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PAPER

Silica-supported 5-(pyrrolidin-2-yl)tetrazole: development of organocatalytic processes from batch to continuous-flow conditions†

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5-(Pyrrolidin-2-yl)tetrazole functionalized silica prepared by photoinduced thiol–ene coupling is packed into a short stainless steel column. The resulting packed-bed microreactor is conveniently heated to perform environmentally benign continuous-flow aldol reactions with good stereoselectivities, complete conversion efficiencies, and long term stability of the packing material.

Introduction

In the context of a growing competition in which time, cost, and sustainability issues of the synthesis play an increasingly important role even at a research stage, chemical efficiency has become one of the leading concepts for chemists working in both industry and academia. Key criteria include intrinsic (yield, (stereo)selectivity, atom economy) and extrinsic (time, waste, equipment, environment, safety) factors of the synthetic process.[1] Hence, the booming field of asymmetric organocatalysis is opening, on the one hand, new and unique opportunities towards efficient and highly stereoselective metal-free catalytic syntheses.[2] On the other hand, microreactor technology is offering safe, environmentally benign, and high-throughput processes typically intensified by a fast postreaction phase (workup and purification) and direct scalability.[3] Very recently, we have embarked on a research program aimed at preparing and testing organocatalytic packed-bed microreactors[4] to prove the potential benefits arising from the combination of the above synthetic methodology and production technology.[5] Currently, this program is being developed on the basis of the following general thread: (i) heterogenization of a successful asymmetric organocatalyst on silica and optimization of its performance (yield and stereoselectivity) under batch conditions; (ii) preparation of the corresponding packed-bed microreactor and preliminary testing in continuous-flow regime; (iii) development of a suitable in-line analysis method and final optimization of the continuous-flow process based on kinetic and thermodynamic characterization thereof. It is worth noting that while a (limited) number of notable examples of asymmetric syntheses in continuous-flow have been reported,[6] only a few studies have dealt with the use of immobilized organocatalysts.[7] Indeed, peculiar benefits of heterogeneous organocatalysis in conjunction with microreactor technology are the absence of metal leaching (a problematic issue especially in pharmaceutical applications), the enhanced resistance of supports to mechanical degradation, and the potential long-term usage of (micro)reactors that is highly desirable for complex and costly immobilized catalysts. As a matter of fact, the main limitation encountered in our first investigation[4] on the proline-catalyzed continuous-flow aldol reaction of cyclohexanone with *p*-nitro benzaldehyde was the progressive loss of catalytic activity of the packing material **1** (Fig. 1). Deactivation of immobilized proline **1** occurred through irreversible decarboxylation[8] after 24 h on stream at room temperature and was greatly accelerated by increasing the process temperature. Herein, we report on the synthesis and catalytic activity under batch conditions of immobilized proline mimetics, namely heterogeneous prolyl amide **2**,[9] sulfonamide **3**,[10] and pyrrolidinyl tetrazole **4**,[11] which are not prone to the above deactivation pathway and thus are expected to provide organocatalytic packed-bed

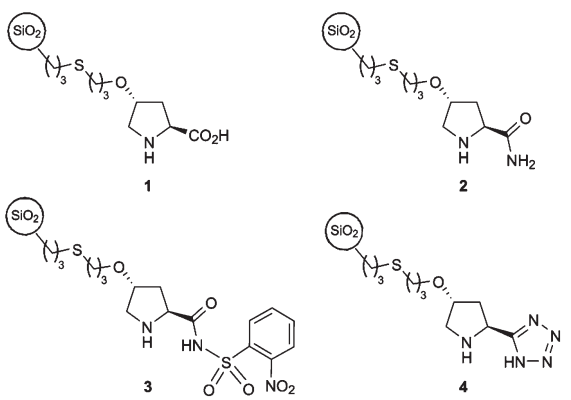

Fig. 1 Silica-immobilized proline and proline-like organocatalysts **1–4**.

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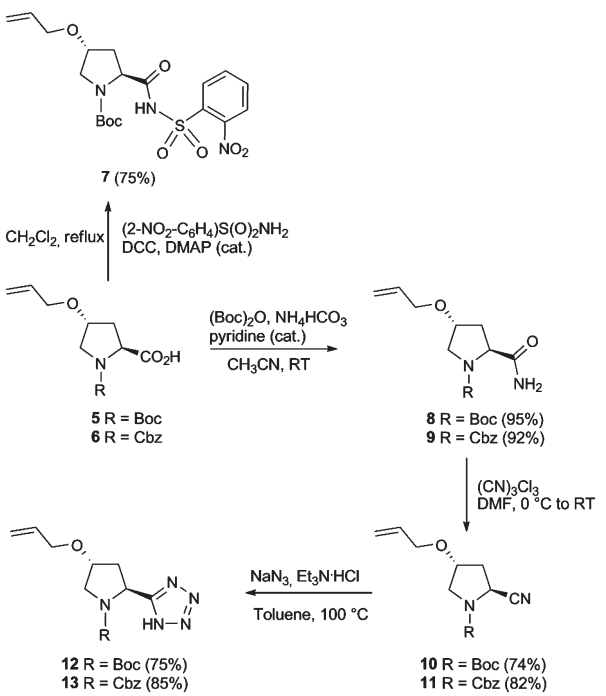
microreactors with improved stability and, eventually, better reaction profiles.[9–11] Preliminary results on the continuous-flow aldol reaction promoted by the best performing silica-supported 5-(pyrrolidin-2-yl)tetrazole catalyst **4** are finally presented.

Results and discussion

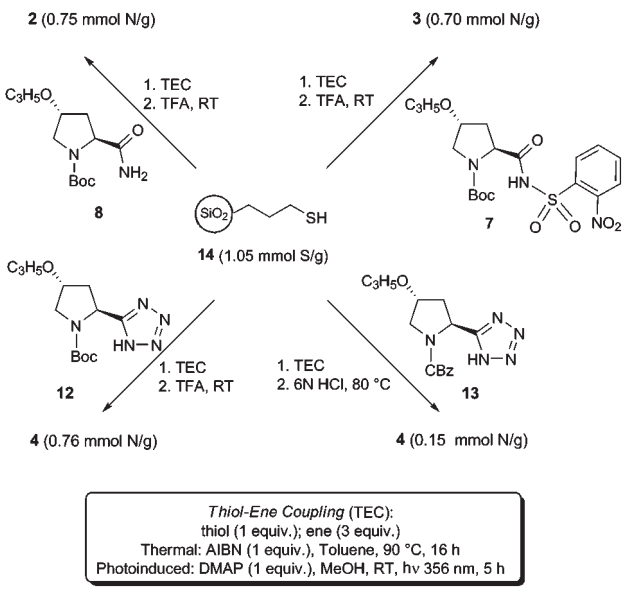
The thermal/photoinduced thiol–ene coupling (TEC)[12] was chosen as the covalent immobilization strategy for the preparation of heterogeneous proline-like organocatalysts **2–4** in analogy with the synthesis of the previously reported immobilized proline **1**. Accordingly, the novel *N*-Boc pyrrolidine 2-carboxyamide **7** and sulfonamide **8** equipped with the ene functionality (4-allyloxy group) were readily prepared in a single step from (2*S*,4*R*)-*N*-Boc-4-*O*-allyl-hydroxyproline **5**[4] by standard chemistry (Scheme 1). The tetrazolyl alkene **13** bearing a Cbz protecting group at the pyrrolidine nitrogen atom was next synthesized by adapting the procedures already optimized by Ley *et al.*,[11m] Hartikka and Arvidsson,[11i] and Saito, Yamamoto *et al.*[11j] for the synthesis of a *N*-Cbz protected pyrrolidinyl tetrazole analogue. Accordingly, (2*S*,4*R*)-*N*-Cbz-4-*O*-allyl-hydroxyproline **6**[13] was almost quantitatively converted to the corresponding amide **9** by *in situ* activation of the carboxylic acid. Subsequent dehydration promoted by cyanuric chloride gave the nitrile **11** in high yield (82%), which in turn was transformed into the corresponding tetrazole **13** (85%) by cycloaddition with sodium azide.

