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Continuous Flow Enantioselective Three-Component *anti*-Mannich Reactions Catalyzed by a Polymer-Supported Threonine Derivative

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Abstract: A series of primary amino acid-derived polystyrene-supported organocatalysts was tested in *anti*-selective Mannich reactions. The polystyrene-immobilized threonine derivative showed the best performance in three-component (hydroxyacetone, anilines and aldehydes) Mannich reactions to provide *anti*- β -amino- α -hydroxycarbonyl compounds (11 examples; up to 95% ee) and its use could be extended to dihydroxyacetone and protected hydroxyacetones (7 examples; up to 90% ee). The high activity depicted by the catalyst has allowed its implementation in continuous flow. Under this operation mode, the supported threonine catalyst

produces *anti*-Mannich adducts with generally higher diastereo- and enantioselectivity than in batch. A family of five different enantioenriched *anti*-Mannich adducts has been sequentially prepared in flow by passing different combinations of anilines and aromatic aldehydes over the same sample of catalyst. This confirms the suitability of this methodology for the rapid access to small libraries of enantioenriched compounds.

1. INTRODUCTION

The asymmetric Mannich reaction¹ is one of the most versatile methodologies for the preparation of valuable chiral amino carbonyl compounds and their derivatives.² In 2000, List described the utility of L-proline as an excellent organocatalyst³ for three-component intermolecular asymmetric Mannich reactions,⁴ and L-proline became a routine catalyst for this transformation affording *syn*-products with high stereoselectivity.⁵ While *syn*-Mannich products are readily accessible, *anti*-Mannich products are more difficult to synthesize. Recently, different organocatalysts have been found to catalyze Mannich reactions to selectively achieve either *syn*- or *anti*-Mannich products.^{2f,6} When α -hydroxyacetone and *O*-protected derivatives are used as acyclic ketone donors in asymmetric Mannich-type transformations, adducts with up to four adjacent functional carbons featuring a central, stereodefined 1,2-amino alcohol unit are obtained. These synthons are common building blocks for the synthesis of complex α -amino acid derivatives^{5b,5e} as well as important precursors for different types of bioactive compounds with high pharmaceutical value.⁷ The development of a simple and efficient way for the preparation of these compounds in enantiomerically pure form is thus of utmost importance for synthetic organic chemistry.

Natural primary amino acids and their derivatives have recently caught attention as successful catalysts for different asymmetric transformations such as Mannich,^{8,9} aldol,^{8b,8e,8k,10} Michael,¹¹ α -

amination¹² and cyanosilylation reactions.¹³ While proline catalyzes Mannich reactions of hydroxyacetone to form adducts with a *syn*-1,2-amino alcohol arrangement,^{5b,5e} with primary amino acids the corresponding *anti* adducts are formed.^{8b-1} This is due to the fact that primary amino acids mediate Mannich reactions *via* the (*Z*)-enamine intermediate, this configurational preference results from an extra hydrogen bonding interaction between the NH group and the oxygen atom of the hydroxy group of the enamine. Therefore, primary amino acid catalysis is complementary to proline catalysis when hydroxyacetone and their *O*-protected derivatives are used.^{8b,8h}

The high polarity of organocatalysts (e.g., free amino acids) converts the isolation of similarly polar reaction products (e.g., Mannich adducts) into wasteful and tedious processes. A successful strategy to overtake this problem is catalyst immobilization onto solid supports, which allows catalyst separation by simple filtration and the possibility of catalyst recycling.¹⁴ In addition, properly designed, heterogenized catalysts often replicate the properties of their homogeneous analogues, with the advantage of being suitable for continuous flow processes without co-elution of the catalyst.^{5f,6d,15,16} Mannich reactions catalyzed by homogeneous primary amino acid derivatives usually require high catalyst loadings (up to 30%);^{8a-b,8e-f,8i-k,9} thus, immobilization of these species appears to be a very good alternative. In the literature, only two examples of recyclable primary amino acid derivatives are reported to catalyze *anti*-Mannich reactions. One of them involves a soluble catalyst and, therefore, extraction is required before the catalyst can be reused.^{8m} The other example reports the use of a cysteine-derivative anchored onto magnetic nanoparticles, however non-enantioenriched Mannich products were obtained.¹⁷

