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Enantioselective Direct Aldol Addition of Acetone to Aliphatic Aldehydes

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ABSTRACT The asymmetric direct aldol addition of acetone to aliphatic aldehydes catalyzed by D-proline, L-proline, and its derivatives was studied. While excellent results could be obtained in neat acetone using α-branched aldehydes, unbranched and β-branched aldehydes gave moderate results. Two dipeptide derivatives, L-Pro-L-Try-CH_2OH and L-Pro-L-Trp-OCH_3, were prepared and tested in this reaction and both were found to be able to induce enantioselectivities. The ee-values in the case of some aldehydes approached that obtained with L-proline. Immobilization of L-proline on a polystyrene resin by its carboxylic group provided a catalyst which is able to induce enantioselectivity, can be easily removed from the reaction mixture, and reused without a significant decrease in the enantioselectivity of the β-hydroxyketones obtained in the cross-aldol additions. *Chirality 15:S90–S96, 2003.*

KEY WORDS: asymmetric direct aldol addition; proline; aliphatic aldehydes; acetone; β-hydroxyketones; immobilization; resin

The development of catalytic enantioselective reactions is among the most challenging tasks of organic synthesis.[1,2] The aldol reactions are regarded to be between the synthetically important carbon–carbon bond-forming reactions. Several stereo- and enantioselective catalytic methods are known which require the transformation of the aldol donor to the corresponding enolate or enol ether and the use of chiral promoters or metal complexes.[3–7] Recently, new methods have been developed which use unmodified substrates and enzymes or antibodies as catalyst.[8–12] Metal complexes bearing chiral ligands were also used as catalysts.[13–19] However, further attempts were made to find readily available chiral molecules which could mimic the action of antibody aldolases[11,12] and their natural counterparts, class I aldolase enzymes.[8,9] It has been suggested that the reactions catalyzed by these catalysts proceed via an enamine mechanism[12]; as a consequence, investigations were conducted to find natural amino compounds which are able to enantioselectively catalyze the reaction. A similar well-known reaction is the Hajos-Parrish-Eder-Sauer-Wiechert reaction, an enantiogroup-differentiating aldol cyclodehydration reaction which is catalyzed by L-proline.[20,21] Recently, it was found that in the presence of catalytic amounts of L-proline the direct addition of acetone to aromatic aldehydes results in the enantioselective formation of the aldol adducts in high yields (Fig. 1).[22]

Thorough studies of the reaction[22–30] revealed that low yields and enantioselectivities (ee) can be obtained when

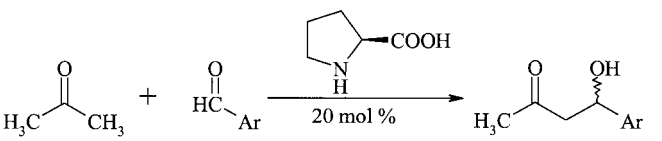

Fig. 1. General scheme of direct asymmetric aldol addition of acetone to aromatic aldehydes catalyzed by L-proline.

aliphatic amino acids were used as catalysts or when the pyrrolidine ring of proline was replaced by an azetidine or piperidine ring.[22,24] Substituents in the fourth position of the pyrrolidine ring (OH or OAc) of proline had limited effects,[24] whereas 2-pyrrolidine carboxamide[22,24] or proline esters[27] failed to catalyze the aldol addition. 5,5-Dimethyl thiazolidinium-4-carboxylate was found to ensure comparable results to those obtained by L-proline[24]. It was concluded that the presence of both a base center and an acidic proton is required. Accordingly, the reaction proceeds through a transition state stabilized by hydrogen bonds in which stereodifferentiation will be imposed by

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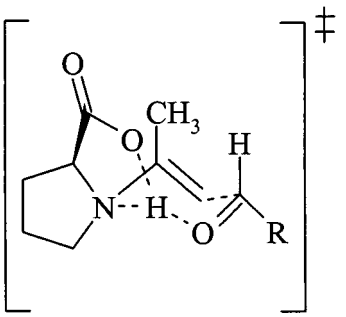


Fig. 2. Transition state of direct asymmetric aldol addition of acetone to aldehydes catalyzed by L-proline.

preferential *re*-facial attack, as shown in Figure 2.[24] The acid group may also be introduced separately; cyclic chiral amines in the presence of organic Broensted acids gave good results.[26] The use of other ketones as aldol donors also afforded good ee's[24]; the addition of unsymmetrical ketones proceeded in a highly regio- and enantioselective way; however, in several cases the diastereoselectivity of the reaction was low.[23–25]

