Tetrahedron Letters 52 (2011) 619–622

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Toward the optimization of continuous-flow aldol and α-amination reactions by means of proline-functionalized silicon packed-bed microreactors

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ARTICLE INFO

Article history:
Received 21 October 2010
Revised 24 November 2010
Accepted 30 November 2010
Available online 5 December 2010

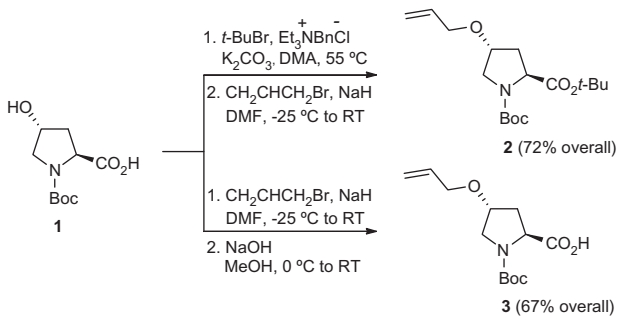
Keywords:
Asymmetric catalysis
Continuous-flow processes
Microreactors
Organocatalysis

ABSTRACT

The activity and stability under flow conditions of covalently and non-covalently silica supported proline and proline-like organocatalysts is herein described. The slow aldol reaction of cyclohexanone with *p*-nitro benzaldehyde and the fast α-amination of isovaleraldehyde with dibenzyl azodicarboxylate have been selected as model reactions for this study. Prospects and limitations of the disclosed continuous-flow organocatalytic approach are widely discussed.

Today, the combination of efficient synthetic methodologies such as organocatalysis[1] with high-throughput techniques such as microreactor technology[2] is actively pursued to create new synthetic platforms for the sustainable, safe, and intensified production of fine chemicals and pharmaceuticals.[3] In light of this new paradigm, Odedra and Seeberger recently reported the first homogeneous organocatalytic asymmetric aldol and Mannich reactions performed in microfluidic devices.[4] Pericàs and co-workers later described the implementation of heterogeneous continuous-flow Mannich reactions by using packed-bed microreactors filled with a proline-functionalized polystyrene resin.[5] For a broad range of microreactor applications it would be desirable, however, that the proline-functionalized packing material be compatible with a wide array of reaction solvents. In general, lightly cross-linked polystyrene resins appear inappropriate for microchannel packing as they may cause high pressure drop along the microreactor and lead to irreproducible flow when swollen with different solvents.[6] Herein, we report on the preparation of proline-functionalized silicas by a covalent immobilization strategy based on the photoinduced thiol-ene coupling (TEC).[7] The synthesis of an ionic counterpart is also described and the nature of immobilization on catalyst activity and stability under batch and flow conditions duly evaluated by using model aldol and α-amination reactions.

The hitherto unreported 4-*O*-allyl-hydroxyproline derivatives **2** and **3** were readily synthesized in two steps from commercially available (2*S*,4*R*)-*N*-Boc-4-hydroxyproline **1** (Scheme 1).[8] The thermally induced TEC of **2** (3 equiv) with commercial 3-mercaptopropyl silica **4** was next performed by using 2,2′-azobis(2-methylpropionitrile) (AIBN, 1 equiv) as the radical initiator and toluene as the solvent (Scheme 2, route *a*).[9] Full conversion into the adduct **5** was achieved under vigorous magnetic stirring at 90 °C in 20 h as established by FT-IR analysis (disappearance of the SH stretching band at 2577 cm^{-1}). The corresponding photochemically initiated TEC was also investigated with the aim to set up a milder procedure for proline immobilization. Indeed, the photoinduced (365 nm) TEC of **4** with **3** (3 equiv) proceeded smoothly (25 °C, 3 h) in MeOH in the presence of 2,2-dimethoxy-2-phenyl-acetophenone (DMAP) as the sensitizer (Scheme 2, route *b*).[10]



Scheme 1. Synthesis of 4-*O*-allyl-hydroxyproline derivatives **2** and **3**.

