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# Multicomponent Approach to Silica-Grafted Peptide Catalysts: A 3D Continuous-Flow Organocatalytic System with On-line Monitoring of Conversion and Stereoselectivity

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*In memory of Prof. Carlos Barbas III for his contribution to the field of organocatalysis*

The derivatization of organocatalysts with functional appendages suitable to anchor onto solid supports is usually achieved by stepwise syntheses. As an alternative to such a strategy, this work describes a one-pot approach to silylated prolyl-peptide catalysts by a multicomponent reaction that enables the simultaneous incorporation of the catalytic and the heterogenizable (triethoxysilane) moieties. A microreactor with high catalytic efficacy and reproducibly in the conjugate addition of aldehydes to nitroolefins was obtained by grafting onto HPLC-grade silica (10 μm) and packing into a column with a selected catalyst. A 3D continuous-flow system that includes the on-line monitoring of the reaction outcome was set up. For that, the microreactor was coupled to a chromatographic column for the separation of the remaining substrates from the Michael adduct in the second dimension, followed by a chiral polysaccharide column for the analysis of conversion and stereoselectivity. This approach represents a new instrumental setup that combines the advantages of multidimensional chromatography and flow catalysis.

## Introduction

The immobilization of organocatalysts onto solid supports such as organic polymers and inorganic materials (e.g., silica gel) has emerged as a powerful and sustainable strategy that integrates the advantages of heterogeneous and organocatalysis.[1] The heterogenization of organocatalysts allows not only catalyst recovery and reuse[2] but also the implementation of continuous-flow catalytic systems that permit the uninterrupted production of chiral building blocks and fine chemicals.[1,3] Recently, excellent reports have proven the potential of continuous-flow catalytic systems based on supported pyrrolidine[4] and imidazolidinone[5] chiral catalysts (e.g., proline and its derivatives, Wennermers, and MacMillan catalysts). Traditionally, approaches to prepare organocatalysts functionalized appropriately for heterogenization (i.e., to anchor to a resin, to graft onto inorganic materials, or to polymerize) require multistep syntheses wherein the assembly of the catalytic motif is performed separately from the installation of the heterogenizable appendage.[4,5] In our endeavor to facilitate access to immobilized organocatalysts, we propose the utilization of multicomponent reactions (MCRs) for the simultaneous incorporation of both the catalytic and the heterogenizable moieties in a one-pot process. Recently, we have described a combinatorial approach based on the Ugi four-component reaction (Ugi-4CR) for the development of new prolyl-peptides that are successful in enamine catalysis.[6] Our interest in the application of MCRs to catalyst discovery derives from their tremendous capacity to generate diversity,[7] which enables the direct and tunable variation of functionalities around a known organocatalytic motif.[8] Herein we report on the utilization of a multicomponent approach for the one-pot synthesis of silylated prolyl-peptide catalysts and their further grafting onto silica, which thus enables the construction of an organocatalytic microreactor for continuous-flow enamine catalysis. A key feature of this strategy is the utilization of the Ugi-4CR to introduce all of the structural fragments in one step to obtain the heterogenizable organocatalyst, that is, the chiral pyrrolidine and triethoxysilane moieties, which thus provides a significant advance over all multistep approaches known previously that comprise a separate assembly and derivatization of the organocatalytic core. Another innovation of this work is the combination, for the first time, of flow organocatalysis with multidimensional chro-

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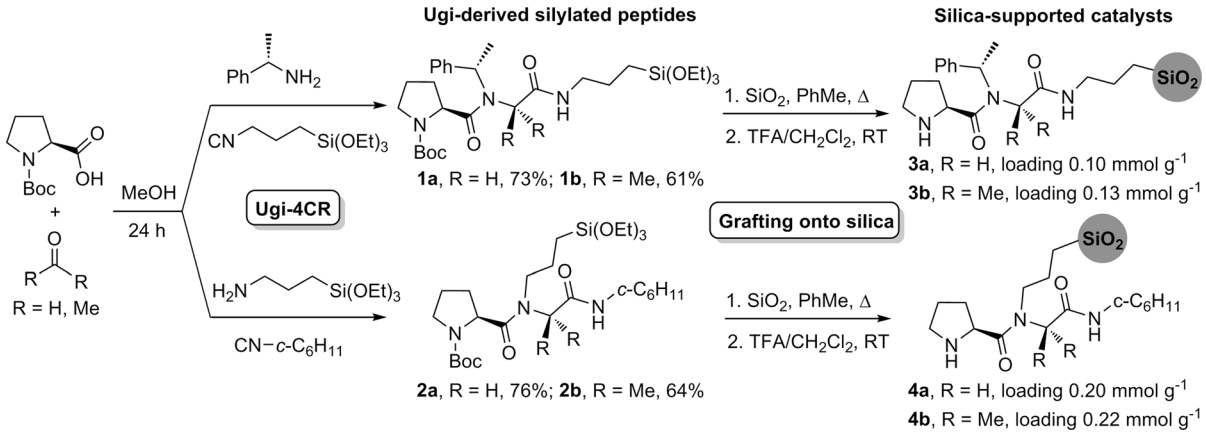



**Scheme 1.** Multicomponent one-pot synthesis of triethoxysilylated prolyl-peptide catalysts and their subsequent grafting onto silica for applications in heterogeneous catalysis. TFA = Trifluoroacetic acid.