The thermally (toluene, 90 °C) and photochemically (MeOH, room temperature, λ_{max} 365 nm) induced TECs of thiol–silica **14**[14] with alkenes **7** or **8** (3 equiv.) were next carried out under the previously optimized conditions[4] by using 2,2′-azobis(2-methylpropionitrile) (AIBN) and 2,2-dimethoxy-2-phenyl-acetophenone (DMAP) as the radical initiators, respectively. Both immobilization strategies resulted equally effective producing, after TFA-promoted Boc deprotection, the target prolyl amide and sulfonamide functionalized silicas **2** and **3**, respectively, with a comparable degree of functionalization (0.75–0.70 mmol g^{-1}), as determined by elemental analysis (Scheme 2). A lower loading (0.15 mmol g^{-1}) was instead achieved for the tetrazole functionalized silica **4** prepared by TEC (thermal or photoinduced) of **14** with *N*-Cbz pyrrolidinyl tetrazole **13**. This unsatisfactory result was determined by the harsh acidic conditions required for Cbz group removal (6N HCl, 80 °C). Nevertheless, while milder Cbz deprotection procedures proved to be unsuccessful on silica support, the synthetic sequence optimized for the preparation of *N*-Cbz pyrrolidinyl tetrazole **13** was practicable and effective for the synthesis of the *N*-Boc analogue **12** as well (Scheme 1). Gratifyingly, TEC of **14** with **12** followed by Boc deprotection afforded the tetrazole functionalized silica **4** with a suitable loading (0.76 mmol g^{-1}; Scheme 2).

Next, on the basis of our previous experience with proline catalyst **1**, the activity of the newly prepared heterogeneous proline mimetics **2–4** was evaluated in selected solvents (acetonitrile, toluene, DMSO, and dichloromethane) by using the aldol condensation of cyclohexanone **15** with *p*-nitro benzaldehyde **16a** as the benchmark (Table 1). Proline amide **2** was the less active catalyst in terms of both chemical yield and stereoselectivity (entries 1–4). As already observed for immobilized proline **1**,[4] the use of the low-polarity toluene produced the best results for the sulfonamide **3** and tetrazole **4** as well, the latter being much more active than the former (entries 6 and 10). Different solvents were then screened to further improve catalyst **4** profile (entries 13–15). Pleasingly, the utilization at room temperature of diisopropyl ether allowed isolation of the mixture of *anti–syn* adducts (d.r. = 2 : 1) in quantitative yield and high enantioselectivity (95% ee_{anti}) after 12 h reaction time (entry 15). It is important to note that tetrazole catalyst **4** outperforms the supported proline **1**, which promoted the formation of **17a** (d.r. = 4 : 1) in lower yield (67%) and enantioselectivity (78% ee_{anti}; entry 16).[4] Finally,

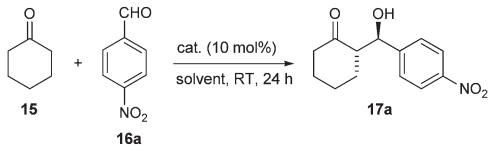


Scheme 1 Synthesis of the ene-functionalized proline mimetics **7**, **8**, **12**, and **13**.



Scheme 2 Thermally and photochemically induced TEC of thiol silica **14** with 4-*O*-allyl-hydroxyroline derivatives **7**, **8**, **12**, and **13**.

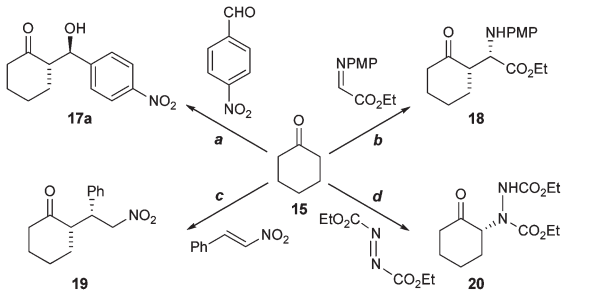
Table 1 Evaluation of catalysts **2–4** performance under batch conditions[a]



Entry	Cat.	Solvent	Yield[b] [%]	d.r. *anti–syn*[c]	ee$_{anti}$[d] [%]
1	**2**	CH_3CN	24	2 : 1	26
2	**2**	Toluene	45	4 : 1	23
3	**2**	DMSO	12	3 : 1	23
4	**2**	CH_2Cl_2	18	4 : 1	8
5	**3**	CH_3CN	21	4 : 1	9
6	**3**	Toluene	58	3 : 1	30
7	**3**	DMSO	25	2 : 1	9
8	**3**	CH_2Cl_2	15	4 : 1	15
9	**4**	CH_3CN	75	4 : 1	74
10	**4**	Toluene	>95	3 : 1	82
11	**4**	DMSO	>95	1 : 1	50
12	**4**	CH_2Cl_2	84	3 : 1	51
13	**4**	MeOH	45	3 : 1	32
14	**4**	Et_2O	>95	2 : 1	90
15	**4**	$(iPr)_2O$	>95[e]	2 : 1	95
16	**1**	Toluene	68	4 : 1	78
17	**4**	$(iPr)_2O$[f]	>95	2 : 1	92

[a] Reactions performed in the stated solvent with 0.25 mmol of aldehyde (0.15 M) and 0.75 mmol of ketone. [b] Isolated yield of the *anti–syn* diastereomeric mixture. [c] Estimated by ^{1}H NMR analysis of crude reaction mixtures. [d] Determined by chiral HPLC analysis. [e] Reaction time: 12 h. [f] Reactions performed with recycled catalyst.

