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Novel Prolinamide-Supported Polystyrene as Highly Stereoselective and Recyclable Organocatalyst for the Aldol Reaction

Michelangelo Gruttadauria,[a,*] Francesco Giacalone,[a] Adriana Mossuto Marculescu,[a] and Renato Noto[a]

[a] Dipartimento di Chimica Organica "E. Paternò", Università di Palermo, Viale delle Scienze, Pad. 17, 90128 Palermo, Italy
Fax: (+39)-091-596-825; e-mail: mgrutt@unipa.it

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Dedicated to the memory of Prof. G. C. Cusmano.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A new prolinamide derivative anchored to a polystyrene support has been straightforwardly prepared and employed as heterogeneous catalyst in the direct asymmetric aldol reaction with good results in terms of yield and stereoselectivity. The optimal reaction conditions were found when a 1:2 (v/v) water/chloroform mixture was used. This mixture was the best compromise between the good swelling properties of chloroform and the formation of a concentrated organic phase due to the presence of water. Noticeably, the enantioselectivities obtained employing acetone as ketone were, to the best of our knowledge, the highest achieved with a supported proline derivative. This catalyst can be easily recovered, regenerated and recycled, without loss of activity, at least for twelve cycles.

Keywords: aldol reactions; immoblization; organic catalysis; polymers; proline

Introduction

Asymmetric organocatalysis, especially with L-proline and its derivatives, has experienced a huge interest and development in the recent years.[1] In fact, L-proline and several its derivatives have emerged as powerful catalysts in the asymmetric intermolecular aldol reaction, one of the most important methods of forming carbon-carbon bonds.

On the other hand, since the organocatalyst is usually used in a substantial quantity, in some cases up to 30 mol%, its recovery and reuse became fundamental in order to reduce costs and to facilitate the separation of the products, especially when the catalyst is obtained after several synthetic steps.[2] Immobilization of organocatalyst to the support can be realized both with a non-covalent linkage[3] or with a covalent linkage on supports such as polystyrene,[4] silica,[5] PEG,[6] magnetite[7] or ionic liquids.[8] Recently, the immobilization of L-proline on polystyrene has received interest, and indeed stereoselective and recyclable materials have been prepared.[4] Immobilization of L-proline may be considered useless since proline is inexpensive and available in both enantiomeric forms. However, immobilization of L-proline has allowed one to reach, in several cases,[4b,d,f] higher stereoselectivities compared to the native catalyst. Immobilization of more expensive organocatalysts, such as substituted prolinamides, may be of higher interest from an economical point of view. Substituted prolinamides have been recently found to be active and highly stereoselective catalysts for direct aldol reaction in aqueous medium.[9] Indeed, since 2006, when Barbas[10] and Hayashi[11] independently reported the highly stereoselective aldol reactions using proline derivatives as organocatalysts in the presence of water,[12] this point has received attention.[13] Particularly, compound **1** (Figure 1) gave excellent results in the direct aldol reaction.[9a]

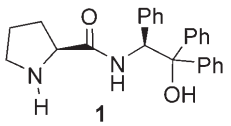

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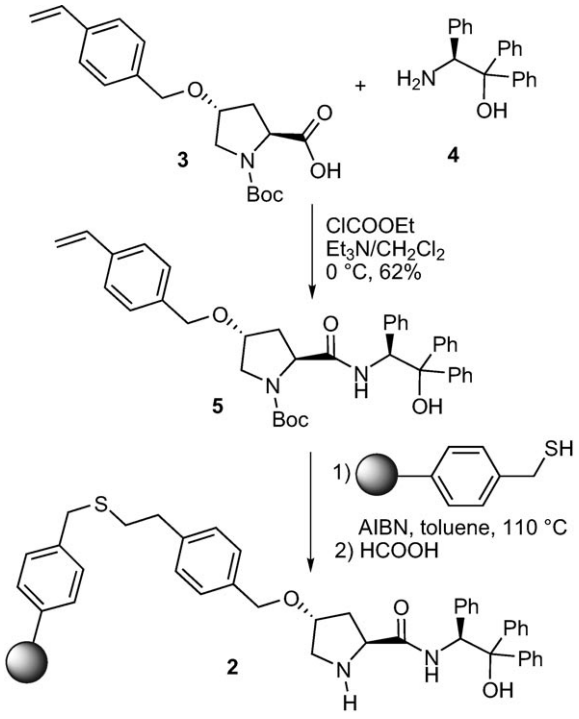
Figure 1. Prolinamide catalyst for direct aldol reactions.