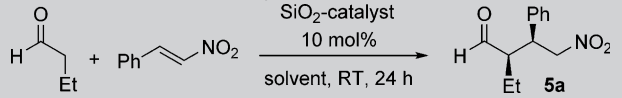
matography. The separation capacity of the connection of orthogonal chromatographic columns has been successful for the analysis of complex mixtures previously.[9] Herein we take advantage of this capability for the design of a 3D catalytic/chromatographic system that enables the on-line monitoring of the asymmetric transformation. The system comprises i) a microreactor packed with a silica-supported organocatalyst, ii) a first chromatographic column to separate the reaction product from the substrates and solvent, and iii) a second chiral-stationary-phase chromatographic column for the analysis of conversion and stereoselectivity.

## Results and Discussion

As a result of the feasible covalent derivatization of silica gel as well as its intrinsic properties (i.e., high surface area, thermal and mechanical stability, etc.), this material has been used widely as a solid support in heterogeneous catalysis in batch[10] and in continuous-flow reactors.[4c,5b] Two distinctive types of triethoxysilylated prolyl-peptide catalysts were prepared by the Ugi-4CR followed by grafting onto Luna silica gel (pore diameter, 100 Å; mean particle size, 10 μm; surface area, 400 $m^2 g^{-1}$; Scheme 1). The classic Ugi-4CR is the one-pot condensation of a primary amine, an oxo compound (i.e., ketone or aldehyde), a carboxylic acid, and an isocyanide to produce an N-substituted dipeptide backbone.[11] To take advantage of the multicomponent nature of the process, a variation of three components (i.e., the amine, the oxo, and the isocyanide) was made from the knowledge gained in the previous catalytic screening of Ugi-derived prolyl-peptide catalysts that have an internal N substitution.[6] Such a combinatorial approach provided important information on the key structural elements for this new family of hybrid peptide–peptoid catalysts to be effective in asymmetric conjugate addition reactions, which rely on enamine catalysis. These results aided the selection of the most suitable Ugi components for the preparation of the silylated prolyl-peptide catalyst described in this work. For example, it was demonstrated that the utilization of acetone as the oxo component leads to catalysts that provide greater stereoselectivity than those derived from paraformaldehyde.[6] As proven by a molecular modeling study, the reason for this is the greater conformational rigidity and better shielding of one of the faces in enamines derived from catalysts that have the sequence Pro-*N*-alkyl-Aib (Aib = α-aminoisobutyric acid) compared those that have the sequence Pro-*N*-alkyl-Gly.[6] Nevertheless, we decided to prepare catalysts derived from acetone and paraformaldehyde to address their catalytic efficacy in heterogeneous enamine catalysis. Thus, the other two tunable components (amine and isocyanide) were selected to allow the incorporation of the heterogenizable triethoxysilane moiety as proline is a fixed component required for enamine formation. Such a rational selection of the components led to the one-pot synthesis of silylated organocatalysts **1a**–**b** and **2a**–**b**, derived from *N*-Boc-proline (Boc = *tert*-butoxycarbonyl) and either paraformaldehyde or acetone in combination with (*S*)-α-methylbenzylamine, 3-isocyanoprolpyltriethoxysilane, 3-aminoprolpyltriethoxysilane, and cyclohexyl isocyanide, respectively (Scheme 1).

The grafting onto Luna silica was accomplished conventionally by mixing and heating the silylated organocatalyst with commercially available silica, followed by N-terminal deprotection of the peptide moiety to render the silica-supported prolyl-peptides **3** and **4**. Catalyst loading onto the silica ranged from 0.1 mmol $g^{-1}$ for **3a** to 0.22 mmol $g^{-1}$ for **4b**, which shows that the anchoring of catalysts **2a**–**b** derived from 3-aminoprolpyltriethoxysilane was more effective than that of 3-isocyanopropyltriethoxysilane-derived catalysts **1a**–**b**. To seek preliminary information on the catalytic efficiency and stereoselectivity, the four silica-supported catalysts (**3a**, **3b**, **4a**, and **4b**) were screened in batch mode for the asymmetric Michael addition that relies on heterogeneous enamine catalysis. For this, the model organocatalytic system that comprises the conjugate addition of *n*-butanal to *trans*-β-nitrostyrene was studied using 10 mol% of the solid-supported catalysts and toluene as the solvent. The best results (entry 4) in terms of conversion and stereocontrol were obtained for catalyst $SiO_2$-**4b** (96:4 diastereomeric ratio (*dr*), 90% *ee*; Table 1). Notably, the Ugi-based peptide catalysts derived from acetone (**3b** and **4b**)

**Table 1.** Screening of silica-supported prolyl-peptide catalysts and reaction conditions in batch heterogeneous Michael addition.




