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## ARTICLE

## Monolithic 5-(pyrrolidin-2-yl)tetrazole flow microreactor for the asymmetric aldol reaction in water-ethanol solvent†

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(S)-5-(pyrrolidin-2-yl)-1*H*-tetrazole organocatalyst has been prepared in the form of monolithic column through the radical copolymerization of a styryl-functionalized pyrrolidinyl-tetrazole derivative, styrene and divinylbenzene in the presence of porogens (dodecanol and toluene). The activity of the monolithic pyrrolidinyl-tetrazole organocatalyst (triturated polymer) has been initially tested under batch conditions using the asymmetric aldol reaction of cyclohexanone and *p*-nitro benzaldehyde as the benchmark. A prerequisite of the study has been the utilization of the ecofriendly water-ethanol mixture as the solvent. After having established the high efficiency and recyclability of the catalyst under these conditions, it has been evaluated the effect of the flow regime by fabricating the corresponding monolithic microreactor (pressure-resistant stainless-steel column). It has been demonstrated by a brief substrate scope study that the flow regime contributes to preserve the activity of the pyrrolidinyl-tetrazole catalyst over the time (5 days on stream) with an almost twofold increase of productivity moving from batch to flow conditions. Added value of the flow procedure has been the optimization of a suitable 2D instrumental setup for simultaneous flow reaction and online flow-injection analysis.

### Introduction

Continuous-flow meso- and micro-reactors can be considered nowadays useful scale-down versions of industrial reactors for transformations at the lab-scale;<sup>1</sup> conversely, the scale-up of optimized microflow reactions is emerging as a new opportunity for the fine chemical industry with advantages in terms of safety, sustainability and ease of automation/monitoring of the production processes.<sup>2</sup> In this scenario, continuous-flow asymmetric catalysis is receiving a great deal of attention as highlighted in recent reviews;<sup>3</sup> indeed, utilization of microflow technologies as synthetic platforms for the production of multifunctional chiral molecules is very attractive, promising and worth investigation. Surprisingly, the implementation of organocatalyzed stereoselective flow processes has scarcely been considered until recently despite the peculiar benefits associated with the use of an organic molecule as a catalyst, which include stability in air and water, absence of metal leaching and compatibility with a number of unprotected functionalities. Very likely, this lack of initial interest had been directly related to the difficult recycling of organocatalysts and the high catalyst loadings often required for several

transformations. Nevertheless, ours<sup>4</sup> and other groups<sup>3a,b</sup> have recently demonstrated that heterogeneization of organocatalysts may represent a viable solution to overcome the above drawbacks allowing the set-up of effective continuous-flow procedures endowed with high levels of stereoselectivity and productivity. The majority of the reported studies on asymmetric flow organocatalysis utilize the active catalyst immobilized on either polymeric or inorganic particles as packing material of fixed-bed reactors. In view of an easy scaling-up for potential industrial applications, this type of system, however, suffers from several limitations such as uncontrolled fluid dynamics, broad distribution of residence times, formation of hot-spots and stagnation zones.<sup>5</sup> Monolithic reactors characterized by a regular or irregular network of meso- and micro-porous channels typically offer improved flow properties in virtue of the high void volume, which guarantees a large contact area of the catalyst with the fluid and the absence of pressure drop.<sup>6</sup> The immobilization of organocatalysts in the form of continuous-flow monolithic columns is, however, still scant in literature. Our group<sup>4c</sup> and that of Luis and García-Verdugo<sup>7</sup> reported umpolung processes promoted by achiral azolium salts, while the group of Benaglia described stereoselective cycloadditions and Friedel-Crafts alkylations catalyzed by an imidazolidinone derivative.<sup>8</sup> As part of our ongoing studies on heterogeneous flow organocatalysis, we herein describe the fabrication of a polystyrene monolithic microreactor functionalized with the Ley- Arvidsson -Yamamoto (S)-5-(pyrrolidin-2-yl)-1*H*-tetrazole organocatalyst and its utilization in the stereoselective aldol reaction of cyclic ketones and acetone with activated aromatic

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aldehydes in the ecofriendly water-ethanol mixture. The asymmetric aldol reaction is one of the most versatile carbon-carbon bond-forming reaction leading to the widely diffused chiral  $\beta$ -hydroxyketone functionality.<sup>9</sup> Continuous-flow heterogeneous organocatalysis has been applied to this fundamental reaction in a few studies using proline, proline mimetics and small peptides (Figure 1);<sup>4d,e,10-14</sup> each of the disclosed processes is characterized by strengths and limitations, although the procedure described by Pericàs and co-workers with a polystyrene immobilized proline derivative seems to excel in terms of diastereoselectivity of the aldol products.<sup>11</sup>

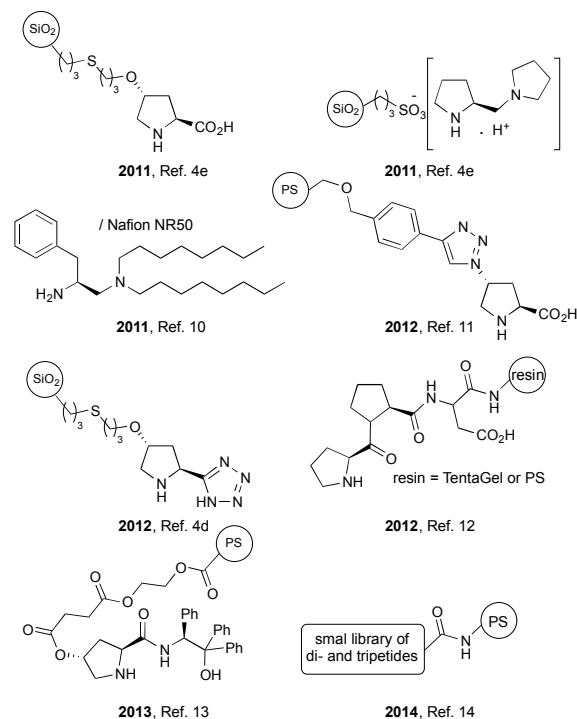


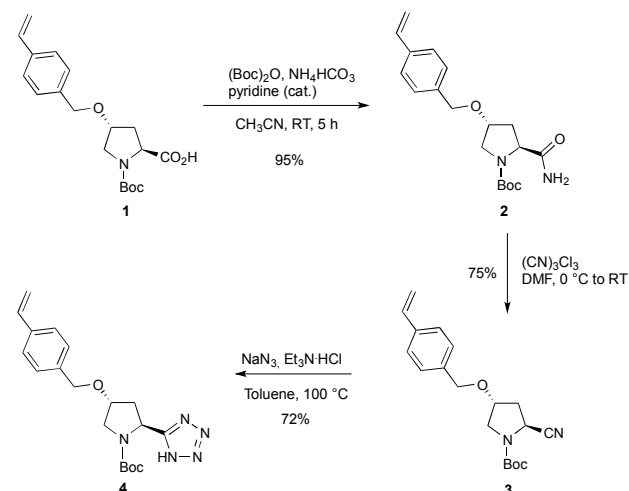
Fig. 1 Organocatalysts utilized for the continuous-flow asymmetric aldol reaction.

The main goal of the present study is the disclosure of a monolithic microreactor with improved fluid dynamics and high long-term stability of the catalytic material for the effective production of chiral aldol products under environmentally benign conditions. A suitable 2D instrumental arrangement for simultaneous flow reaction and online flow-injection analysis has also been devised by coupling the pyrrolidinyl tetrazole-functionalized monolithic reactor to a chiral HPLC column for conversion and stereoselectivity determination.<sup>15</sup>

## Results and discussion

In recent years, (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole has emerged as a 'privileged' organocatalyst that mediates a wide range of useful asymmetric reactions, including aldol, Michael, Mannich,  $\alpha$ -amination reactions and so forth.<sup>16</sup> In a previous study we described a novel strategy based on photoinduced

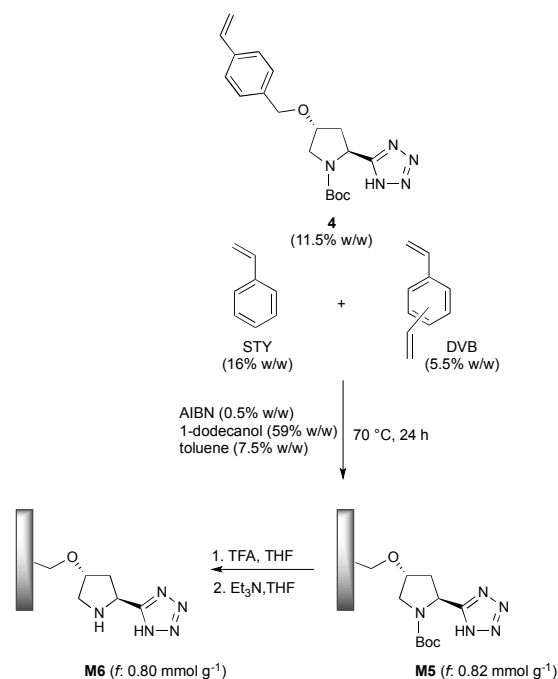
thiol-ene coupling (TEC) for the immobilization of pyrrolidinyl-tetrazole catalyst on silica support and demonstrated its activity in continuous-flow asymmetric aldol reactions.<sup>4d</sup> The use of low polarity solvents such as diisopropyl ether and toluene resulted to be crucial to prevent the free hydroxyls on silica from perturbing the hydrogen-bonding network responsible for the high selectivities detected in the homogeneous catalysis. In the present study we reversed our strategy and planned to create a favorable catalytic microenvironment in water medium by the occurrence of hydrophobic interactions between the polystyrene support and the catalytic sites through a simplified enzyme-like mechanism. Accordingly, the synthesis of the styryl pyrrolidinyl-tetrazole derivative **4** was initially addressed for its subsequent utilization as co-monomer in the polymerization furnishing the target polystyrene monolithic column **M6** (Schemes 1 and 2). Hence, the known styryl proline derivative **1**<sup>17</sup> was almost quantitatively converted into the amide **2** by in situ activation of the carboxylic acid. Subsequent dehydration of crude **2** promoted by cyanuric chloride afforded the nitrile **3** in good yield (75%), which in turn was transformed into the corresponding tetrazole **4** (72%) by cycloaddition with sodium azide (Scheme 1).



Scheme 1. Synthesis of the styryl-functionalized pyrrolidinyl-tetrazole **4**.

The synthesis of tetrazole-functionalized polystyrene monoliths was next investigated using the conditions first described by Fréchet and Svec.<sup>18</sup> Therefore, an extensive polymerization study was conducted to identify the optimal ratio between styrene (STY), divinylbenzene (DVB), the co-monomer **4** and the porogens (toluene and 1-dodecanol). It is important to emphasize that monoliths were molded into both glass and stainless-steel columns (4.6 mm internal diameter, 10 cm length) in parallel experiments to evaluate, on the one hand, the batch reactivity and the analytical/morphological properties of the prepared materials by SEM, FT-IR and elemental analysis; technically, the polymers prepared inside the glass columns were triturated and tested in the form of powder. On the other hand, this approach also allowed us to

estimate the influence of the polymerization parameters on the flow-through behavior of the monolith inside the metal column since wall effects and high backpressures needed to be carefully avoided for the correct functioning of the reactors in flow regime. Hence, after some experimentation, the optimal composition of the polymerization mixture resulted as follows: 1-dodecanol (59% w/w), toluene (7.5% w/w), STY (16% w/w), DVB (5.5% w/w), **4** (11.5% w/w) and AIBN (0.5% w/w). Elemental analysis of the resulting monolith **M5** indicated a satisfactory loading of pyrrolidinyl-tetrazole units ( $f$ : 0.82 mmol g<sup>-1</sup>); at the same time, <sup>1</sup>H NMR analysis of the THF solution used to wash the polymer **M5** confirmed the complete incorporation of the co-monomer **4** into the monolith. The *N*-Boc deprotection of triturated **M5** was finally carried out with TFA/THF followed by treatment with Et<sub>3</sub>N/THF to give the target active catalyst **M6**. Several experiments were also attempted to directly polymerize the co-monomer **4** in its *N*-deprotected form; by this approach, however, the resulting monoliths **M6** displayed detrimental pore clogging determining high backpressures in the flow regime and a very low reactivity under batch conditions, likely because of the reduced accessibility of the catalytic sites buried inside the micropores.



Scheme 2. Synthesis of polystyrene monolithic pyrrolidinyl-tetrazole **M6**.

Preliminary batch experiments were performed with optimal **M6** using the test reaction between cyclohexanone **7a** and *p*-nitro benzaldehyde **8a** in different solvents systems, with particular attention to the environmentally benign water-ethanol mixture<sup>19</sup> for the development of subsequent green applications of the newly prepared monolithic reactors (Table 1). Gratifyingly, the polystyrene pyrrolidinyl-tetrazole catalyst **M6** resulted highly active in pure water affording the aldol

product **9a** in quantitative yield and high stereoselectivity (*anti/syn* = 10:1; 95% *ee*<sub>anti</sub>) in 4 h reaction time (entry 1). The addition of ethanol for achieving the full solubilization of the substrates (H<sub>2</sub>O/EtOH 1:1) determined a partial erosion of enantioselectivity (90% *ee*<sub>anti</sub>) accompanied by a marked decrease of diastereoselectivity (*anti/syn* = 5:1; entry 2). Unfortunately, and contrary to previous findings on the beneficial effect of temperature on the activity of pyrrolidinyl-tetrazole organocatalysts,<sup>4d,20</sup> warming the reaction mixture to 50 °C produced a further drop of enantioselectivity (82% *ee*<sub>anti</sub>, entry 3). Next, a short solvent screening confirmed the necessary presence of water for obtaining satisfactory levels of conversion and stereoselectivity (entries 4-7). The maintenance of catalyst activity was finally ascertained in recycling experiments performed in H<sub>2</sub>O-EtOH, which was selected as the optimal solvent mixture for the subsequent flow experiments based on solubility reasons; catalyst **M6** could be recycled up to eight times affording the aldol product **9a** with almost constant yield (turnover number TON<sub>batch</sub> = 80) and only moderate decrease of stereoselectivity in every cycle (entry 8). On the other hand, peculiar advantage of the 1*H*-tetrazole moiety of **M6** as isosteric replacement of the carboxylic acid functionality is the impossibility to undergo irreversible decarboxylation, which is a known side reaction occurring in the presence of activated aromatic aldehydes with analogue proline organocatalysts and leading to a progressive loss of catalytic activity.<sup>21</sup>

Table 1. Evaluation of catalyst **M6** performance under batch conditions.<sup>a</sup>

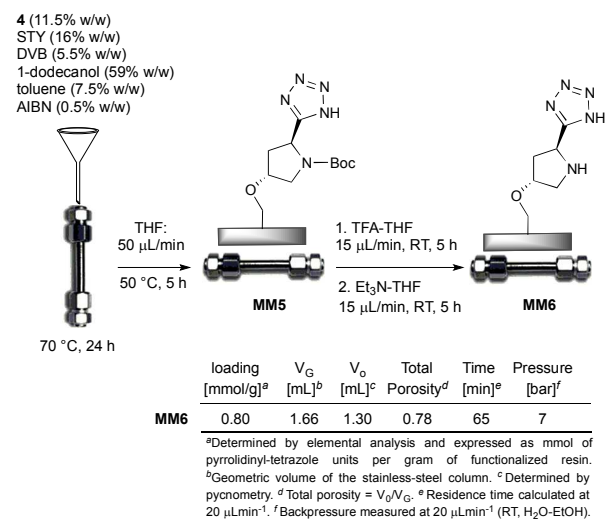
Entry	Solvent	Yield [%] <sup>b</sup>	Time	d.r. <i>anti/syn</i> <sup>c</sup>	<i>ee</i> <sub>anti</sub> [%] <sup>d</sup>
1	H <sub>2</sub> O	95	4	10:1	95
2	H <sub>2</sub> O-EtOH <sup>e</sup>	95	4	5:1	90
3 <sup>f</sup>	H <sub>2</sub> O-EtOH <sup>e</sup>	95	1	4:1	82
4	CH <sub>2</sub> Cl <sub>2</sub>	nr	24	-	-
5	EtOH	15	24	3:1	84
6	DMF	17	24	3:1	75
7	H <sub>2</sub> O-DMF <sup>e</sup>	85	4	8:1	90
8 <sup>g</sup>	H <sub>2</sub> O-EtOH <sup>e</sup>	95	4	5:1	88

<sup>a</sup> Reactions performed in the stated solvent with 0.40 mmol of **8a** (0.4 M) and 2.00 mmol of **7a**. <sup>b</sup> Isolated yield of the *anti/syn* diastereomeric mixture. <sup>c</sup> Estimated by <sup>1</sup>H NMR analysis of crude reaction mixtures. <sup>d</sup> Determined by chiral HPLC analysis. <sup>e</sup> 1:1 mixture. <sup>f</sup> Reaction performed at 50 °C. <sup>g</sup> 8<sup>th</sup> recycle.

At this stage of the study, we evaluated the performance of **M6** as a monolithic microreactor (hereafter designed as **MM**). Thus, the optimized polymerization mixture containing the monomer **4** was transferred into the stain-steel column, which was next sealed at both ends and heated at 70 °C for 24 h in a standard convection oven (Scheme 3). After cooling, the resulting monolithic microreactor **MM5** was connected to a HPLC instrument and then washed with THF (50 μL min<sup>-1</sup>; HPLC



oven 50 °C, 5 h) to remove the porogen and residual non-polymeric material. The *N*-Boc deprotection step was next performed by sequentially flowing (15  $\mu\text{L min}^{-1}$ ; 25 °C; 5 h) TFA/THF and Et<sub>3</sub>N/THF solutions through the column.



Scheme 3. Fabrication of monolithic microreactor **MM6**.

The void volume and the total porosity of the monolithic microreactor **MM6** were established by pycnometry. The main features of **MM6** including the observed backpressure, residence time and catalyst loading are summarized in Scheme 3. The macroporous nature of **MM6** was determined by SEM analysis (Figure S1); additionally, **MM6** displayed nearly no swelling in water-ethanol (1:1) solvent as verified by dedicated experiments showing a linear relationship between backpressure and flow rate.<sup>22</sup>

As anticipated, integration of an analytical platform for monitoring the reaction progress in flow regime was an important objective of this study. The devised injection-reaction-analysis system consisted in the monolithic microreactor **MM6** connected to pump-1 through a mixer chamber (direction-1). The solutions of ketone **7** and aldehyde **8** were continuously fed into **MM6** through the channels A and B, respectively (Figure 2). The outflow of the microreactor was redirected to a 6-port 2-position switching valve. In direction-2, the binary pump-2 delivered a hexane/*i*-PrOH solution into a chiral HPLC column by passing through the valve. This was controlled by software and allowed to switch from the 'load' position of the valve, where the sampling loop is filled with the effluent from **MM6**, to the 'inject' position, where the content of the loop is flushed into the chiral HPLC column for conversion and stereoselectivity determination. The developed 2D system greatly facilitated the study of the transition from batch to flow conditions of the model **7a/8a** coupling, in which different flow rates and substrate concentrations were evaluated. Keeping in mind that reaction completion was a prior condition for an easier purification of the target aldol products, the optimal compromise between aldehyde solubility and process productivity (*P*) was found by injecting into **MM6** a solution of *p*-nitro benzaldehyde **7a** (0.5

M) and cyclohexanone **8a** (2.5 M) in H<sub>2</sub>O-EtOH (1:1.5) at 20  $\mu\text{L min}^{-1}$  (residence time = 65 min) (Table 2, entry 1). Under these conditions, the steady-state regime was reached in ca. 4 h. Interestingly, the diastereoselectivity of the flow process (*anti/syn* = 7:1) slightly exceeded that of the batch reaction, while the enantioselectivity remained unmodified (90% *ee*<sub>anti</sub>). Isolation of the  $\beta$ -hydroxyketone **9a** was simply achieved by extraction of the collected eluate with dichloromethane after 5 h operation of **MM6** under steady-state conditions. Notably, the yield of isolated **9a** was compared with that evaluated using the online analysis method, which resulted in a very similar value.

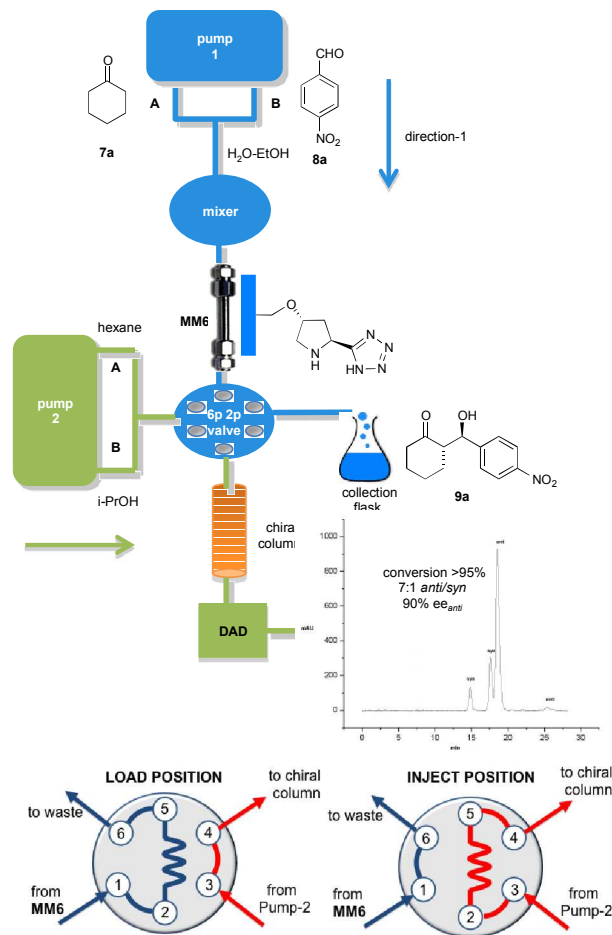


Fig. 2. 2D continuous-flow catalytic system for the production and online analysis of chiral  $\beta$ -hydroxyketones (6p2p valve: 6-port, 2-position switching valve; DAD: diode array detector). Magnification of the 6-port 2-position valve shows the 'load' and the 'inject' positions.

The long-term stability of monolithic microreactor **MM6** was next examined to determine the effect of the flow regime on the deactivation rate of the heterogeneous pyrrolidiny-tetrazole catalyst. The analysis of the reaction parameters *versus* process time plot shows that the steady-state conversion, diastereomeric excess (*de*) and *ee* are maintained unaltered for ca. 120 h on stream (TON<sub>flow</sub> = 147; Figure 3). A

progressive loss of efficiency is instead observed after that time, with a more pronounced effect at the level of reaction stereoselectivity.<sup>23</sup>

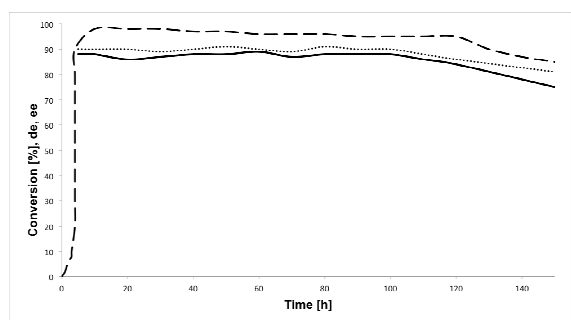


Fig. 3. Continuous-flow model aldol reaction in microreactor **MM6** operated for 150 h. Conversion %, dashed line; *de*, plain line; *ee*, dotted line.

