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Enhanced Activity and Stereoselectivity of Polystyrene-Supported Proline-Based Organic Catalysts for Direct Asymmetric Aldol Reaction in Water

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Several polystyrene-supported proline dipeptides and a prolinamide derivative were prepared by thiol–ene coupling. These materials were used as catalysts for the direct asymmetric aldol reaction in water, and results compared with unsupported catalysts in water. Such an approach gave more active or stereoselective catalysts compared to the unsupported compounds, showing that our immobilization procedure may be useful to develop catalytic materials with enhanced performance. Moreover, these catalysts can be recovered and reused for at least nine times without loss of activity or can be easily regenerated when their activity has decreased.

Introduction

Immobilization and recycling of asymmetric catalysts is of current interest and many efforts have been devoted both to organic catalysts and metal-based catalysts.[1] Polymeric materials are widely used in organic synthesis and catalysis.[2] During the last years we have been involved in research regarding immobilization and recycling of organic catalysts such as proline and proline derivatives[3] and their use under aqueous conditions.[4] Indeed, water plays an important role both when used with nonsupported or supported catalysts. One of the most important challenges with catalyst immobilization is to retain the activity and stereoselectivity of the immobilized catalysts. Usually, performances similar to homogeneous catalysts can be reached, but sometimes lower activity and stereoselectivity are observed in the first cycle or after a few cycles.[1] Moreover, another important aspect of immobilized catalysts is the separation, which should be achieved by a simple operation such as filtration. For these reasons, immobilization of organic catalysts on insoluble supports can give very useful catalytic materials to be used in highly stereoselective transformations such as the aldol reaction, one of the most powerful carbon–carbon bond-forming reactions.[5] Even if the mere use of water does not make a reaction "green" because of the necessity of disposal or clean up of the aqueous waste, its use can result in higher activities of catalysts and more stereoselective transformations, in addition to other advantages such as safety and economy. Since several years many researchers have examined the use of catalysts based on amino acids for asymmetric reactions in water.[6] Looking at the proline-catalyzed aldol reactions, it could be seen that immobilized proline on highly hydrophobic supports, such as a polystyrene backbone, furnished excellent results in terms of yield and stereoselectivity if compared to native proline under aqueous conditions.[7] These are not trivial examples of how immobilization can give more active and selective catalysts. Moreover, as stated before, immobilization on insoluble supports allows recovery and recycling of organic catalysts, thus counterbalancing the higher cost of the immobilization procedure. In this context, we have reported that supported prolinamides **1** and **2** (Figure 1) gave excellent results[8] compared to the unsupported catalysts, although used in higher quantities (10 mol-%) compared to the unsupported catalysts (down to 0.5 mol-%).[9] Indeed, we obtained high stereoselectivities without the need of performing the reaction at low temperature (–40 °C in $CHCl_3$, and –5/–10 °C in brine).[9]

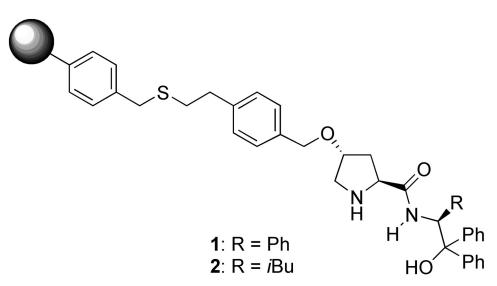

Figure 1. Supported prolinamides **1** and **2**.

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Encouraged by these results we wondered if our immobilization procedure would provide more active and stereoselective catalysts. The synthetic strategy we are currently using is very simple and relies on a thiol–ene coupling (TEC) reaction between a preformed commercially available mercaptomethyl–polystyrene resin and an organic catalyst bearing a styrene linker. The importance of the TEC reaction as a click process for materials and bioorganic chemistry has been recently highlighted.[10]