The aldehydes studied were mostly aromatic or cycloaliphatic compounds, although the highest yields and ee's were obtained in the addition of acetone to an α-substituted aliphatic aldehyde, i.e., isobutyraldehyde.[22–25] Furthermore, these aldehydes also afforded high diastereoselectivities in their reaction with hydroxyacetone.[23–25] The lack of a detailed study on the influence of the structure of aliphatic aldehydes on the ee may be explained by the relatively poor results obtained by the use of pentanal.[22,24]

It was found that the nature of the solvent had a significant effect on the reaction. The best results were obtained in polar aprotic solvents, supporting the conclusions regarding the hydrogen-bonded transition state[22,24]. These conclusions were also confirmed by density functional calculations.[30] The use of dimethyl sulfoxide (DMSO) or N,N-dimethylformamide (DMF) afforded the highest ee's. However, their use (especially DMSO) made product isolation and purification more laborious. The attempt to carry out the reaction of pentanal in neat acetone led to good yield and ee comparable with those obtained in DMSO; however, due to the high concentration of acetone self-aldolization products also resulted.[24]

Recovery and reuse of the catalyst is of paramount importance when application on a larger scale is considered. The use of a solvent in which L-proline is insoluble (i.e., $CHCl_3$) resulted in easy recovery of the catalyst but low ee. The initial attempts at heterogenization of L-proline by immobilization on silica gel gave poor results.[24] Recently, (2*S*,4*R*)-4-hydroxyproline was immobilized on poly(ethylene glycol) by means of a succinate spacer and the poly(ethylene glycol)-supported L-proline derivative was used as catalyst, affording yields and ee's comparable to those obtained in the homogeneous reaction.[31]

Continuing our studies on base-catalyzed asymmetric organic reactions,[32] we investigated the direct aldol addition of acetone to aliphatic aldehydes. Our aim was to search for correlations between the structure of the aldehyde and the results of this synthetically useful asymmetric reaction and to make the method economically more attractive by heterogenization of the catalyst and its reuse.

MATERIALS AND METHODS

Materials

L-Proline, D-proline, N-(tert-butoxycarbonyl)-L-proline (Boc-L-Pro), N-(benzyloxycarbonyl)-L-proline (Z-L-Pro), N-(tert-butoxycarbonyl)-L-4-hydroxyproline (Boc-L-Hyp), L-prolinol, L-tryptophan methyl ester hydrochloride (L-Trp-OCH_3 HCl), and 4-methylbenzhydrylamine resin hydrochloride (MBHA-polystyrene, cross-linked with 1% divinylbenzene, 1.3 mmol NH_2/g resin, 100–200 mesh) were purchased from Sigma-Aldrich (Milwaukee, WI) or Fluka (Buchs, Switzerland). Reagents used in the synthesis of the amino acid derivatives and in the immobilization of L-proline on the resin were of analytical grade and used without further purification. All organic solvents, minimum purity 99.5%, were purchased from Aldrich, Fluka, or Reanal (Budapest, Hungary) and were used as received.

The aldehydes used in our study, butanal (**1**), 2-methyl propanal (**2**), pentanal (**3**), 2-methyl butanal (**4**), 3-methyl butanal (**5**), 2,2-dimethyl propanal (**6**), hexanal (**7**), 2-ethyl butanal (**8**), 3,3-dimethyl butanal (**9**), and octanal (**10**) were Aldrich or Fluka products.

Preparation of Catalysts

L-Proline methyl ester (L-Pro-OCH_3) was prepared by a published procedure.[33] To 120 mL (2.96 mol) CH_3OH cooled to 0°C 30 mL (0.4 mol) $SOCl_2$ was added dropwise. To this solution 15 g (0.13 mol) L-proline was added and stirred at 0°C for 1 h. The mixture was allowed to warm to room temperature and further stirred for 48 h. After evaporation of the CH_3OH, the resulted oil was stored overnight at 0°C. During this time the crude L-proline methyl ester hydrochloride crystallized and the crystalline product was washed with cold $(C_2H_5)_2O$ affording 21.6 g (0.13 mol, yield 97%) of product. This product was suspended in 80 mL $(C_2H_5)_2O$, 25 mL (0.18 mol) $N(C_2H_5)_3$ was added at room temperature, and stirred for 2 h. The white precipitate was filtered and washed several times with $(C_2H_5)_2O$. The $(C_2H_5)_2O$ was evaporated from the combined ethereal solutions affording a pale yellow liquid that after distillation in vacuo (bp.: 85°C/30 mmHg) gave 15 mL (0.12 mol, yield 89%) of pure (98% determined by GC) L-proline methyl ester as a colorless liquid. MS (EI, 70eV); *m/z* (%): 129 $[M]^+$ (2), 101 (2), 70 (100), 43 (20), 41 (30).