Interestingly, there are no reports in the literature about the use of immobilized organocatalysts giving high *ee* values (>90%) in the reaction between acetone and substituted benzaldehydes. We considered it possible to obtain high *ee* values for the above reaction using an immobilized organocatalyst. We coupled the idea of using compound **1** with our immobilization procedure with the aim to obtain a recyclable catalyst. Our intention was to prepare a recyclable supported version of **1** while trying to maintain its excellent behaviour. Here, we report the results of the direct asymmetric aldol reaction between several ketones and substituted benzaldehydes catalyzed by a substituted prolinamide anchored to a polystyrene resin.

Results and Discussion

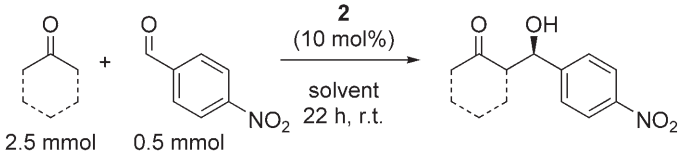
Resin **2** has been prepared by following a straightforward synthetic strategy in two steps, as depicted in Scheme 1. Firstly, L-Pro derivative **3**[4b] has been reacted with commercial (2*S*)-2-amino-1,1,2-triphenylethanol (**4**) in the presence of ethyl chloroformate[14] to afford the corresponding prolinamide derivative **5**. Secondly, due to the presence of a styrenic moiety in its structure, **5** can be promptly linked to a commercially available mercaptomethyl-functionalized polystyrene (1% cross-linked with DVB, spherical beads, particle size 100–200 mesh) *via* a radical reaction in the presence of AIBN. Finally, the Boc group has been removed under smooth conditions by using formic acid. This procedure gave the supported-prolinamide resin **2** in high yield with a prolinamide loading of *ca.* 0.74 $mmol\,g^{-1}$, as determined by elemental analysis and weight gain.



Scheme 1. Synthesis of polystyrene-supported prolinamide.

Once the catalyst was prepared, we focused our attention on the aldol reaction between two ketones (acetone and cyclohexanone) and 4-nitrobenzaldehyde (Table 1). First, we tried to determine the best solvent system and, in the mean time, recycling studies were performed. Indeed, because one of the most important features of a supported catalyst should be its high reusability, we decided to carry out recycling experiments at the beginning of our study in order to find the best conditions for catalyst reuse for further applications. As a first approach we studied the reaction between acetone and 4-nitrobenzaldehyde using brine, water and $CHCl_3$ (Table 1, entries 1–3) in order to compare these different reaction media. Using brine we were able to reproduce the *ee* value obtained under homogeneous conditions, however, the yield was modest. No differences were observed using water. The reaction carried out in $CHCl_3$ afforded the product in a very low yield (entry 3). Reuse of catalyst in brine gave a decreased yield (Table 1, entry 4) although the *ee* value was unaffected. We reasoned that a certain amount of catalyst was probably disactivated by an excess of acetone with formation of the corresponding imidazolidinone.[15] Therefore, we decided to regenerate the catalyst by treatment with formic acid in order to hydrolyze the imidazolidinone.[16] Interestingly, a beneficial effect was observed after regeneration of the resin because we obtained again the same yield as displayed by fresh catalyst (entries 1 and 5). However, such a yield was still disappointing. Because we were interested both in high yield and *ee* values and high recyclability of the catalyst, new regenerations were carried out after each cycle. Contrasting effects were obtained in terms of enantioselectivity when no solvent was used and a negative effect of dilution was observed when 10 equiv. of acetone were used (entries 6 and 7). Then we decided to try a 1:2 (v/v) water/chloroform mixture. To our delight, excellent results were achieved by adopting this solvent system. In fact, both yields and enantioselectivities were boosted to 96 and 95%, respectively (entry 8). It is worthy to note that such an *ee* value was higher than that obtained with **1** under homogeneous conditions. The reaction performed at −5 °C gave an improved enantioselectivity but, a dramatic drop in activity was observed (entry 9). Use of other solvents such as CH_2Cl_2, tetrahydrofuran, toluene and diethyl ether gave very low yields (entries 10–13) while the reaction took place, with high *ee* values, when the above solvents were used as a 1:2 (v/v) water/solvent mixture (entries 14–17).