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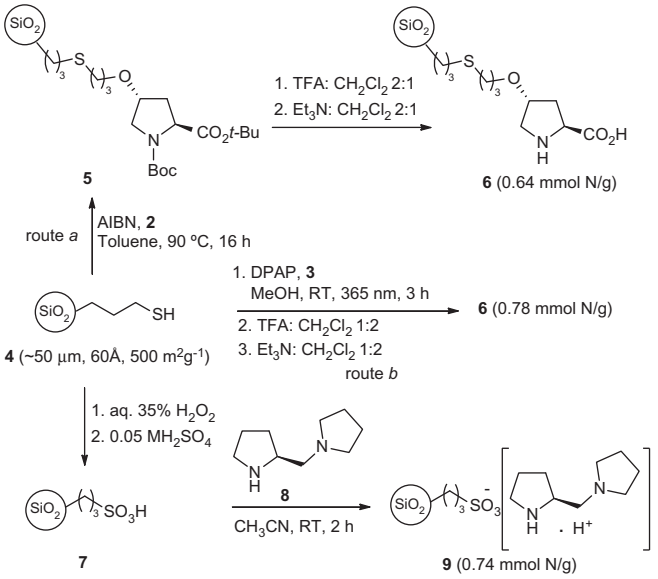
doi:10.1016/j.tetlet.2010.11.157



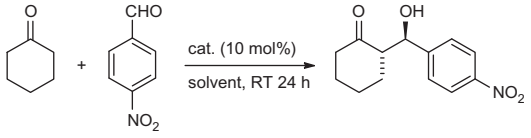
Scheme 2. Thermally and photochemically induced TEC of thiol-silicas **4a** with 4-*O*-allyl-hydroxyproline derivatives **2** and **3**.

Considering the final deprotection step, it should be noted that the harsher acid conditions required for simultaneous Boc and *t*-butyl ester removal (route *a*) resulted in the partial loss (elemental analysis) of supported proline, thus confirming route *b* as the optimal synthetic strategy toward the covalently proline-functionalized silica **6**. In a divergent approach, the non-covalently supported chiral amine catalyst **9** was readily prepared from commercial thiol-silica **4** and (*S*)-(+)-1-(2-pyrrodinylmethyl)-pyrrolidine **8** by adapting a two-step procedure already reported for chiral amine catalysts supported on polystyrene resins.[11]

Activity and stability of covalently and non-covalently anchored organocatalysts **6** and **9** were first evaluated under batch conditions in different solvents by using the aldol condensation of cyclohexanone with *p*-nitro benzaldehyde as a benchmark (Table 1). To our delight, we found that catalyst **6** efficiently promoted the model reaction in the apolar solvent toluene (entry 6), showing levels of activity (67% yield) and stereoselectivity (*anti*/*syn* = 4:1; 78% ee_{anti}) comparable to those observed for homogeneous proline catalysis.[12a,13]

Bearing in mind the execution of a continuous-flow process as the ultimate goal of this study, stability (recyclability) of catalyst **6** was also investigated. A progressive loss of activity was observed with recycled **6** in the polar solvent acetonitrile (entry 2; only data

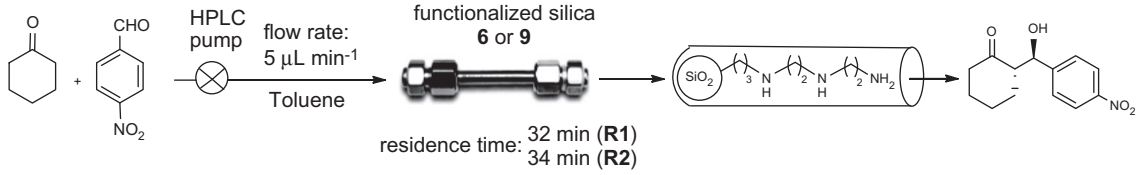
Table 1
Optimization of catalysts **6** and **9** performance under batch conditions[a]