L-Prolyl-L-tryptophan methyl ester (L-Pro-L-Trp-OCH_3) was prepared by dissolving 1.16 g (4 mmol) L-Trp-OCH_3 HCl, 0.99 g (4 mmol) Z-L-Pro and 0.54 g (4 mmol) 1-hydroxybenzotriazole (HOBt) in 20 mL DMF. The mixture was cooled to 0°C and 0.51 mL (4 mmol) 4-methylmorpholine and 0.91 g (4.4 mmol) N,N′-dicyclohexylcarbodiimide (DCC) were added. The solution was stirred at 0°C for 1 h, then at room temperature for another 3 h. The precipitate formed was filtered and the filtrate was evaporated in vacuo to dryness. After adding 30 mL of $CH_3COOC_2H_5$ to the remaining substance, the organic solution was washed with water, 10% $NaHCO_3$, water (20 mL each), and dried over Na_2SO_4. The solvent was evaporated and the residue was crystallized from CH_3OH/water 9/1 to give 1.62 g (3.4

mmol, yield 84%) product (Z-L-Pro-L-Trp-OMe). Mp.: 63–66°C, ESMS: *m/z* calculated 449, found 450 (MH^+). The Z-protecting group of 0.45 g (1 mmol) of this product was cleaved by catalytic hydrogenolysis using 10% Pd/charcoal in 40 mL CH_3OH in the presence of 0.1 mL 37% HCl. The catalyst was filtered and the filtrate was evaporated in vacuo to dryness. The deprotected product was crystallized from $CH_3OH/(C_2H_5)_2O$ 2/1 in the form of pale pink powder. Yield: 0.25 g (0.8 mmol, yield 80%), mp.: 165–170°C, ESMS: *m/z* calculated 315, found 316 (MH^+). The free amine was obtained by suspending the hydrochloride in $(C_2H_5)_2O$ and treatment with excess $N(CH_2CH_3)_3$. The white precipitate was filtered and the ethereal solution evaporated in vacuo to dryness.

L-Prolyl-L-tryptophanol (L-Pro-L-Try-CH_2OH) was prepared by dissolving 0.7 g (1.56 mmol) Z-L-Pro-L-Trp-OMe in 20 mL CH_3OH and 0.8 g (21 mmol) $NaBH_4$ was added in small portions at room temperature. The product was precipitated with water, filtered, and recrystallized from CH_3OH/water 9/1. Yield: 0.55 g (1.31 mmol, yield 85%), mp.: 163–164°C, ESMS: *m/z* calculated 421, found 422 (MH^+). Deprotection of 0.42 g (1 mmol) of the dipeptide alcohol was achieved as described above to give a white crystalline powder. Yield: 0.20 g (0.7 mmol, yield 70%), mp.: 120–125°C, ESMS: *m/z* calculated 287, found 288 (MH^+).

L-Pro-MBHA. Immobilization of L-proline on polystyrene resin was carried out by a coupling procedure used in peptide chemistry. 0.77 g (1 mmol NH_2) MBHA-polystyrene was deprotected by shaking for 5 min in F_3CCOOH/CH_2Cl_2 1/1, neutralized by treatment with 10% $N(CH_2CH_3)_3$ in CH_2Cl_2 and washed several times with CH_3OH and CH_2Cl_2. This resin was shaken in 15 mL CH_2Cl_2 in the presence of 0.65 g (3 mmol) Boc-L-Pro, 0.62 g (3 mmol) DCC, 1.14 g (3 mmol) N,N,N′,N′-tetramethyl-O-(1H-benzotriazoL-1-yl)uranium hexafluorophosphate, 0.41 g (3 mmol) HOBt and 0.4 mL (4 mmol) $HN(C_2H_5)_2$ for 5 h. The ninhydrin spray reagent on the resulting resin showed that the condensation was successful. The Boc-protecting group was removed by 5-min treatment with F_3CCOOH/CH_2Cl_2 1/1, neutralization with 10% $N(CH_2CH_3)_3$ in CH_2Cl_2 and thorough washing with CH_3OH and CH_2Cl_2, resulting the L-Pro-MBHA resin.