Finally, the scope and applicability of the disclosed process and analysis method were briefly investigated in the aldol reactions of cyclohexanone **7a**, cyclopentanone **7b** or acetone **7c** with the activated aromatic aldehydes **8a-e** (Table 2). Gratifyingly, high conversion efficiencies could be achieved for all the substrate combinations by suitably adjusting the flow rate (10–20  $\mu\text{L min}^{-1}$ ) of the optimized feed solutions. As for the model reaction, the monolithic column **MM6** produced the aldol products **9b-e** from cyclohexanone **7a** with good enantioselectivity and satisfactory diastereoselectivity (entries 1-5). With cyclopentanone **7b** as donor, the aldol products **10a-e** were obtained as almost equimolar mixtures of diastereoisomers (entries 6-10). For the challenging aldol reaction of acetone in water medium, an acceptable level of enantioselectivity (71–88% *ee*) of the corresponding aldols **11a-e** could be achieved by reducing the reaction temperature to 0 °C (entries 11-15).

## Conclusions

In summary, we have presented a heterogeneous version of the valuable Ley-Arvidsson-Yamamoto catalyst in the form of polystyrene monolithic column (**MM6**) and demonstrated its efficacy in the continuous production of optically active aldol products using the environmentally benign water-ethanol mixture as the reaction medium. A remarkable long-term stability of the catalytic bed (ca. five days on stream) could be achieved thanks to the resistance of the *1H*-tetrazole moiety of **MM6** toward known side reactions occurring with activated aldehydes as acceptor substrates.

The devised 2D injection-reaction-analysis system together with the ease of product/catalyst separation and the detected twofold increase of productivity considerably enhanced the value of the optimized flow procedure compared to the corresponding batch protocol.

Monolithic columns of type **MM6** can be fabricated at low cost without the need for specialist equipment; an easy scale-up of

Table 2. Scope of the continuous-flow asymmetric aldol reaction.<sup>a</sup>

Entry	Product <b>9-11</b>	Flow rate [ $\mu\text{L/min}$ ] <sup>b</sup>	d.r. <i>anti/syn</i> <sup>c</sup>	<i>ee</i> <sub>anti</sub> [%] <sup>d</sup>	<i>P</i> <sup>e</sup>
1	 <b>9a</b>	20	7:1	90	1.22
2	 <b>9b</b>	20	7:1	95	1.22
3	 <b>9c</b>	15	6:1	89	0.92
4	 <b>9d</b>	15	6:1	91	0.92
5	 <b>9e</b>	20	5:1	95	1.22
6	 <b>10a</b>	20	1:1	76	1.22
7	 <b>10b</b>	15	2:1	81	0.92
8	 <b>10c</b>	15	1.5:1	71	0.92
9	 <b>10d</b>	15	1.2:1	75	0.92
10	 <b>10e</b>	15	1:1	90	0.92
11 <sup>f</sup>	 <b>11a</b>	15	–	81	0.92
12 <sup>f</sup>	 <b>11b</b>	10	–	80	0.61
13 <sup>f</sup>	 <b>11c</b>	10	–	88	0.61
14 <sup>f</sup>	 <b>11d</b>	10	–	71	0.61
15 <sup>f</sup>	 <b>11e</b>	10	–	82	0.61

<sup>a</sup> Experiments performed at 25 °C for 5 h (steady-state regime) in H<sub>2</sub>O-EtOH 1:1.5 ([**7**] = 2.5 M, [**8**] = 0.5 M). <sup>b</sup> Flow rate required for the complete conversion of aldehyde **8**. <sup>c</sup> Estimated by <sup>1</sup>H NMR analysis of the collected crude reaction mixtures. <sup>d</sup> Determined by chiral HPLC analysis. <sup>e</sup> *P* (productivity) is measured in mmol(product) h<sup>-1</sup> mmol(catalyst)<sup>-1</sup>. <sup>f</sup> Experiments performed at 0 °C in H<sub>2</sub>O-acetone 1.5:1 ([**8**] = 0.5 M).

the disclosed aldol process can be envisaged by the operation of multiple columns and the design of monoliths with larger diameters. Therefore, we hope that the methodology described herein may encourage further progress in the field of flow asymmetric catalysis and its utilization above the bench-scale.

## 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 chromatography was performed on silica gel 60 (230-400 mesh). Reactions were monitored by TLC on silica gel 60 F<sub>254</sub> with detection by charring with sulfuric acid and/or phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230-400 mesh). Optical rotations were measured at 20 ± 2 °C in the stated solvent; [ $\alpha$ ]<sub>D</sub> values are given in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. <sup>1</sup>H (300 MHz) and <sup>13</sup>C (75 MHz) NMR spectra were recorded for CDCl<sub>3</sub> solutions at room temperature unless otherwise specified. Peaks assignments were aided by <sup>1</sup>H-<sup>1</sup>H COSY and gradient-HMQC experiments. Enantiomeric excess (*ee*) values were determined by HPLC using the suitable chiral column (see below for details). Elemental analyses were performed with FLASH 2000 Series CHNS/O analyzer (ThermoFisher Scientific). FT-IR analyses were performed with the Bruker Instrument Vertex 70. ESI-MS routine analyses were performed in positive ion mode with samples dissolved in 10 mM solution of ammonium formate in 1:1 MeCN/H<sub>2</sub>O. For accurate mass measurements, the compounds were analyzed in positive ion mode by Agilent 6520 HPLC-Chip Q/TOF-MS (nanospray) using a quadrupole, a hexapole, and a time-of-flight unit to produce spectra. The capillary source voltage was set at 1700 V; the gas temperature and drying gas were kept at 350 °C and 5 L/min, respectively. MS analyzer was externally calibrated with ESI-L low concentration tuning mix from *m/z* 118 to 2700 to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 40/60 H<sub>2</sub>O/ACN 0.1% TFA into the system at a flow-rate of 0.4  $\mu$ L/min. SEM analyses were performed with a Zeiss Gemini 1530 scanning electron microscope.

(2*S*,4*R*)-1-(*Tert*-butoxycarbonyl)-4-((4-vinylbenzyl)oxy)pyrrolidine-2-carboxylic acid **1**<sup>17</sup> was synthesized as described. Adducts **9a-e**, **10a-e** and **11a-e** are known compounds. The self-disproportionation of enantiomers (SDE) test for achiral chromatography<sup>24</sup> has been carried out for derivatives **9a-e**, **10a-e** and **11a-e** without noting any significant magnitude of SDE.

**(2*S*,4*R*)-*Tert*-butyl 2-carbamoyl-4-((4-vinylbenzyl)oxy)pyrrolidine-1-carboxylate (2).** To a stirred mixture of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-((4-vinylbenzyl)oxy)pyrrolidine-2-carboxylic acid **1**<sup>17</sup> (1.00 g, 2.88 mmol), di-*tert*-butyl dicarbonate (940 mg, 4.32 mmol), NH<sub>4</sub>HCO<sub>3</sub> (341 mg, 4.32 mmol) and anhydrous CH<sub>3</sub>CN (15 mL) anhydrous pyridine (175  $\mu$ L, 2.16 mmol) was added in one portion. The mixture was stirred at room temperature for 5 h,

then the volume was reduced under vacuum to approximately 5 mL. Subsequently, AcOEt (20 mL) and H<sub>2</sub>O (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<sub>2</sub>SO<sub>4</sub>), and concentrated to give the amide **2** (947 mg, 95%) at least 90% pure as judged by <sup>1</sup>H NMR analysis. <sup>1</sup>H NMR:  $\delta$  = 7.40 (d, 2 H, *J* = 8.1 Hz, Ar), 7.32 (d, 2 H, *J* = 8.1 Hz, Ar), 7.28-7.20 (m, 2 H, Ar), 6.70 (dd, 1 H, *J* = 10.5 Hz, *J* = 17.0 Hz, HHC=CH), 5.75 (d, 1 H, *J* = 17.0 Hz, HHC=CH), 5.22 (d, 1 H, *J* = 10.5 Hz, HHC=CH), 4.55-4.38 (m, 4 H, CH<sub>2</sub>O, H-2, H-4), 3.58-3.40 (m, 2 H, 2 H-5), 2.45-2.11 (m, 2 H, 2 H-3), 1.45 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (two rotamers, selected data):  $\delta$  = 175.9, 174.7, 156.8, 155.5, 137.6, 136.4, 127.8, 126.5, 114.5, 113.9, 80.7, 80.6, 76.8, 76.0, 70.9, 70.5, 59.6, 58.4, 52.0, 51.7, 37.6, 37.1, 28.3, 28.1. ESI MS (346.4): 347.8 (M + H<sup>+</sup>).

**(2*S*,4*R*)-*Tert*-butyl 2-cyano-4-((4-vinylbenzyl)oxy)pyrrolidine-1-carboxylate (3).** To a cooled (0 °C), stirred solution of crude amide **2** (900 mg, 2.60 mmol) in anhydrous DMF (20 mL) cyanuric chloride (311 mg, 1.69 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<sub>2</sub>O (15 mL) and extracted with AcOEt (3 × 50 mL). The combined organic phases were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and eluted from a column of silica gel with 3:1 cyclohexane-AcOEt to give **3** (640 mg, 75%) as a pale yellow oil. [ $\alpha$ ]<sub>D</sub> = -44.9 (c 1.4, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  = 7.36 (d, 2 H, *J* = 8.1 Hz, Ar), 7.25 (d, 2 H, *J* = 8.1 Hz, Ar), 6.71 (dd, 1 H, *J* = 10.5 Hz, *J* = 17.5 Hz, HHC=CH), 5.75 (d, 1 H, *J* = 17.5 Hz, HHC=CH), 5.25 (d, 1 H, *J* = 10.5 Hz, HHC=CH), 4.58-4.36 (m, 3 H, CH<sub>2</sub>O, H-2), 4.26-4.05 (m, 1 H, H-4), 3.77-3.37 (m, 2 H, 2 H-5), 2.53-2.21 (m, 2 H, 2 H-3), 1.51 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (two rotamers, selected data):  $\delta$  = 153.3, 137.8, 136.3, 128.2, 127.9, 126.4, 118.9, 114.2, 81.9, 75.2, 70.9, 50.7, 45.7, 37.4, 28.3. ESI MS (328.4): 329.6 (M + H<sup>+</sup>). HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 329.1865, found 329.1891.

**(2*S*,4*R*)-*Tert*-butyl 2-(1*H*-tetrazol-5-yl)-4-((4-vinylbenzyl)oxy)pyrrolidine-1-carboxylate (4).** A mixture of nitrile **3** (700 mg, 2.13 mmol), NaN<sub>3</sub> (181 mg, 2.78 mmol), Et<sub>3</sub>N·HCl (382 mg, 2.78 mmol), and toluene (10 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<sub>2</sub>SO<sub>4</sub>), concentrated, and eluted from a column of silica gel with 6:4:1 cyclohexane-AcOEt-AcOH to give **4** (569 mg, 72%) as a white amorphous solid. [ $\alpha$ ]<sub>D</sub> = -50.3 (c 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  = 7.41 (d, 2 H, *J* = 8.1 Hz, Ar), 7.37 (d, 2 H, *J* = 8.1 Hz, Ar), 6.72 (dd, 1 H, *J* = 10.5 Hz, *J* = 17.5 Hz, HHC=CH), 5.77 (d, 1 H, *J* = 17.5 Hz, HHC=CH), 5.24 (d, 1 H, *J* = 10.5 Hz, HHC=CH), 5.18 (t, 1 H, *J* = 7.3 Hz, H-2), 4.61-4.45 (m, 2 H, CH<sub>2</sub>O), 4.38-4.29 (m, 1 H, H-4), 3.65-3.58 (m, 1 H, H-5a), 3.45-3.37 (m, 1 H, H-5b), 3.10-2.96 (m, 1 H, H-3a), 2.65-2.50 (m, 1 H, H-3b), 1.49 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (two rotamers, selected data):  $\delta$  = 175.5, 156.5, 137.4, 136.3, 128.2, 127.9,

126.4, 114.2, 82.1, 76.2, 71.2, 52.1, 49.5, 34.5, 28.3. ESI MS (371.4): 372.5 (M + H<sup>+</sup>). HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>26</sub>N<sub>5</sub>O<sub>3</sub> [M + H]<sup>+</sup> 372.2036, found 372.2054.

**Synthesis of monolithic pyrrolidiny-tetrazole M6.** A homogeneous mixture of tetrazole derivative **4** (180 mg, 0.49 mmol), styrene (280  $\mu$ L, 2.43 mmol), divinylbenzene (technical grade, 80%; 100  $\mu$ L, 0.70 mmol), toluene (140  $\mu$ L, 1.31 mmol), 1-dodecanol (1.14 mL, 5.10 mmol), and AIBN (6 mg, 0.04 mmol) was degassed under vacuum, and saturated with argon (by an Ar-filled balloon) three times. The mixture was then poured in a glass column (length: 10 cm, 0.46 cm internal diameter), sealed at both ends and placed in a vertical position in a standard convection oven. The polymerization was allowed to proceed for 24 h at 70 °C, then the column was cooled to room temperature, the glass broken, and the resulting monolith **M5** triturated to obtain a yellow powder. This powder was suspended in THF (5 mL), centrifuged with 5-mL portions of THF (2  $\times$ ) and dried under reduced pressure (0.1 mbar, 40 °C, 6 h). The collected supernatants were analyzed (<sup>1</sup>H NMR analysis) to verify the complete incorporation of monomer **4** into the polymer. The triturated **M5** resin was utilized for elemental and FT-IR analyses and the subsequent N-Boc deprotection step. Elemental analysis (%) found: N 5.74 (*f* = 0.82 mmol g<sup>-1</sup>). FT-IR (KBr):  $\nu$  3025, 2952, 1648, 1530 cm<sup>-1</sup>. To a cooled (0 °C), stirred mixture of triturated **M5** resin and THF (0.8 mL) was slowly added a solution of TFA (0.8 mL) and THF (0.8 mL). The mixture was then warmed to room temperature, stirred for 12 h, and centrifuged with 5-mL portions of THF (2  $\times$ ), 1:2/Et<sub>3</sub>N-THF (2  $\times$ ; addition at 0 °C) and THF (2  $\times$ ). The resulting monolith **M6** was finally dried at reduced pressure (0.1 mbar, 40 °C, 6 h). Elemental analysis (%) found: N 5.60 (*f* = 0.80 mmol g<sup>-1</sup>). FT-IR (KBr):  $\nu$  3022, 2950, 1521 cm<sup>-1</sup>.

**Procedure for the model aldol reaction under batch conditions (Table 1).** A mixture of *p*-nitro benzaldehyde (60 mg, 0.40 mmol), cyclohexanone (207  $\mu$ L, 2.00 mmol), triturated monolith **M6** (50 mg, 0.040 mmol) and the stated solvent (0.8 mL) was stirred at the stated temperature for the stated time, and then centrifuged with 2.5 mL-portions of CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$ ). The combined centrifugates were concentrated and the resulting residue analyzed by <sup>1</sup>H 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 isolated yield of the *anti/syn* diastereomeric mixture and the enantiomeric excess value<sup>23</sup> of the *anti* diastereoisomer by chiral HPLC analysis: Lux-1 Cellulose (hexanes/*i*-PrOH 98:2 v/v, 400  $\mu$ L min<sup>-1</sup>;  $\lambda_{\text{max}}$  = 258 nm); *t*<sub>R</sub> (major) = 18.5 min; *t*<sub>R</sub> (minor) = 25.4).

#### Preparation of monolithic microreactor (MM6)

A homogeneous mixture of tetrazole derivative **4** (180 mg, 0.49 mmol), styrene (280  $\mu$ L, 2.43 mmol), divinylbenzene (technical grade, 80%; 100  $\mu$ L, 0.70 mmol), toluene (140  $\mu$ L, 1.31 mmol), 1-dodecanol (1.14 mL, 5.10 mmol), and AIBN (6 mg, 0.04 mmol) was degassed under vacuum, and saturated

with argon (by an Ar-filled balloon) three times. The mixture was then poured in a stainless-steel columns (length: 10 cm, 0.46 cm internal diameter) sealed at both ends, and placed in a vertical position in a standard convection oven. The polymerization was allowed to proceed for 24 h at 70 °C, then the column **MM5** was cooled to room temperature and the seals removed. The column was provided with fittings, connected to the HPLC pump, and warmed to 50 °C. Then, THF was pumped through the warmed column at a flow rate of 50  $\mu$ L min<sup>-1</sup> for 5 h to remove the porogenic solvents and residual non-polymeric materials. The column **MM5** was cooled to room temperature; then, it was pumped an input stream of 1:2 TFA-THF solution (5 mL) at 15  $\mu$ L min<sup>-1</sup> for 5 h followed by an input stream of 1:2 Et<sub>3</sub>N-THF solution (5 mL; 15  $\mu$ L min<sup>-1</sup> for 5 h). The resulting column **MM6** was finally washed at room temperature with THF at a flow rate of 50  $\mu$ L min<sup>-1</sup> for 2 h. The whole procedure was performed with a reference microreactor in a parallel experiment with the aim to establish the main feature of **MM6** (level of functionalization, the void volume *V*<sub>0</sub>, the total porosity, the residence time and the observed backpressure; see Scheme 3).

#### Determination of microreactor void-volume

Microreactor void volume (*V*<sub>0</sub>) was determined by pycnometry.<sup>25</sup> This method consists in filling the microreactor successively with two distinct solvents (solvent 1: water; solvent 2: *n*-hexane) and weighing the filled microreactors accurately. Simple math shows that:<sup>26</sup>

$$V_0 = (\omega_1 - \omega_2) / (\delta_1 - \delta_2).$$

where  $\omega_1$  and  $\omega_2$  are the weights of the microreactor filled with solvents 1 and 2 and  $\delta_1$  and  $\delta_2$  the densities of the solvents.

#### Description of the experimental set-up for simultaneous flow-reaction and flow-injection analysis (Figure 2 and Table 2).

The system used for simultaneous flow-reaction and flow-injection analysis was made of two binary pumps (Agilent 1100 and Agilent 1100 micro series), a thermostated microreactor holder (Peltier unit), a diode array detector (DAD), and a data acquisition system (Agilent ChemStation).<sup>4b</sup> On the first direction, pump-1 was connected to the microreactor **MM6** through a mixer chamber (200  $\mu$ L). Channel-A was used to deliver a solution of ketone **7** (3.75 M) in H<sub>2</sub>O-EtOH (1:1.5). Channel-B delivered a solution of aldehyde **8** (0.75 M) in H<sub>2</sub>O-EtOH (1:1.5). The feed solutions were pumped at room temperature and at the stated flow rate through the mixer into **MM6** by operating channel-A and -B of pump-1 at 2:1 ratio. Experiments with acetone **7c** as donor were performed at 0 °C in H<sub>2</sub>O-acetone 1.5:1 ([**8**] = 0.5 M). The effluent from **MM6** was redirected to a 6-port 2-position switching valve. On the second direction, the binary pump-2 delivered a hexanes/*i*-PrOH solution (see below for compositions) into the suitable chiral HPLC column by passing through the switching valve. The 6-port 2-position valve (Rheodyne) was controlled by software<sup>27</sup> and allowed the switching between the 'load' and 'inject' positions for conversion and stereoselectivity

determination. Microreactor **MM6** was operated for 5 h under steady-state conditions, then the collected solution was extracted with  $\text{CH}_2\text{Cl}_2$  (ca. 20 min for the separation of the phases) to give the target  $\beta$ -hydroxyketone **9** as diastereomeric mixture at least 90% pure as judged by  $^1\text{H}$  NMR analysis.

The long-term stability experiment was performed using cyclohexanone **7a** (0.25 M) and *p*-nitro benzaldehyde **8a** (0.5 M) as the substrates; microreactor **MM6** was operated at 25 °C with a flow rate of 20  $\mu\text{L min}^{-1}$  for ca. 150 h. After the achievement of the steady-state regime (ca. 4 h), full conversion of **7a** was maintained for ca. 120 h, while a progressive loss of catalytic activity was observed after that time ( $\text{TON}_{\text{flow}} = 147$ ).

**(S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone (9a).** Yield: 98% (0.73 g).  $^1\text{H}$  NMR:  $\delta = 8.23$  (d, 2 H,  $J = 8.7$  Hz, Ar), 7.53 (d, 2 H,  $J = 8.7$  Hz, Ar), 4.92 (dd, 1 H,  $J = 3.2$  Hz,  $J = 8.4$  Hz, H-1'), 4.10 (d,  $J = 3.2$  Hz, OH), 2.38-2.62 (m, 3 H), 2.11-2.16 (m, 1 H), 1.38-1.87 (m, 5 H);  $^{13}\text{C}$  NMR:  $\delta = 214.8, 148.4, 147.6, 127.9, 123.6, 74.0, 57.2, 42.7, 30.8, 27.7, 24.7$ ; HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 98:2 v/v, 0.4  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 258$  nm);  $t_R$  (major) = 18.5 min;  $t_R$  (minor) = 25.4).

**(S)-2-((R)-Hydroxy(4-cyanophenyl)methyl)cyclohexanone (9b).** Yield: 97% (0.67 g).  $^1\text{H}$  NMR:  $\delta = 7.64$  (d, 2 H,  $J = 8.4$  Hz, Ar), 7.45 (d, 2 H,  $J = 8.4$  Hz, Ar), 4.84 (d, 1 H,  $J = 8.4$  Hz, H-1'), 2.54-2.61 (m, 1 H), 1.26-2.51 (m, 8 H).  $^{13}\text{C}$  NMR:  $\delta = 214.8, 146.3, 132.1, 127.7, 118.7, 111.6, 74.1, 57.1, 42.6, 30.7, 27.6, 24.6$ . HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 95:5 v/v, 1  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 13.9 min;  $t_R$  (minor) = 18.0).

**(S)-2-((R)-Hydroxy(4-bromophenyl)methyl)cyclohexanone (9c).** Yield: 99% (0.63 g).  $^1\text{H}$  NMR:  $\delta = 7.51$ -7.38 (m, 2 H, Ar), 7.24-7.12 (m, 2 H, Ar), 4.74 (d, 1 H,  $J = 8.7$  Hz, H-1'), 4.03 (bs, 1 H, OH), 2.63-2.25 (m, 3 H), 2.15-1.94 (m, 1 H), 1.93-1.15 (m, 5 H).  $^{13}\text{C}$  NMR:  $\delta = 215.3, 140.0, 131.5, 128.7, 121.7, 74.2, 57.3, 42.6, 30.7, 27.7, 24.7$ . HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 95:5 v/v, 1  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 13.9 min;  $t_R$  (minor) = 18.0).

**(S)-2-((R)-Hydroxy(4-chlorophenyl)methyl)cyclohexanone (9d).** Yield: 98% (0.52 g).  $^1\text{H}$  NMR:  $\delta = 7.31$  (d, 2 H,  $J = 8.4$  Hz, Ar), 7.25 (d, 2 H,  $J = 8.6$  Hz, Ar), 4.76 (d, 1 H,  $J = 8.8$  Hz, H-1'), 2.58-2.43 (m, 2 H), 2.38-2.30 (m, 1 H), 2.11-2.04 (m, 1 H), 1.86-1.75 (m, 1 H), 1.72-1.48 (m, 3 H), 1.33-1.26 (m, 1 H).  $^{13}\text{C}$  NMR:  $\delta = 215.4, 139.4, 133.6, 128.5, 128.4, 74.1, 57.3, 42.7, 30.7, 27.7, 24.7$ . HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 99:1 v/v, 1  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 29.4 min;  $t_R$  (minor) = 40.0).