We have recently reported on the use of polymer-supported prolines and pyrrolidines as highly active and selective heterogenized catalysts for Mannich reactions under batch and continuous

flow conditions leading respectively to *syn*-products and *anti*-products, with excellent diastereo- and enantioselectivities.^{5f,6d} However, to the best of our knowledge there are no examples of three-component enantioselective *anti*-Mannich reactions catalyzed by supported organocatalysts. Herein, we report the use of a polymer-supported threonine derivative as a highly active and stereoselective catalyst for three-component *anti*-Mannich reactions, and its use for the implementation of a single pass, continuous flow process for the preparation of a small library of *anti*- β -amino- α -hydroxycarbonyl compounds in high enantiomeric purity.

2. RESULTS AND DISCUSSION

We have recently reported the preparation of a series of polymer-supported primary amino acid derivatives **1-6** (Figure 1) and their use as heterogeneous catalysts for aldol reactions.^{10j} Among them, catalyst **6** showed the best catalytic performance regarding activity and stereoselectivity, yielding aldol products of high enantiopurity.

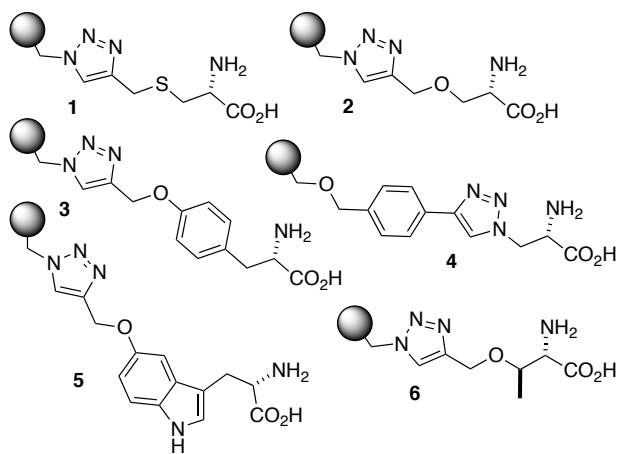
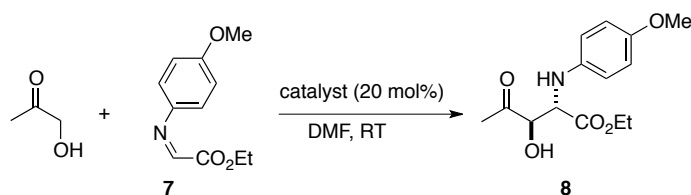


Figure 1. Primary amino acid derived catalysts.

With these catalysts in hand, we proceeded to evaluate them in Mannich reactions, using hydroxyacetone and preformed *N*-(*p*-methoxyphenyl) (*N*-PMP) ethyl glyoxylate imine **7** as the

benchmark process (Table 1). DMF was used as the solvent for this transformation due to both its good swelling ability for polymer-supported organocatalysts and previous experience in the laboratory.^{5f,6d}

Table 1. Evaluation of PS-supported primary amino acids as catalysts for the *anti*-selective Mannich reaction.^a



entry	catalyst	time (h)	conv. ^b (%)	<i>syn:anti</i> ^b	ee ^c (%)
1	1	17	>99	58:42	43
2	2	12	>99	50:50	69
3	3	6	>99	55:45	58
4	4	3	>99	40:60	36
5	5	6	>99	50:50	78
6	6	6	>99	35:65	85
7	6^d	8	>99	40:60	73
8	6^e	8	>99	45:55	80

^aReactions were performed with catalyst **1-6** (20 mol%), preformed imine **7** (0.125 mmol) and hydroxyacetone (6 equiv.) in DMF (0.25 mL). ^bBy ¹H NMR of the crude mixture. ^c*anti*-Isomer; by chiral HPLC after purification. ^d10 mol% of **6** was used. ^e15 mol% of **6** was used.