Then, we looked at the literature, searching for some organic catalysts that need additives or low temperatures to reach a good yield and level of stereoselectivity in order to investigate if the corresponding supported catalysts may be more active and/or stereoselective. We focused our attention on small peptide-[11] and prolinamide-based[12] organocatalysts for aldol reactions carried out in the presence of water.[13,14] Several small peptides have also been immobilized on insoluble supports such as polystyrene or silica in order to get easily recyclable catalytic materials.[15] In contrast, simple polystyrene-supported prolinamides have been very scarcely investigated.[7a,8a] Recently, few examples have regarded the use of prolinamide dendrons.[16] Among the unsupported organocatalysts, it has been reported that several L-proline-based dipeptides have been used in the aldol reaction between cyclohexanone and several aromatic aldehydes; the dipeptide L-Pro-L-Trp was the most promising (Figure 2).[17,18] Extensive studies on reaction conditions showed that the presence of a base and a surfactant was essential for the success of the reaction. Usually, NMM/SDS or DABCO/PEG400 were employed as additive, and the reactions were carried out in water at 0 °C. Our idea was that immobilization may avoid the use of such additives. In order to expand this investigation, and considering that polystyrene-supported prolinamides have not been extensively investigated, we also studied prolinamide **3** (Figure 2) as catalyst for the aldol reaction in water. Also, in this case, we compared such catalyst with the corresponding supported catalyst, immobilized by using our procedure. Recently, prolinamide **3** was tested as a catalyst for the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde under solvent-free conditions.[19]

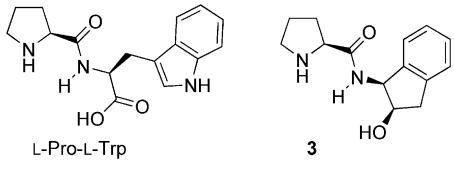
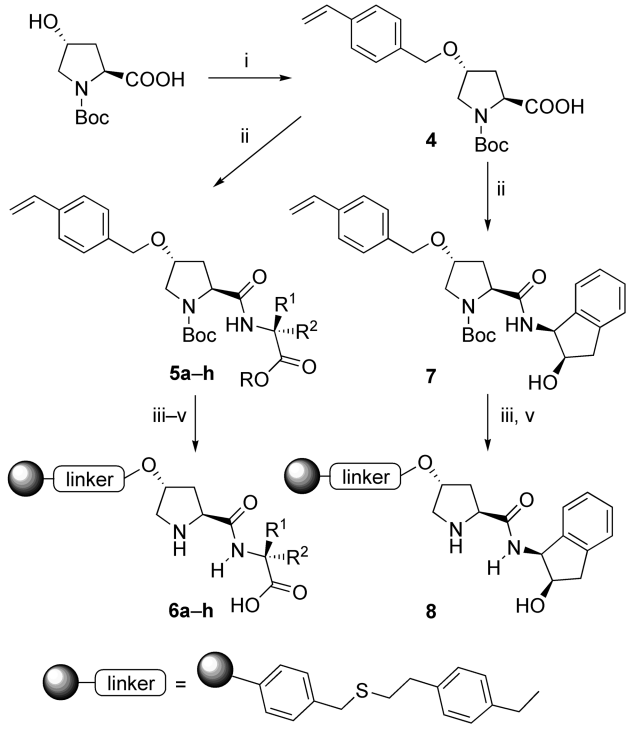


Figure 2. L-Pro-L-Trp and prolinamide **3**.

Here we report the results obtained in the aldol reaction performed in water as a reaction medium in the presence of several polystyrene-supported proline derivatives. The main aim of this research was to show that immobilization may furnish more highly active and/or stereoselective catalysts compared to the unsupported catalysts.

Results and Discussion

Supported catalysts were prepared as outlined in Scheme 1. First, the styrene derivative of *N*-Boc-protected *trans*-4-hydroxy-L-proline **4** was prepared.[7b] This compound was used as a starting material for generating molecular diversity (Figure 3). Indeed, compound **4** can be used to obtain polystyrene-supported proline, prolinamides, and proline-based dipeptides through immobilization on a preformed resin (Figure 3, routes a–d) or could be used as a monomer for the synthesis of functionalized polystyrene resins (Figure 3, route e). Very recently, this approach was developed by using other 4-substituted-hydroxy L-proline derivatives as monomers.[20,21] In the present work a series of dipeptides **5a**–**h** was obtained by reaction with the proper amino ester in the presence of triethylamine and ethyl chloroformate in dichloromethane. In the same way, prolinamide **7** was also prepared. In our case we anchored styrene derivatives **5a**–**h** and **7** on a preformed polystyrene resin. Immobilization was carried out by using the thiol–ene coupling reaction between a mercaptomethyl polymer-bound (1% cross-linked with DVB, spherical beads, particle size 100–200 mesh, 2.5 mmol g^{-1} loading) and the styrene derivative of protected dipeptides **5a**–**h**.