| Entry[a] | Catalyst | Solvent | Conversion [%][b] | *dr* (*syn*/*anti*)[b] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | $SiO_2$-**3a** | PhMe | 55 | 94:6 | 18 |
| 2 | $SiO_2$-**3b** | PhMe | 80 | 91:9 | 14 |
| 3 | $SiO_2$-**4a** | PhMe | 68 | 95:5 | 72 |
| 4 | $SiO_2$-**4b** | PhMe | 91 | 96:4 | 90 |
| 5 | $SiO_2$-**4b** | THF | 93 | 94:6 | 88 |
| 6 | $SiO_2$-**4b** | $CHCl_3$ | 92 | 97:3 | 87 |
| 7 | $SiO_2$-**4b** | $Et_2O$ | 91 | 97:3 | 90 |
| 8 | $SiO_2$-**4b** | *i*PrOH | 96 | 91:9 | 88 |
| 9 | $SiO_2$-**4b** | EtOH | 92 | 93:7 | 89 |
| 10 | $SiO_2$-**4b** | $CH_3CN$ | 94 | 92:8 | 90 |
| 11[c] | $SiO_2$-**4b** | hexane/*i*PrOH | 95 | 96:4 | 86 |

[a] Reactions were conducted using 3 equiv. of aldehyde. [b] Determined by chiral-stationary-phase HPLC analysis. [c] Solvent mixture 9:1 (v/v).

showed a higher catalytic efficiency than those derived from paraformaldehyde, which agrees with our previous studies on this type of catalyst in homogeneous catalysis.[6]

Intriguingly, catalyst **4b**, which has a C-terminal cyclohexyl carboxamide and propyl silica as the N substituent, provided greater enantioselectivity than **3b**, which has the propyl silica linked at the C terminus and (*S*)-α-methylbenzyl as the N substituent. This may be because of a conformational difference between the *anti* enamines derived from **3b** and **4b**, of which the latter allows a better shielding to one of the faces (i.e., the *Re*-face according to the resulting 2*R*,3*S* configuration: see Experimental Section) during the attack on the nitroolefin. The effectiveness of **4b** was further assessed in a variety of solvents, and it provided good enantioselectivity and excellent diastereoselectivity in quite different reaction media, which include both apolar and polar protic solvents (Table 1, entries 5–11). This behavior is quite different from that of homogeneous organocatalytic Michael reactions described with similar prolyl-peptide catalysts, in which the catalyst efficacy and enantioselection is highly dependent on the chosen solvent.[6,12]

After we established which silica-supported catalyst provides the best results under batch heterogeneous conditions, we focused on the implementation of the 3D flow system by integrating the microreactor and the multidimensional chromatography platform. Thus, the immobilized catalyst $SiO_2$-**4b** was employed to prepare the packed-bed microreactor by using an HPLC column (2.1 mm internal diameter × 50 mm length). In general, on-flow catalytic systems reported previously lack the integration of an analytical platform to monitor the reaction progress.[4,5] Recently, a catalytic microreactor coupled to a chromatographic system was used in a 2D setup for the online analysis of reaction kinetics by nonlinear chromatography.[13] The 3D continuous-flow system[14] described here is a further advance in the field of flow asymmetric catalysis as it allows the real-time investigation of important reaction parameters such as conversion and stereoselectivity.

The 3D catalytic flow system designed for the simultaneous production and analysis of chiral γ-nitroaldehydes is illustrated in Figure 1. The system comprises a sample loop interface that stores the microreactor outflow and couples it to a chromatographic column for the purification of the reaction product. The band of the pure product is then transferred as a heart-cut by using a switching-valve system to a polysaccharide chiral column for the analysis of the stereoselectivity and conversion. A typical procedure includes the continuous injection of a solution of β-nitrostyrene (0.25 M, 1 equivalent) and butanal (0.75 M, 3 equivalent) in *n*-hexane/*i*PrOH (9:1, v/v) to the organocatalytic microreactor (filled with catalyst $SiO_2$-**4b**) by using a syringe pump. To seek the most favorable conditions, various flow rates were tested to reach a compromise between retention time and reaction yield. Finally, a flow rate of 1 μL min$^{-1}$ was set, and the steady-state regime was reached in 18 h. These conditions were kept for the first during 48 h to produce the Michael adduct continuously in 95% yield, 96:4 *dr*, and 92% *ee*. The outflow of the microreactor was accumulated in the sample loop (≈2 μL) and then injected by using pump A onto the homemade Boc-protected peptide $SiO_2$-**4b** column. The selection of the same peptide in a protected form ($SiO_2$-Boc-**4b**) as the stationary phase for the second dimension was not arbitrary. Instead, it was the material that furnished adequate retention for the Michael adduct, which shows selectivity with respect to β-nitrostyrene. The direct analysis is accomplished in the third dimension by a transfer of the heart-cut[15] of the γ-nitroaldehyde chromatographic band (≈2 μL) to the chiral column by using a switching valve (Figure 1). Such a first-hand analysis of the reaction progress allows the continuous-flow to be stopped if the reaction parameters reach undesired values, for example, a decreased conversion and stereoselectivity. This feature represents an important operational advance in terms of cost and time as it enables conventional collection, purification, and analysis of the chiral product in separate operations to be circumvented.