Table 2 Short study on the catalytic activity of **4** in model organocatalytic reactions[a]



Entry	React.	Solvent	Yield[b] [%]	d.r. *anti–syn*[c]	ee[d] [%]
1	*a*	$(iPr)_2O$	90 (**17a**)	2 : 1	95$_{anti}$
2	*a*	DMSO	92 (**17a**)	1 : 1	50$_{anti}$
3[e]	*b*	$(iPr)_2O$	82[f] (**18**)	1 : >19	90$_{syn}$
4[e]	*b*	Toluene	>95[f] (**18**)	1 : >19	95$_{syn}$
6	*c*	$(iPr)_2O$	80 (**19**)	1 : 15	55$_{syn}$
5	*c*	DMSO	92 (**19**)	1 : 9	45$_{syn}$
7[e]	*d*	CH_3CN	95[f] (**20**)	—	42
8[e]	*d*	Toluene	72[f] (**20**)	—	71
9[g]	*a*	DMSO	92 (**17a**)	1 : 1	95$_{anti}$

[a] Reactions performed at room temperature for 24 h in the stated solvent with 0.25 mmol of acceptor (0.1 M), 0.75 mmol of cyclohexanone, and 0.075 mmol of **4**. [b] Isolated yield of the stereomeric mixture of adducts. [c] Estimated by ^{1}H NMR analysis of crude reaction mixtures. [d] Determined by chiral HPLC analysis. [e] Reaction performed with 20 vol % of **15**. Reaction time: 2 h. [f] Yield determined by ^{1}H NMR analysis. [g] Reaction performed under homogeneous conditions with (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole catalyst (10 mol%).

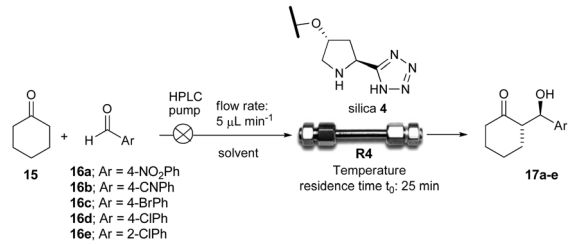
a substantial maintenance of catalyst efficiency was detected in diisopropyl ether for recycled **4** (entry 17). Indeed, the evaluation of catalyst stability (recyclability) was a crucial experiment to envisage the potential application of **4** in continuous-flow processes.

Since its discovery,[11g,h,j] the unsupported (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole has proven to be a successful catalyst due to its efficacy in a wide range of organocatalytic reactions.[11a] Therefore, with the aim to gain more information about the potential applications of the supported analogue **4** in continuous-flow heterogeneous catalysis, the activity of **4** was tested in model Mannich (eq. *b*, Table 2), Michael (eq. *c*), and α-amination (eq. *d*) reactions. Table 2 summarizes the results of this short study reporting for each transformation the best reaction profiles based on product yield and/or stereoselectivity.[15] Selected outcomes of the model aldol reaction are also included in Table 2 (eq. *a*). It appears from these preliminary results that heterogeneous catalyst **4** behaves in a comparable manner to the unsupported counterpart in terms of yield[16] and diastereo- and enantioselectivity. A direct comparison with literature data was, in fact, possible for the Mannich,[11c] Michael,[11c,16] and α-amination reactions.[11b] As far as the aldol reaction is concerned (entries 1–2), the observed poor diastereoselectivity was demonstrated to be an intrinsic feature of tetrazole catalysis. Indeed, an experiment (entry 9) performed in DMSO (room temperature, 24 h) with the unsupported (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole catalyst (10 mol%) gave the mixture of aldol products in identical quantitative yield and 1 : 1 diastereomeric ratio (entries 9 and 2).

Mechanistically, though the general mode of pyrrolidinyl tetrazole catalysis is still the subject of debate and discussion,[11a] it can be speculated that the suitable choice of low-polarity solvents such as diisopropyl ether and toluene prevents the free hydroxyls on the silica support of **4** from perturbing the hydrogen-bonding network responsible for the high selectivities detected in homogeneous catalysis.[17]

As anticipated, the tetrazole catalyst **4** was finally tested in the continuous-flow aldol reaction of cyclohexanone with *p*-nitro benzaldehyde with the hope of setting up an effective process with potential long term stability.[18] Thus, a micro-HPLC was suitably adapted for this study with minimized extra-columns volumes. The packed-bed microreactor **R4** (Table 3) was then prepared by filling (packing by gravity) a stainless steel column (50 mm length, 2.1 mm diameter) with tetrazole-functionalized silica **4** (pore size 60 Å, particle size ~50 μm, superficial area 500 m^2 g^{-1}, loading 0.76 mmol g^{-1}). Main features of **R4** were determined by pycnometry and included the hold-up (dead) volume (V_0 = 125 μL), and the total porosity (0.72). The packing amount of silica (154 mg) was calculated by weighing the column before and after filling. In addition, chromatographic retention factors k' of cyclohexanone and *p*-nitro benzaldehyde were measured under linear conditions in diisopropyl ether (DIP) and toluene.[19] These solvents, in fact, were selected as the optimal reaction media for the subsequent continuous-flow experiments (Table 3). Importantly, the determination of k' values was crucial for roughly calculating the retention times (t_r) of the above reactants at different flow rates,[19] and thus for

Table 3 Optimization of continuous-flow aldol reaction in packed-bed microreactors **R4** and short substrate scope study[a]



Entry	Solvent	**16** (c [M])	$k'_{\mathbf{16}}$[b]	$t_{r(\mathbf{16})}$[b] (min)	Temp.[c] [°C]	Conv.[d] [%]	Productivity[e]/10^3 [mmolh^{-1} mmol$_{cat}^{-1}$]	d.r. *anti–syn*[f]	ee$_{anti}$[g] [%]
1	$(iPr)_2O$	**16a** (0.03)	8.56	239	25	65	50	2 : 1	95
2	Toluene	**16a** (0.10)	0.91	48	25	62	159	3 : 1	82
3	$(iPr)_2O$[h]	**16a** (0.10)	—	—	25	58	149	2 : 1	85
4	$(iPr)_2O$[i]	**16a** (0.03)	8.56	239	50	>95	77	1 : 1	92
5	Toluene	**16a** (0.10)	0.91	48	50	95	256	2 : 1	80
6	Toluene	**16b** (0.10)	0.60	45	50	>95	256	3 : 1	75
7	Toluene	**16c** (0.10)	0.26	31	50	95	256	3 : 1	78
8	Toluene	**16d** (0.10)	0.27	32	50	>95	256	3 : 1	82
9	Toluene	**16e** (0.10)	0.28	32	50	>95	236	2 : 1	68

[a] See the Experimental section for a description of the experimental setup. All reactions were performed with a three-fold excess of cyclohexanone. [b] Chromatographic retention factors k' and retention times t_r have been estimated at RT in the reaction solvent as described in ref. 19. $k'_{\mathbf{15}}$(DIP) = 0.84 (t_r = 46 min); $k'_{\mathbf{15}}$(Tol) = 0.30 (t_r = 33 min)). [c] All temperatures were measured by a thermometer placed inside the thermostatted unit containing the microreactor. [d] Instant conversion in steady-state regime as established by ^{1}H NMR analysis. [e] Productivities are measured in mmol(product) h^{-1} mmol(catalyst)$^{-1}$ × 10^3. [f] Estimated by ^{1}H NMR analysis of crude reaction mixtures. [g] Determined by chiral HPLC analysis. [h] Reaction performed with 10 vol% of DMF. [i] The same reaction outcome was observed in a control experiment performed at the end of the substrate scope study.

