Poly(Ethylene Glycol)-Supported Proline: A Versatile Catalyst for the Enantioselective Aldol and Iminoaldol Reactions

Maurizio Benaglia,[a,*] Mauro Cinquini,[a] Franco Cozzi,[a,*] Alessandra Puglisi,[a] Giuseppe Celentano[b]

[a] CNR-ISTM and Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via Golgi 19, 20133 Milano, Italy
Fax: (+39) 02-5835-4159, e-mail: franco.cozzi@unimi.it
[b] Istituto di Chimica Organica, Facoltà di Farmacia, Università degli Studi di Milano, via Venezian 21, 20133 Milano, Italy

Received: December 27, 2001; Accepted: February 22, 2002

Abstract: (2*S*,4*R*)-4-Hydroxyproline has been anchored to the monomethyl ether of poly(ethylene glycol), M_W 5000, by means of a succinate spacer to afford a soluble, polymer-supported catalyst (PEG-Pro) for enantioselective aldol and iminoaldol condensation reactions. This organic catalyst can be considered as a minimalistic version of a type I aldolase enzyme, with the polymer chain replacing the enzyme's peptide backbone, and the proline residue acting as the enzyme's active site. In the presence of PEG-Pro (0.25 – 0.35 mol equiv.), acetone reacted with enolizable and non-enolizable aldehydes and imines to afford β-ketols and β-aminoketones in good yield and high enantiomeric excess (ee), comparable to those obtained using non-supported proline derivatives as the catalysts. Extension of the PEG-Pro-promoted condensation to hydroxyacetone as the aldol donor opened an access to synthetically relevant *anti*-α,β-dihydroxyketones and *syn*-α-hydroxy-β-aminoketones, that were obtained in moderate to good yields, and good to high diastereo- and enantioselectivity. Exploiting its solubility properties, the PEG-Pro catalyst was easily recovered and recycled to promote all of the above-mentioned reactions, that occurred in slowly diminishing yields but virtually unchanged ee's.

Keywords: aldol reactions; asymmetric catalysis; iminoaldol reactions; soluble polymers; supported catalysis

Introduction

Proline has long been known to catalyze enantioselective Robinson annulation processes.[1] On this basis there has recently been a renewed interest in a broader use of this amino acid for the biomimetic approach to catalytic asymmetric C-C bond-forming reactions.[2–4] In the context of aldol condensations,[2] proline plays the role of an oversimplified version of type I aldolase enzymes,[5] promoting the activation of an aldol donor by formation of a ketone enamine and its enantioselective condensation with an aldol acceptor (an aldehyde or an imine). The use of proline represents an "all-organic" (i.e., metal-free) alternative to the metal-based catalysts for enantioselective aldol-type processes.[6,7]

In the course of a project aimed at the immobilization of chiral ligands[8] and catalysts[9] on poly(ethylene glycols) (PEGs),[10] we were attracted by the possibility of using a modified PEG of M_W 5000 (PEG_{5000}) as support for chiral organic catalysts.[11] We hypothesized that a PEG-supported proline (PEG-Pro) could potentially represent a very useful catalyst for the following reasons. First, the solubility profile of PEG[12] would secure PEG-Pro to be soluble in many organic solvents and insoluble in a few other solvents, thus allowing us to operate under homogeneous (and best-performing) catalysis conditions, and to easily recover and recycle the catalyst as if working under heterogeneous conditions. Secondly, being a supported organic catalyst, PEG-Pro would not suffer from metal leaching,[10a] a major problem associated with the use and the recycling of metal-based, polymer-supported catalytic systems, which often require addition of fresh metal species to fully restore the original catalytic activity.[13] Finally, PEG-Pro can be considered a less dissimilar model than proline itself of a type I aldolase enzyme, with the polymer backbone roughly acting as the peptide skeleton[14] and proline acting as the catalytic site.

Here, we report that the immobilization of (2*S*,4*R*)-4-hydroxyproline on PEG_{5000} monomethyl ether (MeO-PEG) afforded an efficient and recyclable catalyst for enantioselective aldol and iminoaldol reactions.[15]

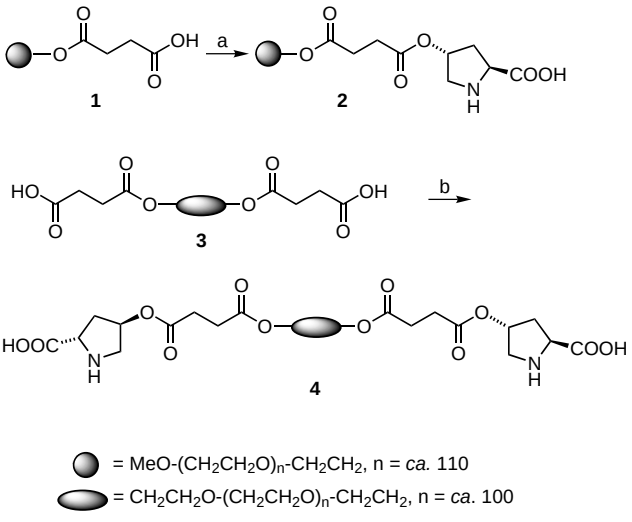
  1615-4150/02/34405-533 – 542 $ 17.50+.50/0

Results and Discussion

Synthesis of the Catalysts

Reaction of MeOPEG monosuccinate **1**[10b] with diisopropylcarbodiimide (DIC, 2.2 mol equiv.) and (2*S*,4*R*)-4-hydroxyproline (2.0 mol equiv.) at 140 °C for 20 h in the absence of solvent (Scheme 1) afforded PEG-Pro **2** in 85 – 95% yield (see the Experimental Section for the determination of the yields of reactions that involve polymer-supported substrates and the purity criteria for polymer-supported products). Lower yields (35 – 40%) were observed by running the reaction for 40 h in refluxing 1,2-dichloroethane using a four-fold excess of DIC and 4-hydroxyproline with respect to MeOPEG.

Formation of product **2** was suggested by 300 MHz ^{1}H NMR spectroscopy which showed that the coincident signals of the succinic methylene groups of **1** (a singlet at 2.60 ppm) became two distinct triplets (at 2.66 and 2. 44 ppm) in **2**. In a control experiment, it was shown that a mechanical mixture of **1** and 4-hydroxyproline gave a singlet for the same protons. Configurational stability of 4-hydroxyproline under the reaction conditions required for the synthesis of **2** was demonstrated when a sample of the amino acid showed an unchanged optical rotation after heating at 150 °C for 40 h. In order to obtain a catalyst with a double loading of catalytic sites, bis-succinate **3** was prepared from unprotected PEG_{4600} and transformed into the bis-proline derivative **4** in 87% yield.



Reagents and conditions. a: DIC (2.2 mol equiv.), (2*S*,4*R*)-4-hydroxyproline (2.0 mol equiv.), 140 °C, 20 h; b: DIC (4.4 mol equiv.), (2*S*,4*R*)-4-hydroxyproline (4.0 mol equiv.), 140 °C, 20 h.