**(S)-2-((R)-Hydroxy(2-chlorophenyl)methyl)cyclohexanone (9e).** Yield: 97% (0.69 g).  $^1\text{H}$  NMR:  $\delta = 7.60$ -7.50 (m, 1 H, Ar), 7.38-7.15 (m, 3 H, Ar), 5.34 (dd, 1 H  $J = 8.1$ , Hz,  $J = 3.9$  Hz, H-1'), 4.03 (d, 1 H,  $J = 3.9$  Hz, OH), 2.72-2.63 (m, 1 H), 2.48-2.28 (m, 2 H), 2.11-2.05 (m, 1 H), 1.86-1.46 (m, 5 H).  $^{13}\text{C}$  NMR:  $\delta = 215.3,$

139.0, 132.9, 129.2, 128.7, 128.2, 127.2, 70.4, 57.6, 42.7, 30.4, 27.8, 24.9. HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 99:1 v/v, 1  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 20.7 min;  $t_R$  (minor) = 25.5).

**(S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)cyclopentanone (10a).** Yield: 96% (0.68 g).  $^1\text{H}$  NMR:  $\delta = 8.17$ -8.13 (m, 2 H, Ar), 7.49-7.45 (m, 2 H, Ar), 4.78 (d, 1 H,  $J = 9.2$  Hz, H-1'), 4.69 (bs, 1 H, OH), 2.44-2.16 (m, 3 H), 2.00-1.90 (m, 1 H), 1.73-1.45 (m, 3 H);  $^{13}\text{C}$  NMR:  $\delta = 222.0, 148.5, 147.5, 127.2, 123.6, 74.4, 55.1, 38.6, 26.9, 20.4$ . HPLC: Chiralpak IC (hexanes/*i*- PrOH 80:20 v/v, 0.5  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 26.8 min;  $t_R$  (minor) = 31.9).

**(S)-2-((R)-Hydroxy(4-cyanophenyl)methyl)cyclopentanone (10b).** Yield: 97% (0.47 g).  $^1\text{H}$  NMR:  $\delta = 7.66$ -7.60 (m, 2 H, Ar), 7.48-7.40 (m, 2 H, Ar), 4.79 (d, 1 H  $J = 9.2$  Hz, H-1'), 4.72 (s, 1 H, OH), 2.50-1.50 (m, 7 H);  $^{13}\text{C}$  NMR:  $\delta = 222.2, 148.3, 132.2, 127.2, 118.7, 111.7, 70.5, 55.0, 38.5, 26.7, 20.3$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 90:10 v/v, 1  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (minor) = 30.8 min;  $t_R$  (major) = 32.7).

**(S)-2-((R)-Hydroxy(4-bromophenyl)methyl)cyclopentanone (10c).** Yield: 99% (0.60 g).  $^1\text{H}$  NMR:  $\delta = 7.48$  (d, 2 H,  $J = 8.4$  Hz, Ar), 7.22 (d, 2 H,  $J = 8.4$  Hz, Ar), 4.68 (d, 1 H,  $J = 8.9$  Hz, H-1'), 2.36-1.89 (m, 5 H), 1.75-1.62 (m, 2 H);  $^{13}\text{C}$  NMR:  $\delta = 222.8, 140.7, 131.5, 128.8, 121.9, 74.7, 55.5, 38.9, 26.9, 20.5$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 80:20 v/v, 1  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (minor) = 8.4 min;  $t_R$  (major) = 8.8).

**(S)-2-((R)-Hydroxy(4-chlorophenyl)methyl)cyclopentanone (10d).** Yield: 97% (0.49 g).  $^1\text{H}$  NMR:  $\delta = 7.35$ -7.21 (m, 4 H, Ar), 4.68 (d, 1 H,  $J = 9.0$  Hz, H-1'), 4.62 (bs, 1 H, OH), 2.45-1.40 (m, 7 H);  $^{13}\text{C}$  NMR:  $\delta = 222.4, 140.3, 133.5, 128.1, 128.6, 74.8, 55.3, 38.3, 27.0, 20.1$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 90:10 v/v, 1  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (minor) = 13.5 min;  $t_R$  (major) = 14.5).

**(S)-2-((R)-Hydroxy(2-chlorophenyl)methyl)cyclopentanone (10e).** Yield: 98% (0.49 g).  $^1\text{H}$  NMR:  $\delta = 7.59$  (d, 1 H,  $J = 7.6$  Hz, Ar), 7.45-7.27 (m, 3 H, Ar), 5.30 (d, 1 H,  $J = 9.2$  Hz, H-1'), 4.52 (s, 1 H, OH), 2.28-2.52 (m, 3 H), 2.03-2.07 (m, 1 H), 1.71-1.80 (m, 3 H);  $^{13}\text{C}$  NMR:  $\delta = 222.8, 139.1, 132.2, 129.1, 128.7, 128.2, 127.1, 70.2, 55.5, 38.6, 26.2, 20.4$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 95:5 v/v, 1  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 33.2 min;  $t_R$  (minor) = 38.2).

**(R)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (11a).** Yield: 98% (0.31 g).  $^1\text{H}$  NMR:  $\delta = 8.20$  (d, 2 H,  $J = 8.8$  Hz, Ar), 7.53 (d, 2 H,  $J = 8.8$  Hz, Ar), 5-31-5.25 (m, 1 H, H-4), 3.57 (d, 1 H,  $J = 3.3$  Hz, OH), 2.88-2.82 (m, 2 H), 2.22 (s, 3 H).  $^{13}\text{C}$  NMR:  $\delta = 208.5, 149.9, 126.4, 123.8, 68.9, 51.5, 30.7$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 80:20 v/v, 0.5  $\text{mLmin}^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 19.7 min;  $t_R$  (minor) = 21.2).

**(R)-4-Hydroxy-4-(4-cyanophenyl)butan-2-one (11b).** Yield: 96% (0.27 g).  $^1\text{H}$  NMR:  $\delta = 7.64$  (d, 2 H,  $J = 8.0$  Hz, Ar), 7.48 (d, 2



H,  $J = 8.0$  Hz, Ar), 5.45-5.38 (m, 1 H, H-4), 2.70-2.55 (m, 2 H), 2.21 (s, 3H).  $^{13}\text{C}$  NMR:  $\delta = 208.3, 148.1, 132.2, 126.3, 118.6, 111.2, 69.0, 51.5, 30.6$ . HPLC: Chiralpak ID (hexanes/*i*-PrOH 85:15 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 280$  nm);  $t_R$  (major) = 37.0 min;  $t_R$  (minor) = 40.2).

**(R)-4-Hydroxy-4-(4-bromophenyl)butan-2-one (11c).** Yield: 98% (0.35 g).  $^1\text{H}$  NMR:  $\delta = 7.47$  (d, 2 H,  $J = 8.4$  Hz, Ar), 7.23 (d, 2 H,  $J = 8.0$  Hz, Ar), 5.11 (q, 1 H,  $J = 4.0$  Hz,  $J = 8.0$  Hz, H-4), 2.83-2.81 (m, 2 H), 2.20 (s, 3 H);  $^{13}\text{C}$  NMR:  $\delta = 208.9, 141.6, 131.4, 127.2, 121.2, 69.0, 51.6, 30.7$ . HPLC: Chiralpak ID (hexanes/*i*-PrOH 80:20 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 280$  nm);  $t_R$  (major) = 9.1 min;  $t_R$  (minor) = 9.8).

**(R)-4-Hydroxy-4-(4-chlorophenyl)butan-2-one (11d).** Yield: 97% (0.29 g).  $^1\text{H}$  NMR:  $\delta = 7.28$ -7.33 (m, 4 H, Ar), 5.11-5.15 (q, 1 H,  $J = 4.0$  Hz,  $J = 8.0$  Hz, H-4), 2.88-2.78 (m, 2 H), 2.20 (s, 3 H);  $^{13}\text{C}$  NMR:  $\delta = 208.9, 141.1, 133.0, 128.4, 126.9, 68.9, 51.6, 30.6$ . HPLC: Chiralpak ID (hexanes/*i*-PrOH 80:20 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 7.8 min;  $t_R$  (minor) = 9.4).

**(R)-4-Hydroxy-4-(2-chlorophenyl)butan-2-one (11e).** Yield: 98% (0.29 g).  $^1\text{H}$  NMR:  $\delta = 7.63$ -7.61 (m, 1 H, Ar), 7.34-7.20 (m, 3 H, Ar), 5.52-5.48 (m, 1 H, H-4), 3.58 (d, 1 H,  $J = 3.2$  Hz, OH), 3.05-2.60 (m, 2 H), 2.22 (s, 3 H).  $^{13}\text{C}$  NMR:  $\delta = 208.9, 140.0, 130.7, 129.0, 128.3, 127.0, 126.8, 66.2, 49.9, 30.3$ . HPLC: Chiralpak ID (hexanes/*i*-PrOH 95:5 v/v, 0.5 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 11.8 min;  $t_R$  (minor) = 12.9).

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Journal Name

ARTICLE

## Monolithic 5-(pyrrolidin-2-yl)tetrazole flow microreactor for the asymmetric aldol reaction in water-ethanol solvent†

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(*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole organocatalyst has been prepared in the form of monolithic column through the radical copolymerization of a styryl-functionalized pyrrolidinyl-tetrazole derivative, styrene and divinylbenzene in the presence of porogens (dodecanol and toluene). The activity of the monolithic pyrrolidinyl-tetrazole organocatalyst (triturated polymer) has been initially tested under batch conditions using the asymmetric aldol reaction of cyclohexanone and *p*-nitro benzaldehyde as the benchmark. A prerequisite of the study has been the utilization of the ecofriendly water-ethanol mixture as the solvent. After having established the high efficiency and recyclability of the catalyst under these conditions, it has been evaluated the effect of the flow regime by fabricating the corresponding monolithic microreactor (pressure-resistant stainless-steel column). It has been demonstrated by a brief substrate scope study that the flow regime contributes to preserve the activity of the pyrrolidinyl-tetrazole catalyst over the time (5 days on stream) with an almost twofold increase of productivity moving from batch to flow conditions. Added value of the flow procedure has been the optimization of a suitable 2D instrumental setup for simultaneous flow reaction and online flow-injection analysis.

### Introduction

Continuous-flow meso- and micro-reactors can be considered nowadays useful scale-down versions of industrial reactors for transformations at the lab-scale;<sup>1</sup> conversely, the scale-up of optimized microflow reactions is emerging as a new opportunity for the fine chemical industry with advantages in terms of safety, sustainability and ease of automation/monitoring of the production processes.<sup>2</sup> In this scenario, continuous-flow asymmetric catalysis is receiving a great deal of attention as highlighted in recent reviews;<sup>3</sup> indeed, utilization of microflow technologies as synthetic platforms for the production of multifunctional chiral molecules is very attractive, promising and worth investigation. Surprisingly, the implementation of organocatalyzed stereoselective flow processes has scarcely been considered until recently despite the peculiar benefits associated with the use of an organic molecule as a catalyst, which include stability in air and water, absence of metal leaching and compatibility with a number of unprotected functionalities. Very likely, this lack of initial interest had been directly related to the difficult recycling of organocatalysts and the high catalyst loadings often required for several

transformations. Nevertheless, ours<sup>4</sup> and other groups<sup>3a,b</sup> have recently demonstrated that heterogeneization of organocatalysts may represent a viable solution to overcome the above drawbacks allowing the set-up of effective continuous-flow procedures endowed with high levels of stereoselectivity and productivity. The majority of the reported studies on asymmetric flow organocatalysis utilize the active catalyst immobilized on either polymeric or inorganic particles as packing material of fixed-bed reactors. In view of an easy scaling-up for potential industrial applications, this type of system, however, suffers from several limitations such as uncontrolled fluid dynamics, broad distribution of residence times, formation of hot-spots and stagnation zones.<sup>5</sup> Monolithic reactors characterized by a regular or irregular network of meso- and micro-porous channels typically offer improved flow properties in virtue of the high void volume, which guarantees a large contact area of the catalyst with the fluid and the absence of pressure drop.<sup>6</sup> The immobilization of organocatalysts in the form of continuous-flow monolithic columns is, however, still scant in literature. Our group<sup>4c</sup> and that of Luis and García-Verdugo<sup>7</sup> reported umpolung processes promoted by achiral azolium salts, while the group of Benaglia described stereoselective cycloadditions and Friedel-Crafts alkylations catalyzed by an imidazolidinone derivative.<sup>8</sup> As part of our ongoing studies on heterogeneous flow organocatalysis, we herein describe the fabrication of a polystyrene monolithic microreactor functionalized with the Ley- Arvidsson -Yamamoto (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole organocatalyst and its utilization in the stereoselective aldol reaction of cyclic ketones and acetone with activated aromatic

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aldehydes in the ecofriendly water-ethanol mixture. The asymmetric aldol reaction is one of the most versatile carbon-carbon bond-forming reaction leading to the widely diffused chiral  $\beta$ -hydroxyketone functionality.<sup>9</sup> Continuous-flow heterogeneous organocatalysis has been applied to this fundamental reaction in a few studies using proline, proline mimetics and small peptides (Figure 1);<sup>4d,e,10-14</sup> each of the disclosed processes is characterized by strengths and limitations, although the procedure described by Pericàs and co-workers with a polystyrene immobilized proline derivative seems to excel in terms of diastereoselectivity of the aldol products.<sup>11</sup>

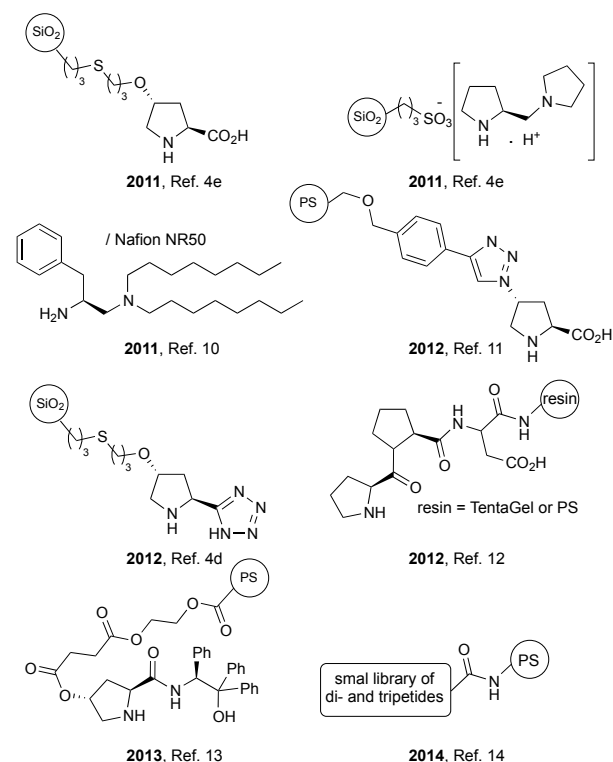


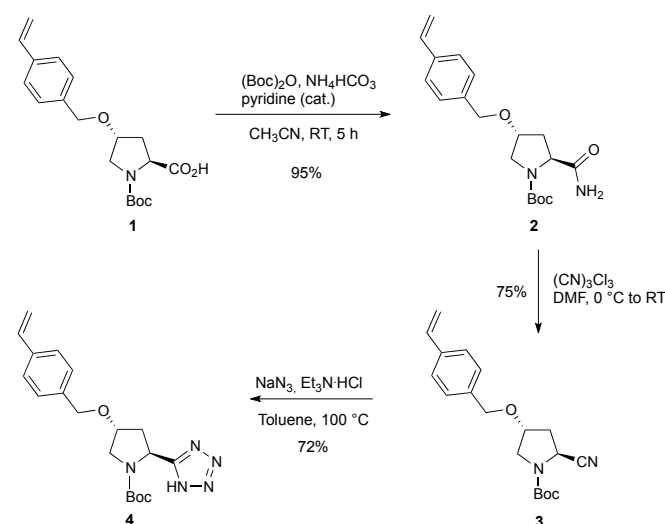
Fig. 1 Organocatalysts utilized for the continuous-flow asymmetric aldol reaction.

The main goal of the present study is the disclosure of a monolithic microreactor with improved fluid dynamics and high long-term stability of the catalytic material for the effective production of chiral aldol products under environmentally benign conditions. A suitable 2D instrumental arrangement for simultaneous flow reaction and online flow-injection analysis has also been devised by coupling the pyrrolidiny tetrazole-functionalized monolithic reactor to a chiral HPLC column for conversion and stereoselectivity determination.<sup>15</sup>

## Results and discussion

In recent years, (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole has emerged as a 'privileged' organocatalyst that mediates a wide range of useful asymmetric reactions, including aldol, Michael, Mannich,  $\alpha$ -amination reactions and so forth.<sup>16</sup> In a previous study we described a novel strategy based on photoinduced

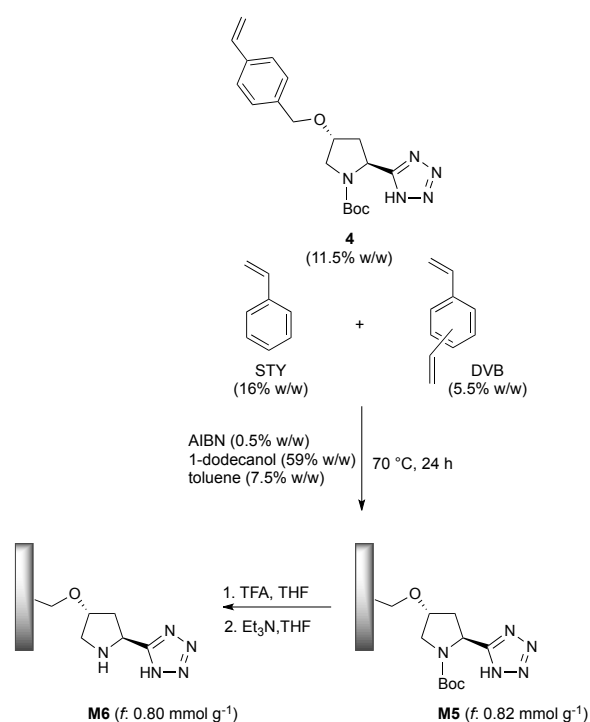
thiol-ene coupling (TEC) for the immobilization of pyrrolidiny-tetrazole catalyst on silica support and demonstrated its activity in continuous-flow asymmetric aldol reactions.<sup>4d</sup> The use of low polarity solvents such as diisopropyl ether and toluene resulted to be crucial to prevent the free hydroxyls on silica from perturbing the hydrogen-bonding network responsible for the high selectivities detected in the homogeneous catalysis. In the present study we reversed our strategy and planned to create a favorable catalytic microenvironment in water medium by the occurrence of hydrophobic interactions between the polystyrene support and the catalytic sites through a simplified enzyme-like mechanism. Accordingly, the synthesis of the styryl pyrrolidiny-tetrazole derivative **4** was initially addressed for its subsequent utilization as co-monomer in the polymerization furnishing the target polystyrene monolithic column **M6** (Schemes 1 and 2). Hence, the known styryl proline derivative **1**<sup>17</sup> was almost quantitatively converted into the amide **2** by in situ activation of the carboxylic acid. Subsequent dehydration of crude **2** promoted by cyanuric chloride afforded the nitrile **3** in good yield (75%), which in turn was transformed into the corresponding tetrazole **4** (72%) by cycloaddition with sodium azide (Scheme 1).



Scheme 1. Synthesis of the styryl-functionalized pyrrolidiny-tetrazole **4**.

The synthesis of tetrazole-functionalized polystyrene monoliths was next investigated using the conditions first described by Fréchet and Svec.<sup>18</sup> Therefore, an extensive polymerization study was conducted to identify the optimal ratio between styrene (STY), divinylbenzene (DVB), the co-monomer **4** and the porogens (toluene and 1-dodecanol). It important to emphasize that monoliths were molded into both glass and stainless-steel columns (4.6 mm internal diameter, 10 cm length) in parallel experiments to evaluate, on the one hand, the batch reactivity and the analytical/morphological properties of the prepared materials by SEM, FT-IR and elemental analysis; technically, the polymers prepared inside the glass columns were triturated and tested in the form of powder. On the other hand, this approach also allowed us to

estimate the influence of the polymerization parameters on the flow-through behavior of the monolith inside the metal column since wall effects and high backpressures needed to be carefully avoided for the correct functioning of the reactors in flow regime. Hence, after some experimentation, the optimal composition of the polymerization mixture resulted as follows: 1-dodecanol (59% w/w), toluene (7.5% w/w), STY (16% w/w), DVB (5.5% w/w), **4** (11.5% w/w) and AIBN (0.5% w/w). Elemental analysis of the resulting monolith **M5** indicated a satisfactory loading of pyrrolidinyl-tetrazole units ( $f$ : 0.82 mmol g<sup>-1</sup>); at the same time, <sup>1</sup>H NMR analysis of the THF solution used to wash the polymer **M5** confirmed the complete incorporation of the co-monomer **4** into the monolith. The *N*-Boc deprotection of trituated **M5** was finally carried out with TFA/THF followed by treatment with Et<sub>3</sub>N/THF to give the target active catalyst **M6**. Several experiments were also attempted to directly polymerize the co-monomer **4** in its *N*-deprotected form; by this approach, however, the resulting monoliths **M6** displayed detrimental pore clogging determining high backpressures in the flow regime and a very low reactivity under batch conditions, likely because of the reduced accessibility of the catalytic sites buried inside the micropores.

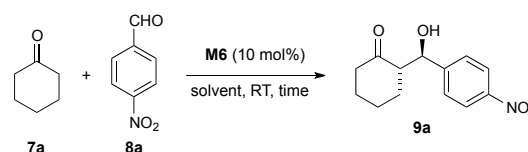


**Scheme 2.** Synthesis of polystyrene monolithic pyrrolidinyl-tetrazole **M6**.

Preliminary batch experiments were performed with optimal **M6** using the test reaction between cyclohexanone **7a** and *p*-nitro benzaldehyde **8a** in different solvents systems, with particular attention to the environmentally benign water-ethanol mixture<sup>19</sup> for the development of subsequent green applications of the newly prepared monolithic reactors (Table 1). Gratifyingly, the polystyrene pyrrolidinyl-tetrazole catalyst **M6** resulted highly active in pure water affording the aldol

product **9a** in quantitative yield and high stereoselectivity (*anti/syn* = 10:1; 95%  $ee_{anti}$ ) in 4 h reaction time (entry 1). The addition of ethanol for achieving the full solubilization of the substrates (H<sub>2</sub>O/EtOH 1:1) determined a partial erosion of enantioselectivity (90%  $ee_{anti}$ ) accompanied by a marked decrease of diastereoselectivity (*anti/syn* = 5:1; entry 2). Unfortunately, and contrary to previous findings on the beneficial effect of temperature on the activity of pyrrolidinyl-tetrazole organocatalysts,<sup>4d,20</sup> warming the reaction mixture to 50 °C produced a further drop of enantioselectivity (82%  $ee_{anti}$ ; entry 3). Next, a short solvent screening confirmed the necessary presence of water for obtaining satisfactory levels of conversion and stereoselectivity (entries 4-7). The maintenance of catalyst activity was finally ascertained in recycling experiments performed in H<sub>2</sub>O-EtOH, which was selected as the optimal solvent mixture for the subsequent flow experiments based on solubility reasons; catalyst **M6** could be recycled up to eight times affording the aldol product **9a** with almost constant yield (turnover number  $TON_{batch}$  = 80) and only moderate decrease of stereoselectivity in every cycle (entry 8). On the other hand, peculiar advantage of the 1*H*-tetrazole moiety of **M6** as isosteric replacement of the carboxylic acid functionality is the impossibility to undergo irreversible decarboxylation, which is a known side reaction occurring in the presence of activated aromatic aldehydes with analogue proline organocatalysts and leading to a progressive loss of catalytic activity.<sup>21</sup>

**Table 1.** Evaluation of catalyst **M6** performance under batch conditions.<sup>a</sup>

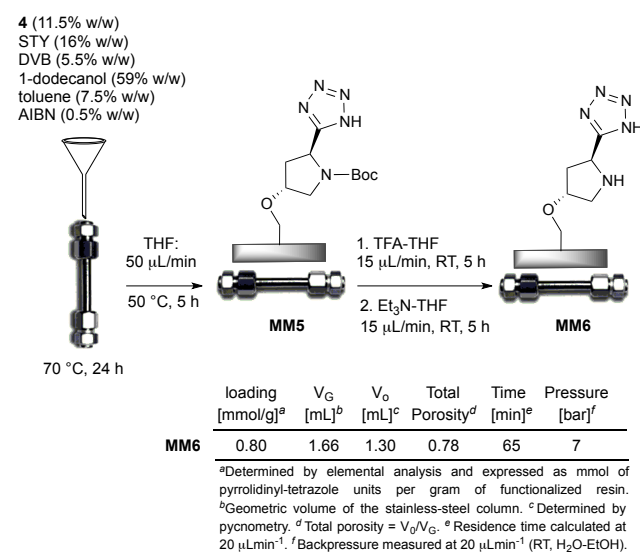


Entry	Solvent	Yield [%] <sup>b</sup>	Time	d.r. <i>anti/syn</i> <sup>c</sup>	$ee_{anti}$ [%] <sup>d</sup>
1	H <sub>2</sub> O	95	4	10:1	95
2	H <sub>2</sub> O-EtOH <sup>e</sup>	95	4	5:1	90
3 <sup>f</sup>	H <sub>2</sub> O-EtOH <sup>e</sup>	95	1	4:1	82
4	CH <sub>2</sub> Cl <sub>2</sub>	nr	24	-	-
5	EtOH	15	24	3:1	84
6	DMF	17	24	3:1	75
7	H <sub>2</sub> O-DMF <sup>e</sup>	85	4	8:1	90
8 <sup>g</sup>	H <sub>2</sub> O-EtOH <sup>e</sup>	95	4	5:1	88

<sup>a</sup> Reactions performed in the stated solvent with 0.40 mmol of **8a** (0.4 M) and 2.00 mmol of **7a**. <sup>b</sup> Isolated yield of the *anti/syn* diastereomeric mixture. <sup>c</sup> Estimated by <sup>1</sup>H NMR analysis of crude reaction mixtures. <sup>d</sup> Determined by chiral HPLC analysis. <sup>e</sup> 1:1 mixture. <sup>f</sup> Reaction performed at 50 °C. <sup>g</sup> 8<sup>th</sup> recycle.