estimating the duration of the process.[20] An initial continuous-flow experiment was performed in DIP by using a three-fold excess of cyclohexanone in analogy to the batch study. The optimal compromise between aldehyde solubility, conversion efficiency, and productivity was obtained by pumping a 0.03 M solution of aldehyde at 5 μL min^{-1} (residence time t_0 = 25 min; $t_{r(\mathbf{16a})}$: 239 min). As previously observed with proline catalyst **1**,[4] the stereoselectivity of the batch experiment with **4** (Table 1, entry 15) was replicated (d.r. 2 : 1; 95 ee$_{anti}$, Table 3, entry 1) and maintained constant during the continuous process in steady-state regime.[20] The use of toluene or a 9 : 1 DIP–DMF mixture as the solvent improved the process productivity because of the higher concentration of reactants but, at the same time, slightly lowered the reaction conversion and the level of enantioselectivity (entries 2–3). Therefore, having in mind that reaction completion is a fundamental goal in continuous process optimization for easier product purification, the effect of temperature on conversion efficiency was finally examined.[21] To our delight, we found that warming the microreactor **R4** in the HPLC oven set a 50 °C resulted in complete conversion and selectivity (no formation of dehydration by-product was detected) both in DIP and toluene, thus allowing the isolation of the aldol product **17a** by simple evaporation of the solvent and excess cyclohexanone (entries 4 and 5). Notably, the increase of the process temperature did not compromise the enantioselectivity of the process, which proceeded with higher productivity (*ca.* 8 mg h^{-1}) in toluene (entry 5).

The scope and the applicability of the method were shortly investigated by reacting cyclohexanone with various aromatic aldehydes having electron-withdrawing substituents (entries 6–9). Gratifyingly, the corresponding mixtures of aldol adducts **17b–e** were produced in toluene at 50 °C with high conversion efficiency (≥95%) and a satisfactory level of enantioselectivity (68–82 ee$_{anti}$). We would like to emphasize that the whole optimization and substrate scope study was carried out with the same packed-bed microreactor **R4**, which functioned at 50 °C for an overall time of 80 hours. Remarkably, the packing silica **4** did not show any evidence of deactivation during that period, as demonstrated by a final control experiment that reproduced the optimal **15**/**16a** coupling outcome (entry 4). A progressive loss of catalytic activity was observed, however, after 120 hours at 50 °C, with catalyst **4** fully deactivated after *ca.* 7 days on stream.

Conclusions

In summary, we have synthesized a heterogeneous version of the valuable Ley–Arvidsson–Yamamoto (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole organocatalyst and ascertained that the utilization of silica as the support and thiol–ene coupling (TEC) as the immobilization strategy enables tetrazole organocatalyst **4** to maintain the level of stereoselectivity of its homogeneous counterpart in model batch transformations. Crucial for successful experiments with supported tetrazole **4** was the selection of low-polarity reaction solvents. In addition, we have provided a further example of the effective combination of heterogeneous asymmetric organocatalysis and microreactor technology by preparing a packed-bed microreactor filled with silica **4** and demonstrating its efficacy in the continuous production of optically active aldol products. Further improvements, in particular pertaining to process productivity, are in progress through chemical optimization of the

described catalytic system and by taking advantage of a deeper understanding of the kinetics and thermodynamics of the continuous-flow-process. Nevertheless, we believe this work may represent a useful contribution to the current search for more efficient, economic, and environmentally benign production strategies of valuable chiral targets.

Experimental section

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agent and freshly distilled prior to use. Flash column chromatograph was performed on silica gel 60 (230–400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid and/or ninhydrin. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified. Peak assignments were aided by ^1H–^1H COSY and gradient-HMQC experiments. Enantiomeric excess (ee) values were determined by HPLC. A two-pump high pressure micro system (Agilent 1100 micro series) equipped with a DAD detector was employed. The column was 150 × 2 mm Lux-1 Cellulose (from Phenomenex), 3 μm particle diameter. The mobile phase was a binary mixture hexanes–i-PrOH 90 : 10 (v/v). ESI MS (LTQ-XL Linear Trap from Thermo Scientific) analyses were performed in positive ion mode with samples dissolved in 10 mM solution of HCO_2NH_4 in 1 : 1 MeCN–H_2O. FT-IR analyses were performed with the Bruker Instrument Vertex 70. Elemental analyses were performed with FLASH 2000 Series CHNS/O analyzer (ThermoFisher Scientific). Vertical agitation was performed with the FirstMate™ synthesizer, Argonaut Technology. The household UVA lamp apparatus was equipped with four 15 W tubes (1.5 × 27 cm each). Photoinduced reactions were carried out in a glass vial (diameter: 1 cm; wall thickness: 0.65 mm), sealed with a natural rubber septum, located 2.5 cm away from the UVA lamp (irradiation on sample: 365 nm, 1.04 W m^{-2}). The system used for continuous-flow reactions was composed of an HPLC pump (Agilent 1100 micro series), an in-line pressure transducer, a thermostated microreactor holder (Peltier unit), a system to collect fractions and a data acquisition system (Agilent ChemStation). The units were connected by peek tubing (internal diameter 0.01 inch from Upchurch Scientific). The system hold-up volume was smaller than 80 μL. The temperature was controlled by inserting a thermometer inside the Peltier unit (temperature measurement error: ±0.5 °C). Silica gel (grade 9385, pore size 60 Å, particle size ~50 μm, superficial area 500 m^2 g^{-1}) was purchased from Sigma-Aldrich. (2*S*,4*R*)-*N*-Boc-4-(allyloxy)proline **5**[4] and (2*S*,4*R*)-*N*-Cbz-4-(allyloxy)proline **6**[13] were synthesized as described. Thiol–silica **14**[22] was prepared according to reported procedures with minor modifications. For microreactor **R4** preparation and characterization see the ESI.† Adducts **17a–e**, **18**, **19**, and **20** are known compounds. The self-disproportionation of enantiomers (SDE) test for achiral chromatography[23] has been carried out for derivatives **17a–e**, **19**, and **20** without noting any significant magnitude of SDE.