Polystyrene-supported cysteine and serine derivatives **1** and **2** catalyzed the formation of compound **8** but showed only low activity (entries 1 and 2). Moreover, in the case of cysteine derivative **1**, the *syn*-Mannich product was obtained as the major diastereomer.¹⁸ Catalyst **4** was

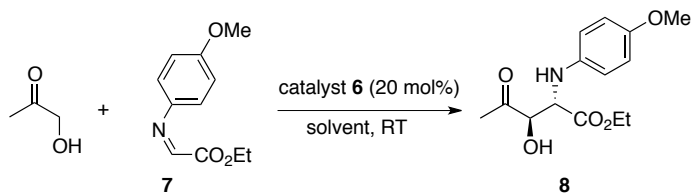
synthesized as a promising potential catalyst due to its close structural similarity with immobilized *trans*-4-azidoproline.^{5f} Although this species did not show catalytic activity for aldol reactions,^{10j} it mediated the formation of *anti*-Mannich product **8** in a remarkable short reaction time (3 h), albeit with disappointingly low enantioselectivity (entry 4). In turn, catalyst **5** derived from 5-hydroxytryptophan afforded product **8** with high levels of enantioselectivity but in poor diastereoselectivity (entry 5).

Threonine derivatives have been reported to display very good catalytic activity for enantioselective *anti*-Mannich reactions.^{8b-f,8i-k} Very gratifyingly, the supported threonine **6** also displayed this behavior and showed the best catalytic performance (entry 6) in terms of both diastereo- and enantioselectivity.

Once **6** was selected as the optimal catalyst, the effect of the solvent nature on the performance of the reaction was studied (Table 2). With DMF, no difference was observed regarding either catalytic activity or selectivity when reagent grade or anhydrous solvent was used (entries 1 and 2). In both cases, reaction rates were low, although good stereoselectivities were achieved. Using THF stereoselectivity was not improved, but a shorter reaction time was required (entry 3). Despite the fact that some examples of *anti*-selective Mannich reactions catalyzed by primary amino acid derivatives using NMP (*N*-methyl-2-pyrrolidone) have been described,^{8b,8f,8i-k} in the presence of catalyst **6** a slow reaction took place and the product was obtained with low enantioselectivity (entry 4). Conversely, the reaction showed to be very fast when CH₂Cl₂, toluene or solvent free conditions were tested; unfortunately, only moderate to very poor enantioselectivities were achieved in these cases (entries 5, 6 and 7). On the other hand, the presence of water as a co-solvent exclusively led to the decomposition of imine **7** (entry 8).^{5f} In the light of these results, we tested different mixtures of DMF (better results regarding

stereoselectivity) and CH₂Cl₂ (better results regarding reaction rate and swelling ability for Merrifield-derived resins) (entries 9, 10 and 11). Gratifyingly, a 1:1 mixture of DMF and CH₂Cl₂ led to a significantly improved yield as well as to excellent enantioselectivity (Table 2, entry 10). As a consequence of the hydrolytic instability of imine **7**, optimal reaction conditions involved performing the reaction in the glovebox with anhydrous solvents (entry 12) and in the presence of molecular sieves (entry 13). In this way, the Mannich adduct **8** could be obtained in very short reaction time (1 h) and with good diastereoselectivity (*syn:anti* = 21:79) and excellent enantioselectivity (96% ee).

Table 2. Solvent screening for the Mannich reaction between hydroxyacetone and preformed imine **7** catalyzed by resin **6**.^a

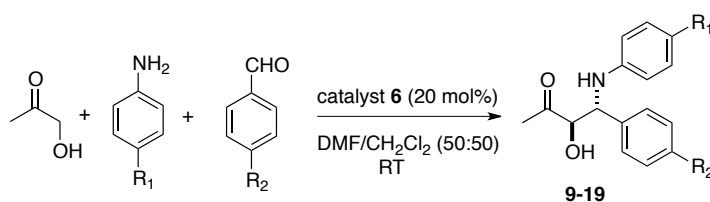


entry	solvent	time (h)	yield ^b (%)	<i>syn:anti</i> ^c	ee ^d (%)
1	DMF ^e	6	35	35:65	85
2	anh. DMF	5	35	37:63	84
3	anh. THF	3	37	50:50	74
4	NMP	6	16	59:41	33
5	anh. CH ₂ Cl ₂	1,5	53	64:36	66
6	Neat	0,5	46	65:35	0
7	anh. Toluene	1	51	63:37	60
8	DMF/H ₂ O (80:20)	7	-	-	-
9	DMF/CH ₂ Cl ₂ (80:20) ^e	3	42	36:64	85
10	DMF/CH ₂ Cl ₂ (50:50) ^e	2	52	26:74	93
11	DMF/CH ₂ Cl ₂ (20:80) ^e	2	45	41:59	88
12 ^f	anh. DMF/ anh. CH ₂ Cl ₂ (50:50)	1,5	56	26:74	94
13 ^{f,g}	anh. DMF/ anh. CH ₂ Cl ₂ (50:50)	1	58	21:79	96