Table 1. Asymmetric aldol reactions in water between acetone or cyclohexanone and 4-nitrobenzaldehyde catalyzed by resin **2** (10 mol%).



Entry	Ketone	Solvent	Cycle	Regeneration[a]	Yield[b] [%]	*anti/syn*[c]	ee[d]
1[e]	acetone	brine	1	-	41	-	85
2[f]	acetone	H_2O	1	-	42	-	85
3[g]	acetone	$CHCl_3$	1	-	5	-	nd
4[e]	acetone	brine	2	-	30	-	85
5[e]	acetone	brine	3	1	42	-	86
6	acetone	none	3	2	34	-	94
7[h]	acetone	acetone	4	3	12	-	86
8[i]	acetone	$H_2O/CHCl_3$	4	3	96	-	95
9[i,j]	acetone	$H_2O/CHCl_3$	4	3	13	-	98
10[g]	acetone	CH_2Cl_2	1	-	5	-	nd
11[g]	acetone	THF	1	-	<5	-	nd
12[g]	acetone	toluene	1	-	7	-	nd
13[g]	acetone	Et_2O	1	-	7	-	nd
14[i]	acetone	H_2O/CH_2Cl_2	2	1	80	-	96
15[i]	acetone	H_2O/THF	2	1	44	-	92
16[i]	acetone	H_2O/toluene	2	1	50	-	94
17[i]	acetone	H_2O/Et_2O	2	1	37	-	92
18[f]	cyclohexanone	H_2O	1	-	50	94/6	95
19[i]	cyclohexanone	$H_2O/CHCl_3$	2	-	97	95/5	97
20[g]	cyclohexanone	$CHCl_3$	3	-	-	-	-
21[k]	cyclohexanone	$H_2O/CHCl_3$	4	-	36	95/5	86
22[i]	cyclohexanone	$H_2O/CHCl_3$	5	-	46	97/3	50
23[i]	cyclohexanone	$H_2O/CHCl_3$	6	1	91	94/6	97
24[i]	cyclohexanone	$H_2O/CHCl_3$	7	1	51	93/7	97
25[i,l]	cyclohexanone	$H_2O/CHCl_3$	8	2	83	98/2	97
26[i]	cyclohexanone	$H_2O/CHCl_3$	9	3	97	96/4	97
27[i]	cyclohexanone	$H_2O/CHCl_3$	10	4	97	96/4	97
28[i]	cyclohexanone	$H_2O/CHCl_3$	11	5	97	96/4	97
29[i]	cyclohexanone	$H_2O/CHCl_3$	12	6	95	96/4	97

[a] Regeneration with formic acid during 2.5 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by HPLC using a chiral stationary phase.
[e] Using 500 μL of brine.
[f] Using 300 μL of H_2O.
[g] Using 300 μL of solvent.
[h] No solvent and 5 mmol (10 equiv.) of acetone were used.
[i] Using 100/200 μL of H_2O/solvent.
[j] Reaction carried out at −5 °C.
[k] Using 50/250 μL, respectively.
[l] Resin treated with formic acid during 1.5 h.

Then, we checked the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde and, in the mean time, other recycling studies were also performed (Table 1).

Following the results obtained using acetone, we used again water, chloroform and 1:2 (v/v) water/chloroform as reaction medium. Although water seemed to work, giving high stereoselectivity, the conversion was low (entry 18). We turned our attention to the 1:2 (v/v) water/chloroform mixture. To our delight, this solvent system again worked nicely with almost quantitative yield and high stereoselectivity (entry 19). Then, we observed that when water was absent or present in a minor amount, the reaction did not take place or proceeded with bad results (entries 20 and 21) demonstrating that again water played a crucial role. In the fifth cycle (entry 22) we