The main characteristics of the packed-bed microreactor, determined by pycnometry and elemental analysis (Supporting Information), are given in Table 2. To assess the robustness of the microreactor and the reproducibility of the catalytic process, seven consecutive rounds were performed initially with the same substrates and reaction flow, albeit with various operation times. After each round, the microreactor was flushed thoroughly with EtOH and rinsed with *n*-hexane/*i*PrOH, a solvent mixture that does not affect the integrity of the chiral stationary phase. During these independent rounds, the microreactor was able to produce γ-nitroaldehyde **5a** in a high yield

**Table 2.** Main characteristics of the catalytic microreactor.

| Loading of **4b** [mmol g$^{-1}$][a] | Amount [mg] | $V_0$ [μL] | $V_G$ [μL][b] | $V_{bed}$ [μL][c] | $t$ [min][d] | Total porosity[e] |
|---|---|---|---|---|---|---|
| 0.217 | 143 | 140 | 173 | 33 | 140 | 0.81 |

[a] Determined by elemental analysis. [b] Geometric volume. [c] $V_{bed} = V_G - V_0$. [d] Residence time calculated at 1 μL min$^{-1}$. [e] Total porosity $\varepsilon_{tot} = V_0/V_G$.

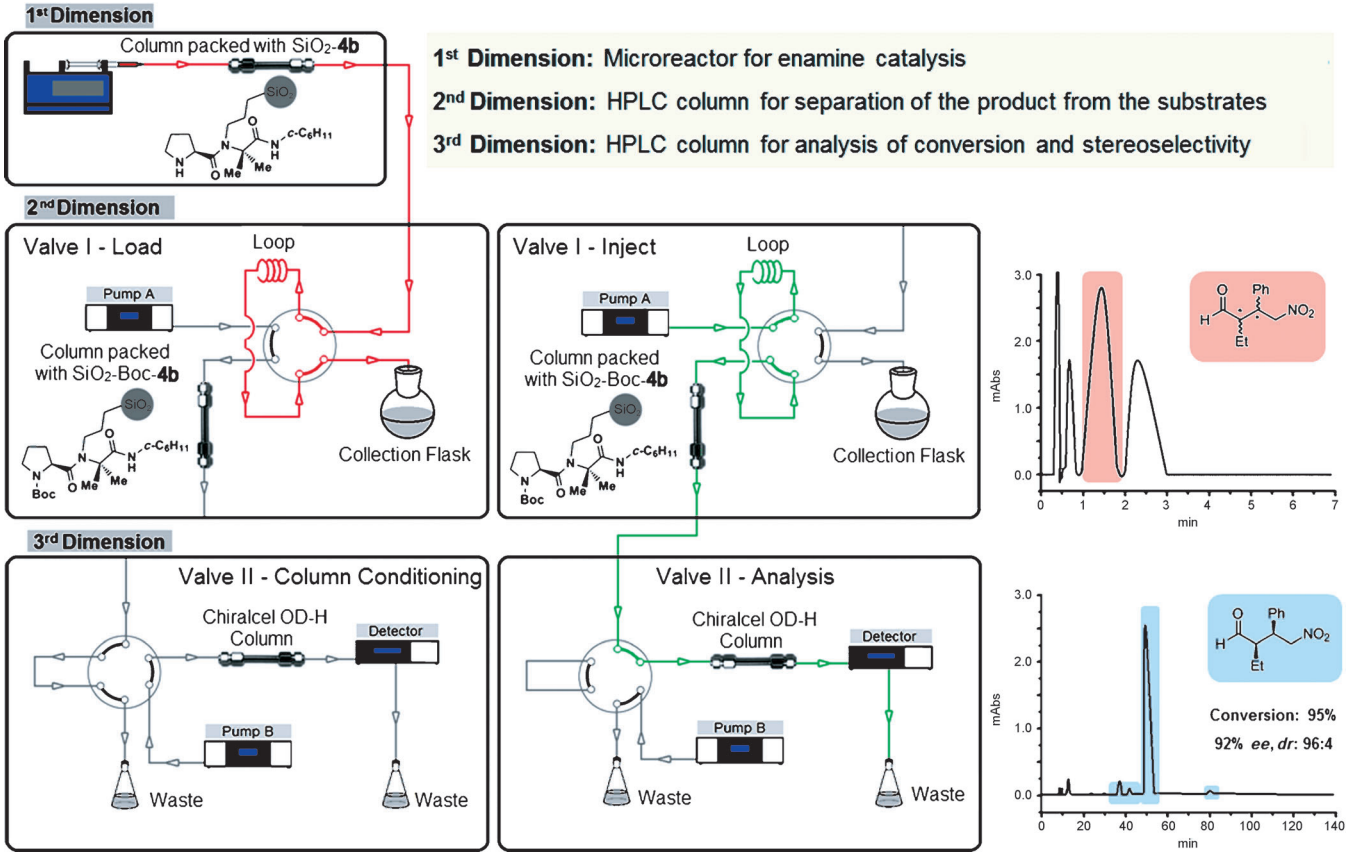



**Figure 1.** 3D continuous-flow catalytic system for the production and on-line analysis of chiral γ-nitroaldehydes.

with excellent stereoselectivity, which corresponds to a turnover number (TON) of 218 for this product (Table 3).