Scheme 1. Synthesis of supported dipeptides **6a**–**h** and prolinamide **8**. Reagents and conditions: (i) 4-vinylbenzyl chloride, NaH, 18-crown-6, THF, 50 °C, 80%; (ii) ethyl chloroformate, triethylamine, RNH_2, CH_2Cl_2, 0 °C to r.t., overnight; (iii) mercaptomethyl polymer-bound, AIBN, toluene, 110 °C, 24 h; (iv) LiOH, THF/H_2O, r.t., 24 h; (v) trifluoroacetic acid, CH_2Cl_2, r.t., 24 h then THF/Et_3N, 98:2. See Table 1 for R^1 and R^2.

Usually, 3 equivalents of compound **5** were employed, but the excess amount was easily recovered after the reaction.[22] Deprotection of the ester group was carried out by

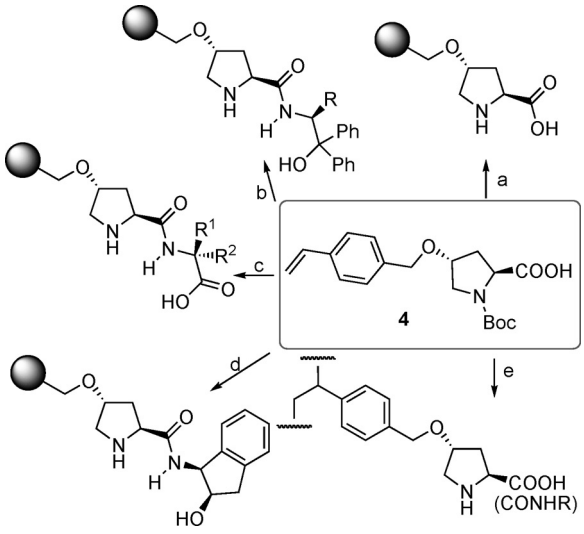
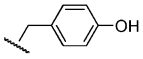
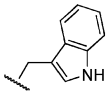
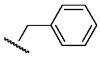
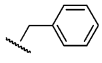


Figure 3. Different routes for proline-based organocatalysts immobilization.

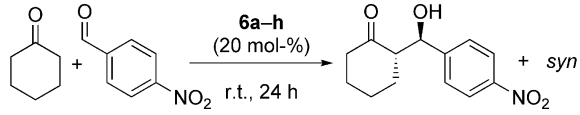
treatment with an excess amount of LiOH in THF/H_2O. Removal of the *tert*-butoxycarbonyl group was carried out with TFA/CH_2Cl_2 (20:80), followed by treatment with Et_3N/THF (2:98). Following this procedure, catalysts **6a**–**h** were prepared (Table 1). Dipeptide loadings, determined by weight gain, were found to be ca. 0.7–1 mmol g^{-1}; catalyst **6f** had the highest loading (1.38 mmol g^{-1}). Compound **8** was also prepared (0.92 mmol g^{-1}) by using the same strategy.

Table 1. Catalysts **6a**–**h** used in this work.

Entry	Catalyst	R^1	R^2	Loading [mmol g^{-1}]
1	**6a**		H	0.70
2	**6b**		H	0.76
3	**6c**		H	0.76
4	**6d**		H	0.76
5	**6e**		H	0.92
6	**6f**	H		1.38
7	**6g**		H	0.67
8	**6h**	H		1.15

With catalytic materials **6a**–**h** in hand we started our investigation by carrying out the reaction between cyclohexanone and 4-nitrobenzaldehyde. First we checked the role of water. When catalysts **6a**–**h** were used under neat conditions no reaction took place. Such results were previously observed by us and an explanation was given.[7b,8a] Also, the presence of the free carboxylic acid group plays an important role. For instance, when catalysts were obtained after mild deprotection with a slight excess amount of LiOH, the aldol products were obtained with lower optical purity with respect to when we deprotected the ester group with a large excess of LiOH. As an example, catalysts **6g** and **6h**, not fully hydrolyzed, gave the aldol product in 54 and 66%*ee*, respectively (Table 2, Entries 23 and 26). When the catalysts were fully hydrolyzed, the *ee* values increased up to 65 and 80%, respectively. Such a result showed that the excess amount of LiOH was needed to fully hydrolyze the ester function and also that the COOH group plays a role in the stereochemical outcome of the reaction, even in the immobilized catalysts.