used same conditions as in entry 19, but both yield and stereoselectivity were lost. Then, we regenerated the resin by treatment with formic acid. Again, the resin worked almost as well as in the second cycle (see entries 23 and 19). A new reaction was performed without regeneration and once again conversion fell down (entry 24). Then, new regenerations were carried out after each cycle, and the resin always showed the same activity (entries 25–29). As can be seen from the data reported, the optimal solvent system was a $CHCl_3/H_2O$ mixture. In our opinion this is a result of a synergistic effect of the two solvents. Chloroform should be able to swell the hydrophobic prolinamide catalyst. However, no reaction took place when only $CHCl_3$ was used simply because it is a good solvent. Ketones and aldehydes are well dissolved, while the catalytic center is supported on a material having a very low surface area ($< 10\ m^2\ g^{-1}$). This strongly favors the repartition of the reactants in the liquid phase. Using water, reactions occurred in a concentrated organic phase, so a higher conversion with respect to $CHCl_3$ was observed, but it was not high because the presence of the bulky hydrophobic moieties on the prolinamide catalyst did not allow an open structure of the catalyst in water (see Figure 2). The water/chloroform mixture was the optimal system because $CHCl_3$ allowed the catalyst to adopt an open structure while water created a concentrated organic phase as depicted in Figure 3. In other words, the above mixture was a good compromise between swelling and formation of a concentrated organic phase. A similar behavior was observed when CH_2Cl_2, tetrahydrofuran, Et_2O or toluene were employed. Interestingly, when the above solvents were used as mixture with water, yields decreased in the order $CHCl_3 > CH_2Cl_2 > \text{toluene} > \text{THF} > Et_2O$. This order is in agreement with the swelling studies carried out on DVB cross-linked polystyrene resins.[17]

Next we carried out aldol reactions using a set of substituted benzaldehydes. In Table 2 the results obtained using acetone as donor are reported. Adopting the optimal conditions, activated aldehydes showed good to excellent results both in terms of conversion and enantiomeric ratio, being the latter in the 89–97% range. In some cases, *ca.* 3–9% of the corresponding α,β-unsaturated compounds were observed. Although under homogeneous conditions the yields were 70–85% and *ee* values were 84–>99% in the case of 4-CF_3-benzaldehyde, with 4-NO_2-benzaldehyde and 2-naphthaldehyde we observed higher *ee* values. Improvements in the yields were achieved both with longer reaction times (compare entries 2 and 13) or by using 30 mol% of catalyst (compare entries 6 and 12). The use of a larger amount of catalyst can be justified by the high recyclability of the catalyst. As can be seen from Table 2, reactions were carried out with catalyst **2** previously employed in the reaction between acetone and 4-nitrobenzaldehyde. Catalyst **2** was used up to 11 cycles, regenerating it after each cycle, without any loss in activity or selectivity.

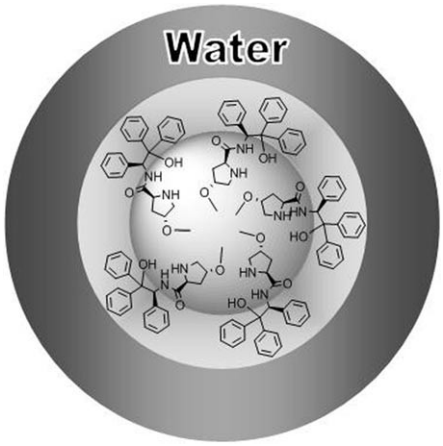


Figure 2. Proposed unswelled catalyst structure in the presence of water.

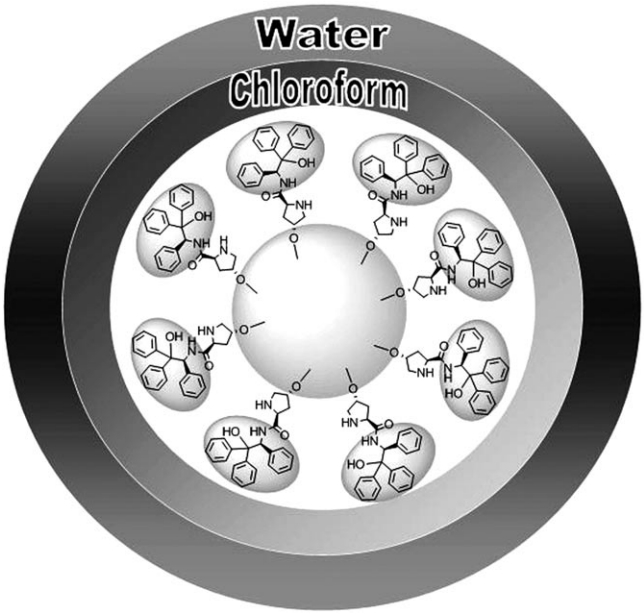
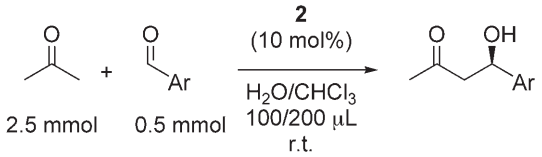