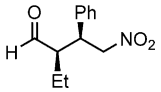
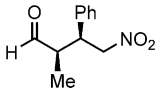
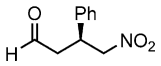
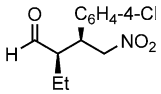
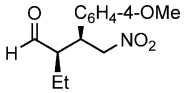
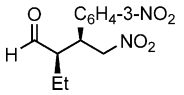
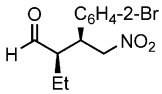
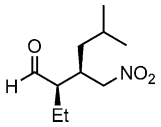
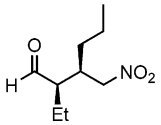
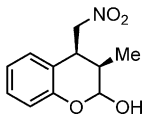
Interestingly, the enantioselectivity was slightly higher using the flow microreactor than under batch conditions, whereas the diastereoselectivity remained the same. The yield of isolated pure products—collected in the second dimension—was compared with the conversion calculated in the third dimension by using the calibration curve method, which resulted in very similar results. The reproducibility of the microreactor was evaluated subsequently in the continuous-flow production of enantiomerically enriched γ-nitroaldehydes (**5b–j**). Importantly, the microreactor was able to catalyze the reaction between dissimilar aldehydes and both aliphatic and aromatic nitroolefins that featured a variety of substitution patterns at the phenyl rings (i.e., electron-donating and -withdrawing groups). To extend the substrate scope of the continuous-flow catalytic microreactor, we explored the possibility to perform a tandem process that comprises the conjugate addition of an aldehyde to *trans*-2-hydroxy-β-nitrostyrene followed by acetalization to produce adduct **5j** in a reasonable yield. This compound was collected in the second dimension and further reduced to facilitate the assessment of the stereoselectivity, exactly as described in the original report.[16]

Michael adducts were obtained in good enantio- and diastereoselectivity, albeit in some cases with lower yields than the model γ-nitroaldehyde **5a**. To determine whether the decrease in the catalytic efficiency was caused by of the microreactor itself because of the structural differences in the aldehydes and the nitroolefins, the original combination of butanal and β-nitrostyrene was submitted to an additional run. Notably, adduct **5a** was produced once again in excellent yield (94%) and stereoselectivity (94:6 *dr* and 91% *ee*), which proves the robustness of the microreactor. At the end of this study, the microreactor had been working for eleven rounds, which corresponds to a total TON of 304, and still showed good efficiency and stereoselectivity. For all γ-nitroaldehydes, the absolute configuration of the major diastereomer was established to be 2*R*,3*S* based on correlations with previous reports.[12a,17]

## Conclusions

We have introduced a multicomponent strategy for the one-pot assembly of organocatalysts functionalized suitably for immobilization onto solid supports. Four silylated prolyl-peptide catalysts were produced by the Ugi four-component reaction through variation of the oxo, amine, and isocyanide components. They were all grafted onto HPLC-grade silica, screened in batch mode for the heterogeneous catalytic Michael addition, and $SiO_2$-**4b** was the most effective catalyst. The $SiO_2$-**4b** flow microreactor showed a high catalytic efficiency and excellent stereoselectivity and reproducibly in organocatalytic conjugate addition for a series of aldehydes to nitroolefins. Neither the deactivation of the catalytic microreactor nor a significant decrease in the stereoselectivity was observed even after 16

**Table 3.** Scope of the catalytic conjugate addition of aldehydes to β-nitroolefins in a continuous-flow system with on-line monitoring of the reaction outcome.

| Round[a,b] | *t* [h] | Product | | Amount of **5** [mmol] | *dr*[c] (*syn/anti*) | *ee*[c] [%] | TON | Yield[d] [%] |
|---|---|---|---|---|---|---|---|---|
| 1 | 48 |  | **5a** | 0.68 | 96:4 | 92 | 22 | 95 |
| 2 | 96 | | | 1.36 | 96:4 | 92 | 44 | 95[e] |
| 3 | 96 | | | 1.36 | 96:4 | 92 | 44 | 95 |
| 4 | 48 | | | 0.68 | 96:4 | 92 | 22 | 95 |
| 5 | 96 | | | 1.34 | 96:4 | 92 | 43 | 93 |
| 6 | 48 | | | 0.67 | 96:4 | 92 | 21 | 93[e] |
| 7 | 48 | | | 0.66 | 96:4 | 92 | 21 | 92 |
| 8 | 24 |  | **5b** | 0.32 | 95:5 | 88 | 10 | 90 |
| 9 | 24 |  | **5c** | 0.24 | – | 82 | 8 | 67 |
| 10 | 24 |  | **5d** | 0.33 | 88:12 | 91 | 11 | 93 |
| 11 | 24 |  | **5e** | 0.28 | 94:6 | 86 | 9 | 78 |
| 12 | 24 |  | **5f** | 0.31 | 96:4 | 86 | 10 | 86 |
| 13 | 24 |  | **5g** | 0.33 | 95:5 | 86 | 11 | 91 |
| 14 | 24 |  | **5h** | 0.30 | 94:6 | 84 | 10 | 84 |
| 15 | 24 |  | **5i** | 0.31 | 94:6 | 85 | 10 | 87 |
| 16[f] | 24 |  | **5j** | 0.26 | 97:3 | 91 | 8 | 72 |