(2*S*,4*R*)-*tert*-Butyl 4-(allyloxy)-2-(2-nitrophenylsulfonylcarbamoyl)pyrrolidine-1-carboxylate (7)

To a stirred solution of (2*S*,4*R*)-*N*-Boc-4-(allyloxy)proline **5**[4] (500 mg, 1.85 mmol) in CH_2Cl_2 (8 mL) were added 2-nitrobenzenesulfonamide (337 mg, 1.67 mmol), 4-(dimethylamino)pyridine (DMAP, 61 mg, 0.50 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 419 mg, 2.03 mmol). The resulting mixture was refluxed for 72 h, then cooled to room temperature, filtered, and washed with fresh portions of CH_2Cl_2 (4 × 5 mL). The combined filtrates were washed with cold 1 M HCl (5 mL) and brine (5 mL) Then, the organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 2.5 : 1 cyclohexane–AcOEt to give the sulfonamide **7** (631 mg, 75%) as a white amorphous solid. $[\alpha]_D = -51.2$ (*c* 1.6, $CHCl_3$). ^1H NMR: δ = 8.50–8.38 (bm, 2 H, Ar), 7.85–7.62 (bm, 3 H, Ar), 5.90–5.78 (m, 1 H, CH_2═C*H*), 5.28–5.15 (m, 2 H, CH_2═CH), 4.50–4.29 (bm, 1 H, H-2), 4.08–3.74 (bm, 3 H, OCH_2, H-4), 3.52 (bdd, 1 H, $J_{4,5a}$ = 2.0 Hz, $J_{5a,5b}$ = 8.5 Hz, H-5a), 3.40 (bdd, 1 H, $J_{4,5b}$ = 5.0 Hz, $J_{5a,5b}$ = 10.5 Hz, H-5b), 2.50–2.00 (bm, 2 H, 2 H-3), 1.42 and 1.38 (2 s, 9 H, C(CH_3)$_3$). ^{13}C NMR (major conformer): δ = 171.1, 157.0, 154.2, 148.1, 134.2, 133.3, 132.3, 124.7, 117.2, 82.3, 76.0, 70.1, 59.5, 51.9, 32.6, 28.2. ESI MS (455.1): 473.4 (M + NH_4^+). Found: C, 50.02; H, 5.78; N, 9.51; S 7.22. $C_{19}H_{25}N_3O_8S$ requires C, 50.10; H, 5.53; N, 9.23; 7.04%.

(2*S*,4*R*)-*tert*-Butyl 4-(allyloxy)-2-carbamoylpyrrolidine-1-carboxylate (8)

To a stirred mixture of (2*S*,4*R*)-*N*-Boc-4-(allyloxy)proline **5**[4] (1.28 g, 4.72 mmol), di-*tert*-butyl dicarbonate (1.54 g, 7.08 mmol,), NH_4HCO_3 (559 mg, 7.08 mmol), and anhydrous CH_3CN (20 mL) anhydrous pyridine (286 μL, 3.54 mmol) was added in one portion. The mixture was stirred at room temperature until TLC analysis revealed the disappearance of the starting acid (*ca.* 5 h), then the volume was reduced under vacuum to approximately 5 mL. Subsequently, AcOEt (20 mL) and H_2O (20 mL) were added and the organic phase separated. The aqueous phase was extracted further with AcOEt (2 × 20 mL) and the combined organic phases washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give the amide **8** (1.21 g, 95%) at least 90% pure as judged by ^1H NMR analysis. An analytical sample of **8** was obtained by column chromatography with 1 : 9 cyclohexane–AcOEt. $[\alpha]_D = -58.8$ (*c* 0.6, $CHCl_3$). ^1H NMR: δ = 6.80 and 5.90 (2 bs, 1 H, NH), 6.00–5.80 (m, 1 H, CH_2═C*H*), 5.60–5.45 (bm, 1 H, NH), 5.35–5.15 (m, 2 H, CH_2═CH), 4.45–4.15 (bm, 2 H, H-2, H-4), 4.05–3.90 (bm, 2 H, OCH_2), 3.80–3.40 (m, 2 H, 2 H-5), 2.55–2.00 (bm, 2 H, 2 H-3), 1.42 (s, 9 H, C(CH_3)$_3$). ^{13}C NMR (major conformer): δ = 173.9, 154.0, 134.3, 117.2, 80.8, 75.9, 70.2, 58.2, 51.8, 33.7, 28.3. ESI MS (270.2): 309.8 (M + K^+). Found: C, 57.48; H, 8.41; N, 10.09. $C_{13}H_{22}N_2O_4$ requires C, 57.76; H, 8.20; N, 10.36%.

(2*S*,4*R*)-Benzyl 4-(allyloxy)-2-carbamoylpyrrolidine-1-carboxylate (9)

To a stirred mixture of (2*S*,4*R*)-*N*-Cbz-4-(allyloxy)proline **6**[13] (1.00 g, 3.28 mmol), di-*tert*-butyl dicarbonate (1.07 g,

4.92 mmol), NH_4HCO_3 (389 mg, 4.92 mmol), and anhydrous CH_3CN (15 mL) anhydrous pyridine (199 μL, 2.46 mmol) was added in one portion. The mixture was stirred at room temperature until TLC analysis revealed the disappearance of the starting acid (*ca.* 5 h), then the volume was reduced under vacuum to approximately 5 mL. Subsequently, AcOEt (20 mL) and H_2O (20 mL) were added and the organic phase separated. The aqueous phase was extracted further with AcOEt (2 × 20 mL) and the combined organic phases washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give the amide **9** (917 mg, 92%) at least 90% pure as judged by ^{1}H NMR analysis. An analytical sample of **9** was obtained by column chromatography with pure AcOEt. $[\alpha]_D = -49.9$ (*c* 1.4, $CHCl_3$). ^{1}H NMR: δ = 7.40–7.20 (m, 5 H, Ar), 6.65 and 5.82 (2 bs, 1 H, NH), 5.92–5.78 (m, 1 H, CH_2═C*H*), 5.45–5.30 (bm, 1 H, NH), 5.28–5.10 (m, 2 H, CH_2═CH), 4.50–4.35 (m, 1 H, H-2), 4.26–4.10 (m, 1 H, H-4), 4.00–3.90 (m, 2 H, OCH_2), 3.86–3.50 (m, 2 H, 2 H-5), 2.60–2.40 and 2.30.2.00 (2 bm, 2 H, 2 H-3). ^{13}C NMR (major conformer): δ = 173.4, 156.2, 136.1, 134.2, 128.5, 128.2, 127.8, 117.3, 76.1, 70.2, 67.5, 58.7, 51.7, 33.9. ESI MS (344.1): 343.9 (M + K^+). Found: C, 63.38; H, 6.51; N, 9.01. $C_{16}H_{20}N_2O_4$ requires C, 63.14; H, 6.62; N, 9.20%.

(2S,4*R*)-*tert*-Butyl 4-(allyloxy)-2-cyanopyrrolidine-1-carboxylate (10)

To a cooled (0 °C), stirred solution of crude amide **8** (1.21 g, 4.48 mmol) in anhydrous DMF (20 mL) cyanuric chloride (537 mg, 2.91 mmol) was added in one portion. The mixture was stirred at 0 °C for 1 h, then warmed to room temperature, and stirred at that temperature for additional 24 h. The mixture was then cooled to 0 °C, diluted with H_2O (15 mL), and extracted with AcOEt (3 × 50 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 4 : 1 cyclohexane–AcOEt to give **11** (835 mg, 74%) as a pale yellow oil. $[\alpha]_D = -65.4$ (*c* 1.1, $CHCl_3$). ^{1}H NMR: δ = 5.98–5.82 (m, 1 H, CH_2═C*H*), 5.34–5.20 (m, 2 H, CH_2═CH), 4.64–4.50 (m, 1 H, H-2), 4.30–4.10 (m, 1 H, H-4), 4.08–3.90 (m, 2 H, OCH_2), 3.70–3.60 and 3.58–3.48 (2 bm, 2 H, 2 H-5), 2.60–2.30 (bm, 2 H, 2 H-3), 1.48 and 1.4 (2 s, 9 H, C(CH_3)$_3$). ^{13}C NMR (major conformer): δ = 152.8, 133.7, 118.7, 117.2, 81.3, 74.9, 69.9, 50.5, 45.4, 37.0, 27.9. ESI MS (252.1): 275.7 (M + Na^+). Found: C, 61.67; H, 7.81; N, 11.28. $C_{13}H_{20}N_2O_3$ requires C, 61.88; H, 7.99; N, 11.10%.