Figure 3. Proposed swelled catalyst structure in the presence of chloroform/water mixture.

Next, a representative selection of aldehydes was examined under the optimized conditions using cyclohexanone as ketone and the results obtained are summarized in Table 3.

Interestingly, aromatic aldehydes gave excellent results, with reaction times ranging between 22 and 120 h. Diastereoselectivities (*anti*/*syn*) and enantioselectivities were excellent in all cases and low yields were observed only for less reactive aldehydes (entries 1, 10 and 12). It is worth mentioning that, since

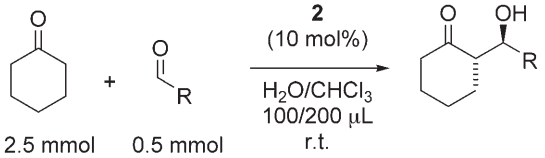
Table 2. Aldol reaction of acetone with substituted benzaldehydes catalyzed by resin **2**.



Entry	Ar	Time [h]	Cycle	Regeneration[a]	Yield[b] [%]	*ee*[c]
1	4-CN-C_6H_4	22	5	4	93	96
2	4-CF_3-C_6H_4	24	5	4	58	95
3	3-Cl-C_6H_4	48	5	4	79	94
4	4-Cl-C_6H_4	72	6	5	67	93
5	Ph	93	6	5	50	92
6	2-naphthyl	95	6	5	30	90
7	2-Cl-C_6H_4	67	7	6	94	89
8	3-MeO-C_6H_4	96	8	7	57	91
9	4-Br-C_6H_4	72	9	8	67	97
10	2-CN-C_6H_4	24	10	9	95	93
11	2-Cl-6-NO_2-C_6H_3	24	10	9	98	96
12[d]	2-naphthyl	95	11	10	44	92
13	4-CF_3-C_6H_4	48	11	10	74	95

[a] Regeneration with formic acid during 2.5 h.
[b] Isolated yield.
[c] Determined by HPLC using a chiral stationary phase.
[d] We employed 30 mol% of catalyst.

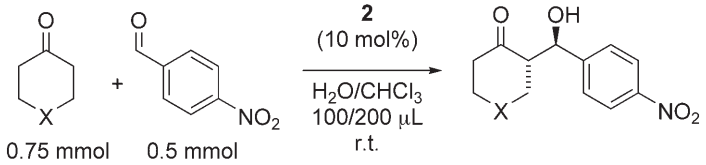
Table 3. Asymmetric aldol reactions in water between cyclohexanone and aldehydes catalyzed by resin **2** (10 mol%).



Entry	R	Time [h]	Cycle	Regeneration[a]	Yield[b] [%]	*anti/syn*[c]	*ee anti*[d]
1	Ph	48	1	-	35	97/3	96
2[e]	Ph	48	1	-	37	98/2	96
3	3-Cl-C_6H_4	72	1	-	91	97/3	97
4	2-naphthyl	90	2	1	52	98/2	95
5	4-CN-C_6H_4	22	3	2	95	96.5/3.5	98
6	cyclohexyl	120	4	3	-	-	-
7	4-CF_3-C_6H_4	48	5	4	84	97.5/2.5	99
8	3-NO_2-C_6H_4	48	6	5	93	96/4	97
9	3-CH_3O-C_6H_4	96	7	6	55	98/2	97
10	4-CH_3-C_6H_4	96	8	7	26	97/3	94
11	4-Cl-C_6H_4	72	9	8	38	98/2	96
12	4-CH_3O-C_6H_4	120	9	8	4	97/3	nd
13[f]	4-Cl-C_6H_4	72	10	9	74	98/2	96
14[f]	4-CH_3-C_6H_4	96	11	10	37	98/2	96

[a] Regeneration with formic acid during 2.5 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by HPLC using a chiral stationary phase.
[e] Using 100 μL of brine instead of water.
[f] We employed 30 mol% of catalyst.