^aUnless otherwise stated, the reactions were performed with catalyst **6** (20 mol%), preformed imine **7** (0.125 mmol) and hydroxyacetone (6 equiv.) in 0.25 mL solvent. ^bIsolated product. ^cBy ¹H NMR of the crude mixture. ^d*anti*-Isomer; by chiral HPLC after purification. ^eSynthesis grade solvents were used. ^fReaction performed in the glovebox. ^g4Å molecular sieves were used.

Once the reaction conditions were optimized, the next step was to explore the scope of the *anti*-Mannich reactions of hydroxyacetone with different amines and aldehydes (Table 3). To avoid possible problems arising from hydrolytic instability of the intermediate imines, the possibility of performing the reactions as "one pot", three component processes was explored. Interestingly, the reactions took place under these conditions without the need for special precautions.

Table 3. Scope of the reaction of hydroxyacetone with different amines and aldehydes catalyzed by resin **6**.^a

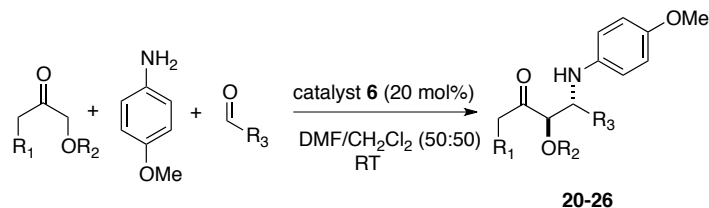


entry	R ₁	R ₂	product	time (h)	yield ^b (%)	<i>syn:anti</i> ^c	ee ^d (%)
1	H	H	9	6	96	8:92	93
2	H	<i>p</i> -NO ₂	10	5	88	9:91	92
3	<i>p</i> -CH ₃ O	H	11	7	90	28:72	82
4	<i>p</i> -CH ₃ O	<i>p</i> -NO ₂	12	4	89	13:87	85
5	<i>p</i> -CH ₃ O	<i>p</i> -CH ₃ O	13	8	62	52:48	49
6	<i>p</i> -CH ₃ O	<i>p</i> -Br	14	4	84	22:78	81
7	<i>p</i> -CH ₃ O	<i>p</i> -CN	15	5	86	19:81	83
8	<i>p</i> -CH ₃ O	<i>p</i> -Cl	16	8	72	37:63	67
9	<i>p</i> -CH ₃ O	<i>o</i> -Cl	17	8	70	15:85	83
10	<i>p</i> -CH ₃	<i>p</i> -NO ₂	18	5	87	11:89	87
11	<i>p</i> -Cl	<i>p</i> -NO ₂	19	3	88	12:88	95

^aReactions were performed with catalyst **6** (20 mol%), amine (0.2 mmol), aldehyde (1.1 equiv.) and hydroxyacetone (6 equiv.) in 1:1 DMF/CH₂Cl₂ (0.4 mL). ^bIsolated product. ^cBy ¹H NMR of the crude mixture. ^d*anti*-Isomer, by chiral HPLC after purification.

The results show that three-component *anti*-Mannich reactions mediated by **6** can be completed in 3-8 hours using unsubstituted aniline (entries 1-2) and *p*-substituted (methoxy, methyl, chloro) derivatives (entries 3-11), yielding *anti*-adducts **9-19** in moderate to good diastereo- (up to 8:92) and enantioselectivities (up to 95% ee), with yields up to 96%. When the reaction was carried out with an aldehyde bearing an electron-donating substituent in *para* position (entry 5) poor enantioselectivity was observed as previously reported in the literature.^{8b} It is worth noting that the present procedure affords *anti*-Mannich products in good enantioselectivities when performing the reactions at room temperature, while most of the reported *anti*-Mannich reactions with hydroxyacetone catalyzed by primary amino acid derivatives require low temperatures for the achievement of high enantioselectivities.^{8b,8i-k}

The scope of the asymmetric, *anti*-selective Mannich reaction mediated by **6** could be further expanded (Table 4) with the use of additional ketones, including 1,3-dihydroxyacetone (entries 1 and 2), protected hydroxyacetones (entries 3-7), aromatic and aliphatic aldehydes, and *p*-anisidine.