(2S,4*R*)-Benzyl 4-(allyloxy)-2-cyanopyrrolidine-1-carboxylate (11)

To a cooled (0 °C), stirred solution of crude amide **9** (1.60 g, 5.26 mmol) in anhydrous DMF (18 mL) cyanuric chloride (630 mg, 3.41 mmol) was added in one portion. The mixture was stirred at 0 °C for 1 h, then warmed to room temperature, and stirred at that temperature for additional 12 h. The mixture was then cooled to 0 °C, diluted with H_2O (10 mL), and extracted with AcOEt (3 × 40 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 2 : 1 cyclohexane–AcOEt to give **11** (1.23 g, 82%) as a white foam. $[\alpha]_D = -61.5$ (*c* 0.7, $CHCl_3$). ^{1}H NMR: δ = 7.45–7.25 (m, 5 H, Ar), 6.00–5.78 (m, 1 H, CH_2═C*H*), 5.40–5.25 (m, 2 H, CH_2═CH), 4.80–4.58 (m, 1 H, H-2), 4.30–4.12 (m, 1 H, H-4), 4.10–3.80 (m, 2 H, OCH_2), 3.80–3.72 and 3.64–3.50 (2 m, 2 H, 2 H-5), 2.60–2.20 (m, 2 H, 2 H-3). ^{13}C NMR (major conformer): δ = 162.0, 135.7, 133.8, 128.6, 128.3, 128.2, 128.1, 128.0, 118.7, 117.8, 75.9, 70.3, 68.1, 51.3, 45.5, 37.6. ESI MS (286.1): 309.5 (M + Na^+). Found: C, 67.42; H, 6.60; N, 9.98. $C_{16}H_{18}N_2O_3$ requires C, 67.12; H, 6.34; N, 9.78%.

(2S,4*R*)-*tert*-Butyl 4-(allyloxy)-2-(1*H*-tetrazol-5-yl)pyrrolidine-1-carboxylate (12)

A mixture of nitrile **10** (800 mg, 3.17 mmol), NaN_3 (268 mg, 4.12 mmol), Et_3N·HCl (567 mg, 4.12 mmol), and toluene (5 mL) was stirred at 95 °C under an atmosphere of argon for 24 h. The mixture was then cooled to room temperature and extracted with AcOEt (3 × 40 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 6 : 4 : 1 cyclohexane–AcOEt–AcOH to give **12** (701 mg, 75%) as a white amorphous solid. $[\alpha]_D = -92.0$ (*c* 0.6, $CHCl_3$). ^{1}H NMR: δ = 6.02–5.88 (m, 1 H, CH_2═C*H*), 5.37–5.22 (m, 2 H, CH_2═CH), 5.17 (dd, 1 H, $J_{2,3a}$ = 7.0 Hz, $J_{2,3b}$ = 7.5 Hz, H-2), 4.35–4.25 (m, 1 H, H-4), 4.15–4.00 (m, 2 H, OCH_2), 3.64 (dd, 1 H, $J_{4,5a}$ = 3.0 Hz, $J_{5a,5b}$ = 11.5 Hz, H-5a), 3.48 (dd, 1 H, $J_{4,5b}$ = 5.0 Hz, $J_{5a,5b}$ = 11.5 Hz, H-5b), 3.10–3.00 (m, 1 H, H-3a), 2.63–2.51 (m, 1 H H-3b), 1.42 (s, 9 H, C(CH_3)$_3$). ^{13}C NMR (major conformer): δ = 157.0, 155.9, 134.1, 117.3, 81.6, 76.0, 70.1, 52.0, 49.7, 35.5, 28.2. ESI MS (295.2): 296.6 (M + H^+). Found: C, 52.55; H, 7.41; N, 23.46. $C_{13}H_{21}N_5O_3$ requires C, 52.87; H, 7.17; N, 23.71%.

(2S,4*R*)-Benzyl 4-(allyloxy)-2-(1*H*-tetrazol-5-yl)pyrrolidine-1-carboxylate (13)

A mixture of nitrile **11** (800 mg, 2.80 mmol), NaN_3 (237 mg, 3.64 mmol), Et_3N·HCl (501 mg, 3.64 mmol), and toluene (5 mL) was stirred at 95 °C under an atmosphere of argon for 24 h. The mixture was then cooled to room temperature, diluted with cold 1 M HCl until pH = 3, and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 6 : 4 :1 cyclohexane–AcOEt–AcOH to give **13** (783 mg, 85%) as a white amorphous solid. $[\alpha]_D = -42.2$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (DMSO-d_6 + D_2O, 120 °C): δ = 7.45–7.15 (m, 5 H, Ar), 6.00–5.84 (m, 1 H, CH_2═C*H*), 5.32–5.05 (m, 2 H, CH_2═CH), 5.29 (dd, 1 H, $J_{2,3a}$ = 5.0 Hz, $J_{2,3b}$ = 5.5 Hz, H-2), 4.36–4.28 (m, 1 H, H-4), 4.04–3.98 (m, 2 H, OCH_2), 3.72 (dd, 1 H, $J_{4,5a}$ = 5.0 Hz, $J_{5a,5b}$ = 11.5 Hz, H-5a), 3.64 (dd, 1 H, $J_{4,5b}$ = 1.5 Hz, $J_{5a,5b}$ = 11.5 Hz, H-5b), 2.42 (ddd, 1 H, $J_{2,3a}$ = 5.0 Hz, $J_{3a,4}$ = 7.5 Hz, $J_{3a,3b}$ = 12.5 Hz, H-3a), 2.21 (ddd, 1 H, $J_{2,3a}$ = 5.5 Hz, $J_{3a,4}$ = 6.0 Hz, $J_{3a,3b}$ = 12.5 Hz, H-3b). ^{13}C NMR (major conformer): δ = 156.7, 156.3, 135.8, 134.1, 128.5, 128.2, 128.0, 127.8, 117.4, 75.7, 70.2, 67.7, 51.9, 50.3, 35.5. ESI MS (329.1): 330.5 (M + H^+). Found: C, 58.62; H,

5.99; N, 21.58. $C_{16}H_{19}N_5O_3$ requires C, 58.35; H, 5.81; N, 21.26%.