At this stage of the study, we evaluated the performance of **M6** as a monolithic microreactor (hereafter designed as **MM**). Thus, the optimized polymerization mixture containing the monomer **4** was transferred into the stain-steel column, which was next sealed at both ends and heated at 70 °C for 24 h in a standard convection oven (Scheme 3). After cooling, the resulting monolithic microreactor **MM5** was connected to a HPLC instrument and then washed with THF (50 μL min<sup>-1</sup>; HPLC

oven 50 °C, 5 h) to remove the porogen and residual non-polymeric material. The *N*-Boc deprotection step was next performed by sequentially flowing (15  $\mu\text{L min}^{-1}$ ; 25 °C; 5 h) TFA/THF and  $\text{Et}_3\text{N}$ /THF solutions through the column.

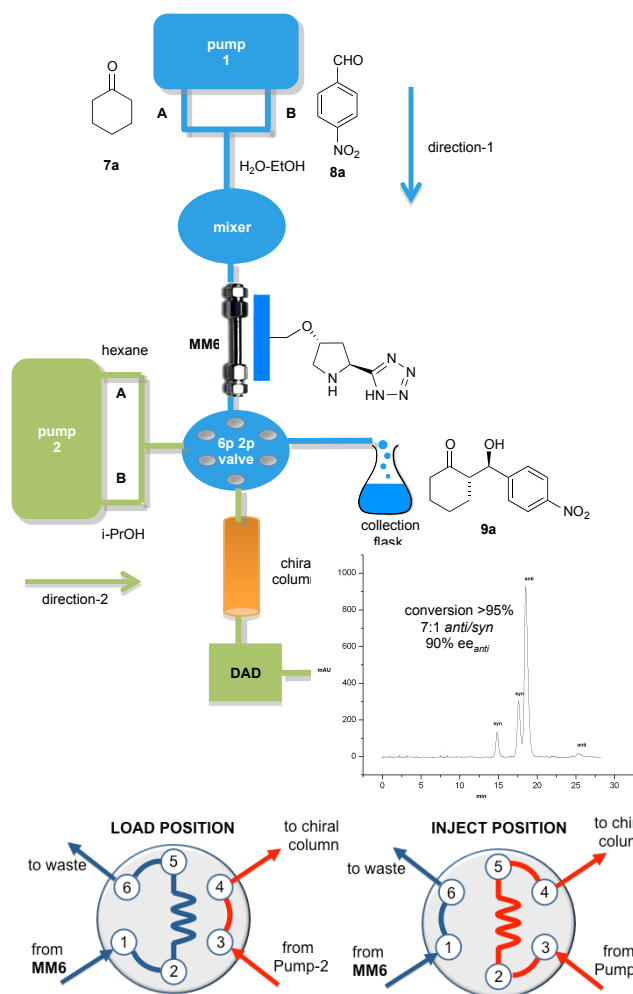


**Scheme 3.** Fabrication of monolithic microreactor **MM6**.

The void volume and the total porosity of the monolithic microreactor **MM6** were established by pycnometry. The main features of **MM6** including the observed backpressure, residence time and catalyst loading are summarized in Scheme 3. The macroporous nature of **MM6** was determined by SEM analysis (Figure S1); additionally, **MM6** displayed nearly no swelling in water-ethanol (1:1) solvent as verified by dedicated experiments showing a linear relationship between backpressure and flow rate.<sup>22</sup>

As anticipated, integration of an analytical platform for monitoring the reaction progress in flow regime was an important objective of this study. The devised injection-reaction-analysis system consisted in the monolithic microreactor **MM6** connected to pump-1 through a mixer chamber (direction-1). The solutions of ketone **7** and aldehyde **8** were continuously fed into **MM6** through the channels A and B, respectively (Figure 2). The outflow of the microreactor was redirected to a 6-port 2-position switching valve. In direction-2, the binary pump-2 delivered a hexane/*i*-PrOH solution into a chiral HPLC column by passing through the valve. This was controlled by software and allowed to switch from the 'load' position of the valve, where the sampling loop is filled with the effluent from **MM6**, to the 'inject' position, where the content of the loop is flushed into the chiral HPLC column for conversion and stereoselectivity determination. The developed 2D system greatly facilitated the study of the transition from batch to flow conditions of the model **7a/8a** coupling, in which different flow rates and substrate concentrations were evaluated. Keeping in mind that reaction completion was a prior condition for an easier purification of the target aldol products, the optimal compromise between aldehyde solubility and process productivity (*P*) was found by injecting into **MM6** a solution of *p*-nitro benzaldehyde **7a** (0.5

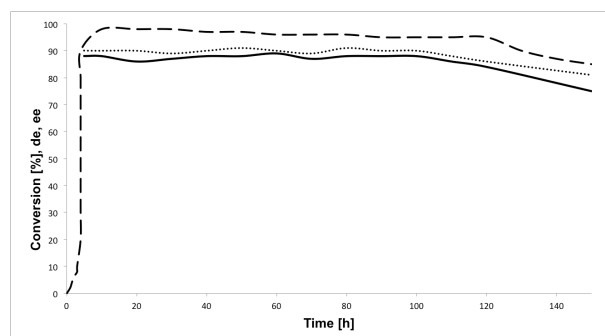
M) and cyclohexanone **8a** (2.5 M) in H<sub>2</sub>O-EtOH (1:1.5) at 20  $\mu\text{L min}^{-1}$  (residence time = 65 min) (Table 2, entry 1). Under these conditions, the steady-state regime was reached in ca. 4 h. Interestingly, the diastereoselectivity of the flow process (*anti/syn* = 7:1) slightly exceeded that of the batch reaction, while the enantioselectivity remained unmodified (90% *ee*<sub>anti</sub>). Isolation of the  $\beta$ -hydroxyketone **9a** was simply achieved by extraction of the collected eluate with dichloromethane after 5 h operation of **MM6** under steady-state conditions. Notably, the yield of isolated **9a** was compared with that evaluated using the online analysis method, which resulted in a very similar value.



**Fig. 2.** 2D continuous-flow catalytic system for the production and online analysis of chiral  $\beta$ -hydroxyketones (6p2p valve: 6-port, 2-position switching valve; DAD: diode array detector). Magnification of the 6-port 2-position valve shows the 'load' and the 'inject' positions.

The long-term stability of monolithic microreactor **MM6** was next examined to determine the effect of the flow regime on the deactivation rate of the heterogeneous pyrrolidiny-tetrazole catalyst. The analysis of the reaction parameters *versus* process time plot shows that the steady-state conversion, diastereomeric excess (*de*) and *ee* are maintained unaltered for ca. 120 h on stream (TON<sub>flow</sub> = 147; Figure 3). A

progressive loss of efficiency is instead observed after that time, with a more pronounced effect at the level of reaction stereoselectivity.<sup>23</sup>



**Fig. 3.** Continuous-flow model aldol reaction in microreactor **MM6** operated for 150 h. Conversion %, dashed line; *de*, plain line; *ee*, dotted line.

Finally, the scope and applicability of the disclosed process and analysis method were briefly investigated in the aldol reactions of cyclohexanone **7a**, cyclopentanone **7b** or acetone **7c** with the activated aromatic aldehydes **8a-e** (Table 2). Gratifyingly, high conversion efficiencies could be achieved for all the substrate combinations by suitably adjusting the flow rate (10–20  $\mu\text{L min}^{-1}$ ) of the optimized feed solutions. As for the model reaction, the monolithic column **MM6** produced the aldol products **9b-e** from cyclohexanone **7a** with good enantioselectivity and satisfactory diastereoselectivity (entries 1–5). With cyclopentanone **7b** as donor, the aldol products **10a-e** were obtained as almost equimolar mixtures of diastereoisomers (entries 6–10). For the challenging aldol reaction of acetone in water medium, an acceptable level of enantioselectivity (71–88% *ee*) of the corresponding aldols **11a-e** could be achieved by reducing the reaction temperature to 0 °C (entries 11–15).

## Conclusions

In summary, we have presented a heterogeneous version of the valuable Ley-Arvidsson-Yamamoto catalyst in the form of polystyrene monolithic column (**MM6**) and demonstrated its efficacy in the continuous production of optically active aldol products using the environmentally benign water-ethanol mixture as the reaction medium. A remarkable long-term stability of the catalytic bed (ca. five days on stream) could be achieved thanks to the resistance of the *1H*-tetrazole moiety of **MM6** toward known side reactions occurring with activated aldehydes as acceptor substrates.

The devised 2D injection-reaction-analysis system together with the ease of product/catalyst separation and the detected twofold increase of productivity considerably enhanced the value of the optimized flow procedure compared to the corresponding batch protocol.

Monolithic columns of type **MM6** can be fabricated at low cost without the need for specialist equipment; an easy scale-up of

**Table 2.** Scope of the continuous-flow asymmetric aldol reaction.<sup>a</sup>

Entry	Product <b>9-11</b>	Flow rate [mL/min] <sup>b</sup>	d.r. <i>anti/syn</i> <sup>c</sup>	<i>ee</i> <sub>anti</sub> [%] <sup>d</sup>	<i>P</i> <sup>e</sup>
1	 <b>9a</b>	20	7:1	90	1.22
2	 <b>9b</b>	20	7:1	95	1.22
3	 <b>9c</b>	15	6:1	89	0.92
4	 <b>9d</b>	15	6:1	91	0.92
5	 <b>9e</b>	20	5:1	95	1.22
6	 <b>10a</b>	20	1:1	76	1.22
7	 <b>10b</b>	15	2:1	81	0.92
8	 <b>10c</b>	15	1.5:1	71	0.92
9	 <b>10d</b>	15	1.2:1	75	0.92
10	 <b>10e</b>	15	1:1	90	0.92
11 <sup>f</sup>	 <b>11a</b>	15	–	81	0.92
12 <sup>f</sup>	 <b>11b</b>	10	–	80	0.61
13 <sup>f</sup>	 <b>11c</b>	10	–	88	0.61
14 <sup>f</sup>	 <b>11d</b>	10	–	71	0.61
15 <sup>f</sup>	 <b>11e</b>	10	–	82	0.61

<sup>a</sup> Experiments performed at 25 °C for 5 h (steady-state regime) in H<sub>2</sub>O-EtOH 1:1.5 ([**7**] = 2.5 M, [**8**] = 0.5 M). <sup>b</sup> Flow rate required for the complete conversion of aldehyde **8**. <sup>c</sup> Estimated by <sup>1</sup>H NMR analysis of the collected crude reaction mixtures. <sup>d</sup> Determined by chiral HPLC analysis. <sup>e</sup> *P* (productivity) is measured in mmol(product) h<sup>-1</sup> mmol(catalyst)<sup>-1</sup>. <sup>f</sup> Experiments performed at 0 °C in H<sub>2</sub>O-acetone 1.5:1 ([**8**] = 0.5 M).

the disclosed aldol process can be envisaged by the operation of multiple columns and the design of monoliths with larger diameters. Therefore, we hope that the methodology described herein may encourage further progress in the field of flow asymmetric catalysis and its utilization above the bench-scale.

## 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 chromatography 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 phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230-400 mesh). Optical rotations were measured at  $20 \pm 2$  °C in the stated solvent;  $[\alpha]_D$  values are given in  $10^{-1}$  deg  $\text{cm}^2 \text{g}^{-1}$ .  $^1\text{H}$  (300 MHz) and  $^{13}\text{C}$  (75 MHz) NMR spectra were recorded for  $\text{CDCl}_3$  solutions at room temperature unless otherwise specified. Peaks assignments were aided by  $^1\text{H}$ - $^1\text{H}$  COSY and gradient-HMQC experiments. Enantiomeric excess (*ee*) values were determined by HPLC using the suitable chiral column (see below for details). Elemental analyses were performed with FLASH 2000 Series CHNS/O analyzer (ThermoFisher Scientific). FT-IR analyses were performed with the Bruker Instrument Vertex 70. ESI-MS routine analyses were performed in positive ion mode with samples dissolved in 10 mM solution of ammonium formate in 1:1 MeCN/ $\text{H}_2\text{O}$ . For accurate mass measurements, the compounds were analyzed in positive ion mode by Agilent 6520 HPLC-Chip Q/TOF-MS (nanospray) using a quadrupole, a hexapole, and a time-of-flight unit to produce spectra. The capillary source voltage was set at 1700 V; the gas temperature and drying gas were kept at 350 °C and 5 L/min, respectively. MS analyzer was externally calibrated with ESI-L low concentration tuning mix from *m/z* 118 to 2700 to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 40/60  $\text{H}_2\text{O}/\text{ACN}$  0.1% TFA into the system at a flow-rate of 0.4 mL/min. SEM analyses were performed with a Zeiss Gemini 1530 scanning electron microscope.

(2*S*,4*R*)-1-(*Tert*-butoxycarbonyl)-4-((4-vinylbenzyl)oxy)pyrrolidine-2-carboxylic acid **1**<sup>17</sup> was synthesized as described. Adducts **9a-e**, **10a-e** and **11a-e** are known compounds. The self-disproportionation of enantiomers (SDE) test for achiral chromatography<sup>24</sup> has been carried out for derivatives **9a-e**, **10a-e** and **11a-e** without noting any significant magnitude of SDE.

**(2*S*,4*R*)-*Tert*-butyl 2-carbamoyl-4-((4-vinylbenzyl)oxy)pyrrolidine-1-carboxylate (2).** To a stirred mixture of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-((4-vinylbenzyl)oxy)pyrrolidine-2-carboxylic acid **1**<sup>17</sup> (1.00 g, 2.88 mmol), di-*tert*-butyl dicarbonate (940 mg, 4.32 mmol),  $\text{NH}_4\text{HCO}_3$  (341 mg, 4.32 mmol) and anhydrous  $\text{CH}_3\text{CN}$  (15 mL) anhydrous pyridine (175  $\mu\text{L}$ , 2.16 mmol) was added in one portion. The mixture was stirred at room temperature for 5 h,

then the volume was reduced under vacuum to approximately 5 mL. Subsequently, AcOEt (20 mL) and  $\text{H}_2\text{O}$  (20 mL) were added and the organic phase separated. The aqueous phase was extracted further with AcOEt (2  $\times$  20 mL) and the combined organic phases washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to give the amide **2** (947 mg, 95%) at least 90% pure as judged by  $^1\text{H}$  NMR analysis.  $^1\text{H}$  NMR:  $\delta$  = 7.40 (d, 2 H,  $J$  = 8.1 Hz, Ar), 7.32 (d, 2 H,  $J$  = 8.1 Hz, Ar), 7.28-7.20 (m, 2 H, Ar), 6.70 (dd, 1 H,  $J$  = 10.5 Hz,  $J$  = 17.0 Hz,  $\text{HHC}=\text{CH}$ ), 5.75 (d, 1 H,  $J$  = 17.0 Hz,  $\text{HHC}=\text{CH}$ ), 5.22 (d, 1 H,  $J$  = 10.5 Hz,  $\text{HHC}=\text{CH}$ ), 4.55-4.38 (m, 4 H,  $\text{CH}_2\text{O}$ , H-2, H-4), 3.58-3.40 (m, 2 H, 2 H-5), 2.45-2.11 (m, 2 H, 2 H-3), 1.45 (s, 9 H,  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C}$  NMR (two rotamers, selected data):  $\delta$  = 175.9, 174.7, 156.8, 155.5, 137.6, 136.4, 127.8, 126.5, 114.5, 113.9, 80.7, 80.6, 76.8, 76.0, 70.9, 70.5, 59.6, 58.4, 52.0, 51.7, 37.6, 37.1, 28.3, 28.1. ESI MS (346.4): 347.8 ( $\text{M} + \text{H}^+$ ).

**(2*S*,4*R*)-*Tert*-butyl 2-cyano-4-((4-vinylbenzyl)oxy)pyrrolidine-1-carboxylate (3).** To a cooled (0 °C), stirred solution of crude amide **2** (900 mg, 2.60 mmol) in anhydrous DMF (20 mL) cyanuric chloride (311 mg, 1.69 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  $\text{H}_2\text{O}$  (15 mL) and extracted with AcOEt (3  $\times$  50 mL). The combined organic phases were washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), concentrated and eluted from a column of silica gel with 3:1 cyclohexane-AcOEt to give **3** (640 mg, 75%) as a pale yellow oil.  $[\alpha]_D = -44.9$  (c 1.4,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR:  $\delta$  = 7.36 (d, 2 H,  $J$  = 8.1 Hz, Ar), 7.25 (d, 2 H,  $J$  = 8.1 Hz, Ar), 6.71 (dd, 1 H,  $J$  = 10.5 Hz,  $J$  = 17.5 Hz,  $\text{HHC}=\text{CH}$ ), 5.75 (d, 1 H,  $J$  = 17.5 Hz,  $\text{HHC}=\text{CH}$ ), 5.25 (d, 1 H,  $J$  = 10.5 Hz,  $\text{HHC}=\text{CH}$ ), 4.58-4.36 (m, 3 H,  $\text{CH}_2\text{O}$ , H-2), 4.26-4.05 (m, 1 H, H-4), 3.77-3.37 (m, 2 H, 2 H-5), 2.53-2.21 (m, 2 H, 2 H-3), 1.51 (s, 9 H,  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C}$  NMR (two rotamers, selected data):  $\delta$  = 153.3, 137.8, 136.3, 128.2, 127.9, 126.4, 118.9, 114.2, 81.9, 75.2, 70.9, 50.7, 45.7, 37.4, 28.3. ESI MS (328.4): 329.6 ( $\text{M} + \text{H}^+$ ). HRMS (ESI) *m/z* calcd for  $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_3$  [ $\text{M} + \text{H}$ ]<sup>+</sup> 329.1865, found 329.1891.

**(2*S*,4*R*)-*Tert*-butyl 2-(1*H*-tetrazol-5-yl)-4-((4-vinylbenzyl)oxy)pyrrolidine-1-carboxylate (4).** A mixture of nitrile **3** (700 mg, 2.13 mmol),  $\text{NaN}_3$  (181 mg, 2.78 mmol),  $\text{Et}_3\text{N}\cdot\text{HCl}$  (382 mg, 2.78 mmol), and toluene (10 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  $\times$  40 mL). The combined organic phases were washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), concentrated, and eluted from a column of silica gel with 6:4:1 cyclohexane-AcOEt-AcOH to give **4** (569 mg, 72%) as a white amorphous solid.  $[\alpha]_D = -50.3$  (c 1.0,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR:  $\delta$  = 7.41 (d, 2 H,  $J$  = 8.1 Hz, Ar), 7.37 (d, 2 H,  $J$  = 8.1 Hz, Ar), 6.72 (dd, 1 H,  $J$  = 10.5 Hz,  $J$  = 17.5 Hz,  $\text{HHC}=\text{CH}$ ), 5.77 (d, 1 H,  $J$  = 17.5 Hz,  $\text{HHC}=\text{CH}$ ), 5.24 (d, 1 H,  $J$  = 10.5 Hz,  $\text{HHC}=\text{CH}$ ), 5.18 (t, 1 H,  $J$  = 7.3 Hz, H-2), 4.61-4.45 (m, 2 H,  $\text{CH}_2\text{O}$ ), 4.38-4.29 (m, 1 H, H-4), 3.65-3.58 (m, 1 H, H-5a), 3.45-3.37 (m, 1 H, H-5b), 3.10-2.96 (m, 1 H, H-3a), 2.65-2.50 (m, 1 H, H-3b), 1.49 (s, 9 H,  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C}$  NMR (two rotamers, selected data):  $\delta$  = 175.5, 156.5, 137.4, 136.3, 128.2, 127.9,

126.4, 114.2, 82.1, 76.2, 71.2, 52.1, 49.5, 34.5, 28.3. ESI MS (371.4): 372.5 (M + H<sup>+</sup>). HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>26</sub>N<sub>5</sub>O<sub>3</sub> [M + H]<sup>+</sup> 372.2036, found 372.2054.

**Synthesis of monolithic pyrrolidinyl-tetrazole M6.** A homogeneous mixture of tetrazole derivative **4** (180 mg, 0.49 mmol), styrene (280 μL, 2.43 mmol), divinylbenzene (technical grade, 80%; 100 μL, 0.70 mmol), toluene (140 μL, 1.31 mmol), 1-dodecanol (1.14 mL, 5.10 mmol), and AIBN (6 mg, 0.04 mmol) was degassed under vacuum, and saturated with argon (by an Ar-filled balloon) three times. The mixture was then poured in a glass column (length: 10 cm, 0.46 cm internal diameter), sealed at both ends and placed in a vertical position in a standard convection oven. The polymerization was allowed to proceed for 24 h at 70 °C, then the column was cooled to room temperature, the glass broken, and the resulting monolith **M5** triturated to obtain a yellow powder. This powder was suspended in THF (5 mL), centrifuged with 5-mL portions of THF (2 ×) and dried under reduced pressure (0.1 mbar, 40 °C, 6 h). The collected supernatants were analyzed (<sup>1</sup>H NMR analysis) to verify the complete incorporation of monomer **4** into the polymer. The triturated **M5** resin was utilized for elemental and FT-IR analyses and the subsequent N-Boc deprotection step. Elemental analysis (%) found: N 5.74 (*f* = 0.82 mmol g<sup>-1</sup>). FT-IR (KBr): ν 3025, 2952, 1648, 1530 cm<sup>-1</sup>. To a cooled (0 °C), stirred mixture of triturated **M5** resin and THF (0.8 mL) was slowly added a solution of TFA (0.8 mL) and THF (0.8 mL). The mixture was then warmed to room temperature, stirred for 12 h, and centrifuged with 5-mL portions of THF (2 ×), 1:2/Et<sub>3</sub>N-THF (2 ×; addition at 0 °C) and THF (2 ×). The resulting monolith **M6** was finally dried at reduced pressure (0.1 mbar, 40 °C, 6 h). Elemental analysis (%) found: N 5.60 (*f* = 0.80 mmol g<sup>-1</sup>). FT-IR (KBr): ν 3022, 2950, 1521 cm<sup>-1</sup>.