[a] Solutions of the β-nitroolefin (0.25 M) and the aldehyde (0.75 M) dissolved in *n*-hexane/*i*PrOH (9:1) were pumped into the microreactor packed with $SiO_2$-**4b**. [b] The microreactor column was flushed with EtOH and rinsed with *n*-hexane/*i*PrOH before each new round. [c] Determined by chiral-stationary-phase HPLC analysis. [d] Yield of isolated pure product in the second dimension. [e] Conversion determined by calibration curve. [f] Solvent: EtOH. Enantio- and diastereoselectivity determined for the reduced product as reported in Ref. [16] (Supporting Information).

rounds. A new instrumental setup that combines the power of multidimensional chromatography and microreactor technologies was designed with success. This consists of a 3D continuous-flow system that couples the microreactor to a column for the separation of the γ-nitroaldehyde from the remaining starting materials followed by a chiral column for analysis of the conversion ratio and stereoselectivity. We believe that both the exploitation of the multicomponent reaction efficiency in the assembly of heterogenizable organocatalysts and the design of the multidimensional platform represent important innovations that may encourage further progress in the field of flow catalysis.

## Experimental Section

### General

All reagents and solvents were purchased and used as received. Enantiomeric excess and diastereoisomeric ratio values were determined by HPLC. Flash column chromatography was performed using silica gel 60 ($F_{254}$ 230–400 mesh), and analytical TLC was performed using silica gel aluminum sheets (0.2 mm $F_{254}$), which were developed using visualizing agents: UV fluorescence (254 nm), iodine, potassium permanganate/heat. $^1$H and $^{13}$C NMR spectra were recorded at 400 MHz for $^1$H and 100 MHz for $^{13}$C. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent signals chemical shifts are given relative to tetramethylsilane (TMS), and coupling constants (*J*) are reported in Hz. HRMS were recorded by using ESI (hybrid linear ion trap-orbitrap FT-MS and QqTOF/MS–Microtof–QII models). HPLC chromatograms were obtained on an apparatus with two LC-10AT pumps, a FCV-10ALvp low-pressure gradient valve, DGU-14A degasser unit, CTO-10A oven, SIL-10ADvp, SPD-10A UV/Vis detector, and a SCL-10Avp system controller with Chiralpak OD-H (Ø = 4.6 mm, *l* = 250 mm, particle size = 5 μm), Chiralpak AD-H (Ø = 4.6 mm, *l* = 250 mm, particle size = 5 μm), Chiralpak IC (Ø = 2.1 mm, *l* = 150 mm, particle size = 3 μm), Chiralpak AS-H (Ø = 4.6 mm, *l* = 250 mm, particle size = 5 μm), and $SiO_2$-**4a**-Boc (Ø = 2.1 mm, *l* = 150 mm, particle size = 10 μm) columns under reported conditions. Two valves of a six-port VICI Valco system were used. Optical rotations were measured by using a Schmidt + Haensch Polartronic H Polarimeter at 589 nm, 25 °C. Silica gel was purchased from Phenomenex (Luna $NH_2$, particle size: 10 μm, pore size: 100 å, surface area 400 $m^2 g^{-1}$, calculated bonded phase coverage 5.80 μmol $m^{-2}$, loading of $NH_2$ 2.32 mmol $g^{-1}$). A high-pressure slurry packer fitted with a Haskel 780-3 pump was used for the analytical column packing. Microanalyses were performed by using a CHNS analyzer Model EA 1108 from Fisons Instruments. An FEI Inspect F50 field-emission scanning electron microscope (FESEM) was used to image the morphology of silica before and after the grafting of the organocatalysts (Supporting Information).

### General Ugi-4CR procedure

A suspension of the amine (1.0 mmol) and the aldehyde (or ketone) (1.0 mmol) in MeOH (5 mL) was stirred for 1 h at RT. The carboxylic acid (1.0 mmol) and the isocyanide (1.0 mmol) were added, and the reaction mixture was stirred at RT for 24 h. The volatiles were removed under reduced pressure, and the resulting crude product was purified by flash column chromatography.

Silylated prolyl-peptide **1a**: (*S*)-α-Methylbenzylamine (514 μL, 4 mmol, 1.0 equiv.), paraformaldehyde (120 mg, 4 mmol, 1.0 equiv.), Boc-L-Pro-OH (862 mg, 4 mmol, 1.0 equiv.), and 3-isocyanopropyltriethoxysilane[18] (928, 4 mmol, 1.0 equiv.) were reacted in MeOH (10 mL) according to the general procedure for Ugi-4CR. Flash