Table 4. Asymmetric aldol reactions in water between ketones and 4-nitrobenzaldehyde catalyzed by resin **2**.



Entry	X	Time [h]	Cycle	Regeneration[a]	Yield[b] [%]	*anti/syn*[c]	*ee anti*[d]
1	-	22	2	1	44	41/59	71
2	CH_2	22	2	1	80	97/3	98
3[e]	O	22	2	1	94	98/2	95
4	O	22	3	2	90	98/2	95
5	S	48	4	3	60	96/4	98
6	NBoc	22	7	6	59	98/2	93
7	$CHCH_3$	48	8	7	54	97/3	96

[a-d] As for Table 3.
[e] 5 equivalents of ketone used.

the catalyst proved to be highly recyclable, resin **2** can be used in a higher amount with the less reactive aldehydes. We used **2** in 30 mol% with 4-chlorobenzaldehyde and 4-methylbenzaldehyde (entries 13 and 14). Yields were improved and the higher amount of catalyst used did not negatively affect the *anti*/*syn* ratio and enantioselectivity.[18]

Moreover, if compared with our previously reported proline-supported resin,[4b] catalyst **2** proved to be more active in the aldol reaction between cyclohexanone and aromatic aldehydes. In fact, almost all the values of yield, diastereo- and enantioselectivities were improved. Noticeably, even if compared with results obtained under homogeneous conditions,[9a] in some case resin **2** showed some better results (i.e., entries 8, 26–29 Table 1, entries 5, 7 and 11 Table 3). Again, reactions were performed with recovered and regenerated catalyst.

To increase the scope of the methodology, the aldol reaction was extended to other ketones with 4-nitrobenzaldehyde, and the results are summarized in Table 4. Cyclopentanone gave a modest result (Table 4, entry 1). Due to the higher cost of tetrahydro-4*H*-pyran-4-one and tetrahydro-4*H*-thiopyran-4-one with respect to commercial aliphatic cyclic ketones, we performed the reactions with a lower excess of ketone (1.5 equiv. *vs.* 5 equiv.). Surprisingly, even under such conditions the reactions worked pretty well, with the same stereoselectivity and only with slight differences in terms of yields (compare: entries 3 and 4 in Table 4, entry 2 in Table 4 with entry 19 in Table 1). Once again, catalyst **2** showed enhanced activity in comparison with the proline-supported resin.

Conclusions

In summary, we have prepared a new, efficient, heterogeneous organocatalyst by employing a rapid and straightforward synthetic strategy. Such a prolinamide-supported polystyrene successfully worked in the asymmetric direct aldol reaction using both cyclic and acyclic ketones and various aryl aldehydes. The optimal reaction conditions were found when a 1:2 (v/v) water/chloroform mixture was used. This mixture was the best compromise between the good swelling properties of chloroform and the formation of a concentrated organic phase due to the presence of water. The performances obtained in some cases improved the values observed under homogeneous conditions or with a proline-based polystyrene. Particularly, the enantioselectivities obtained employing acetone as ketone were, to the best of our knowledge, the highest achieved with a supported proline-derivative. It is worthy to note that our catalyst worked nicely at room temperature while the excellent results displayed by prolinamide **1** under homogeneous condition were obtained on carrying out the reactions at −5 or −10 °C. Finally, although resin **2** needed a simple regeneration treatment, that may be considered as a drawback, its high recyclability, at least for twelve cycles, counterbalanced this aspect and makes resin **2** a promising catalyst.