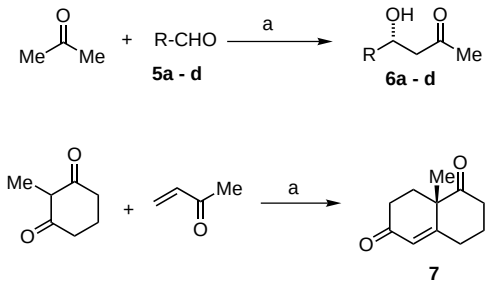
Scheme 1. Synthesis of PEG-supported catalysts **2** and **4**.

Aldol Condensations

The aldol condensation between acetone (68 mol equiv.) and 4-nitrobenzaldehyde **5a** carried out at room temperature (23 – 25 °C) in the presence of catalyst **2** (0.3 mol equiv.) was selected to establish the best reaction conditions (Scheme 2 and Table 1, Entries 1 – 8). These involved the use of an aprotic dipolar solvent (with DMF performing better than DMSO or acetonitrile, Entries 2, 4, 8), and of a reaction time of at least 48 h (Entries 1 *vs.* 2, and 3 *vs.* 4). Under the best conditions (Entry 4) aldol (*R*)-**6a** was obtained in 68% isolated yield and 77% enantiomeric excess (ee), as determined by HPLC analysis on a chiral stationary phase. The absolute configuration was determined by comparison of the sign of optical rotation.[2a,2e] Less polar solvents (Entries 5 – 7) performed poorly both in terms of chemical yield and enantioselectivity. Remarkably, and quite surprisingly, the use of acetone as the reaction solvent (Entry 7) gave an aldol of the opposite absolute configuration.

A comparison of these results with those obtained working with non-supported proline derivatives at the same catalyst loading (0.3 – 0.4 mol equiv.)[2a] showed that the use of PEG-Pro achieved similar yield and enantioselectivity. Among the non-supported catalysts, the best term of comparison is perhaps represented by (2*S*,4*R*)-4-acetoxyproline, which features an ester linkage at C-4 as in **2**. Working with this catalyst in DMSO at room temperature, aldol **6a** was obtained in 70% yield and 74% ee; proline (68% yield, 76% ee), and *trans*-4-hydroxyproline (85% yield, 78% ee) performed similarly.[2a] With our catalyst, the use of DMSO rather than DMF led to marginally higher yield but lower ee (Entries 1 *vs.* 3 and 2 *vs.* 4).

Extension of this methodology to other aldehydes (**5b – d**, Entries 9 – 12) was also possible. The corre-



a, R = 4-NO_2Ph; **b**, R = Ph; **c**, R = 4-BrPh; **d**, R = *c*-C_6H_{11}.

Reagents and conditions. a: **2** (0.3 mol equiv.) or **4** (0.15 mol equiv.), solvent, room temperature, 20 - 130 h.

Scheme 2. Synthesis of β-hydroxyketones **6a – d** and ketone **7**.

Table 1. Catalytic enantioselective synthesis of β-hydroxyketones **6a – d**.

Entry	Aldehyde	Solvent/Time [h]	Product	Yield [%][a]	ee [%][b]
1	**5a**	DMSO/20	(*R*)-**6a**	36	60
2	**5a**	DMSO/48	(*R*)-**6a**	73	62
3	**5a**	DMF/20	(*R*)-**6a**	35	67
4	**5a**	DMF/48	(*R*)-**6a**	68	77
5	**5a**	CH_2Cl_2/48	**6a**	8	undetermined
6	**5a**	Toluene/48	**6a**	15	undetermined
7	**5a**	Acetone/48	(*S*)-**6a**	23	21
8	**5a**	CH_3CN/48	(*R*)-**6a**	50	41
9	**5b**	DMF/60	(*R*)-**6b**	45	59
10	**5c**	DMF/60	(*R*)-**6c**	55	63
11	**5d**	DMF/60	(*R*)-**6d**	33	93
12	**5d**	DMSO/130	(*R*)-**6d**	81	$\geq$98
13	**5a**[c]	DMSO/24	(*R*)-**6a**	67	74
14	**5a**[d]	DMF/48	(*R*)-**6a**	63	77
15	**5a**[e]	DMF/48	(*R*)-**6a**	58	77
16	**5a**[f]	DMF/48	(*R*)-**6a**	51	75
17	**5d**[g]	DMSO/130	(*R*)-**6d**	77	96
18	**5a**[h]	DMSO/24	(*R*)-**6a**	60	74

[a] Isolated yields. For each aldehyde the highest yields were average values of at least duplicate experiments run on different scales. The variations in yield were $\leq$4%.
[b] As determined by HPLC on a chiral stationary phase. The ee values for the highest yielding reactions were average values of at least duplicate experiments. The variations in ee were $\leq$2%.
[c] With catalyst **4**.
[d] Carried out with a catalyst sample recycled after use in Entry 4.
[e] Carried out with a catalyst sample recycled after use in Entries 4 and 14.
[f] Carried out with a catalyst sample recycled after use in Entries 4, 14, and 15.
[g] Carried out with a catalyst sample recycled after use in Entry 10.
[h] Carried out with a sample of catalyst **4** recycled after use in Entry 13.

sponding aldols **6b – d** were obtained in yields and ee comparable to those reported using the non-supported catalysts.[2a] The result obtained with the α-branched cyclohexanecarboxyaldehyde **6d** (Entry 12) was particularly relevant both in terms of yield (81%) and enantioselectivity (ee > 98%). Although in this case the use of DMSO and a long reaction time was necessary, the efficiency of the process was superior to that of the corresponding proline-catalyzed reaction.[2e]

The condensation between acetone and aldehyde **5a** (Entry 13) was used to test the bis-proline substituted catalyst **4**. At a 15% molar concentration this compound was shown to behave virtually as catalyst **2**, promoting the synthesis of aldol **6a** in 67% yield and 74% ee (DMSO, 24 h). This result seems to indicate that the two "catalytic sites" of **4** act independently from, and do not interfere with, one another. It also shows that an increase of the catalyst "loading" (i.e., of the number of active groups per gram of polymer) is a viable protocol to reduce the weight amount of these high M_w polymer-supported reagents.[16]

The possibility of catalyst recovery and recycling was studied using the synthesis of **6a** and the experiments reported in Entries 14 – 18. The data showed that catalyst **2**, readily recovered by precipitation with diethyl ether and filtration (70 – 80% yield), could be re-used at least three times (Entries 14 – 16) with some loss of chemical efficiency but almost no effect on the enantioselectivity. Indeed, while the chemical yield of aldol **6a** showed a slow but steady decrease of about 5% for each cycle (from 68%, 1st cycle, to 51%, 4th cycle), the ee remained practically unchanged at the >75% level. A single recycling of catalyst **4** showed the same trend (Entries 13 and 18).[17] Finally, a sample of **2** employed for the synthesis of aldol **6c** could be re-used to promote the formation of compound **6d** with virtually unchanged stereoselectivity (Entries 10 and 17). These recovery/recycling experiments can be compared to those performed on non-supported proline.[2e] Proline recovery was achieved by two different approaches: simply running the aldol condensation in chloroform, a solvent in which the catalyst is barely soluble and thus easily recovered by filtration, or by performing the reaction with a sample of proline non-covalently immobilized on a silica gel column. However, both modifications clearly depressed the efficiency of the process, and it was concluded that the results did not justify these approaches toward catalyst recycling.[2e]

From a more general point of view, it is worth mentioning that the effect exerted by recycling a PEG-

supported chiral catalyst is different from that exerted by recycling a PEG-supported chiral ligand,[8] a process that, over three cycles, led to less stereoselective reactions (from 96% ee, 1st cycle, to 88% ee, 3rd cycle) that occurred in almost unchanged chemical yield (from 95 to 93%).