Table 4. Scope of the reaction using different ketone donors.^a

entry	R ₁	R ₂	R ₃	product	time (h)	yield ^b (%)	syn:anti ^c	ee ^d (%)
1	^e OH	H	<i>p</i> -BrC ₆ H ₄	20	8	74	34:66	67
2	^e OH	H	<i>p</i> -CNC ₆ H ₄	21	8	76	29:71	82
3	H	Bn	<i>p</i> -NO ₂ C ₆ H ₄	22	38	94	23:77	80
4	H	Bn	<i>p</i> -CNC ₆ H ₄	23	36	80	25:75	90
5	H	Bn	2,4-Cl ₂ C ₆ H ₃	24	38	84	12:88	77
6	H	Bn	<i>i</i> -Bu	25	22	52	47:53	82
7	H	TBS	<i>p</i> -NO ₂ C ₆ H ₄	26	24	77	67:33	51 ^f

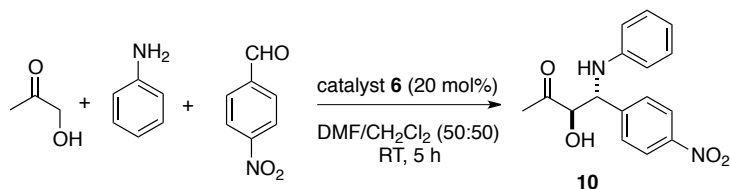
^aReactions were performed with **6** (20 mol%), *p*-anisidine (0.2 mmol), aldehyde (1.1 equiv.) and ketone (6 equiv.) in a 1:1 mixture of DMF/CH₂Cl₂ (0.4 mL). ^bIsolated product. ^cBy ¹H NMR of the crude mixture. ^d*anti*-Isomer; by chiral HPLC after purification. ^eDihydroxyacetone dimer (3 equiv.) and acetic acid (10 mol%) were used. ^f*anti*-Isomer; by chiral HPLC of the desilylated product.

Notably, resin **6** catalyzed the three-component *anti*-Mannich reactions of dihydroxyacetone¹⁹ affording *anti*-dihydroxy-β-aminoketone **20-21** (entries 1 and 2). These densely functionalized compounds are of high synthetic importance for the preparation of aminosugars.²⁰ Despite only moderate stereoselectivities were recorded (and to 82% *ee*), these results are among the best previously reported for the same transformation.^{8b} In the case of *O*-benzylhydroxyacetone, we studied this transformation with both electron-deficient aromatic aldehydes (entries 3, 4 and 5) and aliphatic aldehydes (entry 6), leading to the formation of the orthogonally protected β-

amino- α -hydroxyketones **22-25**. In these cases, the reactions were slower but took place with high enantioselectivity. Notably, when the reaction was performed with TBS-protected α -hydroxyacetone, the diastereoselectivity of the process could be reversed, the *syn*-Mannich adduct being obtained as the major product, and poor enantiomeric excess of the *anti*-isomer was recorded (Table 4, entry 7).^{8d}

To exploit one of the advantages offered by catalyst immobilization, we explored the recyclability of PS-supported threonine **6** in the Mannich reaction between α -hydroxyacetone, aniline and *p*-nitrobenzaldehyde to afford *anti*- β -amino- α -hydroxyketone **10** (Table 5). After each run, the catalyst was recovered by simple filtration and directly used in the next cycle. Working under the specified reaction conditions, a decrease in the activity and selectivity of the catalyst was observed after the third cycle in a highly reproducible manner. Starting from the preformed imine (see Supporting Information) or performing the recycling in the glovebox entailed no improvement of these results. Attempts to reactivate the resin by washing with AcOH also proved unsuccessful (entry 5). To understand the origin of the deactivation process, the initial and the deactivated resins were studied by elemental analysis and by IR spectroscopy (see Supporting Information). No change in the functionalization level (%N) was observed, suggesting that no cleavage of the monomer has taken place. On the other hand, the IR spectrum shows an almost complete disappearance of the carboxylate bands and the appearance of a weak absorption at 1715 cm⁻¹, suggesting that the excess of hydroxyacetone required for the reaction to proceed, slowly reacts with the supported amino acid leading to some catalytically less active and less stereoselective derivative. In any case, the recycling process allows achieving an accumulated TON >20, which compares very favorably with the values (3-5) achieved with the reference homogeneous catalysts.^{8b}