column chromatography purification (*n*-hexane/EtOAc 1:1) afforded prolyl-peptide **1a** (1.63 g, 73%) as a colorless oil. $R_f = 0.30$ (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{25} = -0.044$ ($c = 0.48$, EtOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 8.14$ (m, 1H, N*H*); 7.20–7.50 (m, 5H); 5.40, 6.11 (2×q, 1H); 4.34, 4.88 (2 m, 1H); 3.80 (q, $J = 7.0$ Hz, 6H); 3.51–3.66 (m, 2H); 3.45 (m, 2H); 3.03–3.29 (m, 1H); 2.11 (m, 2H); 1.88 (m, 3H); 1.64 (m, 2H); 1.51 (d, 3H, $J = 7.2$ Hz); 1.47 (s, 9H, Boc); 1.22 (t, $J = 7.0$ Hz, 9H); 0.49, 0.63 ppm (2×m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 172.9$, 168.9, 154.9, 140.5, 128.6, 127.8, 127.6, 127.1, 80.1, 60.4, 58.3, 57.3, 55.2, 51.3, 47.3, 47.2, 42.6; 29.3, 28.5, 24.7, 22.7, 18.3, 8.0 ppm; HRMS [Fourier transform triple quadrupole (FT-QQTOF)] *m/z*: calcd for $C_{29}H_{50}N_3O_7Si$: 580.34125 $[M+H]^+$; found 580.34076.

Silylated prolyl-peptide **1b**: 3-Aminopropyltriethoxysilane (936 μL, 4 mmol, 1.0 equiv.), paraformaldehyde (120 mg, 4 mmol, 1.0 equiv.), Boc-L-Pro-OH (862 mg, 4 mmol, 1.0 equiv.), and cyclohexyl isocyanide (500 μL, 4 mmol, 1.0 equiv.) were reacted in MeOH (10.0 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded prolyl-peptide **1b** (1.43 g, 61%) as a colorless oil. $R_f = 0.35$ (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{25} = -0.030$ ($c = 0.47$, EtOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 6.84$ (d, $J = 8.3$ Hz, 1H, N*H*); 4.75, 4.60 (2×d, $J = 16.4$ Hz, 1H); 4.54 (m, 1H); 3.67–3.87 (m, 8H); 3.40–3.60 (m, 4H); 3.09–3.21 (m, 1H); 2.07–2.15 (m, 2H); 1.53–1.99 (m, 10H); 1.46 (s, 9H, Boc); 1.06–1.37 (m, 14H); 0.58 ppm (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 173.5$, 168.1, 154.6, 79.7, 60.4, 58.5, 56.5, 55.4, 51.0, 48.5, 47.2, 32.8, 30.3, 28.6, 25.5, 25.2, 24.4, 18.2, 14.2, 7.4 ppm; HRMS (ESI-FT-QQTOF) *m/z*: calcd for $C_{27}H_{51}N_3NaO_7Si$: 580.33885 $[M+Na]^+$; found 580.33997.

Silylated prolyl-peptide **2a**: (*S*)-α-Methylbenzylamine (485 μL, 4 mmol, 1.0 equiv.), acetone (294 μL, 4 mmol, 1.0 equiv.), Boc-L-Pro-OH (862 mg, 4 mmol, 1.0 equiv.), and 3-isocyanopropyltriethoxysilane[15] (925 mg, 4 mmol, 1.0 equiv.) were reacted in MeOH (10.0 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded prolyl-peptide **2a** (1.78 g, 76%) as a colorless oil. $R_f = 0.25$ (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{25} = -0.035$ ($c = 0.44$, EtOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$–$7.20$ (m, 5H); 6.43 (m, 1H, N*H*); 5.09 (m, 1H); 3.80 (q, $J = 7.0$ Hz, 6H); 3.51–3.10 (m, 4H); 2.88 (m, 1H); 1.91 (m, 2H); 1.71–1.51 (m, 12H); 1.42 (s, 9H, Boc); 1.22 (t, $J = 7.0$ Hz, 9H); 0.63 ppm (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 175.3$, 168.9, 154.5, 142.7, 128.7, 127.2, 79.2, 64.6, 60.4, 58.3, 47.5, 47.2, 42.3; 29.3, 28.5, 26.6, 23.9, 22.7, 18.3, 7.7 ppm; HRMS (ESI-FT-QQTOF) *m/z*: calcd for $C_{31}H_{54}N_3O_7Si$: 608.37255 $[M+H]^+$; found 608.37943.

Silylated prolyl-peptide **2b**: 3-Aminopropyltriethoxysilane (936 μL, 4 mmol, 1.0 equiv.), acetone (300 μL, 4 mmol, 1.0 equiv.), Boc-L-Pro-OH (862 mg, 4 mmol, 1.0 equiv.), and cyclohexyl isocyanide (500 μL, 4 mmol, 1.0 equiv.) were reacted in MeOH (10.0 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded prolyl-peptide **2b** (1.56 g, 64%) as a colorless oil. $R_f = 0.25$ (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{25} = -0.093$ ($c = 0.39$, EtOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (m, 1H, N*H*); 4.50 (m, 1H); 3.84 (m, 3H); 3.52–3.70 (m, 7H); 3.40 (m, 2H); 3.28 (m, 1H); 2.11 (m, 2H); 1.57–2.10 (m, 10H); 1.46, 1.47 (2 s, 6H); 1.44, 1.45 (2 s, 9H, Boc); 1.20–1.37 (m, 8H); 0.94–1.19 (m, 3H); 0.60 ppm (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 174.1$, 173.5, 154.5 (*C*=O), 79.3 (*C*), 62.8 (*C*), 60.4 (*C*H), 58.5, 56.9 ($CH_2$), 48.6 (CH), 47.2, 33.0, 30.3 ($CH_2$), 18.2 ($CH_3$), 25.5, 25.2, 24.4, 23.1 ($CH_2$), 28.6 ($CH_3$), 14.2 ppm ($CH_3$); HRMS (ESI-FT-QQTOF) *m/z*: calcd for $C_{29}H_{55}N_3NaO_7Si$: 608.37015 $[M+Na]^+$; found 608.36749.