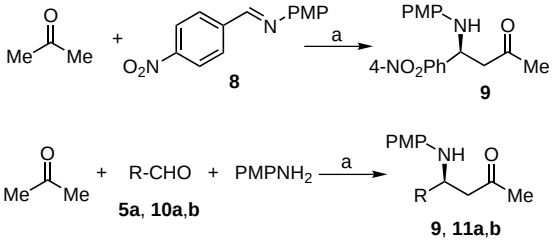
Synthesis of the Wieland–Mischler Ketone

As mentioned in the introduction, the original procedure in which proline was recognized as an enantioselective catalyst was the Eder–Sauer–Wiechert–Hajos synthesis of bicyclic ketones, including the Wieland–Mischler ketone **7**, a useful starting material for natural product synthesis.[1] When the PEG-Pro catalyst **2** (0.35 mol equiv.) was employed in the Robinson annulation between 2-methyl-1,3-cyclohexanedione and 3-propen-2-one (1.5 mol equiv.) at room temperature, ketone (*S*)-**7** was obtained in up to 55% yield and 75% ee (Scheme 2). Optimum conditions involved the use of DMSO for a reaction time of 90 h, whereas the use of DMF led to lower yield (37%) and ee (66%). An attempt to improve the yield of the reaction in DMSO by prolonging the reaction time to 6 days failed, affording **7** in 37% yield and 72% ee. At its best, the PEG-Pro-catalyzed reaction nicely compares with the proline-promoted process (same catalyst loading, DMSO as solvent, 89 h at room temperature) that afforded (*S*)-**7** in 49% yield and 76% ee.[2c]

Iminoaldol Reactions

To the best of our knowledge [10a] a single report in the literature has described the use of a polymer-supported catalyst for the enantioselective iminoaldol reaction.[18,19] In this example a BINAP ligand immobilized on polystyrene was used for the Pd-catalyzed addition of the trimethylsilyl enol ether of acetophenone to a glyoxylate-derived imine, that occurred in 95% yield and 81% ee. After catalyst recovery and regeneration by a basic treatment a second, less efficient cycle was possible (72% yield, 71% ee). Since proline and its analogues have been shown to promote the enantioselective iminoaldol condensation between acetone and pre-formed or *in situ* generated imines,[2e,3] catalyst **2** was tested in this type of process.

The reaction of acetone (36 mol equiv.) with imine **8** in the presence of 0.3 mol equiv. of **2** at room temperature (Scheme 3) afforded β-aminoketone (*S*)-**9** in yields and ee that depended on the reaction time and the solvent (Table 2, Entries 1–5). Best results (81% yield and 96% ee, Entry 5) were obtained in DMSO with a reaction time of 72 h, whereas shorter condensations (Entries 2–4) or the use of DMF (Entry 1) were less satisfactory.



PMP = 4-MeOPh; **10a** and **11a**, R = *i*-Pr; **10b** and **11b**, R = *i*-Bu.

Reagents and conditions. a: **2** (0.3 mol equiv.) , DMSO, room temperature, 24 - 72 h.

Scheme 3. Synthesis of β-aminoketones **9**, **11a**, and **11b**.

A comparison of these results with those obtained under similar conditions with non-supported proline[3] is difficult, since the reported syntheses of compound **9** involved samples of imine **8** generated *in situ* (see below). It must be noted, however, that the use of the *ortho*-methoxy isomer of **8**,[3b] led to the corresponding adduct in 50% yield and 40% ee. The reported results for the proline-catalyzed three-component syntheses of **9**[3] differ slightly. List, working with 0.35 mol equiv. of catalyst (DMSO, 48 h), claimed a 50% yield for a product having a 94% ee;[3a] Barbas, working with 0.2 mol equiv. of catalyst (DMSO, 24 h), isolated compound **9** in 52% yield and 89% ee.[3b] In both cases the yields and the ee's were lower than those observed with catalyst **2** in the two-component reaction. In addition, undisclosed amounts of the aldol product **6a** and of the corresponding α,β-unsaturated ketone were also obtained in the proline-catalyzed three-component procedure.[3]

When PEG-Pro **2** (0.3 mol equiv.) was used to catalyzed the three-component synthesis of β-aminoketone **9** (DMSO, 48 h, RT; Entry 6), a 50:50 mixture of this product and aldol **6a** was obtained in only 20% combined yield. With the aim of speeding up the imine formation, 4 Å molecular sieves were added to the reaction mixture. This increased the **9**/**6a** ratio to 80:20 but exerted a marginal effect on the yield (36%, combined). Slow addition of the aldehyde to the other reagents was not beneficial either (**9**/**6a** ratio = 60:40; 27% combined yield). These results suggested that the iminoaldol reaction catalyzed by **2** is slower than that catalyzed by proline, and therefore the aldol process remains an available pathway in the PEG-Pro-promoted three-component reaction.

β-Ketols were also observed as separable by-products (10–20%) when the three-component condensation was extended to imines derived from aliphatic aldehydes **10a** and **10b** (Entries 9–14, Table 2).[20] The

Table 2. Catalytic enantioselective synthesis of β-aminoketones **9**, **11a**, **11b**.