Preparation of 3-mercaptopropyl silica gel 14

To preserve silica particles from mechanical degradation, this derivatization step was carried out in a standard rotary evaporator in which a two-necked flask was fitted with solvent condenser, solvent collector, and nitrogen inlet for syringe addition of reactant solutions under an inert atmosphere. Mixing was obtained by spinning the flask around its axis and warming by means of a standard oil-bath. Silica gel (grade 9385, pore size 60 Å, particle size ~50 μm, superficial area 500 $m^2\ g^{-1}$) was dried before its use (0.1 mbar, T = 110 °C, 2 h).

To a stirred slurry of silica gel (5.00 g), anhydrous toluene (60 mL), and freshly distilled triethylamine (0.25 mL) was slowly added a solution of (3-mercaptopropyl)-trimethoxysilane (2.5 mL) in anhydrous toluene (10 mL). The resulting mixture was then warmed to 60 °C and stirred for 20 h. Subsequently, the mixture was refluxed until *ca.* 15 mL of solvent were collected (eventually by the aid of a nitrogen stream). The mixture was then refluxed for an additional 1 h, cooled to room temperature, and centrifuged with 20 mL portions of toluene, MeOH, EtOH, and cyclohexane. The resulting thiol-functionalized silica gel **14** was finally dried at reduced pressure (0.1 mbar, 60 °C, 6 h). FT-IR (KBr): ν 2577(SH) cm^{-1}. Elemental analysis (%) found: S 3.36 (estimated loading f = 1.05 mmol g^{-1}).

General procedure for the synthesis of silica-supported proline mimetics 2–4 *via* thermally induced TEC

To preserve silica particles from mechanical degradation, this derivatization step was carried out with the FirstMate™ synthesizer.

A vertically-stirred mixture of thiol–silica **14** (1.00 g, 1.05 mmol; f = 1.05 mmol S g^{-1}), (4-allyloxy)pyrrolidine derivative **7**, **8** or **12** (3.15 mmol), 2,2′-azobis(2-methylpropionitrile) (AIBN, 172 mg, 1.05 mmol), and anhydrous toluene (8 mL) was degassed under vacuum, and saturated with argon (by an Ar-filled balloon) three times. The mixture was then warmed to 90 °C, stirred for 16 h, cooled to room temperature, diluted with AcOEt (8 mL), and centrifuged with 5 mL portions AcOEt (4×). The resulting *N*-Boc protected silica-supported proline mimetic ***N*-Boc 2**, ***N*-Boc 3** or ***N*-Boc 4** was finally dried at reduced pressure (0.1 mbar, 40 °C, 6 h). Excess pyrrolidine derivative **7**, **8** or **12** can be easily recycled by column chromatography of the centrifugate.

Silica *N*-Boc 2. Elemental analysis (%) found: N 2.15 (estimated loading f = 0.77 mmol g^{-1}). FT-IR (KBr): ν 1745 (CO), 1690 (CO), 1455 (*t*-Bu), 1370 (*t*-Bu) cm^{-1}.

Silica *N*-Boc 3. Elemental analysis (%) found: N 3.18 (estimated loading f = 0.76 mmol g^{-1}). FT-IR (KBr): ν 1740 (CO), 1610 (CO), 1545 (SO_2N), 1450 (*t*-Bu), 1370 (*t*-Bu) cm^{-1}.

Silica *N*-Boc 4. Elemental analysis (%) found: N 5.45 (estimated loading f = 0.78 mmol g^{-1}). FT-IR (KBr): ν 1699 (CO), 1650 (CO), 1457 (*t*-Bu), 1396 (*t*-Bu) cm^{-1}.

To a cooled (0 °C), vertically-stirred mixture of silica-supported proline mimetic ***N*-Boc 2**, ***N*-Boc 3** or ***N*-Boc 4** (~1.00 g) and anhydrous CH_2Cl_2 (4 mL) was slowly added a solution of TFA (4 mL) in anhydrous CH_2Cl_2 (4 mL). The mixture was then warmed to room temperature, stirred for 12 h, and centrifuged with 5 mL portions of CH_2Cl_2 (2×), 1 : 2/Et_3N–CH_2Cl_2 (2×; addition at 0 °C), CH_2Cl_2 (2×), MeOH (2×), CH_2Cl_2 (2×). The resulting silica-supported proline mimetics **2**, **3** or **4** was finally dried at reduced pressure (0.1 mbar, 40 °C, 6 h).

Silica 2. Elemental analysis (%) found: N 2.10 (estimated loading f = 0.75 mmol g^{-1}). FT-IR (KBr): ν 2938 (CH), 1681 (CO) cm^{-1}.

Silica 3. Elemental analysis (%) found: N 2.94 (estimated loading f = 0.70 mmol g^{-1}). FT-IR (KBr): ν 2930 (CH), 1613 (CO), 1546 (SO_2N), 1130 (SO_2N) cm^{-1}.

Silica 4. Elemental analysis (%) found: N 5.32 (estimated loading f = 0.76 mmol g^{-1}). FT-IR (KBr): ν 2938 (CH), 1674 (CO), 1445 (CN) cm^{-1}.

General procedure for the synthesis of silica-supported proline mimetics 2–4 *via* photoinduced TEC

To preserve silica particles from mechanical degradation, this derivatization step was carried out with the FirstMate™ synthesizer.

A vertically-agitated mixture of thiol–silica **14** (1.00 g, 1.05 mmol; f = 1.05 mmol S g^{-1}), (4-allyloxy)pyrrolidine derivative **7**, **8** or **12** (3.15 mmol), 2,2-dimethoxy-2-phenyl-acetophenone (DMAP, 269 mg, 1.05 mmol), and MeOH (6 mL) was irradiated at room temperature for 5 h, and then centrifuged with 5 mL portions of MeOH (4×). The resulting *N*-Boc protected silica-supported proline mimetic ***N*-Boc 2**, ***N*-Boc 3** or ***N*-Boc 4** was finally dried at reduced pressure (0.1 mbar, 40 °C, 6 h). Excess pyrrolidine derivative **7**, **8** or **12** can be easily recycled by column chromatography of the centrifugate. Silicas ***N*-Boc 2**, ***N*-Boc 3**, and ***N*-Boc 4** were obtained with levels of functionalization which were comparable to those detected in the corresponding thermally induced TECs.

To a cooled (0 °C), vertically-agitated mixture of silica-supported proline mimetic ***N*-Boc 2**, ***N*-Boc 3** or ***N*-Boc 4** (~1.00 g) and anhydrous CH_2Cl_2 (4 mL) was slowly added a solution of TFA (4 mL) in anhydrous CH_2Cl_2 (4 mL). The mixture was then warmed to room temperature, stirred for 12 h, and centrifuged with 5 mL portions of CH_2Cl_2 (2×), 1 : 2/Et_3N–CH_2Cl_2 (2×; addition at 0 °C), CH_2Cl_2 (2×), MeOH (2×), CH_2Cl_2 (2×). The resulting silica-supported proline mimetics **2**, **3** or **4** was finally dried at reduced pressure (0.1 mbar, 40 °C, 6 h). Silicas **2**, **3**, and **4** were obtained with levels of functionalization which were comparable to those detected in the corresponding thermally induced TECs.