Entry	Cat.	Solvent	Yield[b] (%)	dr *anti*/*syn*[c]	ee_{anti}[d] (%)
1	**6**	DMSO	25	2:1	46
2	**6**	CH_3CN	52(31)[e]	3:1(3:1)[e]	42(42)[e]
3	**6**	DMF	11	1:1	32
4	**6**	H_2O	32	2:1	40
5	**6**	CH_2Cl_2	16	3:1	55
6	**6**	Toluene	67(65)[e]	4:1(4:1)[e]	78(78)[e]
7	**10**[f]	Toluene	<5	—	—
8	**9**	DMSO	92	1.5:1	52
9	**9**	CH_3CN	52	2.5:1	5
10	**9**	DMF	95	2:1	45
11	**9**	H_2O	78	2:1	38
12	**9**	CH_2Cl_2	44	3:1	47
13	**9**	Toluene	>95(92)[e]	2:1(2:1)[e]	55(52)[e]
14	**7**	Toluene	60	4:1	-

[a] Reactions performed in the stated solvent with 0.25 mmol of aldehyde (0.25 M) and 0.75 mmol of ketone.
[b] Isolated yield.
[c] Estimated by ^{1}H NMR analysis of crude reaction mixtures.
[d] Determined by chiral HPLC analysis.
[e] Reactions performed with recycled catalysts.
[f] Catalyst **10** (0.8 mmol/g) prepared by capping the thiol-silica **4** with 1-hexene under the photochemical conditions described in Scheme 2.

Table 2
Optimization of continuous-flow aldol reaction in packed-bed microreactors **R1**and **R2**[a]



Entry	Reactor (Cat.)	Aldehyde (*c* [M])	Ketone (*c* [M])	Temperature[b] (°C)	Conversion[c] (%)	Productivity[d] (mmol h^{-1} $mmol_{cat}^{-1}$)	dr *anti*/*syn*[e]	ee_{anti}[f] (%)
1	**R1** (**6**)	0.22	0.66	25	60	0.43	4:1	78
2	**R1** (**6**)	0.44	0.22	25	18	0.13	3:1	77
3	**R1** (**6**)	0.22	4.8	25	88	0.64	5:1	76
4	**R1** (**6**)	0.22	0.66	0[g]	38	0.27	5:1	82
5	**R1** (**6**)	0.22	0.66	50	82	0.59	4:1	78
6	**R1** (**6**)[h]	0.22	0.66	70	>95	—	2:1	72
7	**R2** (**9**)	0.22	0.66	25	50	—	2:1	40

[a] See note 15 for a description of the experimental setup.
[b] All temperatures were measured by a thermometer placed inside the thermostated unit containing the microreactor.
[c] Instant conversion as established by ^{1}H NMR analysis of the eluate after 2 h reaction time.
[d] Productivities are measured in mmolproduct h^{-1} $mmolcatalyst^{-1}$.
[e] Estimated by ^{1}H NMR analysis of crude reaction mixtures.
[f] Determined by chiral HPLC analysis.
[g] Microreactor placed in a ice-bath.
[h] Temperature determined a partial degradation of supported catalyst (see main text for discussion).

of the second run are shown), whereas a substantial maintenance of efficiency (yield and stereoselectivity) was detected in toluene (entry 6). This evidence agrees with previous observations by Armstrong, Blackmond and their co-workers on the solvent/additive effect in the irreversible deactivation via decarboxylation of proline or proline-like catalysts in the presence of electron-deficient aromatic aldehydes.[14] Indeed, when the integrity of recycled **6** (entry 2, second run) was checked by FT-IR analysis, a much lower intensity of the carbonyl band (1641 cm^{-1}) was observed. In a parallel solvent screening, toluene resulted to be the best performing for the ionic catalyst **9** as well (entry 13), activity and recyclability of **9** being comparable to those previously detected for polystyrene-supported analogs.[11] Control reactions were also carried out in toluene in the presence of the 1-hexene-capped thiol-silica **10** (entry 7) and sulfonic acid silica **7** (entry 14). These experiments demonstrated the absence of background conversion in the reaction catalyzed by the covalently proline-functionalized silica **6** and highlighted the detrimental effect on stereoselectivity in case of incidental amine leaching from ionic catalyst **9**.