Entry	Imine [a]	Time [h]	Product	Yield [%][b]	ee [%][c]
1	**8**	12	**9**	18[d]	undetermined
2	**8**	12	**9**	29	undetermined
3	**8**	24	(*S*)-**9**	43	60
4	**8**	48	(*S*)-**9**	57	93
5	**8**	72	(*S*)-**9**	81	96
6	**5a** + $PMPNH_2$	48	**9** + **6a**	10 + 10	undetermined
7	**5a** + $PMPNH_2$	48	**9** + **6a**	29 + 7	undetermined
8	**5a** + $PMPNH_2$	48	**9** + **6a**	16 + 11	undetermined
9	**10a** + $PMPNH_2$	24	(*S*)-**11a**	41	78
10	**10a** + $PMPNH_2$	48	(*S*)-**11a**	35	73
11	**10a** + $PMPNH_2$	72	(*S*)-**11a**	38	55
12	**10b** + $PMPNH_2$	24	(*S*)-**11b**	45	83
13	**10b** + $PMPNH_2$	48	(*S*)-**11b**	51	83
14	**10b** + $PMPNH_2$	72	(*S*)-**11b**	37	40
15	**8**[e]	72	(*S*)-**9**	71	96
16	**8**[f]	72	(*S*)-**9**	64	97

[a] In the reactions of Entries 6 – 14 the imines were generated *in situ*.
[b] Isolated yields for reactions in DMSO (unless otherwise stated). Yields of Entries 6 – 8 are for iminoaldol **9** + ketol **6a**. Yields of Entries 9 – 14 are for pure iminoaldols. For each imine the highest yields were average values of at least duplicate experiments run on different scales. The variations in yield were $\leq 4\%$.
[c] As determined by HPLC on a chiral stationary phase or by comparison of optical rotation values. The ee values for the highest yielding reactions were average values of at least duplicate experiments. The variations in ee were $\leq 2\%$.
[d] In DMF.
[e] Carried out with a catalyst sample recycled after use in Entry 5.
[f] Carried out with a catalyst sample recycled after use in Entries 5 and 15.

outcome of these reactions, carried out under conditions similar to those employed for the synthesis of **9** (0.3 mol equiv. of **2**, DMSO, RT), strongly depended on the reaction time. Best enantioselectivities were observed after 24 h for both β-aminoketones **11a** (R = *i*-Pr, 78% ee, Entry 9) and **11b** (R = *i*-Bu, 83% ee, Entry 12). The chemical yields were moderate and decreased for prolonged reaction time, as did the enantioselectivities (Entries 11 and 14). In order to show that a process involving β-elimination of 4-methoxyaniline from the β-aminoketone followed by a non-stereoselective conjugate addition of the latter to the resulting unsaturated ketone could account for the lower ee observed at long reaction time, compound **11a** (78% ee) was stirred for 24 h at RT in DMSO in the presence of 0.3 mol equiv. of PEG-Pro **2**. From this reaction the product was recovered in 87% yield virtually in the racemic form, in agreement with the proposed racemization mechanism. Finally, it is worth mentioning that the results obtained in the PEG-Pro-catalyzed three-component synthesis of **11a** nicely compare to those obtained under similar conditions with proline as catalyst (56% yield, 70% ee).[3a]

Catalyst recovery and recycling, tested in the synthesis of (*S*)-**9** (Entries 5, 15, and 16, Table 2), showed a trend similar to that observed in the aldol condensation reaction, with a constant, slow decrease of chemical yield (from 81%, 1st cycle, to 64%, 3rd cycle), and no erosion of the enantioselectivity ($\geq 96\%$).

Reactions with Hydroxyacetone as Aldol Donor

The extension of the proline-catalyzed enantioselective aldol[2b,2e] and iminoaldol reactions [3a] to hydroxyacetone provided a convenient alternative to Sharpless' asymmetric dihydroxylation [21] and aminohydroxylation protocols[22] for the synthesis of 2,3-dihydroxyketones and 2-hydroxy-3-aminoketones, respectively. In this context, the possibility of obtaining *anti*-2,3-dihydroxyketones,[2b,2e] a class of compounds not available in this configuration *via* the asymmetric dihydroxylation reaction,[23] was particularly appealing.

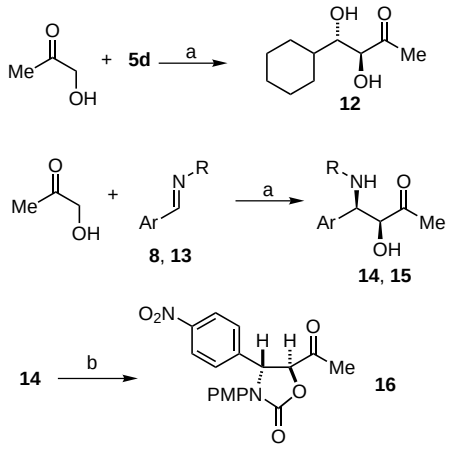
We were pleased to find that the supported catalyst PEG-Pro **2** efficiently promoted also these synthetically relevant reactions in good yields and enantioselectivities (Scheme 4 and Table 3). Condensation of hydroxyacetone (66 mol equiv.) with cyclohexanecarboxyaldehyde carried out in DMF in the presence of 0.25 mol equiv. of catalyst **2** (48 h, RT) afforded adduct (3*S*,4*S*)-**12** in 48% yield, > 20:1 *anti*-diastereoselectivity, and 96% ee. The use of DMSO as solvent (60 h, RT) resulted in identical stereoselectivities and 45% yield. The latter was slightly lower than that observed in the proline-catalyzed reaction carried out under identical conditions (60%).[2b,24]

The condensations between hydroxyacetone (37 mol equiv.) and imines **8** and **13** catalyzed by 0.35 mol equiv. of PEG-Pro **2** were also investigated (Scheme 4 and Table 3). Best conditions were established exploiting

Table 3. Catalytic enantioselective synthesis of α,β-dihydroxyketone **12** and α-hydroxy-β-aminoketones **14** and **15**.

Entry	Acceptor	Time [h]	Product	Yield [%][a]	*anti/syn*[b]	ee [%][c]
1	**5d**	48	(3*S*,4*S*)-**12**	48[d]	20/1	96
2	**5d**	60	(3*S*,4*S*)-**12**	45	>20/1	96
3	**5d**[e]	60	(3*S*,4*S*)-**12**	37	>20/1	96
4	**5d**[f]	60	(3*S*,4*S*)-**12**	28	>20/1	96
5	**8**	48	(3*S*,4*R*)-**14**	21[d]	1/4	80
6	**8**	20	(3*S*,4*R*)-**14**	33	1/5.6	76
7	**8**	48	(3*S*,4*R*)-**14**	73	1/8	83
8	**8**	72	(3*S*,4*R*)-**14**	71	1/9	94[g]
9	**8**[h]	72	(3*S*,4*R*)-**14**	69	1/9	92
10	**13**	72	(3*S*,4*R*)-**15**	70	1/5.6	93[j]

[a] Isolated yields for reactions in DMSO (unless otherwise stated). For products 12 and 14 the highest yields were average values of at least duplicate experiments run on different scales. The variations in yield were $\leq$4%.
[b] As determined by 300 MHz ^{1}H NMR analysis of the crude reaction products.
[c] Reported values refer to the major isomer and were determined by HPLC on a chiral stationary phase. Highest ee values for **12** and **14** were average values of at least duplicate experiments. The variations in ee were $\leq$2%.
[d] In DMF.
[e] Carried out with a catalyst sample recycled after use in Entry 2.
[f] Carried out with a catalyst sample recycled after use in Entries 2 and 3.
[g] The ee of the *anti*-isomer was 40%.
[h] Carried out with a catalyst sample recycled after use in Entry 8.
[j] The ee of the *anti*-isomer was 40%.



PMP = 4-MeOPh; **8** and **14**, Ar = 4-NO_2Ph, R = PMP;
13 and **15**, Ar = Ph, R = 4-ClPh.