L-Hyp-MBHA. Applying the same procedure as described above, we also prepared a catalyst (L-Hyp-MBHA) by immobilization of L-4-hydroxyproline on MBHA-polystyrene resin using Boc-L-Hyp as starting material.

Aldol Additions, General Procedure

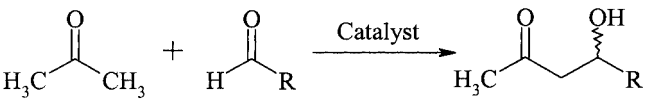
The reactions were carried out in closed glass reactors. The given amount of catalyst was dissolved or suspended in 5 mL (68 mmol) acetone, 1 mmol aldehyde, and 10 μL n-tetradecane (internal standard) were added and the mixture was stirred magnetically at 25°C. After the specified reaction time the products were analyzed by gas chromatography (GC) immediately after removal of the catalyst by treating with saturated NH_4Cl or 10% HCl solution, extracting with $(C_2H_5)_2O$ or $CH_3OC(CH_3)_3$, dried over Na_2SO_4, and concentrated in vacuo. The immobilized catalyst was removed by filtration of the resin. Products were identified by their mass spectra using an HP 5890 GC-HP 5970 MS (Hewlett-Packard Co., Avondale, PA) system equipped with an HP-1 (60 m) capillary column. Quantitative analysis including enantiomeric separation was performed with an HP 5890 GC gas chromatograph equipped with flame ionization detector and Lipodex A, Lipodex C (Macherey-Nagel, Düren, Germany) or Cyclodex-B (J&W Scientific, Köln, Germany) chiral capillary columns. If baseline separation of the product enantiomers was not obtained, derivatization (acetylation or trifluoroacetylation) of the resulting β-hydroxyketone enantiomers was necessary. Acylations were carried out using the corresponding carboxylic acid anhydrides and pyridine. Enantiomeric excess (ee%) was calculated as ee% = ([*E1*] − [*E2*]) × 100/([*E1*] + [*E2*]), where [*E1*] and [*E2*] are the concentrations of the resulting product enantiomers. The reproducibility of the reactions was ±2%. The absolute configurations of the aldol products were assigned by analogy with the previously reported results[22,24] and by comparison of the sense of the optical rotation of the crude products measured by a Polamat A polarimeter (Carl Zeiss, Jena, Germany) with the sense of the rotation of the corresponding known enantiomers.

RESULTS AND DISCUSSION

Effect of the Aldehyde Structure

The aldol addition of acetone to aldehydes catalyzed by L-proline leads to the enantioselective formation of the cross-aldol addition products, β-hydroxyketones (Fig. 3). The yield of the primary products may be lowered by their dehydration, leading to the corresponding α,β-unsaturated ketones. If high excess of acetone is used, diacetone alcohol and mesityl oxide may also be formed.

Our first concern was to avoid the use of the inconvenient solvents (DMSO or DMF) which were found to provide the best results. In the first report on addition of acetone on pentanal (**3**) catalyzed by L-proline, no cross-aldol product was obtained in DMSO/acetone 1/1.[22] Later it was reported that the same reaction proceeds smoothly in neat acetone, giving high yield (75%) and good ee (73%).[24] Accordingly, we carried out the reactions in neat acetone and the results obtained with the selected aldehydes using both L- and D-proline as catalyst are shown in Table 1.



	R		R
(1)	$CH_2CH_2CH_3$;	**(6)**	$C(CH_3)_3$;
(2)	$CH(CH_3)_2$;	**(7)**	$CH_2(CH_2)_3CH_3$;
(3)	$CH_2(CH_2)_2CH_3$;	**(8)**	$CH(CH_2CH_3)_2$;
(4)	$CH(CH_3)CH_2CH_3$;	**(9)**	$CH_2C(CH_3)_3$;
(5)	$CH_2CH_2(CH_3)_2$;	**(10)**	$CH_2(CH_2)_5CH_3$.

Fig. 3. Direct asymmetric aldol addition of acetone to aliphatic aldehydes.