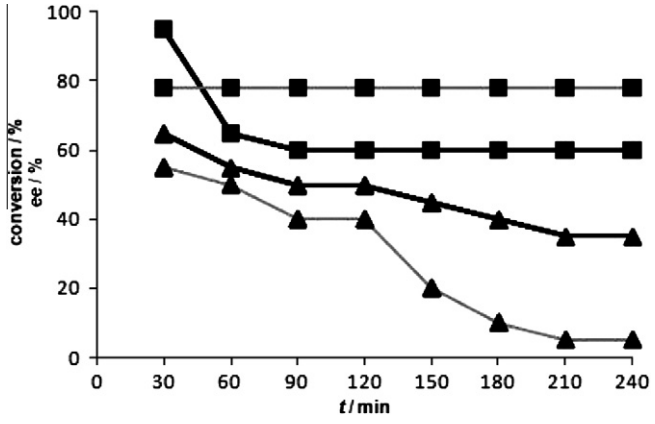


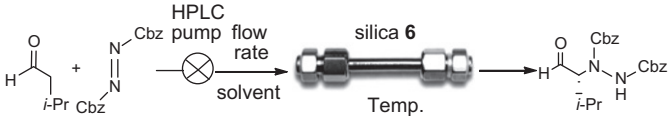
Figure 1. Conversion of the model aldol reaction as a function of time (black lines) in microreactors **R1** (■) and **R2** (▲). Enantioselectivity of the *anti*-aldol as a function of time (gray lines) in microreactors **R1** (■) and **R2** (▲).

Continuous-flow experiments were then performed by means of a micro-HPLC suitably adapted for this study with minimized extra-column volumes. Reactors **R1** and **R2** were prepared by filling (packing by gravity) stainless steel columns (50 mm length, 2.1 mm diameter) with silicas **6** and **9**, respectively (Table 2).[15] The hold-up (dead) volumes (V0) of reactors **R1** and **R2** were determined by pycnometry. Residence times were calculated by dividing V0 by the flow rate. A packed cartridge of commercially available triamine-functionalized silica gel was placed downstream the reactors to selectively remove unreacted *p*-nitro benzaldehyde and thus facilitate isolation of the aldol product. The study on continuous-flow model aldol reaction by using reactor **R1** started with the optimization of flow rate and aldehyde concentration. After some experimentations, the optimal compromise between aldehyde solubility in toluene and conversion efficiency was found by pumping a solution of aldehyde (0.22 M) and cyclohexanone (0.66 M) at 5 μL min^{-1} (residence time: 32 min). Gratifyingly, the stereoselectivity of the batch process (Table 1, entry 6) was replicated (dr 4:1; 78% ee_{anti}, Table 2, entry 1) and maintained constant during the entire flow process (overall time 4 h; Fig. 1).

The working concentrations were chosen by considering the retention behavior of cyclohexanone and *p*-nitro benzaldehyde in **R1**. Under steady-state conditions, the greater affinity of *p*-nitro benzaldehyde for silica **6** (chromatographic retention factor $k' = 1$ vs $k' = 0.45$ for the ketone) causes the preferential occupancy of the packing material by this component, thus limiting the formation of the reactive enamine intermediate and lowering the conversion efficiency. This hypothesis seemed to be supported by experiments conducted at different ketone/aldehyde ratios (entries 2 and 3) and by an in depth analysis of the conversion versus process time profile (Fig. 1).