Reagents and conditions. a: **2** (0.25 - 0.35 mol equiv.) , DMF or DMSO, room temperature, 20 - 72 h. b: $COCl_2$, TEA, DMAP, 0 °C to RT, 1 h.

Scheme 4. Synthesis of α,β-dihydroxyketone **12** and of α-hydroxy-β-aminoketones **14** and **15**.

the synthesis of α-hydroxy-β-aminoketone **14** (Entries 5–8), that, after reaction in DMSO for 72 h, was obtained in 71% yield as a 9:1 mixture of diastereoisomers. The relative configuration at the stereocenters of the major isomer was determined as *syn* by its conversion into the corresponding *trans*-oxazolidinone **16** (20% phosgene in toluene, TEA, DMAP, 0 °C to RT, 1 h, 55% yield). HPLC analysis showed a 94% ee for adduct **14** to which the (3*S*,4*R*) configuration was tentatively assigned, on the basis of the reasonable assumption that the stereocenters at C-3 in **12** and **14** should be the same, and by analogy with the inversion of configuration at C-4 observed on passing from aldol **6a** to iminoaldol **9a**. α-Hydroxy-β-aminoketone **15** (Entry 9) was also obtained in almost identical yield (70%) and ee (93%), but lower diastereoselectivity (*syn*:*anti* = 5.6:1).

In order to compare the efficiency of the supported catalyst to that of non-supported proline, the synthesis of **14** was repeated using the latter as the catalyst. The product was obtained in the same yield (71%) and diastereoselection (*syn*:*anti* ratio 9:1), and a marginally higher ee (96%) after 20 h reaction in DMSO at room temperature, showing that also in this condensation PEG-Pro **2** is a chemically less efficient catalyst than proline.[25]

Recovery and recycling of catalyst **2** in the reactions in which hydroxyacetone acted as the aldol donor were studied both in the case of the synthesis of α,β-dihydroxyketone **12** (Entries 3 and 4, Table 3) and in that of α-hydroxy-β-aminoketone **14** (Entry 8, Table 3). The results confirmed the trend emerged in the previous recycling experiments (see above), showing that catalyst recycling was indeed possible and allowed us to perform equally stereoselective reactions occurring in slowly decreasing chemical yields.

Conclusion

In conclusion, succinic acid-modified poly(ethylene glycol)s were shown to be suitable polymers for the immobilization of (2*S*,4*R*)-4-hydroxyproline to afford

soluble, polymer-supported catalysts for the an enantioselective version of the aldol and iminoaldol reactions. Both acetone and hydroxyacetone could be successfully employed as the aldol donors in these processes. The PEG-Pro-catalyzed condensations gave synthetically relevant products in yields and ee comparable to those observed in the reactions promoted by non-supported proline derivatives. The immobilized catalysts were recovered and recycled to perform reactions occurring in slowly diminishing yields but virtually unchanged enantioselectivities. These results expand the scope of organic catalysts in the field of enantioselective synthesis, making the search for these reagents more and more appealing.

Experimental Section

General

All PEG samples, with the exception of the recovered catalysts, were melted at 90 °C under vacuum for 30 min before use to remove traces of moisture. After reaction, PEG-supported product purification involved evaporation of the reaction solvent in vacuum and addition of the residue dissolved in a few mL of CH_2Cl_2 to diethyl ether (50 mL g^{-1} of polymer), which was stirred and cooled at 0 °C. After 20 – 30 min stirring at 0 °C, the obtained suspension was filtered through a sintered glass filter, and the solid repeatedly washed on the filter with diethyl ether (up to 100 mL/g of polymer, overall). ^{1}H NMR spectra were recorded at 300 MHz as solutions in $CDCl_3$ at 25 °C; δ were in ppm downfield from TMS; IR spectra were recorded on thin film or as solutions in CH_2Cl_2.

Yield and Purity Determination of PEG-Supported Compounds

The yields of the PEG-supported compounds were determined by weight with the assumption that the M_w of the PEG fragment is 5000 Da (for compound **2**) or 4600 Da (for compound **4**). The M_w actually ranged from 4500 to 5500 (4200 to 5000). The indicated yields were for pure compounds. The purity of these compounds was determined by ^{1}H NMR analysis in $CDCl_3$ at 300 MHz with pre-saturation of the methylene signals of the polymer centered at δ = 3.63. In recording the NMR spectra, a relaxation time of 6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of the integration. The relaxation delay was selected after T_1 measurements. The integration of the signals of the PEG CH_2OCH_3 fragment at δ = 3.30 and 3.36 were used as internal standard. The estimated integration error was ± 5%.

Synthesis of the Catalysts

To a mixture of **1** (3.0 g, 0.6 mmol, loading 0.196 meq/g), previously dried under vacuum at 90 °C, and (*2S,4R*)-4-hydroxyproline (0.156 g, 1.2 mmol) kept at 140 °C under N_2, DIC (0.204 mL, 1.32 mmol) was added dropwise. After 20 h stirring at 140 °C, the thick mixture was cooled at RT, dissolved in CH_2Cl_2 (5 mL), and poured dropwise in Et_2O (200 mL). The precipitated pale brown solid was filtered, washed first with Et_2O (150 mL) and then with ice-cold absolute EtOH (150 mL), and dried under vacuum to give **2**; yield: 2.67 – 2.93 g (85 – 95%, 0.52 – 0.57 mmol, loading 0.191 meq/g); ^{1}H NMR: δ = 5.58 – 5.67 (m, 1H, HC-4 of proline), 4.25 [t, ^3J(H,H) = 4.4 Hz, 2H, PEG-CH_2OCO], 4.00 – 4.17 (m, 1H, HC-2 of proline), 3.30 (s, 3H, CH_3O), 2.66 [t, ^3J(H,H) = 6.8 Hz, 2H, CH_2COO-proline), 2.58 – 2.70 (m, 2H, H_2C-3 of proline), 2.44 [t, ^3J(H,H) = 6.8 Hz, 2H *CH_2*CH_2COO-proline).

Starting from compound **3** (3 g, 0.63 mmol, loading 0.211 meq/g) and following the same procedure, catalyst **4** was isolated; yield: 2.74 g (87%, 0.548 mmol, loading 0.2 meq/g); ^{1}H NMR (D_2O): δ = 4.59-4.65 (m, 2H, HC-4 of proline), 4.25 – 4.35 [dd, ^3J(H,H) = 8.1, 2.1 Hz, 2H, HC-2 of proline), 4.22 [t, ^3J(H,H) = 4.5 Hz, 4H, PEG-CH_2*CH_2*OCO], 3.90 [t, ^3J(H,H) = 4.7 Hz, 4H, PEG-*CH_2*CH_2OCO], 3.43 [dd, ^3J(H,H) = 13.0, 3.8 Hz, 2H, HC-5 of proline], 3.31 [dd, ^3J(H,H) = 13.0, 1.0 Hz, 2H, HC-5 of proline], 2.64 [t, ^3J(H,H) = 6.8 Hz, 4H, *CH_2*COO-proline], 2.46 22 [t, ^3J(H,H) = 6.8 Hz, 4H, *CH_2*CH_2COO-proline], 2.38 [ddd, ^3J(H,H) = 14.0, 8.0, 1.0 Hz, 2H, HC-3 of proline], 2.11 [ddd, ^3J(H,H) = 14.0, 8.0, 2.1 Hz, 2H, HC-3 of proline].

