee* were virtually constant throughout the 20 h, at around 83–91% and 88–92%, respectively, and after reduction with $NaBH_4$, 3.49 g of the corresponding α-hydrazino alcohol was isolated, which gave an overall yield of 81% (Table 2). In this case, the catalyst loading in the continuous reaction became a direct function of the process time; the large-scale flow synthesis permitted an almost 13-fold reduction of the catalyst loading relative to the corresponding batch reactions utilizing the same heterogeneous dipeptide (catalyst **5c**) or its non-supported analogue (catalyst **5b**).

To investigate the scope and applicability of the described methodology, the α-amination of various aldehydes was next investigated with DBAD as the electrophilic nitrogen source utilizing catalyst **5c** under the previously optimized reaction conditions (a 3-fold excess of aldehyde, a flow rate of 0.1 mL min^{-1} and 60 bar). As shown in Table 3, short linear aldehydes (propanal, butanal and pentanal) gave conversions of 86–96% and excellent *ee*s of 90–99% (entries 1–3). Aldehydes with longer linear carbon chains (hexanal and undecylenic aldehyde) were converted quantitatively to the desired adducts with *ee*s of 90% (entries 4 and 5). Quantitative conversion and an excellent *ee* of 95% were achieved in the reaction of DBAD with 3-phenylpropanal (entry 6), affording a key intermediate for the synthesis of (−)-bestatin (Scheme 3), a naturally occurring aminopeptidase inhibitor that exhibits immunostimulatory and cytotoxic activities.[9c,23] After it had been established that catalyst **5c** is a highly robust system, this flow reaction

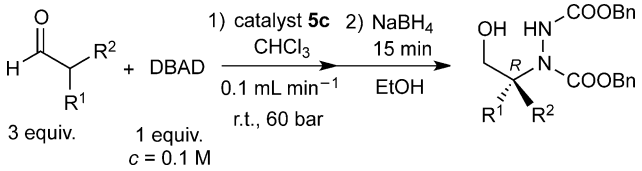
Table 2. Investigation of the large-scale synthetic capability of catalyst **5c** in continuous-flow mode.



Entry[a]	Time [h]	Conv. [%][b]	*ee* [%][c]
1	0–2	84	92
2	2–4	88	90
3	4–6	88	90
4	6–8	91	88
5	8–10	83	89
6	10–12	85	91
7	12–14	90	90
8	14–16	88	90
9	16–18	86	91
10	18–20	87	88

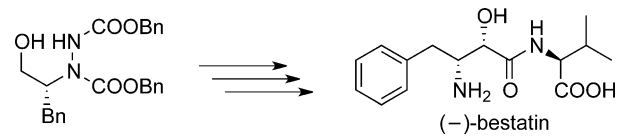
[a] After reduction with $NaBH_4$, 3.49 g of α-hydrazino alcohol were collected in the whole experiment. The overall yield was 81%.
[b] Determined by ^{1}H NMR spectroscopic analysis of the crude material.
[c] Determined by chiral-phase HPLC analysis after reduction with $NaBH_4$.

Table 3. Investigation of the scope and applicability of the continuous-flow α-amination with catalyst **5c**.



Entry	R^1	R^2	Conv. [%][a]	*ee* [%][b]	Prod.[c]
1	Me	H	86	90	5.38
2	Et	H	93	99	5.81
3	*n*-Pr	H	96	93	6.00
4	*n*-Bu	H	100	90	6.25
5	CH_2=$CH(CH_2)_7$	H	100	90	6.25
6	Bn	H	100	95	6.25
7	*i*-Pr	H	92	98	5.75
8	Me	Me	trace	–	–

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude material.
[b] Determined by chiral-phase HPLC analysis after reduction with $NaBH_4$.
[c] Productivity in mmol product × mmol catalyst^{-1} × h^{-1}.