Table 2. Screening of catalysts **6a**–**h** (20 mol-%) in the direct asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of water and recycling studies.[a]



Entry	Catalyst	Cycle	Solvent	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	**6a**	1	H_2O	>99	95	81:19	66
2	**6a**	4	H_2O	>99	94	82:18	64
3	**6a**	1	$CHCl_3$	45	41	84:16	70
4	**6a**	2	DMSO	>99	97	68:32	58
5	**6b**	1	H_2O	>99	96	83:17	72
6	**6b**	4	H_2O	>99	96	83:17	71
7	**6b**	1	$CHCl_3$	>99	93	79:21	54
8	**6c**	1	H_2O	>99	98	83:17	94
9	**6c**	4	H_2O	>99	96	83:17	76
10	**6c**	1	$CHCl_3$	–	–	–	–
11	**6d**	1	H_2O	99	94	83:17	78
12	**6d**	2	H_2O	>99	95	86:14	90
13	**6d**	3	H_2O	>99	95	85:15	85
14	**6d**	4	H_2O	>99	95	86:14	93
15	**6d**	1	$CHCl_3$	5	nd	77:23	nd
16	**6e**	1	H_2O	>99	98	84:16	75
17	**6e**	4	H_2O	>99	98	84:16	84
18	**6e**	1	$CHCl_3$	39	33	83:17	60
19	**6e**	2	DMSO	>99	97	73:27	78
20	**6f**	1	H_2O	>99	97	91:9	86
21	**6f**	4	H_2O	>99	97	91:9	85
22	**6f**	1	$CHCl_3$	–	–	–	–
23[e]	**6g**	1	H_2O	>99	96	83:17	54
24	**6g**	1	H_2O	98	94	82:18	65
25	**6g**	4	H_2O	99	94	84:16	52
26[e]	**6h**	1	H_2O	>99	95	83:17	66
27	**6h**	1	H_2O	95	89	87:13	80
28	**6h**	4	H_2O	98	92	85:15	74

[a] Reaction conditions: cyclohexanone (260 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst (0.1 mmol), H_2O (200 μL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [d] Diastereoisomer (*anti*) determined by HPLC by using a chiral column. [e] Catalyst containing ester function not fully hydrolyzed.

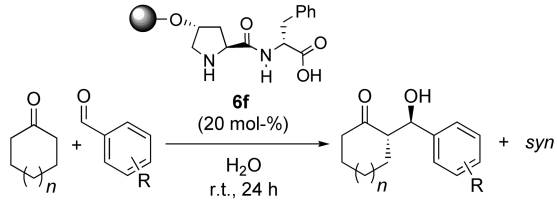
In order to test the recyclability of our catalytic materials, recycling studies were carried out even when *ee* values were not high. Catalyst **6a** gave reproducible results after

four cycles when employed in water: quantitative yields and about 4:1 diastereomeric ratio were observed, but the *ee* values were not high (Table 2, Entries 1 and 2). Similar stereoselectivities were obtained in $CHCl_3$, but the conversion was lower (Table 2, Entry 3), whereas a quantitative yield but a lower stereoselectivity was obtained in DMSO (Table 2, Entry 4). These preliminary data seem to indicate the superior outcome given by water. Also, catalyst **6b** was successfully used for four cycles with unchanged results and a slightly better enantioselectivity compared to **6a** (Table 2, Entries 5 and 6). With this catalyst a quantitative conversion was observed in $CHCl_3$, but the stereoselectivity was not good (Table 2, Entry 7). High enantioselectivity was observed with catalyst **6c**; however, after four cycles, although the yield was still quantitative, a decreased *ee* value was obtained, whereas the diastereomeric ratio was unaffected (Table 2, Entries 8 and 9). No reaction took place in $CHCl_3$ (Table 2, Entry 10). Catalyst **6d** gave also quantitative conversion after four cycles with unchanged diastereoselectivity, whereas the *ee* values ranged from 78 to 95% randomly (Table 2, Entries 11–14). Also, in this case, $CHCl_3$ gave a poor conversion. Catalyst **6e** showed a similar behaviour compared to that of **6a**. Again, water gave better results in terms of conversion and stereoselectivity with respect to $CHCl_3$ and DMSO and a small increase in enantioselectivity was observed after four cycles (Table 2, Entries 16 and 17). Catalyst **6f** behaved differently, giving enhanced diastereoselectivity and reproducible *ee* values after four cycles (Table 2, Entries 20 and 21), whereas no reaction was observed in $CHCl_3$. Catalysts **6g** gave low enantioselectivity, which decreased after four cycles (Table 2, Entries 24 and 25). Catalyst **6h**, having opposite configuration at carbon atom α to the phenylglycine unit, gave higher enantioselectivity even after four cycles (Table 2, Entries 27 and 28). These data showed that water was a better reaction medium compared to DMSO, which gave lower stereoselectivities, and to $CHCl_3$, which gave low yields in many cases.