General Procedure for the Aldol Condensations

The synthesis of **6a** is illustrative of the procedure. To a stirred solution of catalyst **2** (0.160 g, 0.0306 mmol), previously dried under vacuum at 90 °C, in dry DMF (2 mL) and acetone (0.5 mL, 6.8 mmol), 4-nitrobenzaldehyde **5a** (0.0151 g, 0.1 mmol) was added in one portion. The mixture was stirred at RT for 48 h and then poured in Et_2O (100 mL). The precipitated **2** was filtered off, and the solid was washed with Et_2O (50 mL). Average recovery of catalyst ranged from 70 to 80% (0.110 to 0.130 g) when the reaction was run on the above-mentioned scale, and increased to ≥ 90% when the reaction was run on a doubled or a larger scale. The filtrate was washed twice with water, and the Et_2O phase was dried and concentrated under vacuum. The residue was purified by flash chromatography with a 1:1 hexanes:Et_2O mixture as eluant to give the product; yield: 0.010 g (68%). The ee was determined by HPLC (Daicel Chiralpack AS, hexane/*i*-PrOH = 70:30, flow rate 0.8 mL/min, λ = 270): t_R: 13.28 min (major) and 15.94 min (minor). $[\alpha]_D^{23}$: + 55.3 (*c* 0.2, $CHCl_3$) for a sample of 77% ee (Lit.:[2e] $[\alpha]_D^{23}$:+ 46.2, *c* 1.0, $CHCl_3$ for a sample of 76% ee).

Aldols **6a – d**,[2a,2e] and diol **12**[2b] were known compounds. They had spectral data in agreement with those reported. Their absolute configuration was assigned on the basis of comparison of optical rotation sign. **6b** (Daicel Chiralpack OJ, hexane/*i*-PrOH = 70:30, flow rate 0.8 mL/min, λ = 270): t_R: 4.92 min (minor) and 7.35 min (major). $[\alpha]_D^{23}$: + 42.0 (*c* 0.1, $CHCl_3$) for a sample of 59% ee (Lit.:[2a] $[\alpha]_D^{23}$: + 41.8, *c* 1.0, $CHCl_3$ for a sample of 60% ee). **6c** (Daicel Chiralpack AS, hexane/*i*-PrOH = 85:15, flow rate 0.8 mL/min, λ = 270): t_R: 5.55 min (minor) and 7.93 min (major). $[\alpha]_D^{23}$: + 41.0 (*c* 0.1, $CHCl_3$) for a sample of 63% ee. **6d** (Daicel Chiralpack OJ, hexane/*i*-PrOH = 70:30, flow rate 0.8 mL/min, λ = 270): t_R: 3.64 min (minor) and 4.17 min (major). $[\alpha]_D^{23}$: + 45.5 (*c* 0.6, $CHCl_3$) for a

sample of [3] 98% ee (Lit.:[2e] $[\alpha]_D^{23}$: +41.5, *c* 1.0, $CHCl_3$ for a sample of 85% ee). **12** (Daicel Chiralpack AS, hexane/*i*-PrOH = 85:15, flow rate 0.8 mL/min, λ = 270): t_R: 6.84 min (minor) and 7.85 min (major). $[\alpha]_D^{23}$: +82.2 (*c* 0.2, $CHCl_3$) for a sample of 96% ee (Lit.:[2b] $[\alpha]_D^{23}$: +83.0, *c* 1.0, $CHCl_3$ for a sample of the *anti*-isomer of > 20:1 diastereoisomeric purity having a 99% ee). For this compound, the diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude reaction product (the spectrum of the undetected *syn*-isomer has been reported [2b]).

Synthesis of the Wieland–Mischler Ketone (*S*)-7

To a stirred solution of catalyst **2** (0.366 g, 0.070 mmol), previously dried under vacuum at 90 °C, in dry DMSO (2 mL), 2-methyl-1,3-cyclohexanedione (0.0252 g, 0.20 mmol) and freshly distilled 3-buten-2-one (0.025 mL, 0.30 mmol) were added, and the mixture was stirred at room temperature for 90 h. The mixture was then poured in Et_2O (100 mL). The precipitated **2** was filtered off, and the solid was washed with Et_2O (50 mL). The filtrate was washed twice with water, and the Et_2O phase was dried and concentrated under vacuum. The residue was purified by flash chromatography with a 1:1 hexanes:Et_2O mixture as eluant to give the product; yield: 0.020 g (55%), the ^{1}H NMR data were in agreement with those reported;[26a] $[\alpha]_D^{23}$: +77.0 (*c* 0.2, toluene) (Lit.:[26b] $[\alpha]_D^{23}$: +94.0, *c* 1.0, toluene for a sample of 96% ee). HPLC analysis (Daicel Chiralpack OD, hexane/*i*-PrOH = 90:10, flow rate 0.8 mL/min, λ = 270): t_R: 18.90 min (major) and 20.42 min (minor).

Synthesis of β-Aminoketone 9

To a stirred solution of catalyst **2** (0.160 g, 0.0306 mmol), previously dried under vacuum at 90 °C, in dry DMSO (2 mL) and acetone (0.5 mL, 6.8 mmol), *N*-4-methoxyphenyl-4-nitrobenzaldimine **8** (0.0256 g, 0.1 mmol) was added in one portion. The mixture was stirred at RT for 72 h and then poured in Et_2O (100 mL). The precipitated **2** was filtered off, and the solid was washed with Et_2O (50 mL). Average recovery of catalyst ranged from 70 to 80% (0.110 to 0.130 g) when the reaction was run on the above mentioned scale, and increased to ≥ 90% when the reaction was run on a doubled or a larger scale. The filtrate was washed twice with water, and the Et_2O phase was dried and concentrated under vacuum. The residue was purified by flash chromatography with a 1:1 hexanes:Et_2O mixture as eluant to give the product; yield: 0.025 g (81%). Since this compound was known to racemize on standing as such,[3a] its ee was determined immediately after isolation of the product by HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH = 60:40, flow rate 0.8 mL/min, λ = 270): t_R: 9.70 min (minor) and 11.45 min (minor). The product had ^{1}H NMR data in agreement with those reported.[3a] A sample for which an 84% ee was determined had $[\alpha]_D^{23}$: +13.8 (*c* 0.14, $CHCl_3$); no optical rotation has previously been reported for this compound.