This shows a higher conversion (>95%) for the fraction eluted immediately after the hold-up time (32 min) compared to the steady-state conversion (60%),[16] thus confirming that enamine formation happens at maximum level when the less retained cyclohexanone reacts with the bare immobilized proline (first eluted fraction).[17] The effect of temperature on process efficiency was next investigated. A slight improvement of stereoselectivity (dr 5:1; 82% ee_{anti}, entry 4) accompanied by a marked decrease of conversion was observed at 0 °C. Warming the reactor **R1** in

Table 3
Optimization of continuous-flow α-amination reaction in packed-bed microreactors **R1**[a]



Entry	Solvent	Flow rate (μL min^{-1})	Temperature[b] (°C)	Productivity[c]	ee[d] (%)
1[e]	Toluene	25	0	3.60	58
2[e]	CH_2Cl_2	25	0	3.60	42
3[f]	CH_3CN	25	0	1.80	38
4[e]	DMF	25	0	3.60	52
5[e]	Toluene	25	25	3.60	55
6[e]	Toluene	50	25	7.20	55
7[e]	Toluene	75	25	10.8	55
8[g]	Toluene	100	25	13.2	55
9[h]	Toluene	Batch	0	3.33	52

[a] See note 15 for a description of the experimental setup. **R1** fed with 0.22 M DBAD and 0.66 M aldehyde solution in the stated solvent.
[b] Microreactor placed in a ice-bath for processes conducted at 0 °C.
[c] Productivities are measured in mmolproduct h^{-1} mmolcatalyst^{-1}.
[d] Determined by chiral HPLC analysis.
[e] Instant conversion: >95% (^{1}H NMR analysis).
[f] Instant conversion: 50% (^{1}H NMR analysis).
[g] Instant conversion: 92% (^{1}H NMR analysis).
[h] Reaction performed with 0.25 mmol of DBAD (0.25 M), 0.75 mmol of aldehyde, and 10 mol % of **6**. Full conversion after 3 h.

the HPLC column oven set at 50 °C produced an improvement of conversion from 60% to 82% without altering the stereoselectivity of the process (entry 5). Unfortunately, a further increase of temperature (70 °C; entry 6) resulted in a fast (ca. 2.5 h) degradation of packed-bed material, which occurred very likely through decarboxylation of supported proline as indicated by FT-IR analysis of the recovered packing silica. In a parallel investigation, the long-term stability of the covalent packed-bed **6** was also considered, this issue being a key point for the development of effective continuous-flow processes. Gratifyingly, silica **6** did not show any deactivation in terms of productivity and selectivity at ambient temperature for at least 24 h, whereas a progressive decreasing yield with maintenance of stereoselectivity was observed after that time (catalyst fully deactivated after 72 h on stream). Next we focused our attention on microreactor **R2** filled with the ionic silica **9** (entry 7). Degradation of packed-bed catalytic activity took place under flow conditions within 2 h owing to gradual amine **8** leaching as confirmed by MS analysis of eluate samples. The racemic background conversion, in fact, became predominant after that time, thus determining a progressive loss of enantioselectivity of the process (Fig. 1).

To broaden the scope of the methodology and reach higher levels of productivity, the implementation of the fast proline-catalyzed α-amination reaction[12b,c] of isovaleraldehyde with dibenzyl azodicarboxylate (DBAD) in microreactor **R1** was also investigated.[15] After a fast (non exhaustive) solvent screening carried out under flow conditions (Table 3, entries 1–4), toluene was again selected as the optimal solvent (entry 1). Full conversion was achieved at 0 °C with a 5-fold faster flow rate (25 μL min^{-1}) than previous aldol reaction (entry 1). Quite surprisingly, the enantioselectivity of the flow process (58% ee of the α-hydrazino alcohol generated in situ by $NaBH_4$ reduction of the product aldehyde) was noticeably lower compared to that of similar proline-catalyzed homogeneous reactions.[12b,c] Fortunately, conducting the model α-amination at ambient temperature left the stereoselectivity of the process almost unchanged (entry 5). On the other hand, complete conversions could be also achieved at 25 °C with higher flow rates (up to 75 μL min^{-1}, entries 6 and 7), thus further increasing the productivity of the flow process (10.8 mmol h^{-1} mol_{cat}^{-1}; ca. three times greater than the batch process, entry 9).