Table 5. Recycling experiments for the reaction between the α -hydroxyacetone, aniline and *p*-nitrobenzaldehyde.^a



run	conv. ^b (%)	<i>syn:anti</i> ^b	ee ^c (%)
1	>99	9:91	92
2	>99	10:90	92
3	>99	10:90	89
4	82	17:83	55
5 ^d	25	28:72	67

^aReactions were performed with catalyst **6** (20 mol%), aniline (0.2 mmol), *p*-nitrobenzaldehyde (1.1 equiv.) and hydroxyacetone (6 equiv.) in a 1:1 mixture of DMF/CH₂Cl₂ (0.4 mL). ^bBy ¹H NMR of the crude mixture. ^c*anti*-Isomer; by chiral HPLC after purification. ^dAfter washing with acetic acid (10%) in a 1:1 mixture of DMF/CH₂Cl₂.

In view of the results obtained with immobilized catalyst **6** under batch conditions, we envisaged the possibility of performing the asymmetric, three component Mannich reaction in continuous flow. The experimental set-up for the flow synthesis of compound **10** is represented schematically in Figure 2 (see Supporting Information for more details). It consisted of a vertically mounted and fritted, volume adjustable low-pressure glass chromatography column loaded with the polymer-supported catalyst **6**. The reactor inlet was connected to a T-shaped adaptor, which allows switching between two channels, connected to two syringe pumps. One channel was connected to a solution with the three reactants (no reaction occurs in absence of

catalyst) in a 1:1 mixture of DMF/CH₂Cl₂, and the other channel was connected to a flask containing the same solvent mixture, to rinse the system. Continuous inline IR analysis was used to determine the optimal flow rate for complete conversion.²¹

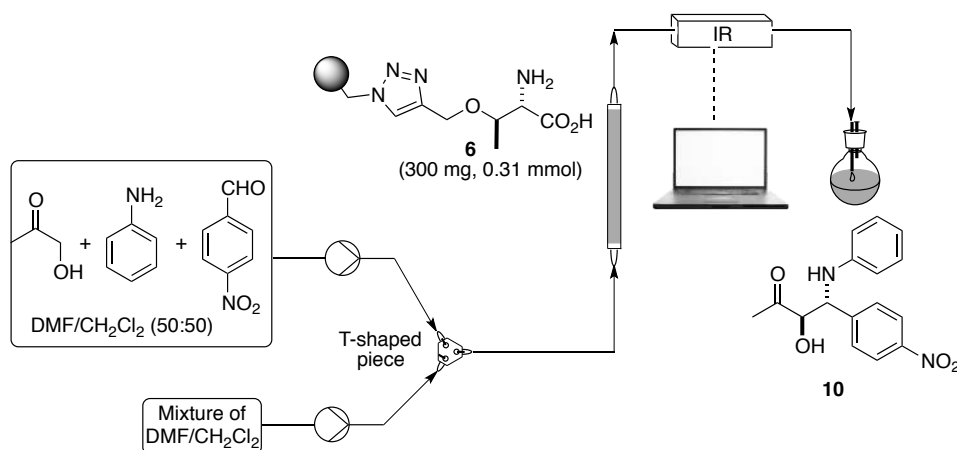
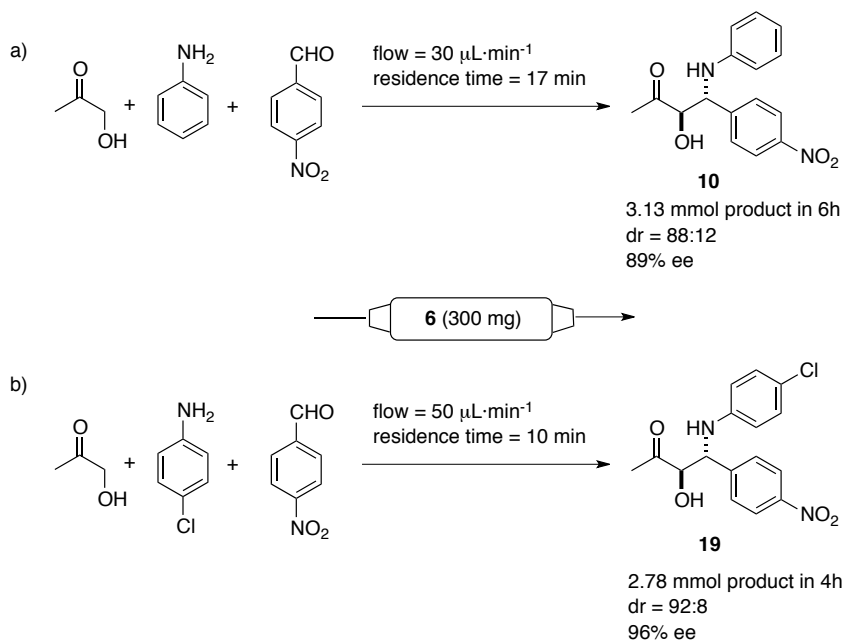