Experimental Section

General Methods

NMR spectra were recorded with a Bruker 300 MHz spectrometer in $CDCl_3$ as solvent. Solid-state ^{13}C MAS NMR spectra were recorded with a Bruker AV 400, 400 MHz

spectrometer with samples packed in zirconia rotors spinning at 5 kHz. FT-IR spectra were recorded with a Shimadzu FTIR 8300 infrared spectrophotometer. Carbon and nitrogen contents were determined by combustion analysis in 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 an SPD-M10 A UV detector and Daicel columns (OD-H, AD-H, AS-H, 4.6 mm × 250 mm) with hexane/isopropyl alcohol as eluent. Aldol products, except (2*S*,1′*R*)-2-(hydroxy-(3-methoxyphenyl)methyl)cyclohexan-1-one, (4*R*)-(2-cyanophenyl)-4-hydroxy-2-butanone and (4*R*)-(2-chloro-6-nitrophenyl)-4-hydroxy-2-butanone are known compounds and showed spectroscopic and analytical data in agreement with their structures.[9a,f,19] The *anti/syn* ratios were determined from the ^{1}H NMR spectra of the crude reaction mixtures. The *ee* values were determined from HPLC traces of the crude reaction mixtures.

(2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-2-[(*S*)-2-hydroxy-1,2,2-triphenylethyl]-4-(4-vinylbenzyloxy)pyrrolidine-2-carboxamide (5)

Triethylamine (776 μL, 5.51 mmol) was slowly added to a solution of acid **3** (1.915 g, 5.51 mmol) in CH_2Cl_2 (18 mL) at 0 °C. Ethyl chloroformate (536 μL, 5.51 mmol) was added dropwise and the solution was stirred at the same temperature for 15 min. Then, amino alcohol (1.414 g, 4.74 mmol) was added and the resulting solution was stirred for 5 h. The solution was diluted with some CH_2Cl_2. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate, 5/1–2/1); yield: 62%; mp 183–185 °C; $[\alpha]_D^{28}$: −159.8 (*c* 0.79, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.08$ and 1.41 (two singlets, rotamers, *tert*-butyl), 1.75–1.81 (m, 1H, H-3, pyrrolidine ring), 2.26–2.33 (m, 1H, H-3, pyrrolidine ring), 3.28–3.62 (m, 3H, OH, H-5 pyrrolidine ring), 3.86–4.31 (m, 4H, H-2 and H-4 pyrrolidine ring, OC*H*$_2$Ph), 5.14 (d, $J = 11.1$ Hz, CH=C*H*$_2$), 5.63 (d, $J = 17.4$ Hz, CH=C*H*$_2$), 5.90 (d, $J = 7.2$ Hz, NH-C*H*), 6.63 (dd, $J = 17.4$ and 11.1 Hz, CH=CH$_2$), 6.95–7.30 (m, 17H, ArH). 7.45–7.50 (m, 2H, ArH), 8.05 (d, $J = 7.2$ Hz, N*H*-CH). IR (nujol): $\tilde{\nu}_{max} = 3385$, 1701, 1650 cm^{-1}; anal. calcd. for $C_{39}H_{42}N_2O_5$: C 75.70, H 6.84, N 4.53; found: C 75.61, H 6.78, N 4.49.

Polystyrene-Supported L-Prolinamide (2)

Mercaptomethylpolystyrene (385 mg, 0.962 mmol) was added to a degassed solution of compound **5** (1.787 g, 2.888 mmol) and AIBN (9.5 mg, 0.057 mmol) in toluene (23 mL). The mixture was stirred at 110 °C overnight under argon. After cooling to room temperature, the resin was filtered and washed with dichloromethane. A brilliant yellow resin was obtained; yield: 676 mg. From the weight increase it was calculated that 0.47 mmol of monomer has been covalently attached to the resin. The dichloromethane solution was evaporated under reduced pressure in order to recover the unreacted prolinamide **5** which was then purified by column chromatography (recovery: 90%). The resin was suspended in HCOOH (1.4 mL) and stirred for 20 h. After this time, water was added and the mixture was filtered. The resin was washed with a saturated solution of $NaHCO_3$, water, methanol and diethyl ether. The resin was dried in an oven at 60 °C for several minutes (629 mg). The weight difference corresponds to the amount of Boc removed, which is identical to the amount of available proline (0.47 mmol/0.629 $g = 0.74$ mmol g^{-1}).