**Procedure for the model aldol reaction under batch conditions (Table 1).** A mixture of *p*-nitro benzaldehyde (60 mg, 0.40 mmol), cyclohexanone (207 μL, 2.00 mmol), triturated monolith **M6** (50 mg, 0.040 mmol) and the stated solvent (0.8 mL) was stirred at the stated temperature for the stated time, and then centrifuged with 2.5 mL-portions of CH<sub>2</sub>Cl<sub>2</sub> (2 ×). The combined centrifugates were concentrated and the resulting residue analyzed by <sup>1</sup>H 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 isolated yield of the *anti/syn* diastereomeric mixture and the enantiomeric excess<sup>23</sup> of the *anti* diastereoisomer by chiral HPLC analysis: Lux-1 Cellulose (hexanes/*i*-PrOH 98:2 v/v, 400 μL min<sup>-1</sup>; λ<sub>max</sub> = 258 nm); *t*<sub>R</sub> (major) = 18.5 min; *t*<sub>R</sub> (minor) = 25.4).

#### Preparation of monolithic microreactor (MM6)

A homogeneous mixture of tetrazole derivative **4** (180 mg, 0.49 mmol), styrene (280 μL, 2.43 mmol), divinylbenzene (technical grade, 80%; 100 μL, 0.70 mmol), toluene (140 μL, 1.31 mmol), 1-dodecanol (1.14 mL, 5.10 mmol), and AIBN (6 mg, 0.04 mmol) was degassed under vacuum, and saturated

with argon (by an Ar-filled balloon) three times. The mixture was then poured in a stainless-steel columns (length: 10 cm, 0.46 cm internal diameter) sealed at both ends, and placed in a vertical position in a standard convection oven. The polymerization was allowed to proceed for 24 h at 70 °C, then the column **MM5** was cooled to room temperature and the seals removed. The column was provided with fittings, connected to the HPLC pump, and warmed to 50 °C. Then, THF was pumped through the warmed column at a flow rate of 50 μL min<sup>-1</sup> for 5 h to remove the porogenic solvents and residual non-polymeric materials. The column **MM5** was cooled to room temperature; then, it was pumped an input stream of 1:2 TFA-THF solution (5 mL) at 15 μL min<sup>-1</sup> for 5 h followed by an input stream of 1:2 Et<sub>3</sub>N-THF solution (5 mL; 15 μL min<sup>-1</sup> for 5 h). The resulting column **MM6** was finally washed at room temperature with THF at a flow rate of 50 μL min<sup>-1</sup> for 2 h. The whole procedure was performed with a reference microreactor in a parallel experiment with the aim to establish the main feature of **MM6** (level of functionalization, the void volume *V*<sub>0</sub>, the total porosity, the residence time and the observed backpressure; see Scheme 3).

#### Determination of microreactor void-volume

Microreactor void volume (*V*<sub>0</sub>) was determined by pycnometry.<sup>25</sup> This method consists in filling the microreactor successively with two distinct solvents (solvent 1: water; solvent 2: *n*-hexane) and weighing the filled microreactors accurately. Simple math shows that:<sup>26</sup>

$$V_0 = (\omega_1 - \omega_2) / (\delta_1 - \delta_2).$$

where  $\omega_1$  and  $\omega_2$  are the weights of the microreactor filled with solvents 1 and 2 and  $\delta_1$  and  $\delta_2$  the densities of the solvents.

#### Description of the experimental set-up for simultaneous flow-reaction and flow-injection analysis (Figure 2 and Table 2).

The system used for simultaneous flow-reaction and flow-injection analysis was made of two binary pumps (Agilent 1100 and Agilent 1100 micro series), a thermostated microreactor holder (Peltier unit), a diode array detector (DAD), and a data acquisition system (Agilent ChemStation).<sup>4b</sup> On the first direction, pump-1 was connected to the microreactor **MM6** through a mixer chamber (200 μL). Channel-A was used to deliver a solution of ketone **7** (3.75 M) in H<sub>2</sub>O-EtOH (1:1.5). Channel-B delivered a solution of aldehyde **8** (0.75 M) in H<sub>2</sub>O-EtOH (1:1.5). The feed solutions were pumped at room temperature and at the stated flow rate through the mixer into **MM6** by operating channel-A and -B of pump-1 at 2:1 ratio. Experiments with acetone **7c** as donor were performed at 0 °C in H<sub>2</sub>O-acetone 1.5:1 ([**8**] = 0.5 M). The effluent from **MM6** was redirected to a 6-port 2-position switching valve. On the second direction, the binary pump-2 delivered a hexanes/*i*-PrOH solution (see below for compositions) into the suitable chiral HPLC column by passing through the switching valve. The 6-port 2-position valve (Rheodyne) was controlled by software<sup>27</sup> and allowed the switching between the 'load' and 'inject' positions for conversion and stereoselectivity

determination. Microreactor **MM6** was operated for 5 h under steady-state conditions, then the collected solution was extracted with  $\text{CH}_2\text{Cl}_2$  (ca. 20 min for the separation of the phases) to give the target  $\beta$ -hydroxyketone **9** as diastereomeric mixture at least 90% pure as judged by  $^1\text{H}$  NMR analysis.

The long-term stability experiment was performed using cyclohexanone **7a** (0.25 M) and *p*-nitro benzaldehyde **8a** (0.5 M) as the substrates; microreactor **MM6** was operated at 25 °C with a flow rate of 20  $\mu\text{L min}^{-1}$  for ca. 150 h. After the achievement of the steady-state regime (ca. 4 h), full conversion of **7a** was maintained for ca. 120 h, while a progressive loss of catalytic activity was observed after that time ( $\text{TON}_{\text{flow}} = 147$ ).

**(S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone (9a).** Yield: 98% (0.73 g).  $^1\text{H}$  NMR:  $\delta = 8.23$  (d, 2 H,  $J = 8.7$  Hz, Ar), 7.53 (d, 2 H,  $J = 8.7$  Hz, Ar), 4.92 (dd, 1 H,  $J = 3.2$  Hz,  $J = 8.4$  Hz, H-1'), 4.10 (d,  $J = 3.2$  Hz, OH), 2.38-2.62 (m, 3 H), 2.11-2.16 (m, 1 H), 1.38-1.87 (m, 5 H);  $^{13}\text{C}$  NMR:  $\delta = 214.8, 148.4, 147.6, 127.9, 123.6, 74.0, 57.2, 42.7, 30.8, 27.7, 24.7$ ; HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 98:2 v/v, 0.4 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 258$  nm);  $t_R$  (major) = 18.5 min;  $t_R$  (minor) = 25.4).

**(S)-2-((R)-Hydroxy(4-cyanophenyl)methyl)cyclohexanone (9b).** Yield: 97% (0.67 g).  $^1\text{H}$  NMR:  $\delta = 7.64$  (d, 2 H,  $J = 8.4$  Hz, Ar), 7.45 (d, 2 H,  $J = 8.4$  Hz, Ar), 4.84 (d, 1 H,  $J = 8.4$  Hz, H-1'), 2.54-2.61 (m, 1 H), 1.26-2.51 (m, 8 H).  $^{13}\text{C}$  NMR:  $\delta = 214.8, 146.3, 132.1, 127.7, 118.7, 111.6, 74.1, 57.1, 42.6, 30.7, 27.6, 24.6$ . HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 95:5 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 13.9 min;  $t_R$  (minor) = 18.0).

**(S)-2-((R)-Hydroxy(4-bromophenyl)methyl)cyclohexanone (9c).** Yield: 99% (0.63 g).  $^1\text{H}$  NMR:  $\delta = 7.51$ -7.38 (m, 2 H, Ar), 7.24-7.12 (m, 2 H, Ar), 4.74 (d, 1 H,  $J = 8.7$  Hz, H-1'), 4.03 (bs, 1 H, OH), 2.63-2.25 (m, 3 H), 2.15-1.94 (m, 1 H), 1.93-1.15 (m, 5 H).  $^{13}\text{C}$  NMR:  $\delta = 215.3, 140.0, 131.5, 128.7, 121.7, 74.2, 57.3, 42.6, 30.7, 27.7, 24.7$ . HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 95:5 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 13.9 min;  $t_R$  (minor) = 18.0).

**(S)-2-((R)-Hydroxy(4-chlorophenyl)methyl)cyclohexanone (9d).** Yield: 98% (0.52 g).  $^1\text{H}$  NMR:  $\delta = 7.31$  (d, 2 H,  $J = 8.4$  Hz, Ar), 7.25 (d, 2 H,  $J = 8.6$  Hz, Ar), 4.76 (d, 1 H,  $J = 8.8$  Hz, H-1'), 2.58-2.43 (m, 2 H), 2.38-2.30 (m, 1 H), 2.11-2.04 (m, 1 H), 1.86-1.75 (m, 1 H), 1.72-1.48 (m, 3 H), 1.33-1.26 (m, 1 H).  $^{13}\text{C}$  NMR:  $\delta = 215.4, 139.4, 133.6, 128.5, 128.4, 74.1, 57.3, 42.7, 30.7, 27.7, 24.7$ . HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 99:1 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 29.4 min;  $t_R$  (minor) = 40.0).

**(S)-2-((R)-Hydroxy(2-chlorophenyl)methyl)cyclohexanone (9e).** Yield: 97% (0.69 g).  $^1\text{H}$  NMR:  $\delta = 7.60$ -7.50 (m, 1 H, Ar), 7.38-7.15 (m, 3 H, Ar), 5.34 (dd, 1 H  $J = 8.1$ , Hz,  $J = 3.9$  Hz, H-1'), 4.03 (d, 1 H,  $J = 3.9$  Hz, OH), 2.72-2.63 (m, 1 H), 2.48-2.28 (m, 2 H), 2.11- 2.05 (m, 1 H), 1.86-1.46 (m, 5 H).  $^{13}\text{C}$  NMR:  $\delta = 215.3,$

139.0, 132.9, 129.2, 128.7, 128.2, 127.2, 70.4, 57.6, 42.7, 30.4, 27.8, 24.9. HPLC: Lux-1 Cellulose (hexanes/*i*- PrOH 99:1 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 20.7 min;  $t_R$  (minor) = 25.5).

**(S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)cyclopentanone (10a).** Yield: 96% (0.68 g).  $^1\text{H}$  NMR:  $\delta = 8.17$ -8.13 (m, 2 H, Ar), 7.49-7.45 (m, 2 H, Ar), 4.78 (d, 1 H,  $J = 9.2$  Hz, H-1'), 4.69 (bs, 1 H, OH), 2.44-2.16 (m, 3 H), 2.00-1.90 (m, 1 H), 1.73-1.45 (m, 3 H);  $^{13}\text{C}$  NMR:  $\delta = 222.0, 148.5, 147.5, 127.2, 123.6, 74.4, 55.1, 38.6, 26.9, 20.4$ . HPLC: Chiralpak IC (hexanes/*i*- PrOH 80:20 v/v, 0.5 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 26.8 min;  $t_R$  (minor) = 31.9).

**(S)-2-((R)-Hydroxy(4-cyanophenyl)methyl)cyclopentanone (10b).** Yield: 97% (0.47 g).  $^1\text{H}$  NMR:  $\delta = 7.66$ -7.60 (m, 2 H, Ar), 7.48-7.40 (m, 2 H, Ar), 4.79 (d, 1 H  $J = 9.2$  Hz, H-1'), 4.72 (s, 1 H, OH), 2.50-1.50 (m, 7 H);  $^{13}\text{C}$  NMR:  $\delta = 222.2, 148.3, 132.2, 127.2, 118.7, 111.7, 70.5, 55.0, 38.5, 26.7, 20.3$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 90:10 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (minor) = 30.8 min;  $t_R$  (major) = 32.7).

**(S)-2-((R)-Hydroxy(4-bromophenyl)methyl)cyclopentanone (10c).** Yield: 99% (0.60 g).  $^1\text{H}$  NMR:  $\delta = 7.48$  (d, 2 H,  $J = 8.4$  Hz, Ar), 7.22 (d, 2 H,  $J = 8.4$  Hz, Ar), 4.68 (d, 1 H,  $J = 8.9$  Hz, H-1'), 2.36- 1.89 (m, 5 H), 1.75-1.62 (m, 2 H);  $^{13}\text{C}$  NMR:  $\delta = 222.8, 140.7, 131.5, 128.8, 121.9, 74.7, 55.5, 38.9, 26.9, 20.5$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 80:20 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (minor) = 8.4 min;  $t_R$  (major) = 8.8).

**(S)-2-((R)-Hydroxy(4-chlorophenyl)methyl)cyclopentanone (10d).** Yield: 97% (0.49 g).  $^1\text{H}$  NMR:  $\delta = 7.35$ -7.21 (m, 4 H, Ar), 4.68 (d, 1 H,  $J = 9.0$  Hz, H-1'), 4.62 (bs, 1 H, OH), 2.45-1.40 (m, 7 H);  $^{13}\text{C}$  NMR:  $\delta = 222.4, 140.3, 133.5, 128.1, 128.6, 74.8, 55.3, 38.3, 27.0, 20.1$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 90:10 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (minor) = 13.5 min;  $t_R$  (major) = 14.5).

**(S)-2-((R)-Hydroxy(2-chlorophenyl)methyl)cyclopentanone (10e).** Yield: 98% (0.49 g).  $^1\text{H}$  NMR:  $\delta = 7.59$  (d, 1 H,  $J = 7.6$  Hz, Ar), 7.45-7.27 (m, 3 H, Ar), 5.30 (d, 1 H,  $J = 9.2$  Hz, H-1'), 4.52 (s, 1 H, OH), 2.28-2.52 (m, 3 H), 2.03-2.07 (m, 1 H), 1.71-1.80 (m, 3 H);  $^{13}\text{C}$  NMR:  $\delta = 222.8, 139.1, 132.2, 129.1, 128.7, 128.2, 127.1, 70.2, 55.5, 38.6, 26.2, 20.4$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 95:5 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 33.2 min;  $t_R$  (minor) = 38.2).

**(R)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (11a).** Yield: 98% (0.31 g).  $^1\text{H}$  NMR:  $\delta = 8.20$  (d, 2 H,  $J = 8.8$  Hz, Ar), 7.53 (d, 2 H,  $J = 8.8$  Hz, Ar), 5.31-5.25 (m, 1 H, H-4), 3.57 (d, 1 H,  $J = 3.3$  Hz, OH), 2.88-2.82 (m, 2 H), 2.22 (s, 3 H).  $^{13}\text{C}$  NMR:  $\delta = 208.5, 149.9, 126.4, 123.8, 68.9, 51.5, 30.7$ . HPLC: Chiralpak ID (hexanes/*i*- PrOH 80:20 v/v, 0.5 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 19.7 min;  $t_R$  (minor) = 21.2).

**(R)-4-Hydroxy-4-(4-cyanophenyl)butan-2-one (11b).** Yield: 96% (0.27 g).  $^1\text{H}$  NMR:  $\delta = 7.64$  (d, 2 H,  $J = 8.0$  Hz, Ar), 7.48 (d, 2

H,  $J = 8.0$  Hz, Ar), 5.45-5.38 (m, 1 H, H-4), 2.70-2.55 (m, 2 H), 2.21 (s, 3H).  $^{13}\text{C}$  NMR:  $\delta = 208.3, 148.1, 132.2, 126.3, 118.6, 111.2, 69.0, 51.5, 30.6$ . HPLC: Chiralpak ID (hexanes/*i*-PrOH 85:15 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 280$  nm);  $t_R$  (major) = 37.0 min;  $t_R$  (minor) = 40.2).

**(R)-4-Hydroxy-4-(4-bromophenyl)butan-2-one (11c).** Yield: 98% (0.35 g).  $^1\text{H}$  NMR:  $\delta = 7.47$  (d, 2 H,  $J = 8.4$  Hz, Ar), 7.23 (d, 2 H,  $J = 8.0$  Hz, Ar), 5.11 (q, 1 H,  $J = 4.0$  Hz,  $J = 8.0$  Hz, H-4), 2.83-2.81 (m, 2 H), 2.20 (s, 3 H);  $^{13}\text{C}$  NMR:  $\delta = 208.9, 141.6, 131.4, 127.2, 121.2, 69.0, 51.6, 30.7$ . HPLC: Chiralpak ID (hexanes/*i*-PrOH 80:20 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 280$  nm);  $t_R$  (major) = 9.1 min;  $t_R$  (minor) = 9.8).

**(R)-4-Hydroxy-4-(4-chlorophenyl)butan-2-one (11d).** Yield: 97% (0.29 g).  $^1\text{H}$  NMR:  $\delta = 7.28$ -7.33 (m, 4 H, Ar), 5.11-5.15 (q, 1 H,  $J = 4.0$  Hz,  $J = 8.0$  Hz, H-4), 2.88-2.78 (m, 2 H), 2.20 (s, 3 H);  $^{13}\text{C}$  NMR:  $\delta = 208.9, 141.1, 133.0, 128.4, 126.9, 68.9, 51.6, 30.6$ . HPLC: Chiralpak ID (hexanes/*i*-PrOH 80:20 v/v, 1 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 7.8 min;  $t_R$  (minor) = 9.4).

**(R)-4-Hydroxy-4-(2-chlorophenyl)butan-2-one (11e).** Yield: 98% (0.29 g).  $^1\text{H}$  NMR:  $\delta = 7.63$ -7.61 (m, 1 H, Ar), 7.34-7.20 (m, 3 H, Ar), 5.52-5.48 (m, 1 H, H-4), 3.58 (d, 1 H,  $J = 3.2$  Hz, OH), 3.05-2.60 (m, 2 H), 2.22 (s, 3 H).  $^{13}\text{C}$  NMR:  $\delta = 208.9, 140.0, 130.7, 129.0, 128.3, 127.0, 126.8, 66.2, 49.9, 30.3$ . HPLC: Chiralpak ID (hexanes/*i*-PrOH 95:5 v/v, 0.5 mLmin $^{-1}$ ;  $\lambda_{\text{max}} = 220$  nm);  $t_R$  (major) = 11.8 min;  $t_R$  (minor) = 12.9).

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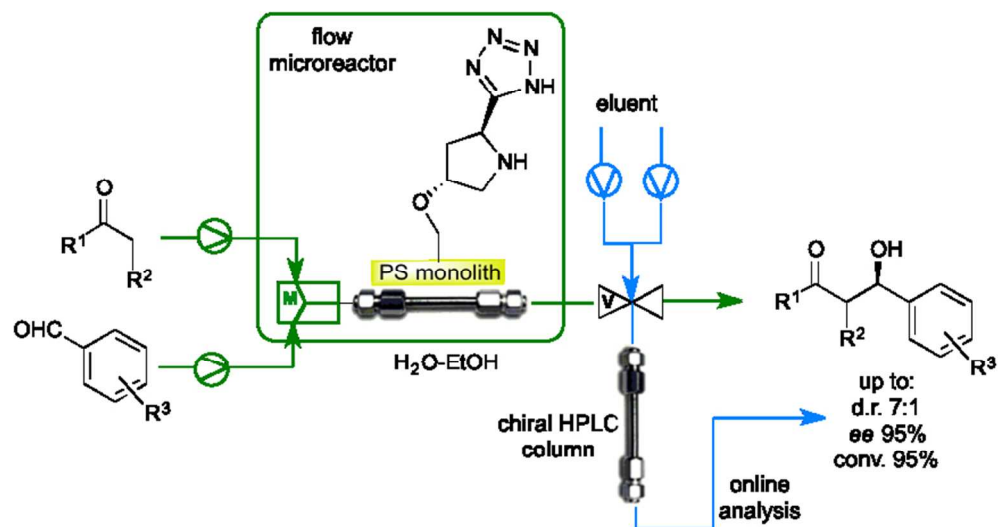
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## Monolithic 5-(pyrrolidin-2-yl)tetrazole flow microreactor for the asymmetric aldol reaction in water-ethanol solvent