Our catalytic systems were much more reactive compared to the unsupported dipeptides,[17] as we did not need to use additives such as a combination of base and surfactant. For instance, a comparison with the catalyst L-Pro-L-Phe[18] showed that our catalytic system was much more reactive and stereoselective when used in water, whereas in DMSO a decreased *ee* value was observed. On the whole, better performances were obtained with D-phenylalanine derivative **6f**. L-Tryptophan derivative **6d**, which gave good performances under homogeneous condition,[17] gave good, but irreproducible, results. Then, we decided to perform additional experiments, employing different aldehydes with catalyst **6f**. Interestingly, by comparing the data from Table 2 we can argue that both the nature of the R group at the α-carbon and the configuration at the same carbon atom play a role in the stereochemical outcome of the reaction, but the key role is played by the C-α configuration of the proline unit. Such role has been recently reported in proline-based dipeptides amides as catalysts for aldol reactions in $CHCl_3$.[23] Sulfonamides of L-Pro-L-Phe and L-Pro-D-Phe[24] and dipeptides L-Pro-L-Phe and L-Pro-D-Phe[18] used in organic solvent gave a decreased enantioselectivity when the D-Phe unit was used. On the contrary, our supported catalyst gave better performances with the D-Phe configuration.

In Table 3 we reported data obtained by using catalyst **6f** along with the recycling investigation performed with the same catalyst. With the only exception of the reaction performed with the use of cyclopentanone, which gave the aldol product with low stereoselectivity (Table 3, Entry 5), in all other cases yields from moderate to high, high diastereoselectivity (>90:10), and good to high enantioselectivity were obtained. Moreover, it is worthy to note that this material was used up to nine times. In the last run, we carried out again the reaction with 4-bromobenzaldehyde, reproducing the result obtained in the sixth cycle. A comparison with several data obtained by using dipeptide L-Pro-L-Trp in the presence of base/surfactant at 0 °C under homogeneous conditions[17] showed comparable stereoselectivities (Table 3, Entries 1, 4, and 7).

Table 3. Direct asymmetric aldol reaction between cyclohexanone or cyclopentanone and aldehydes in the presence of water catalyzed by resin **6f** (20 mol-%) and recycling studies.[a]



Entry	Cycle	Compound	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	1	*n* = 1; R = 4-CN	>99	98	93:7	86
				94[e]	93:7[e]	85[e]
2	2	*n* = 1; R = 4-CF_3	94	91	94:6	99
3	3	*n* = 1; R = 4-Cl	83	79	93:7	81
4	4	*n* = 1; R = 3-NO_2	84	81	94:6	87
				89[e]	90:10[e]	80[e]
5	5	*n* = 0; R = 4-CF_3	97	94	50:50	64
6	6	*n* = 1; R = 4-Br	69	63	91:9	87
7	7	*n* = 1; R = 2-NO_2	95	91	97:3	90
				88[e]	>99:1[e]	89[e]
8	8	*n* = 1; R = 3-OCH_3	40	34	93:7	90
9	9	*n* = 1; R = 4-Br	69	65	92:8	87

[a] Reaction conditions: ketone (2.5 mmol), aldehyde (0.5 mmol), catalyst (0.1 mmol), H_2O (200 μL) at room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] Diastereoisomer (*anti*) determined by HPLC by using a chiral column. [e] Data from ref.[17] with the use of L-Pro-L-Trp.

Because good results were obtained with the use of catalyst **6f**, which has the D configuration in the phenylalanine moiety, we wondered if also an inversion of configuration at C-4 of the L-proline unit may have a role in the stereochemical outcome of the reaction.[25] In order to study this role, we prepared catalyst **9** and checked it in the aldol reaction (Figure 4). Although diastereoselectivities were high (94:6 *anti*/*syn*), the *ee* values were lower than the supported *trans*-4-hydroxy-L-proline.[7b] Because of this deleterious ef-

fect caused by the C-4 configuration, we decided that the synthesis of supported dipeptides based on the *cis*-4-hydroxy-L-proline was, in this case, useless.