Procedure for the model aldol reaction under batch conditions (Table 1)

A mixture of *p*-nitro benzaldehyde (38 mg, 0.25 mmol), cyclohexanone (78 μL, 0.75 mmol), the stated catalyst (0.075 mmol), and the stated solvent (1.7 mL) was vertically-stirred at room temperature for 24 h, and then centrifuged with 2.5 mL-portions of CH_2Cl_2 (2×). The combined centrifugates were concentrated and the resulting residue analyzed by ^1H NMR to determine the

diastereomeric ratio and conversion. Subsequently, the residue was eluted from a column of silica gel with 5 : 1 toluene–AcOEt to determine the yield of the *anti–syn* diastereomeric mixture and obtain the pure *anti*-adduct **17a** whose enantiomeric excess value[23] was determined by chiral HPLC analysis: Lux-1 cellulose (hexanes–i-PrOH 98 : 2 v/v, 400 μL min^{-1}; λ_{max} = 258 nm); t_R (major) = 18.5 min; t_R (minor) = 25.4).

Procedure for the model Mannich reaction under batch conditions (Table 2)

A mixture of *N*-*p*-methoxybenzyl-α-iminoglyoxalate (52 mg, 0.25 mmol), cyclohexanone (340 μL, 20 vol%), catalyst **4** (99 mg, 0.075 mmol), and the stated solvent (1.7 mL) was vertically-stirred at room temperature for 2 h, and then centrifuged with 2.5 mL-portions of CH_2Cl_2 (2×). The combined centrifugates were concentrated and the resulting residue analyzed by ^1H NMR to determine the diastereomeric ratio and estimate the yield of the *syn–anti* diastereomeric mixture. The enantiomeric excess of the *syn*-adduct **18** was determined by chiral HPLC analysis: Lux-1 Cellulose (hexanes–i-PrOH 99 : 1 v/v, 300 μL min^{-1}; λ_{max} = 246 nm); t_R (minor) = 16.5 min; t_R (major) = 17.7).

Procedure for the model Michael reaction under batch conditions (Table 2)

A mixture of *trans*-β-nitrostyrene (37 mg, 0.25 mmol), cyclohexanone (78 μL, 0.75 mmol), the stated catalyst (99 mg, 0.075 mmol), and the stated solvent (1.7 mL) was vertically-stirred at room temperature for 24 h, and then centrifuged with 2.5 mL-portions of CH_2Cl_2 (2×). The combined centrifugates were concentrated and the resulting residue analyzed by ^1H NMR to determine the diastereomeric ratio and conversion. Subsequently, the residue was eluted from a column of silica gel with 2 : 1 cyclohexane–AcOEt to determine the yield of the *anti–syn* diastereomeric mixture and obtain the pure *syn*-adduct **19** whose enantiomeric excess value[23] was determined by chiral HPLC analysis: Lux-1 Cellulose (hexanes–i-PrOH 92 : 8 v/v, 50 μL min^{-1}; λ_{max} = 220 nm); t_R (minor) = 34.8 min; t_R (major) = 36.3).

Procedure for the model α-amination reaction under batch conditions (Table 2)

A mixture of diethyl azodicarboxylate (97% purity, 41 μL, 45 mg, 0.25 mmol), cyclohexanone (340 μL, 20 vol%), catalyst **4** (99 mg, 0.075 mmol), and the stated solvent (1.7 mL) was vertically-stirred at room temperature for 2 h, and then centrifuged with 2.5 mL portions of CH_2Cl_2 (2×). The combined centrifugates were concentrated and the resulting residue analyzed by ^1H NMR to estimate the yield of **20**. The enantiomeric excess of **20** was determined by chiral HPLC analysis: Lux-1 cellulose (hexanes–i-PrOH 95 : 5 v/v, 200 μL min^{-1}; λ_{max} = 220 nm); t_R (minor) = 7.7 min; t_R (major) = 10.4).

Continuous-flow aldol reactions (Table 3)

Microreactor **R4** was fed with a solution in the stated solvent of cyclohexanone and the aromatic aldehyde **16a–e**, and operated at the stated temperature for 4 h (under steady-state conditions) at 5 μL min^{-1} (see Table 3 for molarity concentrations). Instant conversion was determined (^1H NMR analysis) every 30 minutes by taking a sample of the eluate. The collected solution was finally concentrated and eluted from a column of silica gel with the suitable elution system to give the corresponding mixture of *anti–syn* adducts whose diastereomeric ratio was determined by ^1H NMR analysis. The enantiomeric excess[23] of the *anti*-adducts **17a–e** was evaluated by chiral HPLC analysis.

17b. Lux-1 cellulose (hexanes–i-PrOH 99 : 1 v/v, 500 μL min^{-1}; λ_{max} = 220 nm); t_R (major) = 30.5; t_R (minor) = 46.2 min.

17c. Lux-1 cellulose (hexanes–i-PrOH 99 : 1 v/v, 100 μL min^{-1}; λ_{max} = 220 nm); t_R (major) = 57.8; t_R (minor) = 77.9 min.

17d. Lux-1 cellulose (hexanes–i-PrOH 98 : 2 v/v, 500 μL min^{-1}; λ_{max} = 220 nm); t_R (major) = 5.3; t_R (minor) = 7.3 min.

17e. Lux-1 cellulose (hexanes–i-PrOH 99 : 1 v/v, 500 μL min^{-1}; λ_{max} = 220 nm); t_R (major) = 5.4; t_R (minor) = 6.8 min.

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14 Thiol–silica **14** is commercially available from Sigma-Aldrich. Nevertheless, better results in continuous-flow experiments were detected by using immobilized proline mimetics **2–4** obtained from freshly prepared **14** (see Experimental section for details).

15 Screened solvents were toluene, acetonitrile, dichloromethane, DMSO, and diisopropyl ether. The effect of temperature and variation of reagent molar ratios were not considered at this stage of the study.

16 It has to be pointed out that reactions considered in this comparison have been optimized with a lower loading of homogeneous catalyst (typically, 5–15 mol% of unsupported tetrazole *vs.* 30 mol% of **4**). Moreover, modest enantioselectivities were also detected in Michael and α-amination reactions under homogeneous tetrazole catalysis. Higher enantioselectivities were achieved by Ley and co-workers in Michael additions to nitro-olefins by using a homo-proline tetrazole catalyst (ref. 11*f*).

17 The effect on catalyst **4** activity of free hydroxyls capping with hydrophilic and hydrophobic moieties is currently under investigation in our laboratories.

18 A detailed study on the kinetics and thermodynamics of the continuous-flow model aldol reaction promoted by either catalyst **1** or **4** will be reported in due course along with a suitable in-line analysis method.

19 The equation for the experimental determination of the retention factor k' is: $k' = (t_r - t_0)/t_0$, where t_r is the retention time of the species under evaluation and t_0 is the hold-up time of the column. The hold-up time t_0 can be easily calculated by dividing the hold-up volume V_0 by the flow rate. In microreactor technology literature, this is the so called residence time.

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