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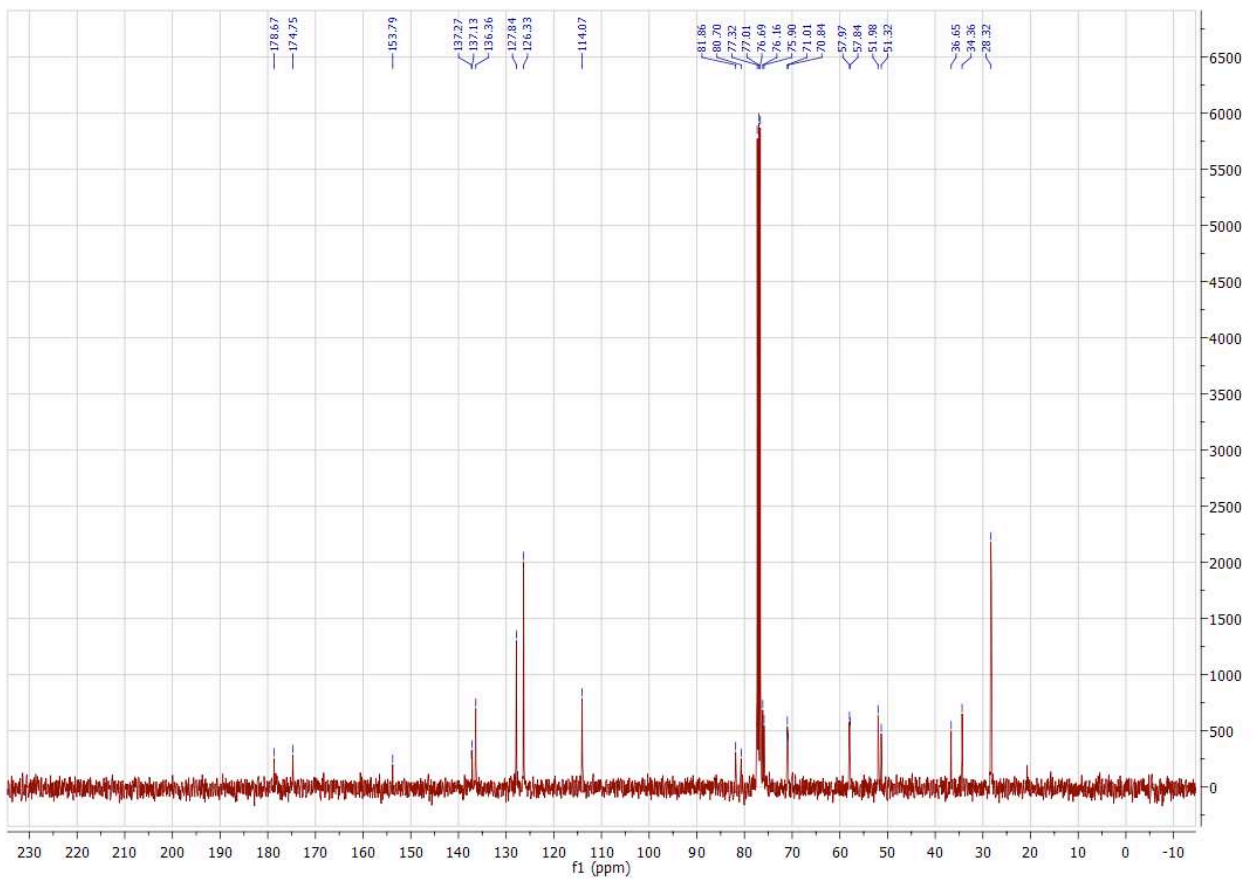
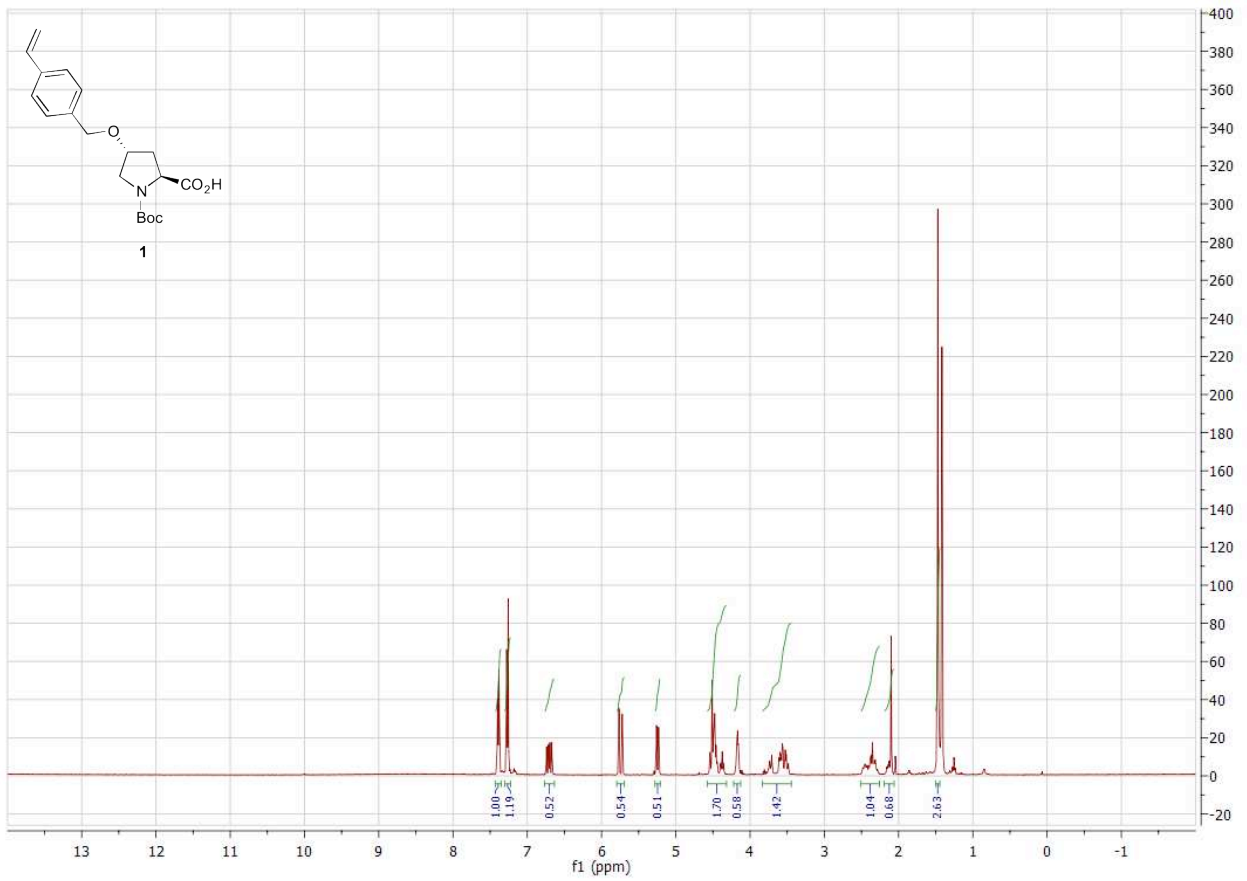
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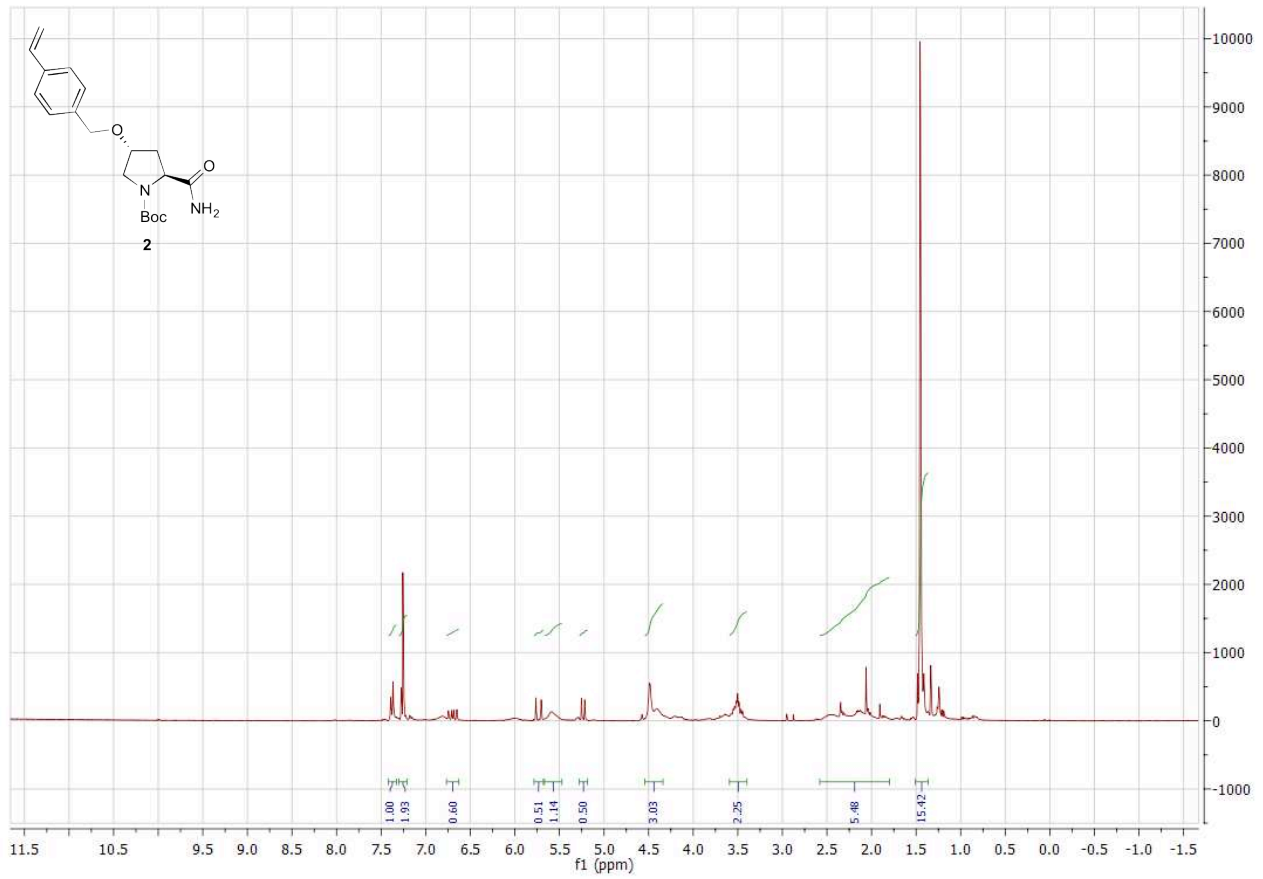
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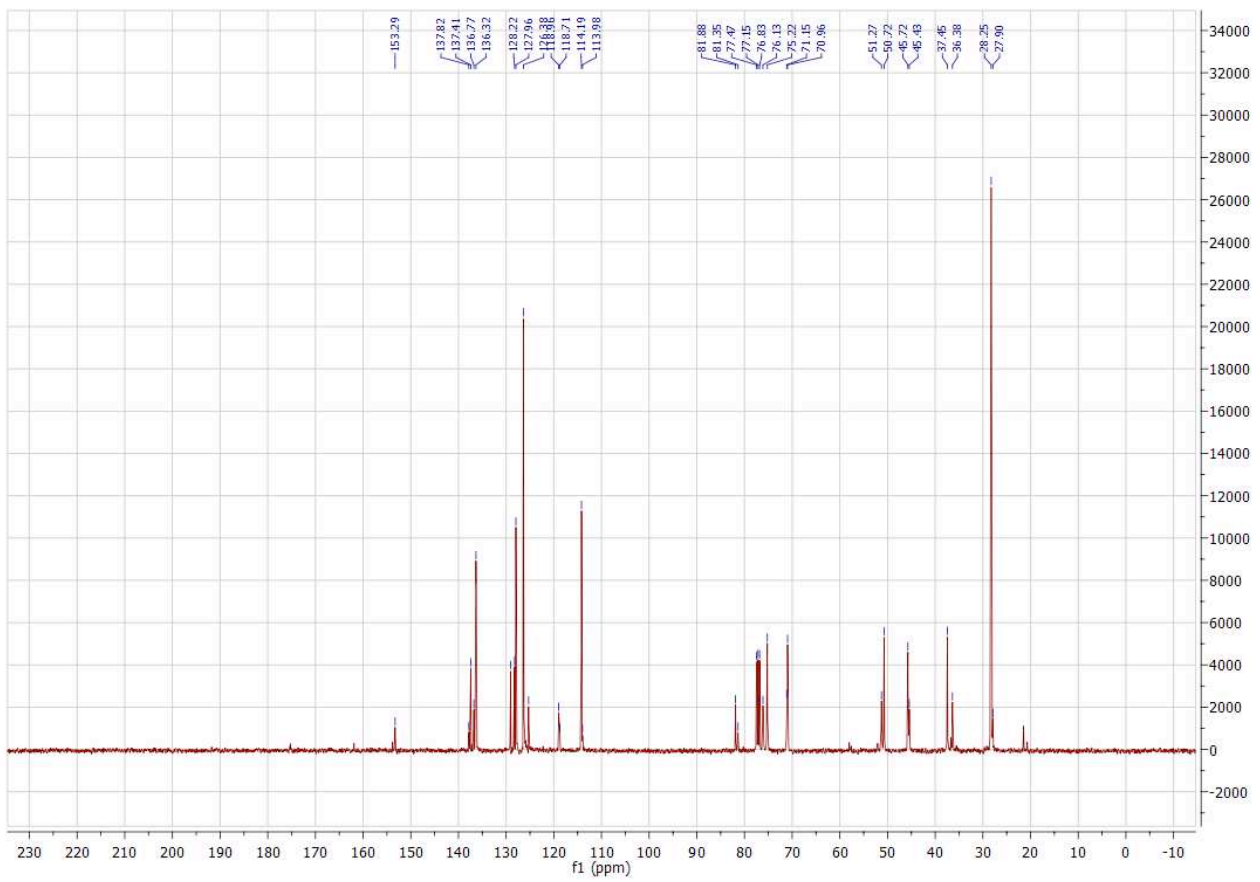
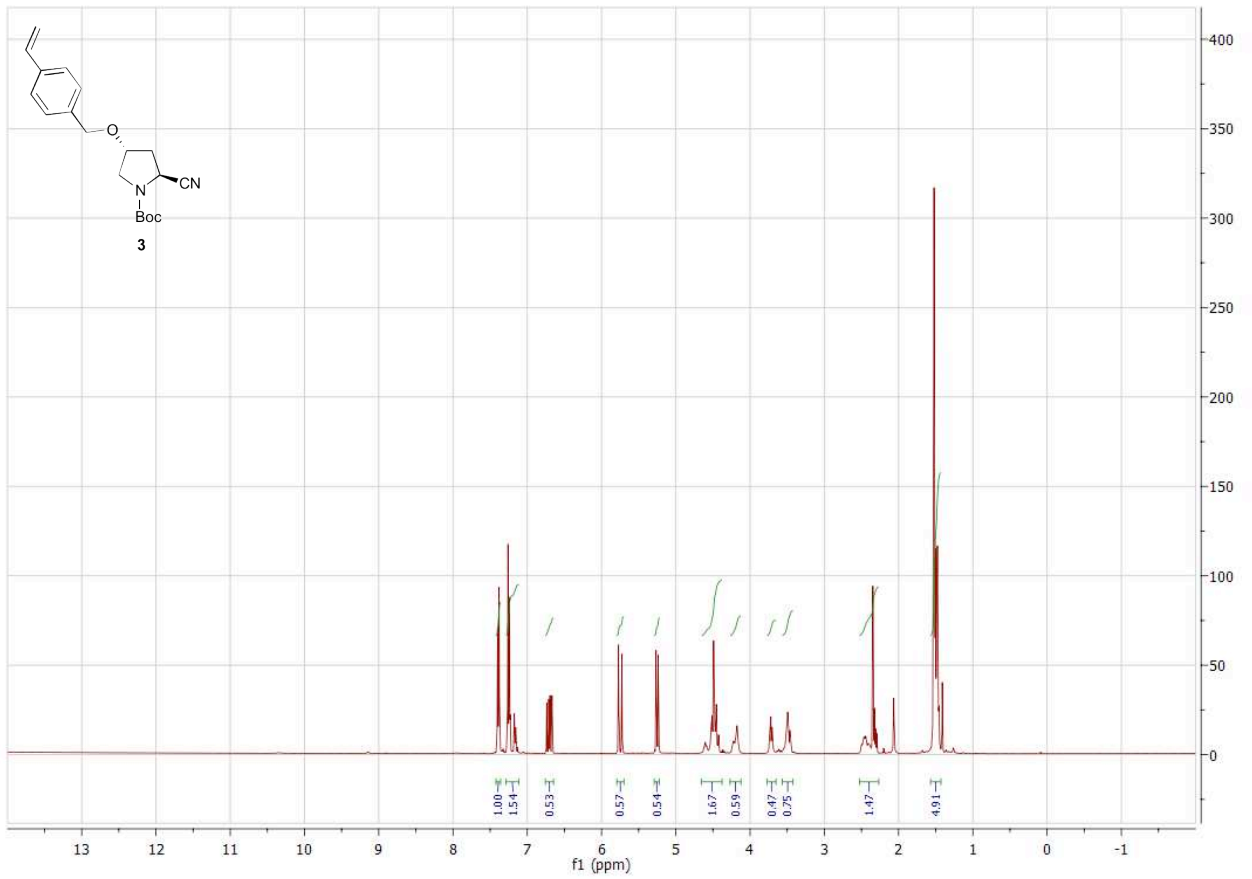
### Electronic supplementary information