Figure 2. Experimental set-up for the continuous flow experiments.

Thus, a solution of aniline, hydroxyacetone and *p*-nitrobenzaldehyde was pumped through a column loaded with 300 mg of catalyst **6** ($f = 1.02 \text{ mmol}\cdot\text{g}^{-1}$) with a flow rate of $30 \mu\text{L}\cdot\text{min}^{-1}$ (corresponding to 17 min residence time) (Scheme 1a).²² The system was operated for 6h producing 3.13 mmol of **10**, with diastereo- and enantioselectivity very close to those recorded under batch conditions (Table 3, entry 2).²³ Likewise, after pumping for 4 hours a solution of *p*-chloroaniline, hydroxyacetone and *p*-nitrobenzaldehyde,²⁴ 2.78 mmol of highly enantioenriched *anti*-Mannich adduct **19** were obtained (Scheme 1b).²⁵ In this case, slightly better diastereo- and enantioselectivity was recorded with respect to the corresponding batch process (Table 3, entry

11). Remarkably, both continuous flow processes allow for a two-fold reduction of the catalyst amount compared to the batch processes mediated by resin **6**.²⁶

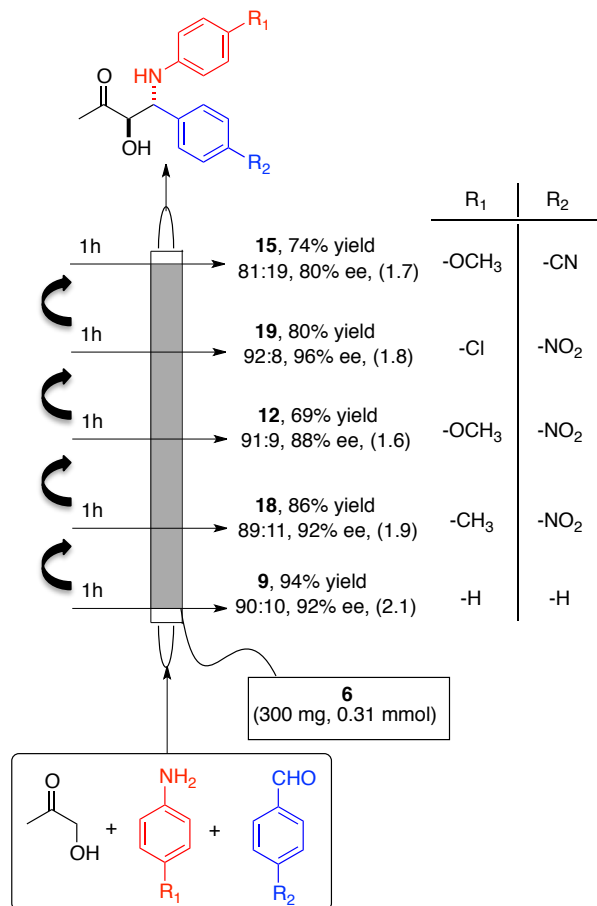
Scheme 1. Continuous production of *anti*-Mannich products **10** and **19**.