Synthesis of β-Aminoketones 11a and 11b

These products were obtained by the three-component version of the iminoaldol reaction (see above), that involved addition of the aldehyde (1 mol equiv.) to the stirred mixture of the catalyst (0.3 mol equiv.) and 4-methoxyaniline (1.1 mol equiv.) in DMSO at room temperature. The products were isolated as described above for **9** and were considered to be likewise configurationally unstable. Their ee's were determined by HPLC (Daicel Chiralpack OD, hexane/*i*-PrOH = 85:15, flow rate 0.8 mL/min, λ = 270). **11a**: t_R: 6.22 min (minor) and 7.64 min (major). **11b**: t_R: 6.00 min (minor) and 8.90 min (major). These products had ^{1}H NMR data in agreement with those reported.[3a] A sample of **11a** for which a 68% ee was determined had $[\alpha]_D^{23}$: +8.1 (*c* 0.2, $CHCl_3$). A sample of **11b** for which an 82% ee was determined had $[\alpha]_D^{23}$: +7.5 (*c* 0.15, $CHCl_3$). No optical rotation has previously been reported for these compounds.

Synthesis of the α-Hydroxy-β-aminoketones 14 and 15

These compounds were prepared by condensing hydroxyacetone with imines **8** and **13** in the presence of **2** following the procedure described above for the synthesis of compound **9**. Yields and diastereoisomeric ratios were reported in Table 3. The diastereoisomeric ratios were determined by ^{1}H NMR analysis of the crude reaction products. The products were purified by flash chromatography with a 3:7 hexanes:Et_2O mixture as eluant.

2-Hydroxy-3-(*N*-4-methoxyphenyl)amino-4-(4-nitrophenyl)-2-butanone 14: The pure *syn*-isomer was a low-melting material. ^{1}H NMR: δ = 8.22 [d, ^3J(H,H) = 8.7 Hz, 2H, H *ortho* to nitro group], 7.57 [d, ^3J(H,H) = 8.7 Hz, 2H, H *meta* to nitro group], 6.70 [d, ^3J(H,H) = 8.9 Hz, 2H, H *meta* to methoxy group], 6.48 [d, ^3J(H,H) = 8.9 Hz, 2H, H *ortho* to methoxy group], 5.03 [d, ^3J(H,H) = 2.3 Hz, 1H, HC-3], 4.45 [d, ^3J(H,H) = 2.3 Hz, 1H, HC-4], 4.33 and 3.93 (2 brs, 2H, OH and NH), 3.70 (s, 3H, methoxy group), 2.40 (s, 3H, methyl group); ^{13}C NMR: δ = 206.4, 153.0,148.0, 147.4, 139.2, 128.2, 124.0, 115.3, 115.1, 80.1, 58.8, 55.7, 25.0. IR (film liquid): ν = 3375,1715, 1345 cm^{-1}. A sample of 94% ee had $[\alpha]_D^{23}$: –12.1 (*c* 0.27, $CHCl_3$); elemental analysis: calcd. (%) for $C_{17}H_{18}N_2O_5$ (330.3): C 61.81, H 5.49, N, 8.48; found: C 61.59, H 5.40, N, 8.64.

The pure *anti*-isomer was a thick oil. ^{1}H NMR: δ = 8.17 [d, ^3J(H,H) = 8.8 Hz, 2H, H *ortho* to nitro group], 7.49 [d, ^3J(H,H) = 8.8 Hz, 2H, H *meta* to nitro group], 6.73 [d, ^3J(H,H) = 9.0 Hz, 2H, H *meta* to methoxy group], 6.56 [d, ^3J(H,H) = 8.9 Hz, 2H, H *ortho* to methoxy group], 4.91 [d, ^3J(H,H) = 3.3 Hz, 1H, HC-3], 4.75 [d, ^3J(H,H) = 3.3 Hz, 1H, HC-4], 3.83 and 3.60 (2 brs, 2H, OH and NH), 3.71 (s, 3H, methoxy group), 2.26 (s, 3H, methyl group). A sample of 40% ee had $[\alpha]_D^{23}$: –11.5 (*c* 0.29, $CHCl_3$). The ee's were determined by HPLC (Daicel Chiralpack OD, hexane/*i*-PrOH = 85:15, flow rate 0.8 mL/min, λ = 270). *Syn*-**14**: t_R: 11.90 min (major) and 13.90 min (minor). *Anti*-**14**: t_R: 9.09 min (minor) and 10.70 min (major).

3-(*N*-4-Chlorophenyl)amino-2-hydroxy-4-phenyl-2-butanone 15: This compound, a thick oil, was isolated as a mixture of diastereoisomers. For the *syn*-isomer: ^{1}H NMR: δ = 7.20–7.30 (m, 5H, Ph), 6.97 [d, ^3J(H,H) = 8.8 Hz, 2H, H *meta* to chloro], 6.38 [d, ^3J(H,H) = 8.7 Hz, 2H, H *ortho* to chloro], 4.83 (brs, 1H, HC-3), 4.50 (brs, 1H, OH or NH), 4.36 [d, ^3J(H,H) = 2.4 Hz, 1H, HC-4], 3.60 (brs, 1H, OH or NH), 2.25 (s, 3H, methyl); ^{13}C NMR: δ = 207.1, 144.7, 138.7, 129.1, 128.7, 126.8, 122.8,115.1, 114.9, 80.6, 58.4, 25.2. For the *anti*-isomer: ^{1}H NMR: δ = 7.20–7.30 (m, 5H, Ph); 7.00 [d, ^3J(H,H) =

8.7 Hz, 2H, H *meta* to chloro], 6.44 [d, ^3J(H,H) = 8.8 Hz, 2H, H *ortho* to chloro], 4.75 (brs, 1H, HC-3), 4.68 (brs, 1H, HC-4), 2.10 (s, 3H, methyl). IR (film liquid): ν = 3380, 1715 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{15}ClNO_2$ (288.8): C 66.55, H 5.24, N, 4.85; found: C 66.33, H 5.07, N, 4.99. The ee's were determined by HPLC (Daicel Chiralpack OD-H, hexane/*i*-PrOH = 85:15, flow rate 0.8 mL/min, λ = 270). *Syn*-**15**: t_R: 10.60 min (minor) and 23.10 min (major). *Anti*-**15**: t_R: 9.10 min (major) and 11.35 min (minor).