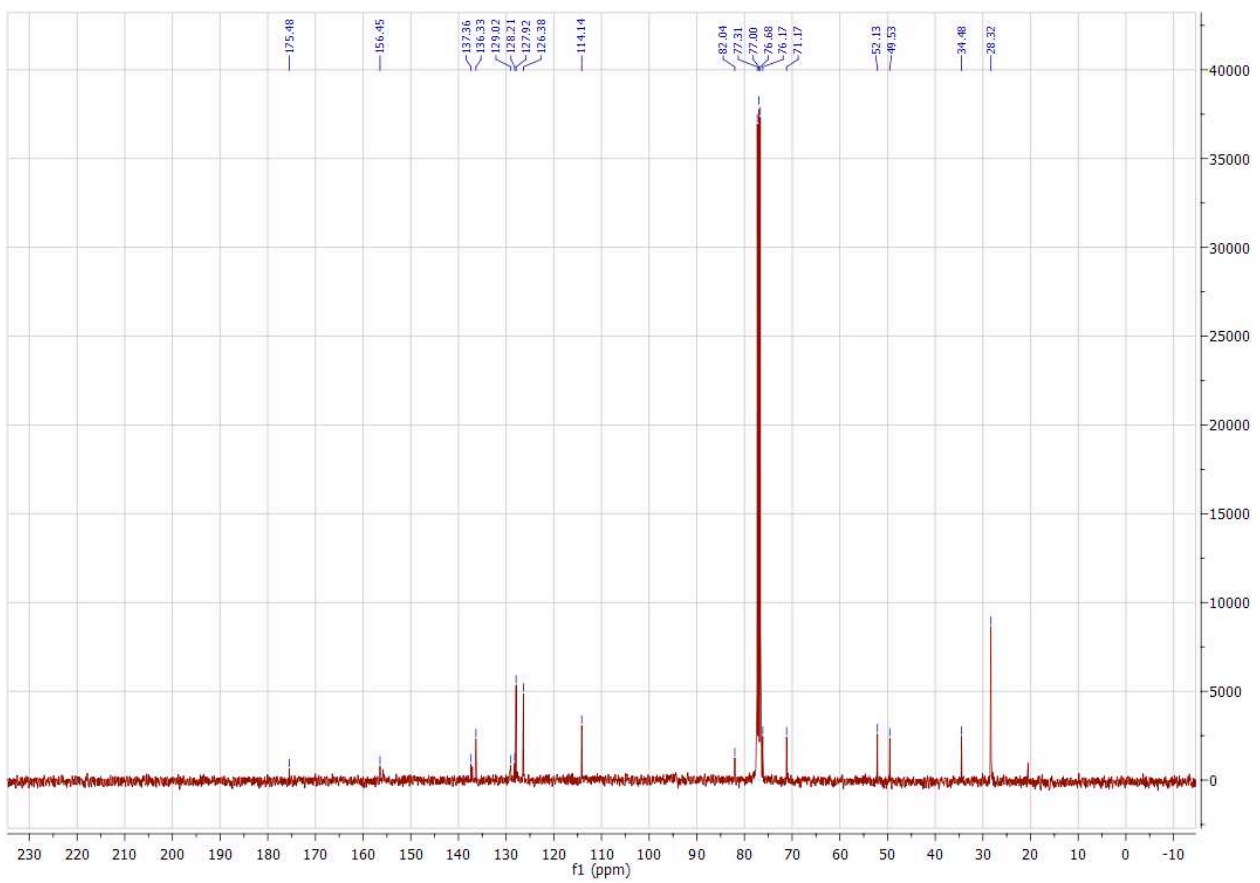
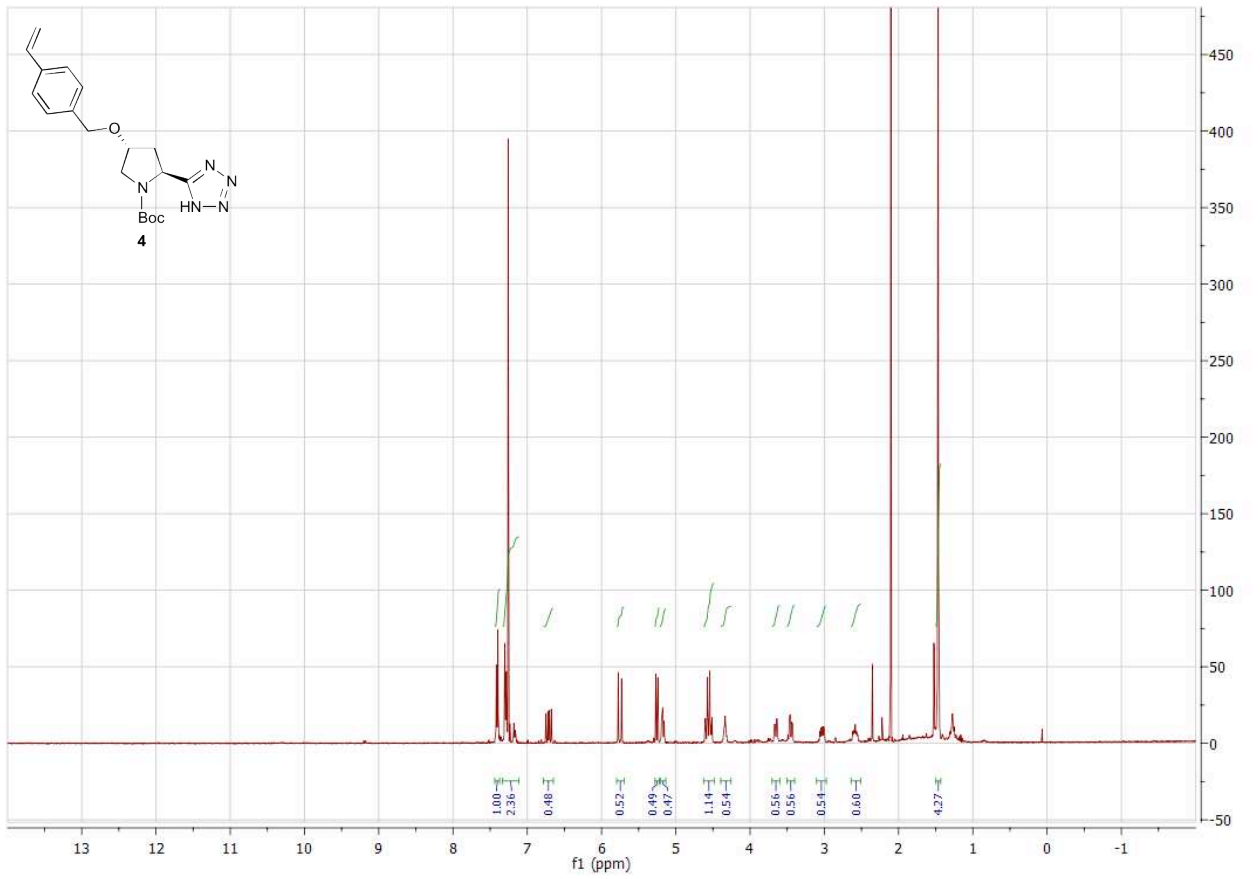
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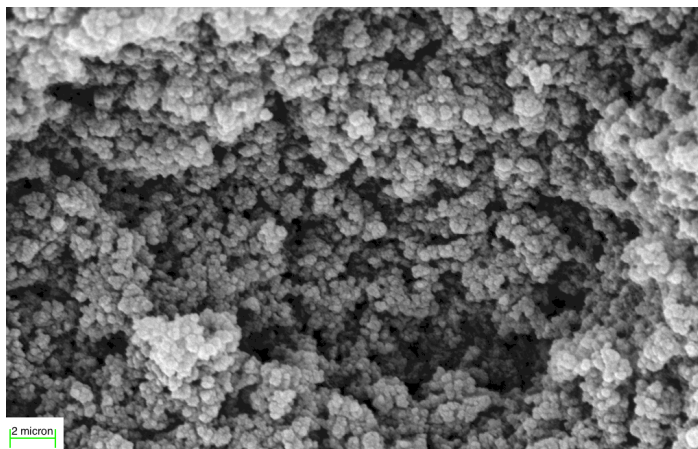
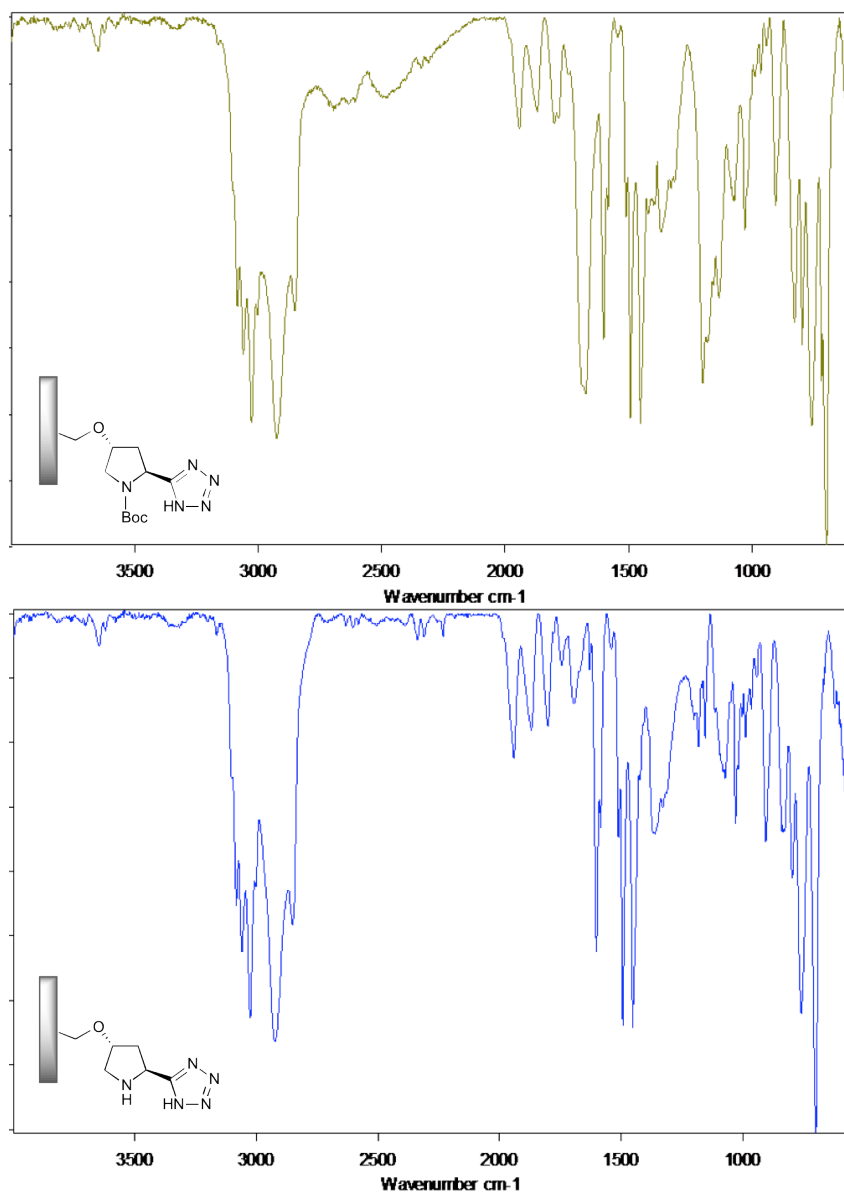
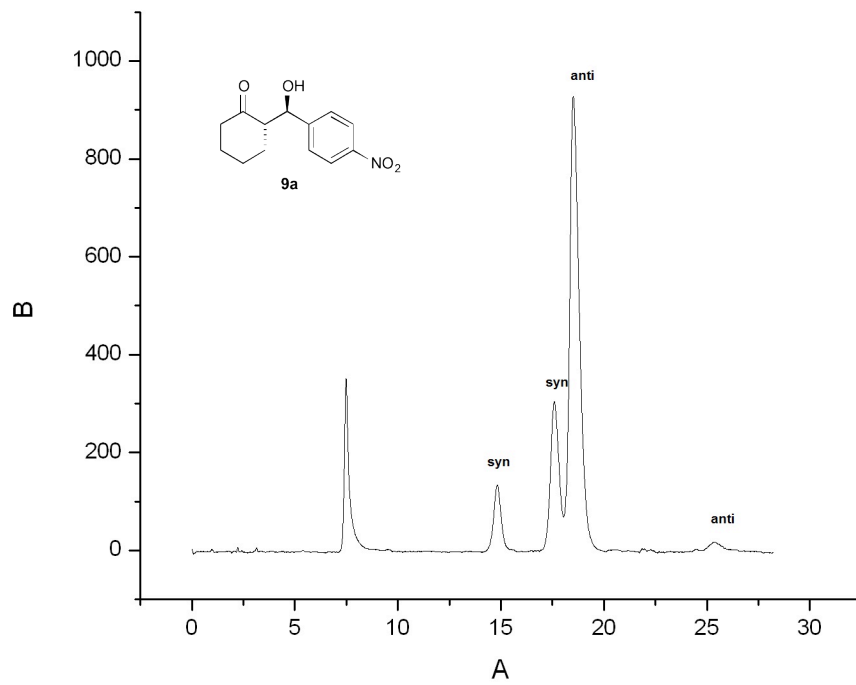
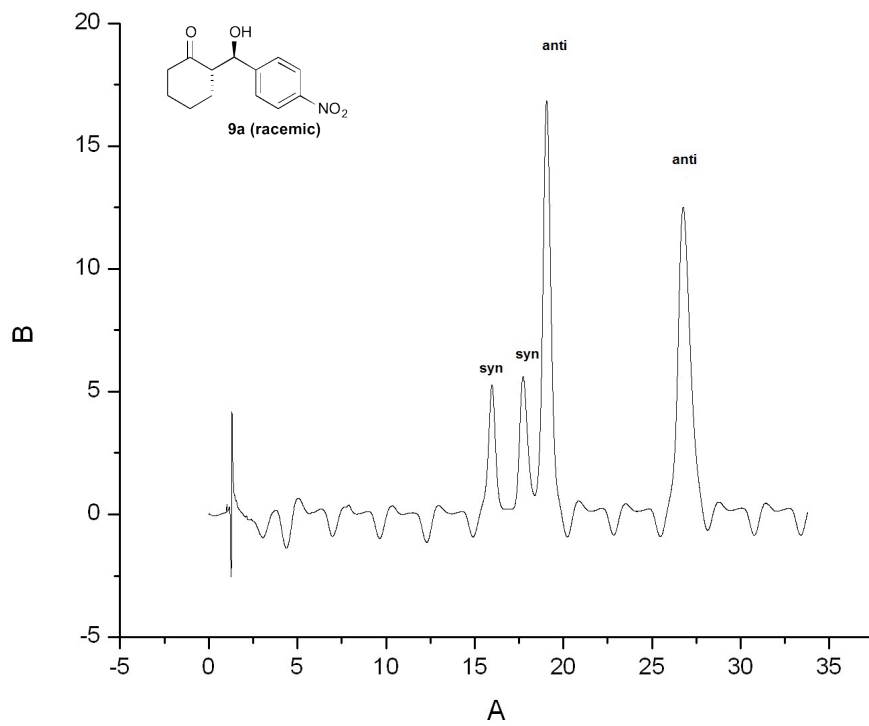
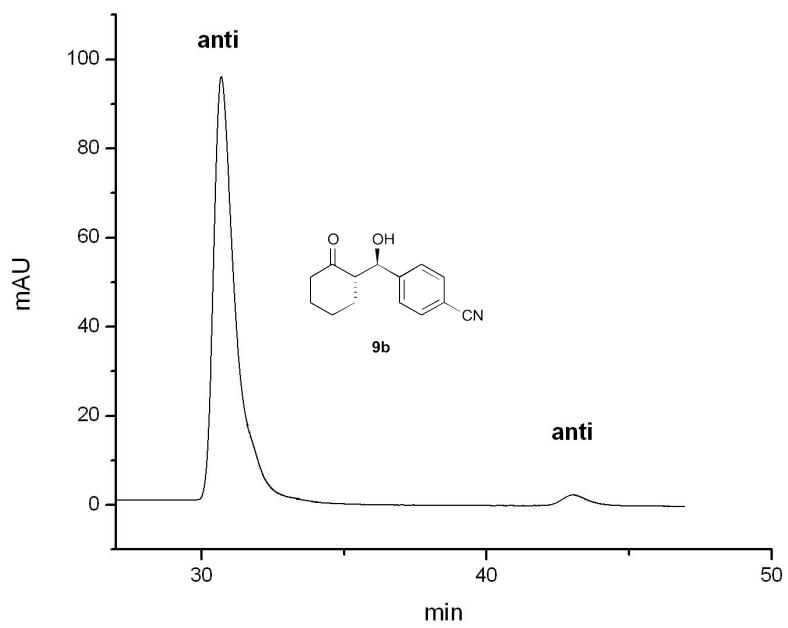
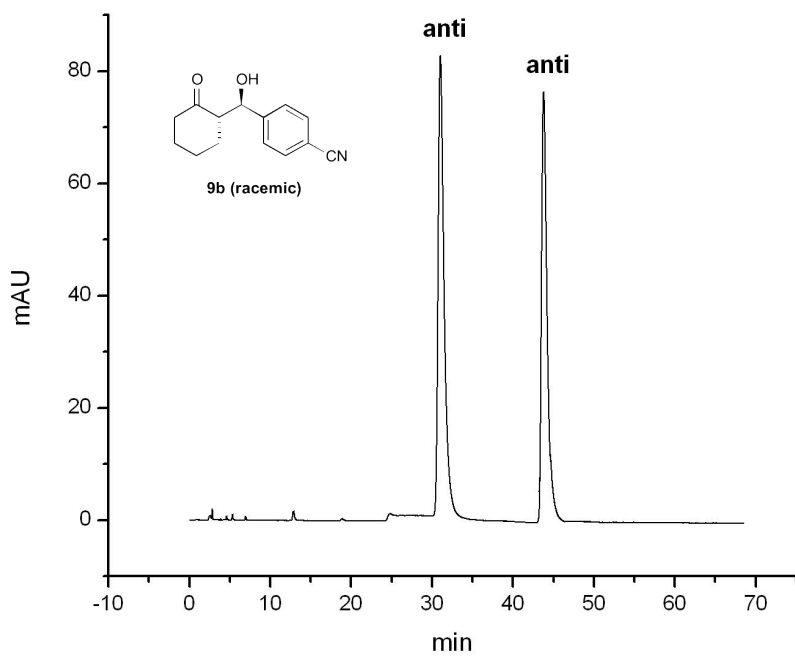
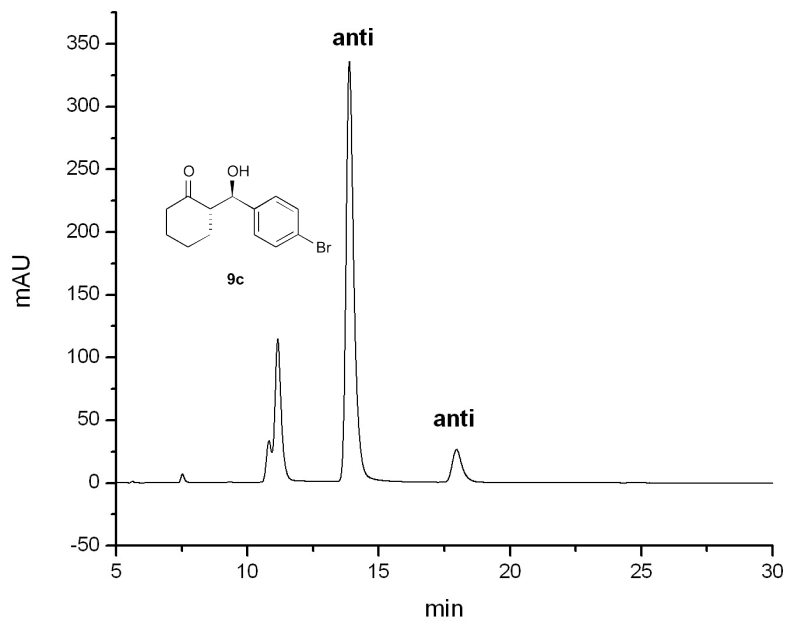
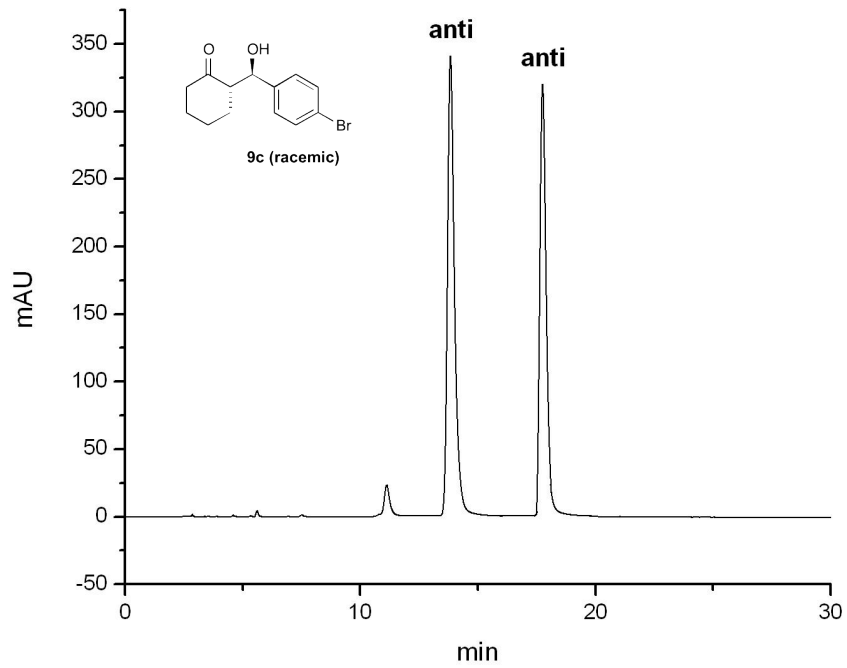


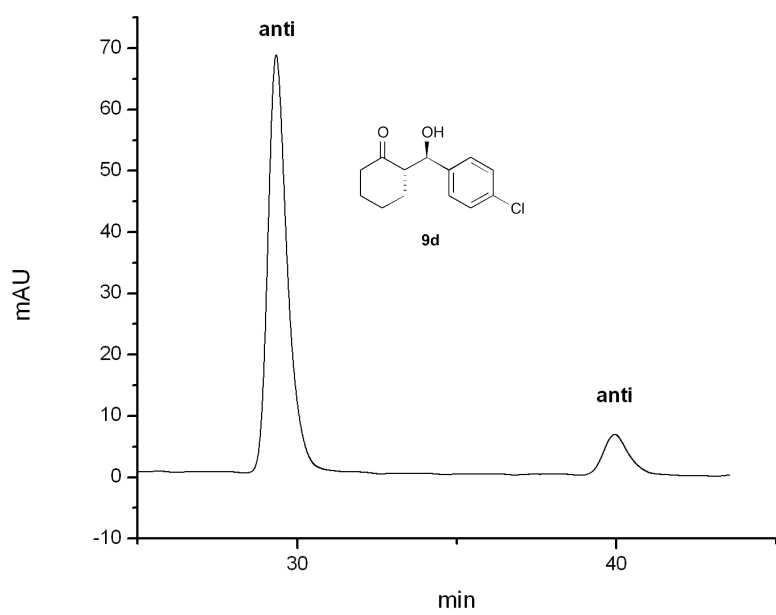
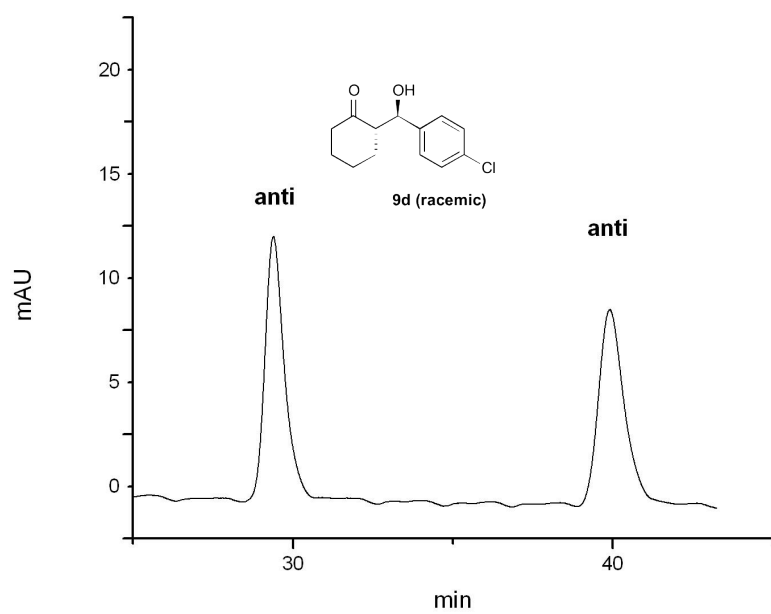
Figure S1. SEM image of MM6 fracture surface.

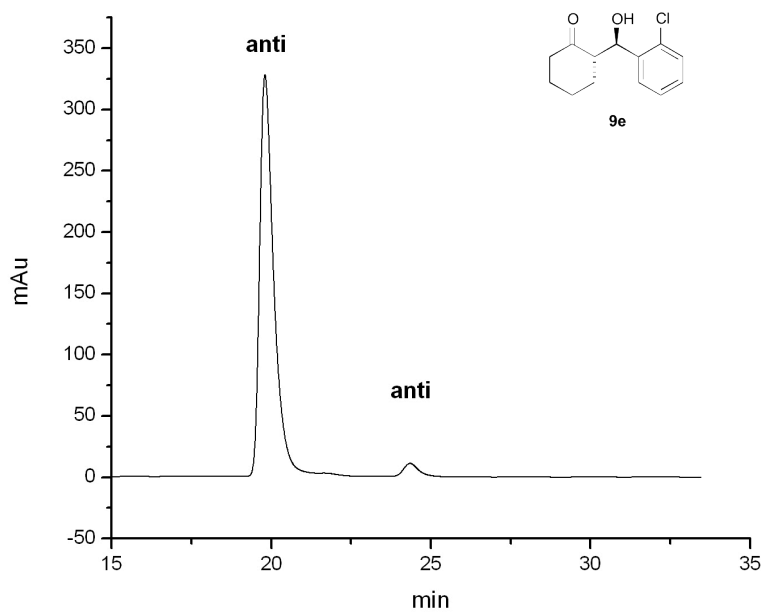
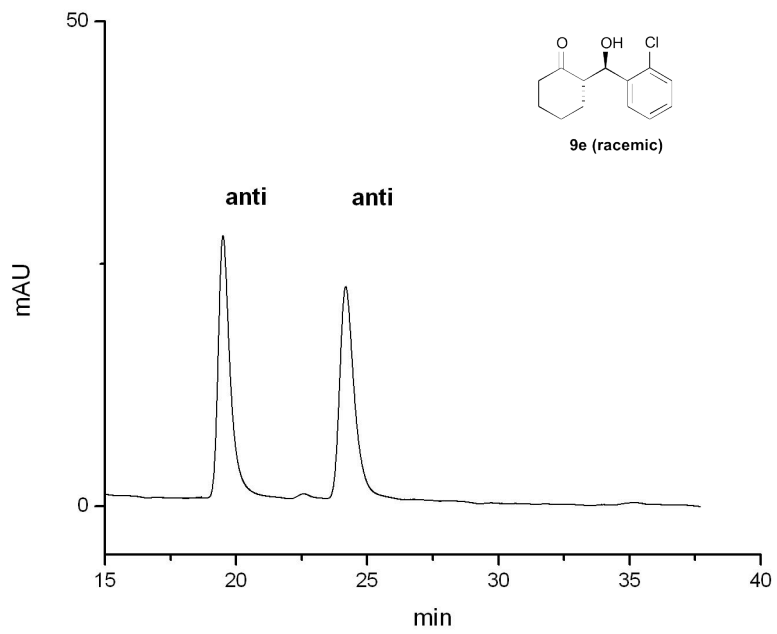


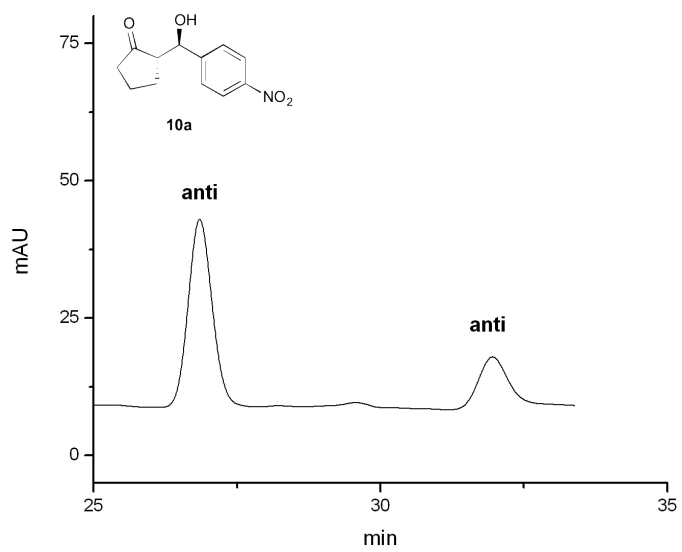
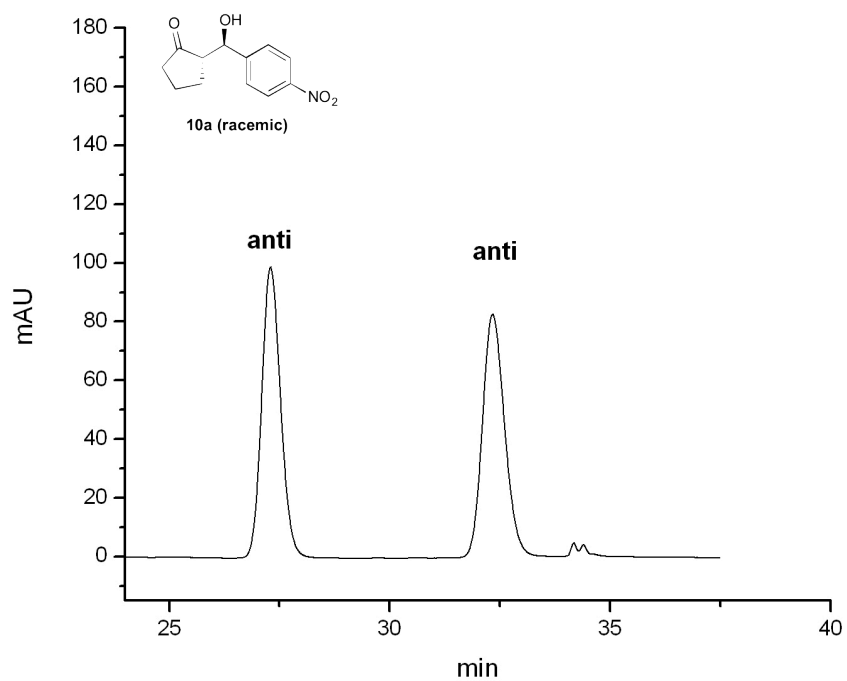


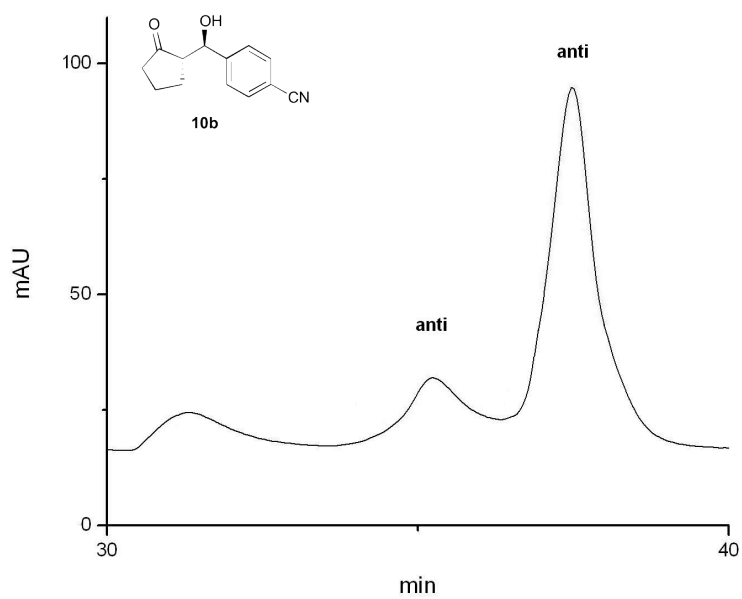
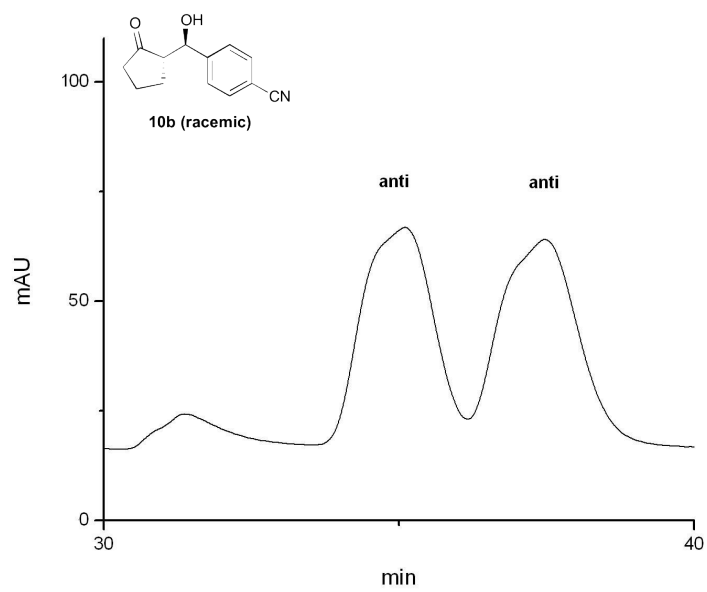