### Grafting the silylated peptide catalysts onto silica

General procedure: Silica (2.60 g) was added to a round-bottomed flask that contained the Ugi-derived silylated peptide (1.0 mmol, 1.0 equiv.) dissolved in toluene (6 mL). Pyridine (0.10 mmol, 0.1 equiv.) was then added, and the reaction mixture was stirred gently under reflux for 24 h. The Boc-protected silica-supported catalyst was collected by filtration and washed consecutively with 25 mL of hexane, isopropanol, methanol/water (1:1), isopropanol, *n*-hexane, and dichloromethane, and then added to a mixture of trifluoroacetic acid/dichloromethane (1:1; 10 mL) and stirred for 12 h. The corresponding silica-supported catalyst was collected by filtration and washed consecutively with 25 mL of hexane, isopropanol, methanol/water (1:1), isopropanol, *n*-hexane, and dichloromethane.

### 1,4-addition of aldehydes to nitroolefins under batch conditions

General procedure: The nitroolefin (0.25 mmol, 1.0 equiv.) and the aldehyde (0.75 mmol, 3.0 equiv.) were added to a solution of the silica-supported catalysts (0.025 mmol, 0.01 equiv.) in an appropriate solvent (1 mL). The reaction mixture was stirred for 24 h and then concentrated under reduced pressure. The conversion of the crude product was determined by HPLC. The *ee* was determined by chiral-phase HPLC analysis by comparison with the authentic racemic material. Assignment of the stereoisomers configuration was performed by comparison with literature data.[16]

### Packing the microreactor column

A slurry of $SiO_2$-**4b** (300 mg, suspended in 15 mL of isopropanol) was packed into a stainless-steel column ($Ø = 2.1$ mm, $l = 50$ mm, particle size = 10 μm). Slurry-packing was performed under constant pressure (6000 psi) using isopropanol (150 mL) as the solvent by using an air-driven liquid pump.

### Packing the chromatographic column

A slurry of $SiO_2$-Boc-**4b** (500 mg, excess, suspended in 25 mL of isopropanol) was packed into a stainless-steel column ($Ø = 2.1$ mm, $l = 150$ mm, particle size = 10 μm). Slurry-packing was performed under constant pressure (6000 psi) using isopropanol (250 mL) as the solvent by using an air-driven liquid pump.

### Organocatalytic addition of aldehydes to nitroolefins under flow conditions

General procedure: A solution of the aldehyde (0.75 M) and the nitroolefin (0.25 M) in *n*-hexane/*i*PrOH (9:1) was pumped at a flow rate of 1 μL min$^{-1}$ into the microreactor column packed with $SiO_2$-**4b** catalyst for a defined period of time (Table 3). Each 140 min (residence time), a volume of approximately 2.0 μL of the microreactor outflow was injected into the $SiO_2$-Boc-**4b** HPLC column. The γ-nitroaldehyde chromatographic band was then transferred to a chiral polysaccharide column to analyze the stereoselectivity by comparison with authentic racemic material and literature data[14] (Supporting Information).

**Supporting information**

$^{1}H$ and $^{13}C$ NMR spectra of silylated prolyl-peptide catalysts, spectroscopic data, NMR spectra, and chiral-phase HPLC analysis of Michael adducts, elemental and microscopy analysis of silica-supported catalysts, and evaluation data of the microreactor and chromatography columns can be found in the Supporting Information.

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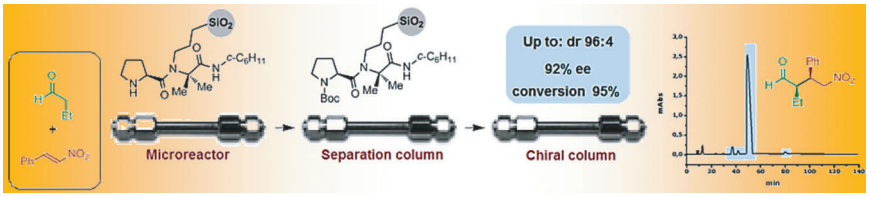
**Multicomponent Approach to Silica-Grafted Peptide Catalysts: A 3D Continuous-Flow Organocatalytic System with On-line Monitoring of Conversion and Stereo-selectivity**




**Fully automated:** A 3D continuous-flow organocatalytic system is designed with the integration of the microreactor and multidimensional chromatography technologies. This enamine catalysis platform enables the production of chiral γ-nitroaldehydes with on-line monitoring of the reaction parameters. Boc = *tert*-Butoxycarbonyl, dr = diastereomeric ratio.