Scheme 3. (−)-Bestatin, a naturally occurring aminopeptidase inhibitor, and the corresponding α-hydrazino alcohol as its key intermediate.[9c,23]

was repeated on a larger scale, resulting in 1.20 g (92% yield) of the desired α-aminated key product after $NaBH_4$ reduction (the *ee* was 95%, similarly as in the small-scale experiment). Isovaleraldehyde, a β-branched aldehyde, also served as a good reaction partner of DBAD (92% conversion and 98% *ee*, entry 7), but isobutyraldehyde proved to be a poor substrate because of the α-branch (entry 8).

These results compare well with those of literature procedures involving the use of various homogeneous or heterogeneous catalysts; detailed comparison with literature batch and continuous-flow experiments are to be found in the Supporting Information (Tables S1 and S2).[3b,4k–m,13p,t,17] The chemical efficacy of the continuous reactions utilizing catalyst **5c** was found to be markedly high. For example, in the propanal–DBAD reaction, the productivity of the flow process proved to be 11–12 times higher than that of the corresponding batch processes in which the same supported peptide or its resin-free analogue (catalyst **5b**) was used. Moreover, the productivities achieved (5.38–6.25 mmol product × mmol catalyst^{-1} × h^{-1}, Table 3) exceeded our previous continuous-flow organocatalytic findings.[13n,o]

Conclusions

In summary, a simple resin-supported dipeptide containing an N-terminal proline unit and an acidic side-chain at the C-terminus was developed as an effective organocatalyst for the direct enantioselective α-amination of aldehydes with DBAD as electrophilic nitrogen source. The heterogeneous catalyst was readily synthetized and immobilized in the same step by SPPS without cleavage of the peptide from the resin. The benefits of continuous-flow processing in combination with strategic control over the residence time were exploited to achieve both high enantioselectivity and high reaction rates. Thus, synthetically useful α-hydrazino alcohols were obtained with high productivities and excellent *ee*s (90–99%). The heterogeneous peptidic catalyst proved prominently robust: no deactivation occurred during 20 h continuous-flow operation. Strategic residence time control has therefore proved to be an efficient tool for the improvement of enantioselectivity in asymmetric syntheses involving configurationally labile products.

Experimental Section

General Information

All the materials and reagents were of analytical grade and were used as received without purification. 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 F254 plates. Compounds were visualized by means of UV or $KMnO_4$. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer at ambient temperature, in $CDCl_3$ as solvent, with TMS as internal standard, at 400.1 and 100.6 MHz, respectively. HPLC analyses were performed on an analytical instrument with a diode array detector from JASCO. MS analyses were carried out with a Thermo Scientific LCQ Fleet/Thermo Scientific Dionex Ulimate 3000 LC/MSD.

Catalyst Synthesis

The heterogeneous peptidic catalysts were prepared manually by means of SPPS, utilizing Fmoc/*t*-Bu chemistry (Fmoc = 9*H*-fluoren-9-ylmethoxycarbonyl). Amino-functionalized non-TFA-labile resins were utilized as solid supports for the SPPS: PS-MBHA (with a loading of 0.59 mmol g^{-1}) and TentaGel (with a loading of 0.48 mmol g^{-1}). With respect to the different swelling properties of the applied resins, DMF was used as solvent in the case of TentaGel, and DMF/CH_2Cl_2 1:1 for couplings with PS-MBHA. Before any synthetic steps, the resin was swollen thoroughly for 1 h in the appropriate solvent. Further treatment with 5% *N*,*N*-diisopropylethylamine (DIEA) solution was carried out in the case of PS-MBHA to liberate the amino function from the HCl salt form. For the couplings, 3 equivalents of Fmoc-protected amino acid and 3 equivalents of 1-[bis(dimethylamino)methyliumyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridine-3-oxide (HATU) were dissolved, and 6 equivalents of DIEA were added. The solution of the activated amino acid was then poured onto the swollen resin, and the coupling was fulfilled by agitation for 3 h. The incorporation of the amino acid was monitored by means of the ninhydrin or isatin test. If the test revealed unreacted amino groups, the coupling was repeated. Fmoc deprotection was performed in a solution of 2% 1,8-diazabicyclo[5.4.0]undec-7-ene and 2% piperidine with agitation for 2 × 15 min, and the peptide chain was then elongated with repetition of the coupling and deprotection steps. After each step, the resin was washed 3 times with CH_2Cl_2, once with MeOH and 3 times with CH_2Cl_2. Finally, the carboxyl side-chain was deprotected without cleavage of the peptide from the solid support by means of agitation for 3 h in a mixture of TFA and H_2O (9:1 v/v). After filtration and washing with the same solvents as described previously, the resin-bound peptide was kept at ambient temperature for 6 h to dry. The immobilized catalysts were obtained in TFA salt form after the SPPS.