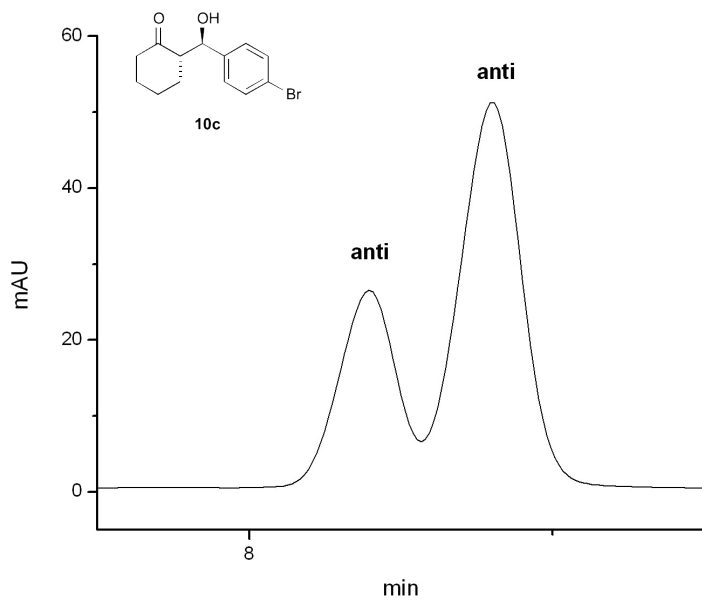
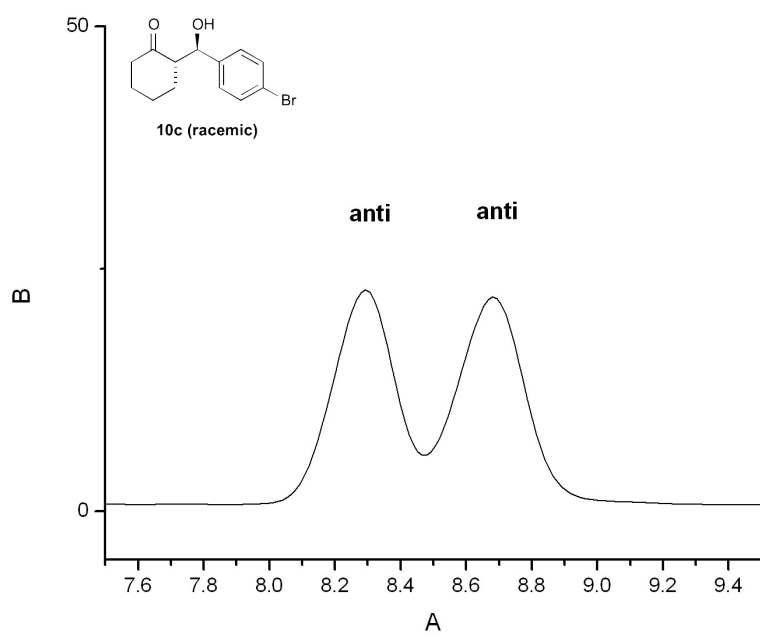




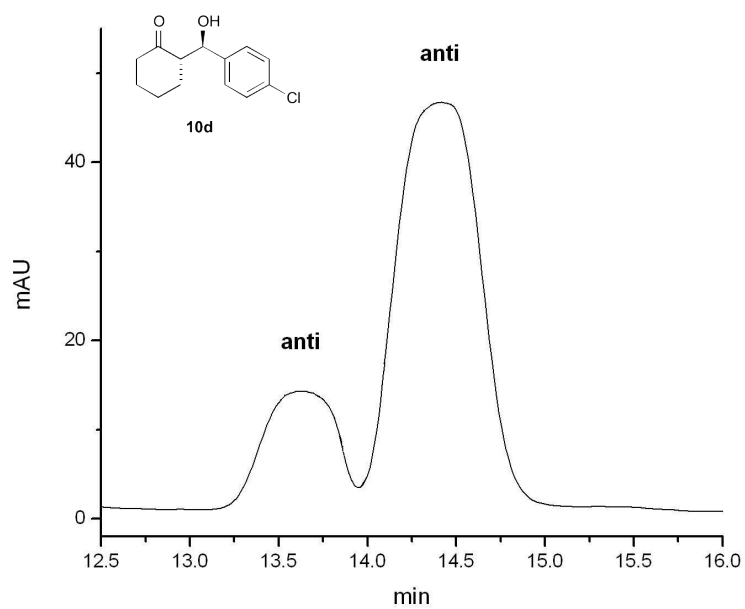
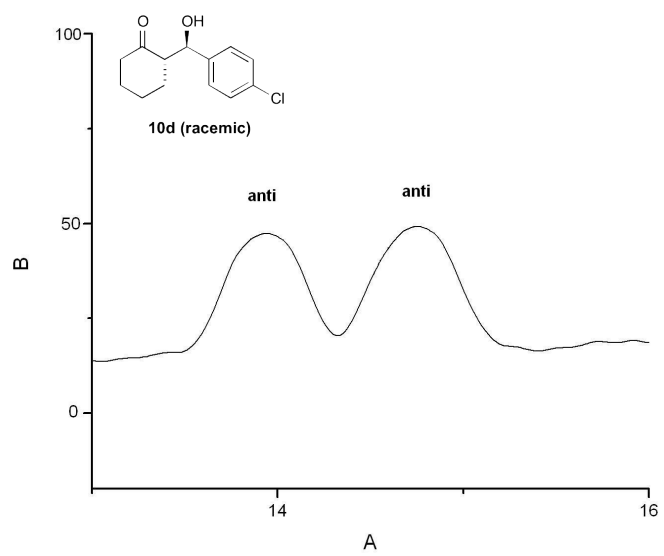


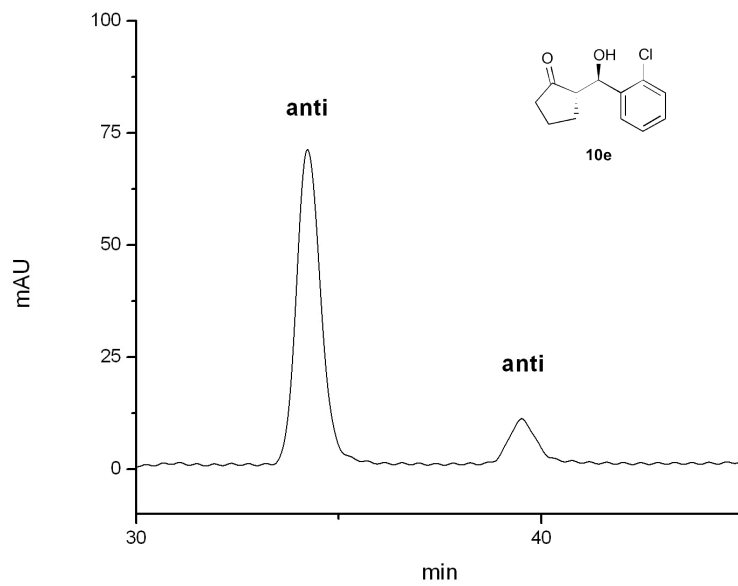
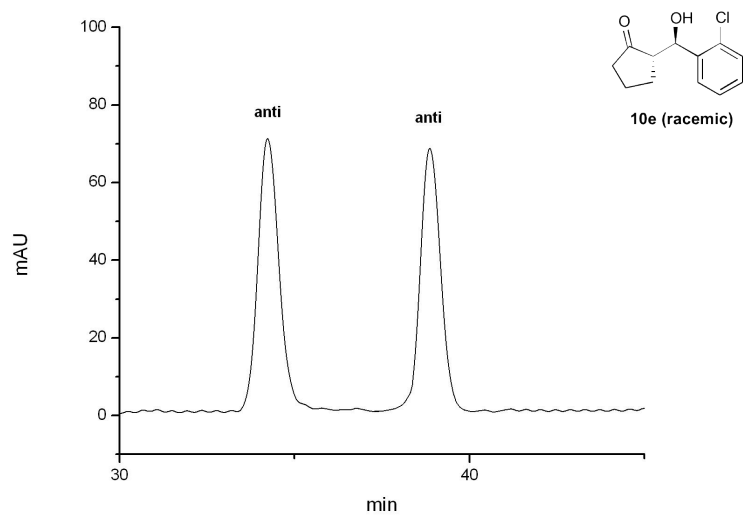


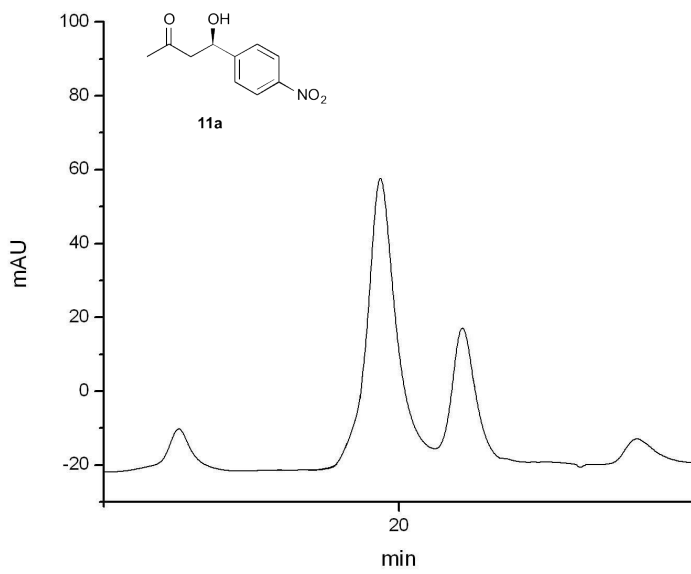
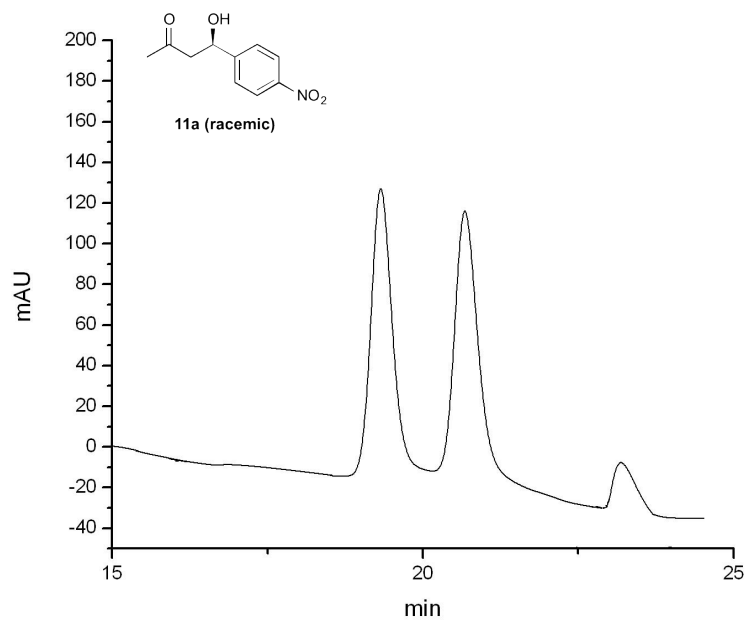


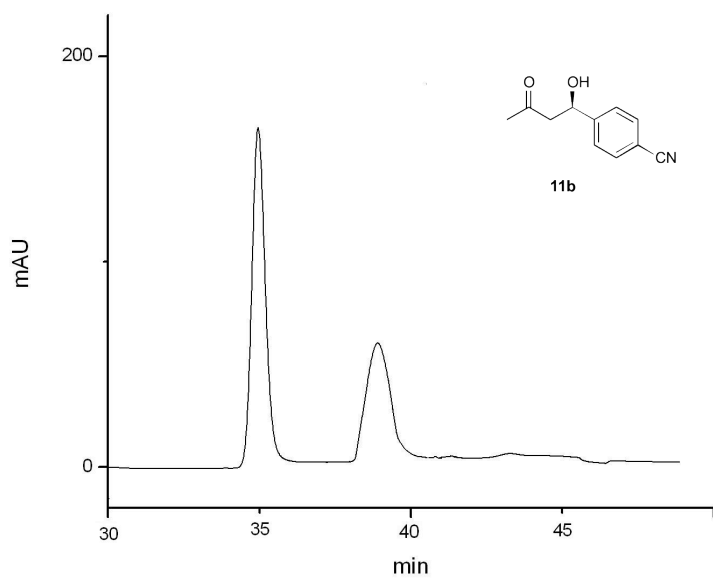
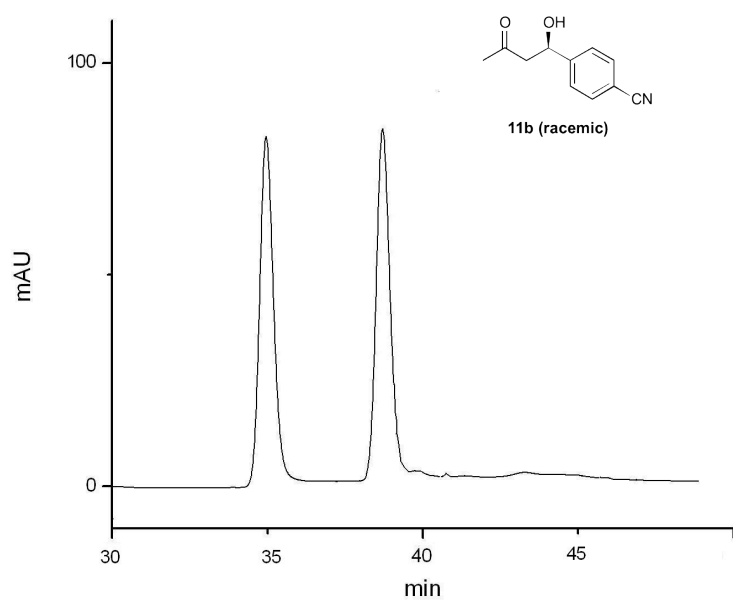


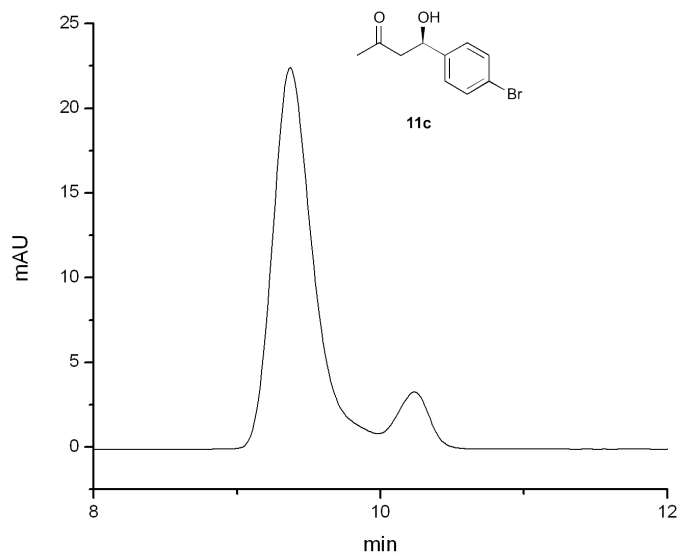
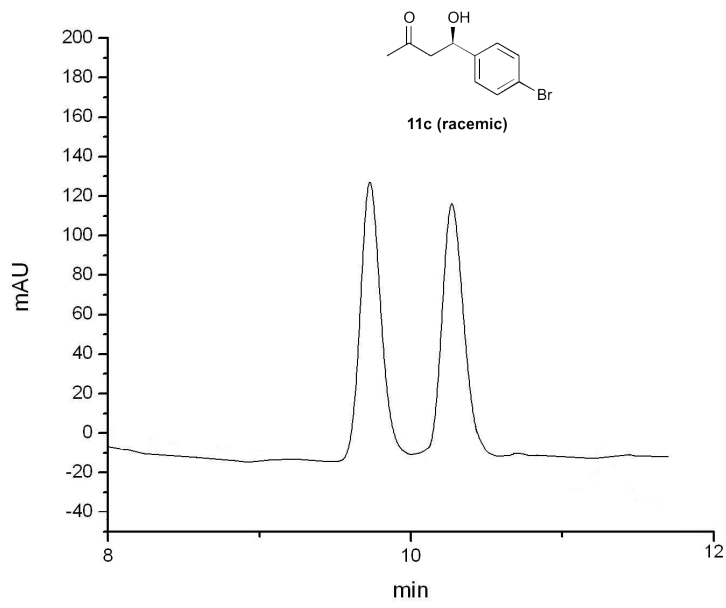


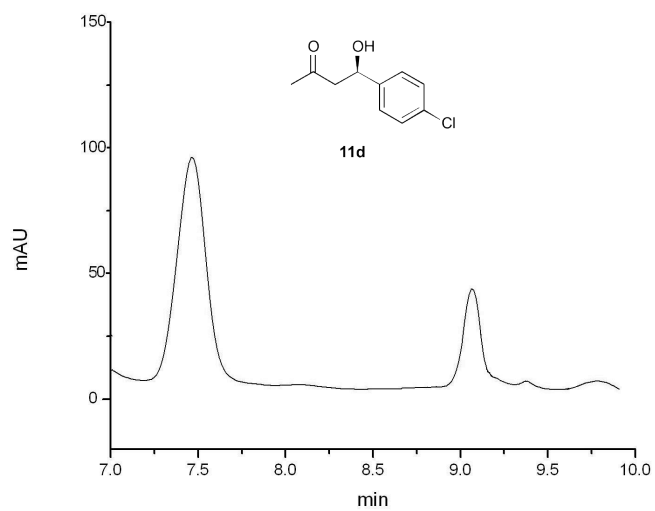
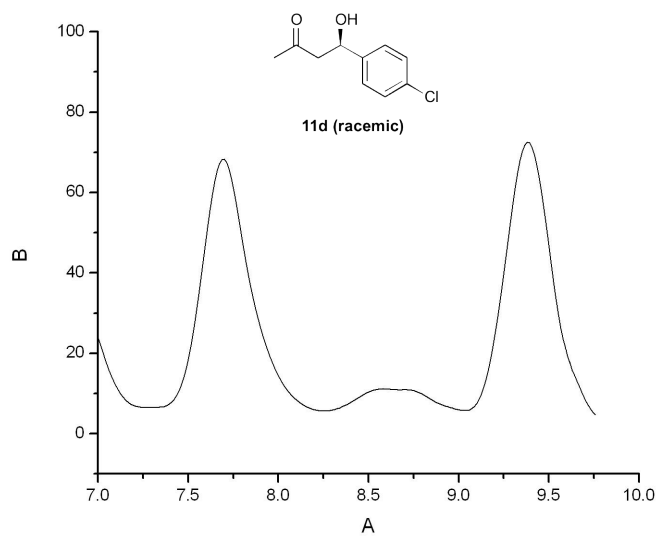


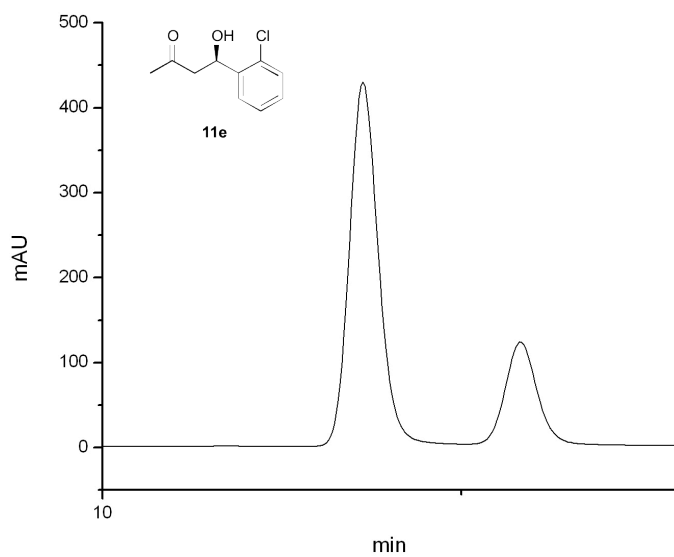
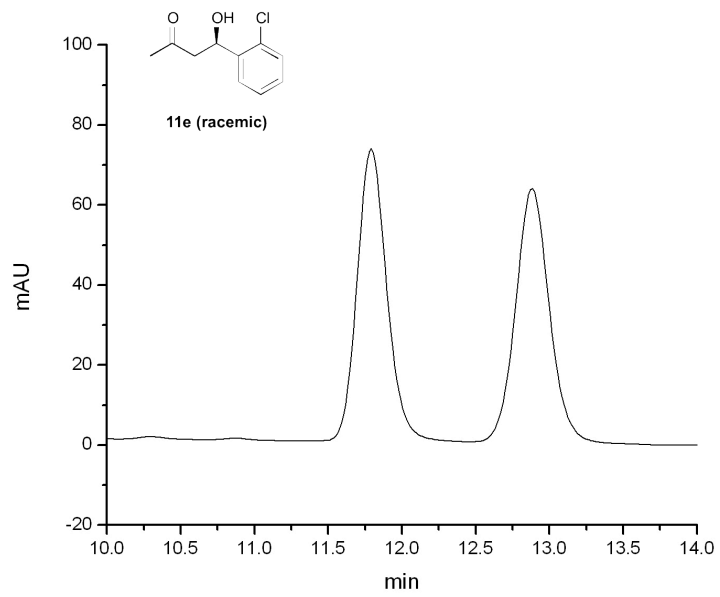












An organocatalytic polystyrene monolithic column produces chiral  $\beta$ -hydroxyketones under benign, continuous-flow conditions with high long-term stability



Referee 1:

We agree with all the points raised by this referee and therefore we have considered *Reaction Chemistry & Engineering* a more suitable journal for our manuscript.

Referee 2:

1. Like all the other contributions on continuous-flow aldol reactions (see Refs. 10-14) we have investigated the classic ketone/aromatic aldehyde coupling for chemoselectivity reasons, thus obtaining a single  $\beta$ -hydroxyketone product. On the other hand, we have reported fifteen substrate combinations in water-ethanol solvent including the challenging acetone/aldehyde coupling. Moreover, the main objectives of the work were more technical in nature, i.e. the fabrication of a monolithic column suitable for continuous-flow experiments and the set-up of a 2D instrument for simultaneous flow reaction and online flow-injection analysis. Therefore we believe that the use of hydroxyacetone and aliphatic aldehydes should be the object of a dedicated study.

2. Note 23 has been added in the text reporting our observation that the FT-IR spectra of the freshly prepared and deactivated catalysts are almost identical and our hypothesis on the loss of activity, which we believe to be related to the accumulation of impurities on the column. In the same note we also indicate that attempts to regenerate the catalyst by washing the monolith column with TFA and Et<sub>3</sub>N solutions are unsuccessful.

3. In our flow experiments the optimal flow rate was selected to achieve the full conversion of the aldehyde that is the limiting reactant. Under these conditions, we could obtain almost quantitative yields of the target  $\beta$ -hydroxyketone products as previously reported. As suggested by this referee, in the revised version of the manuscript we have added the precise values of the yields and the corresponding amounts of isolated products.