(2*S*,1′*R*)-2-(Hydroxy-(3-methoxyphenyl)methyl)cyclohexan-1-one: Oil; $[\alpha]_D^{23}$: +7.9 (*c* 0.982, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.20$–1.34 (m, 1H), 1.50–1.81 (m, 4H), 2.03–2.10 (m, 1H), 2.28–2.35 (m, 1H), 2.37–2.50 (m, 1H), 2.55–2.64 (m, 1H), 3.80 (s, 3H), 3.96 (d, $J = 2.1$ Hz, 1H, OH), 4.75 (d, $J = 8.7$ Hz, 1H), 6.80–6.89 (m, 3H), 7.21–7.26 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 24.7$, 27.8, 30.8, 42.6, 55.2, 57.3, 74.6, 112.4, 113.3, 119.5, 129.3, 142.5, 159.6, 215.5; IR (liquid film): $\tilde{\nu}_{max} = 3498$, 1694, 1601, 1586 cm^{-1}. The optical purity was determined by HPLC on a Chiralpak AS-H column [*n*-hexane/2-propanol, 90:10]; flow rate 1.0 mL min^{-1}; t_R(major) = 15.9 min, t_R(minor) = 20.6 min. Anal. calcd. for $C_{14}H_{18}O_3$: C 71.77, H 7.74; found: C 71.68, H, 7.78.

(4*R*)-(2-Cyanophenyl)-4-hydroxy-2-butanone: Oil; $[\alpha]_D^{23}$: +96.2 (*c* 1.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.10$ (s, 3H), 2.72 (dd. $J = 17.7$ and 9.6 Hz, 1H), 2.90 (dd. $J = 17.7$ and 2.7 Hz, 1H), 3.90 (br s, 1H, OH), 5.40 (dd. $J = 9.6$ and 2.6 Hz, 1H), 7.30 (dt, $J = 7.6$ and 1.1 Hz, 1H), 7.52–7.57 (m, 2H), 7.63 (d $J = 7.6$ Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 30.9$, 51.1, 68.1, 109.9, 117.7, 126.9, 128.3, 133.1, 133.7, 146.7, 208.9; IR (liquid film): $\tilde{\nu}_{max} = 3434$, 2223, 1714 cm^{-1}. The optical purity was determined by HPLC on a Chiralpak OD-H column [*n*-hexane/2-propanol, 95:5]; flow rate 1.0 mL min^{-1}; t_R(minor) = 19.1 min, t_R(major) = 22.7 min. Anal. calcd. for $C_{11}H_{11}NO_2$: C 69.83, H 5.86; found: C 69.91, H 5.90.

(4*R*)-(2-chloro-6-nitrophenyl)-4-hydroxy-2-butanone: White solid; mp 122–124 °C; $[\alpha]_D^{24}$: 414.5 (*c* 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3H), 2.84 (dd, $J =$ 18.2 and 1.9 Hz, 1H), 3.31 (dd, $J = 18.2$ and 10.4 Hz, 1H), 3.46 (br s, 1H, OH), 5.63 (dd, $J = 10.4$ and 1.8 Hz, 1H), 7.26 (dd, $J = 8.0$ and 8.0 Hz, 1H), 7.36 (dd, $J = 8.0$ and 1.1 Hz, 1H), 7.45 (dd, $J = 8.0$ and 1.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 30.8$, 48.4, 67.0, 123.0, 129.3, 132.8, 133.4, 133.7, 151.7, 208.7; IR (nujol): $\tilde{\nu}_{max} = 3381$, 1708, 1543 cm^{-1}. The optical purity was determined by HPLC on a Chiralpak AD-H column [*n*-hexane/2-propanol, 95:5]; flow rate 1.0 mL min^{-1}; t_R(minor) = 29.3 min, t_R(major) = 32.2 min. Anal. calcd. for $C_{10}H_{10}ClNO_4$: C 49.30, H 4.14, N 5.75; found: C 49.36, H 4.19, N 5.80.

Typical Procedure for Aldol Reaction

Catalyst **2** was added (0.05 mmol) to a mixture of the corresponding aldehyde (0.5 mmol) and ketone (0.75 or 2.5 mmol) in distilled water (0.10 mL) and chloroform (0.20 mL) and the reaction mixture was stirred at room temperature. The reaction mixture was filtered, 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 was then purified by chromatography (petroleum ether/ethyl acetate).

Procedure for Catalyst Regeneration

The recovered catalyst was placed in a round-bottom 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 it was dried for a few minutes at 60 °C.

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds, copies of ^{1}H NMR spectra and chromatograms of the reaction mixtures are available as Supporting Information

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