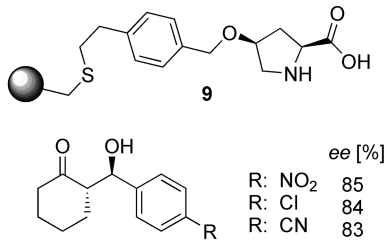
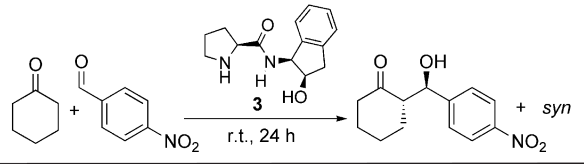


Figure 4. Polystyrene-supported *cis*-4-hydroxy-L-proline **9** and *ee* values of aldol products obtained by using **9**.

Then, we turned our attention to prolinamide **3**. Because this compound was not investigated for the aldol reaction in water, we carried out several reactions. First, we performed the reaction between cyclohexanone and 4-nitrobenzaldehyde by using the same conditions as those used for the dipeptides (aldehyde/cyclohexanone, 5:1; H_2O 200 μL) and by using only 5 mol-% of catalyst **3**. The conversion was good; however, the *ee* value was poor (Table 4, Entry 1). Increasing the amount of catalyst resulted in an even lower *ee* value (Table 4, Entries 2 and 3). Reactions carried out under neat conditions[26] or in chloroform gave also poor enantioselectivity (Table 4, Entries 4 and 5). The minor *syn* diastereoisomer gave a slightly better enantioselectivity. A comparison with the literature datum showed that water and $CHCl_3$ had a detrimental effect on the stereoselectivity of the reaction.[19] After these preliminary data, we carried out several reactions by using supported catalyst **8**.

Table 4. Direct asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehydes in the presence of water catalyzed by prolinamide **3**.[a]

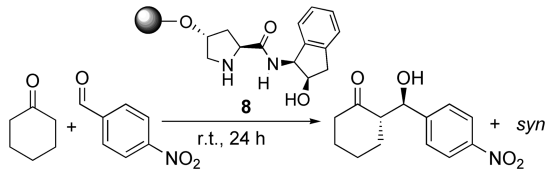


Entry	Catalyst loading [mol-%]	H_2O [μL]	Conv.[b] [%]	*anti*/*syn*[c]	*ee*[d] *anti* [%]	*ee*[d] *syn* [%]
1	5	200	85	81:19	22	52
2	10	200	99	78:22	15	48
3	20	200	>99	78:22	10	37
4	20	0	99	65:35	32	47
5[e]	20	200	80	72:28	24	49

[a] Reaction conditions: cyclohexanone (260 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst, H_2O at room temperature. [b] Yield at ≥95% conversion. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] Determined by HPLC by using a chiral column. [e] $CHCl_3$ as solvent.

When resin **8** was employed in 5–20 mol-% with water we obtained a high yield and good enantioselectivity (Table 5, Entries 1–3). It is worthy to note that, in each case, the enantioselectivity was much higher than that observed with unsupported catalyst **3**. The reaction carried out with the use of resin **8** in 20 mol-% under neat conditions was, as expected, unsuccessful (Table 5, Entry 4). By maintaining the same catalyst loading, we checked the reaction in the presence of different amounts of water (Table 5, Entries 5 and 6). No appreciable differences were observed. This catalyst was used for a further three cycles with unchanged results (Table 5, Entries 7–9). Similar results were obtained when resin **8** was used in lower amount (10 mol-%); however, in the third and fourth cycle a decreased conversion was observed (Table 5, Entries 11 and 12). The diminished activity could be ascribed to the formation of the corresponding imidazolidinone.[8b] In order to regenerate resin **8**, it was treated with formic acid at room temperature for 2.5 h.[27] After this treatment the catalytic activity was restored (Table 5, Entry 13). It is interesting to note that proline-based dipeptides were used up to nine cycles without the need for regeneration. This result could be ascribed to the higher acidity of these catalysts compared to that of **8**. Supported catalyst **8** was more stereoselective with respect to **3** used under solvent-free conditions.[19]

Table 5. Direct asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehydes in the presence of water catalyzed by resin **8**.[a]