In conclusion, we have demonstrated here the potential of packed-bed microreactors filled with covalently silica supported proline to produce chiral targets under flow regime in a stereoselective manner and with a facilitated post reaction phase (workup and purification). Actually, these features along with direct scalability are important prerequisites of a synthetic process for its industrial applications. The proof-of-principle results reported herein are currently being extended to proline-like organocatalysts with extended lifecycle and to other organocatalytic processes.

Acknowledgments

We gratefully acknowledge the Italian Ministry of University and Scientific Research (Progetto FIRB Chem-Profarma-Net Grant RBPR05NWWC 008) for financial supports. Thanks are also given to Professor F. Dondi for useful discussion and support, to Mr. P. Formaglio for NMR experiments and to Professor A. Marchi and Mr. M. Fratta for elemental analyses. We also acknowledge Eka Chemicals for the kind donation of Kromasil silica gel.

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8. Compound **2**: $[\alpha]_D = -26.6$ (*c* 0.6, $CHCl_3$). Compound **3**: $[\alpha]_D = -66.3$ (*c* 0.9, $CHCl_3$).
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13. Under optimized conditions (Table 1, entry 6), the aldol reaction of cyclohexanone with the electron-rich *p*-methoxy benzaldehyde gave the corresponding adduct in lower yield (15%). Hence, the optimization study was continued with the more reactive *p*-nitro benzaldehyde acceptor.
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15. *Description of the experimental setup for the continuous-flow processes*. 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), and either reactor **R1** or **R2** (containing 117 mg and 70 mg of packing material, respectively). In case of aldol reactions, a glass Omnifit® column containing triamine-functionalized silica gel (500 mg, ~1.3 mmol g^{-1}) was placed downstream the reactor. *Continuous-flow model aldol reaction* (Table 2, entry 1). Microreactor **R1** was fed with a 0.22 M aldehyde and 0.66 M ketone solution in toluene and operated for 8 h (under steady state conditions) at 5 μL/min. The collected solution was concentrated to give the pure adduct (78 mg, 60%) as a 4:1 mixture of *anti* and *syn* diastereoisomers (ee_{anti} = 78%). Chiral HPLC analysis: Lux-1 Cellulose (hexanes/*i*-PrOH 90:10 v/v, 200 μL min^{-1}; λ_{max} = 258 nm); t_R (major) = 10.9 min; t_R (minor) = 14.6. *Continuous-flow model α-amination reaction* (Table 3, entry 7). Microreactor **R1** was fed with a 0.22 M DBAD and 0.66 M aldehyde solution in toluene and operated for 8 h (under steady state conditions) at 75 μL/min (25 °C). The collected solution was kept at 0 °C and then diluted with EtOH (40 mL). To the resulting stirred, cooled (0 °C) mixture was then added $NaBH_4$ (629 mg, 16.6 mmol) in one portion. The mixture was stirred at 0 °C for an additional 30 min, then diluted with saturated aqueous NH_4Cl (25 mL), filtered over a pad of Celite, and extracted with Et_2O (2 × 125 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give the target α-hydrazino alcohol (2.75 g, 90%, ee = 55%). Chiral HPLC analysis: Lux-1 Cellulose (hexanes/*i*-PrOH 90:10 v/v, 200 μL min^{-1}; λ_{max} = 210 nm); t_R (major) = 9.9 min; t_R (minor) = 10.9.
16. For all packed-bed microreactors prepared the steady-state was reached within 60 min process time.
17. The prior coverage of silica surface by flowing a 0.66 M solution of cyclohexanone before feeding **R1** under optimized conditions (see note 15) produced, in steady state regime, the same results of entry 1 (Table 2).