H-Pro-Asp-NH_2 was synthesized manually on Tentagel R RAM resin (0.20 mmol g^{-1}). The peptide chain was elongat-

ed through repetition of the coupling and deprotection steps given in the previous paragraph. The peptide was cleaved from the resin by agitation for 3 h in a mixture of TFA and H_2O (95:5 v/v). The TFA was then removed under vacuum, and the free peptide was precipitated in dried diethyl ether, filtered off, dissolved in 10% aqueous acetic acid and lyophilized.

General Procedure for the Batch Reactions

Propanal (0.375 mmol, 1.5 equivalents), DBAD (0.25 mmol, 1 equivalent) and the corresponding catalyst (0.025 mmol, 0.1 equivalent) were combined in $CHCl_3$ (2.5 mL). In some cases, NMM (0.025 mmol, 0.1 equivalent) was also added. The reaction mixture was stirred at ambient temperature until the yellow color of the azodicarboxylate had disappeared or for 24 h at most (the progress of the reaction was also followed by TLC). The catalyst was then filtered off and the solvent was removed under vacuum. EtOH (2.5 mL) and $NaBH_4$ (0.275 mmol, 1.1 equivalents) were added to the filtrate, and the mixture was stirred for 15 min at 0 °C. After completion of the reduction, the mixture was concentrated under vacuum. Brine (10 mL) was next added, and the resulting mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, affording the corresponding α-hydrazino alcohol.

General Procedure for the Continuous-Flow Reactions

The continuous-flow experiments were conducted in a modular instrument consisting of a cylindrical PEEK column (with internal dimensions of 100×4 mm) filled with catalyst **5c** (200 mg), an HPLC pump (a Waters™ 600 pump equipped with a Waters™ 600 controller) and a backpressure valve (IDEX Health & Science high-pressure adjustable BPR P-880). A reaction mixture consisting of the corresponding aldehyde (3 equivalents) and DBAD (1 equivalent, $c = 0.1$ M) in $CHCl_3$ was prepared and carefully homogenized. For small-scale reactions, 5 mL of the starting solution were pumped through the reactor under the appropriate conditions, and elution of the starting materials was continued by washing with $CHCl_3$ for several additional minutes (depending on the set flow rate). Between two continuous-flow experiments, the system was equilibrated for 15 min by pumping $CHCl_3$ at a flow rate of 0.5 mL min^{-1}. For the gram-scale syntheses, the concentrations of the reactants were not varied, and a larger amount of the starting solution was pumped through the instrument. The α-hydrazino aldehydes obtained in the continuous-flow reactions were immediately reduced to the corresponding alcohols with $NaBH_4$, similarly as given for the batch reactions. In the cases of volatile aldehydes and quantitative α-hydrazino aldehyde formation, pure α-hydrazino alcohols could be isolated after the reduction process through a simple extractive work-up and evaporation. If necessary, column chromatographic purification was carried out on silica gel with mixtures of *n*-hexane/EtOAc as eluent.

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