The successful use of resin **6** in continuous flow conditions, together with the importance of the resulting enantioenriched Mannich adducts as advanced synthons for the preparation of biologically active compounds,⁷ prompted us to explore the possibility of preparing a small library of enantioenriched *anti*-Mannich adducts in a sequential manner. This is a rather unique application of flow processes with immobilized catalytic systems, and allows the preparation of focused libraries of drug candidates or drug intermediates with important advantages. Thus, the products are obtained free of contamination by the catalyst, and the scale of production can be simply controlled through the operation time.^{6c,16c,f-g} Not less importantly, these sequential processes are easily amenable to automation. Thus, by operating the same continuous flow setup

described above, a single sample of catalytic resin **6** could be used to prepare five different *anti*-Mannich compounds in a sequential process. In this event, the flow preparation of every adduct was run for 1 h (flow rate of 30 $\mu\text{L}\cdot\text{min}^{-1}$) and the operation only involved washing the resin by circulation of CH_2Cl_2 for 30 min between two different substrates. The results obtained in the preparation of this sequential library are summarized in Scheme 2.

The five target *anti*-Mannich adducts **9**, **12**, **15**, **18** and **19** were obtained in good yields and in high diastereo- and enantiomeric purities. Remarkably **9**, **12**, and **19** were obtained in this manner with slightly better stereoselectivities than under batch conditions (see Table 3, entries 1, 4 and 11). High productivities were recorded with all tested substrates, ranging from 1.6–2.1 $\text{mmol}_{\text{product}}\cdot\text{mmol}_{\text{resin}}^{-1}\cdot\text{h}^{-1}$.



Scheme 2. Continuous flow production of a library of enantioenriched *anti*-Mannich adducts.

Productivities in $\text{mmol}_{\text{product}} \cdot \text{mmol}_{\text{resin}}^{-1} \cdot \text{h}^{-1}$ are shown in parentheses.

3. CONCLUSIONS

In summary, we have identified a threonine derivative immobilized onto polystyrene through a 1,4-disubstituted 1,2,3-triazole linker (**6**) as an efficient organocatalyst for the three-component *anti*-Mannich reaction. The immobilized catalyst depicts high activity and stereoselectivity in dichloromethane/*N,N*-dimethylformamide mixtures and allows recycling and reuse (3 cycles). The good overall performance of **6** allowed adapting its use to single-pass, continuous flow

processes. We have also shown that this flow system can be applied to the diastereo- and enantioselective medium-scale preparation of a diverse library of *anti*-Mannich adducts in a sequential manner. Noteworthy, these are the first examples of *anti*-selective, three component asymmetric Mannich reactions performed in continuous flow.

4. EXPERIMENTAL DETAILS

General Procedure for the Asymmetric Multicomponent Mannich reaction

Polymer-supported catalyst **6** (20 mol%) was swollen in a vial with a 1:1 mixture of DMF/CH₂Cl₂ (0.4 mL). The amine (0.2 mmol), aldehyde (1.1 equiv.) and ketone (6.0 equiv. or 3 equiv. of dihydroxyacetone dimer plus 10 mol% acetic acid) reactants were added and the reaction mixture was shaken at room temperature for the times indicated in Tables 3 and 4. Then, the resin was filtered off, washed with AcOEt (3 x 1 mL) and dried under vacuum. The combined liquid phases were concentrated under reduced pressure. Purification by column chromatography (eluting with cyclohexane/AcOEt) gave the corresponding Mannich products **9-26**. Conversion and diastereomeric ratio were determined by ¹H NMR of the crude samples after removal of the resin. The enantiomeric excess was determined by HPLC on a chiral stationary phase after purification by column chromatography. In the recycling experiments, the dried resin was used in the next run without further treatment.

ASSOCIATED CONTENT

Supporting Information.

Experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (23) The use of continuous flow conditions for six hours results in a turnover number (TON) of 10 (referred to the product formed) and a productivity of $1.7 \text{ mmol}_{\text{product}} \cdot \text{mmol}_{\text{resin}}^{-1} \cdot \text{h}^{-1}$.
- (24) A flow rate of $50 \mu\text{L} \cdot \text{min}^{-1}$ was used (equivalent to 10 min residence time).
- (25) The use of continuous flow conditions results a turnover number (TON) of 9 (referred to the product formed) and a productivity of $2.2 \text{ mmol}_{\text{product}} \cdot \text{mmol}_{\text{resin}}^{-1} \cdot \text{h}^{-1}$.
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