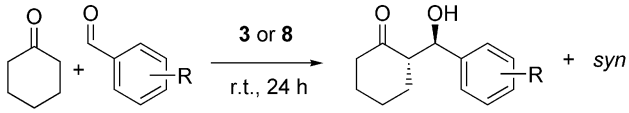


Entry	Cycle	Cat. loading [mol-%]	H_2O [μL]	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	1	5	200	96	93	87:13	79
2	1	10	200	>99	98	86:14	78
3	1	20	200	>99	98	84:16	76
4	1	20	0	–	–	–	–
5	2	20	9[e]	96	92	82:18	71
6	1	20	300	>99	97	83:17	72
7	2	20	200	>99	98	86:14	79
8	3	20	200	>99	97	86:14	83
9	4	20	200	97	93	87:13	81
10	2	10	200	94	89	89:11	82
11	3	10	200	73	70	88:12	83
12	4	10	200	85	78	88:12	86
13[f]	5	10	200	97	94	85:15	82
14[g]	1	20	200	<5	–	–	–

[a] Reaction conditions: cyclohexanone (260 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst, H_2O at room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] Diastereoisomer (*anti*) determined by HPLC by using a chiral column. [e] 1 equiv. [f] After regeneration with HCOOH. [g] $CHCl_3$ as solvent.

These data showed that unsupported prolinamide **3** was not a good catalyst for the asymmetric aldol reaction and it was sensitive to the amount of water with respect to the amount of catalyst. Immobilization of catalyst **3** on a polystyrene backbone resulted in a strong increase in enantioselectivity. Moreover, the optical purity of the *anti* compound was independent from the water/catalyst ratio. In or-

Table 6. Direct asymmetric aldol reaction between cyclohexanone and aldehydes in the presence of water catalyzed by resin **8** or prolinamide **3**.[a]



Entry	R	Cycle	8			3		
			Conv.[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]	Conv.[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	4-CN	2	98	81:19	81	99	56:44	41
2	4-Br	3	60	89:11	78	62	79:21	38
3	2-NO_2	4	98	84:16	78	99	68:32	42
4	3-NO_2	5	31	82:18	75	99	72:28	12
5	3-NO_2	6[e]	99	81:19	75			

[a] Reaction conditions: cyclohexanone (260 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst (20 mol-%), H_2O (200 μL) at room temperature. [b] Yield at ≥95% conversion. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] Diastereoisomer (*anti*) determined by HPLC by using a chiral column. [e] After regeneration with HCOOH.

der to test resin **8** with other substrates, we carried out a set of reactions with four different aldehydes. Again, resin **8** appeared much more stereoselective than catalyst **3**. As a matter of fact, the *ee* values increased from 12–42 to 75–81% without the use of additives (Table 6). A decreased conversion was observed with resin **8** in the fifth cycle. Treatment with HCOOH fully restored its activity without affecting the stereoselectivity (Table 6, Entry 5). The higher stereoselectivity obtained with resin **8** could be attributed to the higher hydrophobicity of the catalyst. The polystyrene backbone plays two roles: it enables the recovery and acts as a large apolar substituent, as in nonsupported proline derivatives carrying large apolar substituents in the C-4 position.[25,28]

Conclusions

The strategy based on TEC reaction is a very simple procedure that allows the preparation of a wide range of useful materials that can be successfully used in water as reaction medium. This approach can be applied to a variety of styrene derivatives of organic catalysts. In this context, styrene–proline derivative **4** proved its potential as a starting material for molecular diversity. Supported proline-based dipeptides showed enhanced activity compared to the unsupported catalysts. Indeed, thanks to the hydrophobic backbone, there is no need for additives such as a combination of base and surfactant. Moreover, good to high yields and stereoselectivities were obtained working at room temperature without the need for lower temperatures. The catalysts can easily be reused over several cycles (so far up to nine). Furthermore, the proline C-4 configuration and the C-α configuration of the second amino acid played a role in determining the *ee* value of the aldol adducts but did not determine the configuration of the final products.

Supported prolinamide **8** is much more stereoselective than unsupported prolinamide **3**. Resin **8** provides a powerful increase in enantioselectivity and a good increase in diastereoselectivity, its use is less dependent on the amount of water. Again, this resin can be recovered and reused for at least six times without loss of stereoselectivity. Moreover, as soon as decreased activity is observed after several cycles, the activity of such catalytic materials can easily be restored by simple treatment with formic acid.

In conclusion, we showed that immobilization of the proper organic catalyst, such as dipeptides or prolinamides, may afford more active and/or stereoselective organic catalysts when employed in water as reaction medium compared to the corresponding unsupported catalysts, although the *ee* values of the aldol products are not excellent. Particularly, the data collected for polystyrene-supported prolinamides in this work and in our previous work[8] indicate that their immobilization furnishes catalytic materials with comparable or better activity than those observed for unsupported catalysts in water. Studies are in progress to further develop and optimize this procedure, not only for the aldol reaction, but for other reactions as well.