(4*R*,5*S*)-5-Methylcarbonyl-3-(4-methoxyphenyl)-4-(4-nitrophenyl)-2-oxazolidinone 16

To a cooled (0 °C), stirred solution of compound *syn*-**14** (0.130 g, 0.394 mmol) in dry toluene (5 mL), triethylamine (0.164 mL, 1.18 mmol), 4-dimethylaminopyridine (0.040 g, 0.33 mmol), and a 20% solution of phosgene in toluene (0.227 mL, 0.44 mmol) were added in this order. After 1 h stirring at 0 °C, water was added to the bright yellow solution. The organic phase was separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over sodium sulfate and filtered, and the filtrate was concentrated under vacuum to give the crude product. This was purified by flash chromatography with a 7:3 hexanes:ethyl acetate mixture as eluant. The product was obtained as a pale yellow solid; yield: 55%; mp 260–262 °C. Longer reaction times led to extensive product decomposition. ^{1}H NMR: δ = 8.23 [d, ^3J(H,H) = 8.0 Hz, 2H, H *ortho* to nitro group], 7.55 [d, ^3J(H,H) = 8.8 Hz, 2H, H *meta* to nitro group], 7.27 [d, ^3J(H,H) = 9.2 Hz, 2H, H *meta* to methoxy group], 6.82 [d, ^3J(H,H) = 9.0 Hz, 2H, H *ortho* to methoxy group], 5.64 [d, ^3J(H,H) = 5.2 Hz, 1H, HC-5], 4.58 [d, ^3J(H,H) = 5.2 Hz, 1H, HC-4], 3.75 (s, 3H, methoxy group), 2.48 (s, 3H, methyl group); ^{13}C NMR: δ = 204.3, 157.0, 154.0,148.0, 144.9, 127.8, 124.8, 123.1, 115.8, 114.5, 82.6, 61.8, 55.5, 27.0; $[\alpha]_D^{23}$: –15.7 (*c* 0.7, CH_2Cl_2); IR ($CHCl_3$): ν = 1764, 1727, 1387 cm^{-1}; elemental analysis calcd. (%) for $C_{18}H_{16}N_2O_6$ (356.3): C 60.67, H 4.53, N, 7.86; found: C 60.53, H 4.44, N, 7.90.

Acknowledgements

Financial support from CNR and MIUR – Progetto Nazionale Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni *is gratefully acknowledged. We thank Prof. Rita Annunziata for valuable NMR assistance.*

References and Notes

[1] a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621; c) P. A. Grieco, N. Fukamiya, M. Miyashita, *J. Chem. Soc. Chem. Commun.* **1976**, 573–575. For discussions on the reaction mechanism see: d) C. Agami, *Bull. Chem. Soc.Fr.* **1988**, *3*, 499–507; e) D. Rajagopal, M. S. Moni, S. Subramanian, S. Swaminathan, *Tetrahedron Asymmetry* **1999**, *10*, 1631–1634.

[2] For recent applications to aldol and related reactions see: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; c) T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951–6954; d) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575; e) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

[3] For recent applications to iminoaldol reactions see: a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; b) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199–201.

[4] For recent applications to conjugated addition reactions see: a) M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520–3530; b) M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shraishi, M. Hirama, *Tetrahedron* **1997**, *53*, 11223–11236; c) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975–2978; d) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425.

[5] C.-H. Wong, R. L. Halcomb, Y. Ichikawa, T. Kajimoto, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 412–432.

[6] For recent reviews see: a) E. M. Carreira, in *Comprehensive Asymmetric Catalysis*, Vol. 3, chapter 29.1, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Heidelberg, **1999**; b) S. G. Nelson, *Tetrahedron Asymmetry* **1998**, *9*, 357–389.

[7] For leading references to chiral Lewis-base catalyzed enantioselective aldol reactions see: S. E. Denmark, R. A. Stavenger, *J. Am. Chem. Soc.* **2000**, *122*, 8837–8847 and references cited therein.

[8] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, M. Pitillo, *J. Org. Chem.* **2001**, *66*, 3160–3166.

[9] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Tocco, *Org. Lett.* **2000**, *2*, 1737–1739.

[10] For an excellent review on the immobilization of ligands and catalysts on polymer supports, see: a) *Chiral Catalyst Immobilization and Recycling*, (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**; for reports concerning the use of PEG as support in this context see: b) C. Bolm, A. Gerlach, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 741–743; c) H. Han, K. D. Janda, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1731–1733; d) M. Glos, O. Reiser, *Org. Lett.* **2000**, *2*, 2045–2048.

[11] For an excellent review on asymmetric organic catalysis see: P. I. Dalko, L. Moisan *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 3726–3748.

[12] D. J. Gravert, K. D. Janda, *Chem. Rev.* **1997**, *97*, 489–509.

[13] For instance, both soluble PEG-supported- (Ref.[8]) and insoluble polystyrene-supported-bisoxazolines/Cu(II) complexes, see: S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, *Angew. Chem. Int. Ed.* **2001**, *40*, 2519–2521, showed considerable decrease of catalytic efficiency upon recovery and recycling.

[14] Obviously, PEG cannot be expected to exert the stereodirecting effect of a peptide chain.

[15] For a preliminary account of the part of this work concerning the PEG-Pro-catalyzed aldol condensation,

see: M. Benaglia, G. Celentano, F. Cozzi, *Adv. Synth. Catal.* **2001**, *343*, 171 – 173.

[16] For different solutions to the problem of loading expansion of reagents supported on high M_w PEG, see: a) M. Benaglia, R. Annunziata, M. Cinquini, F. Cozzi, S. Ressel, *J. Org. Chem.* **1998**, *63*, 8628 – 8629; b) N. N. Reed, K. D. Janda, *Org. Lett.* **2000**, *2*, 1311 – 1313.

[17] The highly hygroscopic nature of PEG can be one of the factors that account for this behavior. In this hypothesis, the observed lower yields could arise from the fact that a wet sample (and thus a lesser amount) of catalyst was actually recycled. Other hypotheses, such as hydrolysis of the ester linkages and/or degradation of the polymer backbone were ruled out by checking by NMR the integrity of the recovered catalyst. A precise evaluation of the water content of the catalyst by NMR was not possible.

[18] A. Fujii, M. Sodeoka, *Tetrahedron Lett.* **1999**, *40*, 8011 – 8014.

[19] For an example of the use of polymer supported catalysts in the asymmetric Strecker reaction, see: M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901 – 4902.

[20] Pre-formed aliphatic aldimines were not employed in the iminoaldol reaction because of their intrinsic instability.

[21] Review: D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059 – 1070.

[22] Review: P. O'Brien, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 326 – 329.

[23] P. J. Wash, K. B. Sharpless, *Synlett* **1993**, 605 – 606.

[24] When aromatic aldehydes were employed in this reaction, both the *anti* selectivity and the ee dropped to less useful levels. For instance, in the case of 2-chrobenzaldehyde a 60:40 mixture of *anti* and *syn* isomers was obtained in 71% yield (DMSO, 60 h, RT). The *anti* isomer had 55% ee; the *syn* isomer had 50% ee. Very similar results were observed using non-supported proline as catalyst (see Refs.[2b,2e]).

[25] List (Ref.[2b]) has reported that the three-component reaction between hydroxyacetone, 2-methylpropanal, and 4-methoxyaniline afforded (57% yield) a 17:1 mixture of *syn* and *anti* isomers, the *syn* isomer having a 65% ee and the same configuration indicated for adducts **14** and **15.** Attempts to use catalyst **2** in this reaction led to the products in very low yields (10 – 15%).

[26] a) E. Wada, J. Funakoshi, S. Kanemasa, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2456 – 2464; b) G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F. Barbas, III, *J. Am. Chem. Soc.* **1997**, *119*, 8131 – 8132.