Experimental Section

General Procedures: NMR spectra were recorded with a Bruker 300 MHz spectrometer in $CDCl_3$ as solvent. FTIR spectra were recorded with a Shimadzu FTIR 8300 infrared spectrophotometer. Carbon and nitrogen contents were determined by combustion analysis with a Fisons EA 1108 elemental analyzer. Optical rotations were measured in chloroform with a Jasco P1010 polarimeter. Chiral HPLC analyses were performed with a Shimadzu LC-10AD apparatus equipped with a SPD-M10A UV detector and Daicel columns (OD-H, AD-H, AS-H, 4.6 mm × 250 mm) with hexane/isopropyl alcohol as the eluent. Aldol products are known compounds and showed spectroscopic and analytical data in agreement with their structures.[8a,9b,12o] The *anti*/*syn* ratios were determined by analysis of the ^1H NMR spectra of the crude reaction mixtures; *ee* values were determined by HPLC chromatograms of the crude reaction mixtures.[8a,9b,12o]

Typical Procedure for the Synthesis of Compounds 5a–h and 7: Triethylamine (344 μL, 2.44 mmol) was slowly added to a solution of acid **5** (0.85 g, 2.44 mmol) in CH_2Cl_2 (9 mL) at 0 °C. Ethyl chloroformate (238 μL, 2.44 mmol) was added dropwise, and the solution was stirred at the same temperature for 15 min. Then, the proper amino ester or (1*S*,2*R*)-(–)-*cis*-1-amino-2-indanol (2.44 mmol) was

added, and the resulting solution was stirred overnight. After this period, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate, 3:1–2:1).

Typical Procedure for the Synthesis of Polystyrene-Supported Dipeptides 6a–h and L-Prolinamide 8: (Mercaptomethyl)–polystyrene (286 mg, 0.72 mmol) was added to a degassed solution of styrene derivative **5a**–**h** or **7** (2.15 mmol) and AIBN (7.5 mg, 2 mol-%) in toluene (17 mL). The mixture was stirred at 110 °C overnight under an atmosphere of argon. After cooling to room temperature, the resin was filtered and washed with dichloromethane. A yellow resin was obtained. From the weight increase the amount of monomer that was covalently attached to the resin was calculated. The dichloromethane solution was evaporated under reduced pressure to recover the unreacted styrene derivative, which was then purified by column chromatography (recovery 90%). The resin was suspended in THF and an aqueous solution of LiOH (5 N). Typical amounts were, for 4.13 mmol of anchored catalyst, THF (19 mL) and LiOH (13.8 mL). The suspension was stirred for 24 h. After this time, the resin was filtered under vacuum, and it was then washed with an aqueous solution of HCl (1 M), water, methanol, and dichloromethane. The resin was dried for a few minutes then suspended in dichloromethane (4 mL) and CF_3COOH (1 mL) and stirred overnight. The resin was filtered and washed with dichloromethane, triethylamine in THF (2%, v/v), water, methanol, and dichloromethane. The resin was dried for a few minutes at 60 °C. The weight difference corresponds to the amount of Boc removed, which was identical to the amount of available proline. In the case of resin **8**, only treatment with TFA was carried out.

Typical Procedure for Aldol Reaction: Catalyst **6a**–**h** or **8** (0.1 mmol) was added to a mixture of the corresponding aldehyde (0.5 mmol) and ketone (2.5 mmol) in distilled water (0.20 mL). The reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered, and the catalyst was washed thoroughly with methanol, ethyl acetate, and diethyl ether. The organic layers were collected and, after evaporation of solvent, the crude product was checked by ^{1}H NMR spectroscopy and HPLC, and then purified by chromatography (petroleum ether/ethyl acetate).

Procedure for Catalyst Regeneration: Catalyst **8** was placed in a round-bottomed flask and HCOOH was added (usually 200 μL for 100 mg of catalyst). The mixture was agitated for 2.5 h, then filtered and washed with water, aqueous $NaHCO_3$, water, MeOH, and diethyl ether. Finally, the product was dried for a few minutes at 60 °C.

Supporting Information (see also the footnote on the first page of this article): Compound characterization and copies of the IR, ^{1}H NMR, and ^{13}C NMR spectra of compounds **5a**–**h** and **7**.

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