TABLE 1. Direct asymmetric aldol addition of acetone to aliphatic aldehydes catalyzed by L-proline and D-proline[a]

Substrate	R	Catalyst	Conversion %[b]	Selectivity %[c]	Ee[d] % (*Conf*)[e]
(1)	$CH_2CH_2CH_3$	L-Proline	100	52	77 (*R*)
		D-Proline	100	50	76 (*S*)
(2)	$CH(CH_3)_2$	L-Proline	100	95	96 (*R*)
		D-Proline	100	95	96 (*S*)
(3)	$CH_2(CH_2)_2CH_3$	L-Proline	95	52	75 (*R*)
		D-Proline	94	52	75 (*S*)
(4)	$CH(CH_3)CH_2CH_3$	L-Proline	95	88	dr*:57/43; 96; 95 (*R*)
		D-Proline	96	91	dr*:58/42; 97; 95 (*S*)
(5)	$CH_2CH(CH_3)_2$	L-Proline	92	43	70 (*R*)
		D-Proline	90	41	69 (*S*)
(6)	$C(CH_3)_3$	L-Proline	85	75	98 (*R*)
		D-Proline	82	72	97 (*S*)
(7)	$CH_2(CH_2)_3CH_3$	L-Proline	93	52	76 (*R*)
		D-Proline	93	49	75 (*S*)
(8)	$CH(CH_2CH_3)_2$	L-Proline	84	85	86 (*R*)
		D-Proline	82	88	85 (*S*)
(9)	$CH_2C(CH_3)_3$	L-Proline	98	41	68 (*R*)
		D-Proline	97	40	66 (*S*)
(10)	$CH_2(CH_2)_5CH_3$	L-Proline	94	69	69 (*R*)
		D-Proline	92	68	71 (*S*)

[a]Reaction conditions: 5 mL (68 mmol) acetone, 1 mmol aldehyde, 0.2 mmol catalyst, 10 μL n-tetradecane, 25°C, 15 h.
[b]Conversion of the aldehyde (GC).
[c]Selectivity of the cross-aldol addition product (β-hydroxyketone).
[d]Ee values determined by chiral capillary GC.
[e]Configuration of the exceeding enantiomer.
*dr: diastereomeric ratio.

In all these reactions the only side-products formed from the aldehydes were the corresponding α,β-unsaturated ketones (5–60% selectivity, see Table 1). Small quantities of diacetone alcohol and mesityl oxide were also formed. The conversions of the aldehydes were over 90%, exceptions being only (**6**) and (**8**) due to the stronger steric hindrance of the three methyl or the two ethyl groups. The two enantiomers of proline provided similar ee values. Unbranched aldehydes gave similar results irrespective of chain length. Although in their case high conversions were obtained, the selectivities were hardly higher than 50% (except (**10**) 69%) and the ee's were 70–77%. Much better results were obtained with α-branched aldehydes. The selectivity of the aldol addition product was high, up to 95% and the ee values were also excellent (see Table 1). Using β-branched aldehydes the conversions were comparable to those obtained with the unbranched substrates and both the selectivities (40–43%) and the ee's (68–70%) were lower.

Accordingly, both the enantioselective addition of acetone to aliphatic aldehydes and the dehydration of the primary products are processes which are significantly influenced by the steric effects of the aliphatic chain. In all these reactions moderate to high ee's could be obtained. Substituents in the α position, besides hindering the reaction on one of the faces of the carbonyl group, also impeded the dehydration of the primary products. Furthermore, the use of racemic mixture of a chiral α-branched aldehyde (**4**), besides high ee's, resulted also in low diastereoselectivity as a consequence of the different reaction rates of the two enantiomers of the starting aldehyde and/or of the different dehydration rates of the product diastereomers. Substituents in the β position had no hindering effect and in these cases dehydration was faster.

Effect of Catalyst Structure and Immobilization of the Catalyst

The practical application of this enantioselective reaction may be decisively influenced by the possibilities of separation and reuse of the catalyst. An easy way to prepare immobilized amino acids is the well-known condensation of these compounds with functionalized resins, often used in the solid-state synthesis of peptides. However, binding L-proline on resin will lead to either the acid or the amino function being engaged in the peptide bond. Thus, it was necessary to ascertain if either of these functional groups could be used in the peptide bond without losing the catalytic property of the parent amino acid. Results obtained by using several natural and synthetic amino acid derivatives led to the conclusion that the secondary amino group plays the role of activating the aldol donor.[22–24] High ee was obtained only if the catalyst contained a pyrrolidine ring.[22–25] As a consequence, L-proline can be bonded to the resin only through the carboxylic acid group. However, proline esters or 2-pyrrolidine carboxamide were found inefficient in catalyzing the reaction[22,24] without the presence of an acidic proton source.[26] To probe the possibilities of L-proline functionalization, two simple proline derivatives, L-Pro-OCH_3 and L-Pro-L-Try-CH_2OH (Fig. 4), were tested as catalysts.

In accordance with previous findings, using L-Pro-OCH_3 as catalyst racemic mixtures of the cross-aldol addition

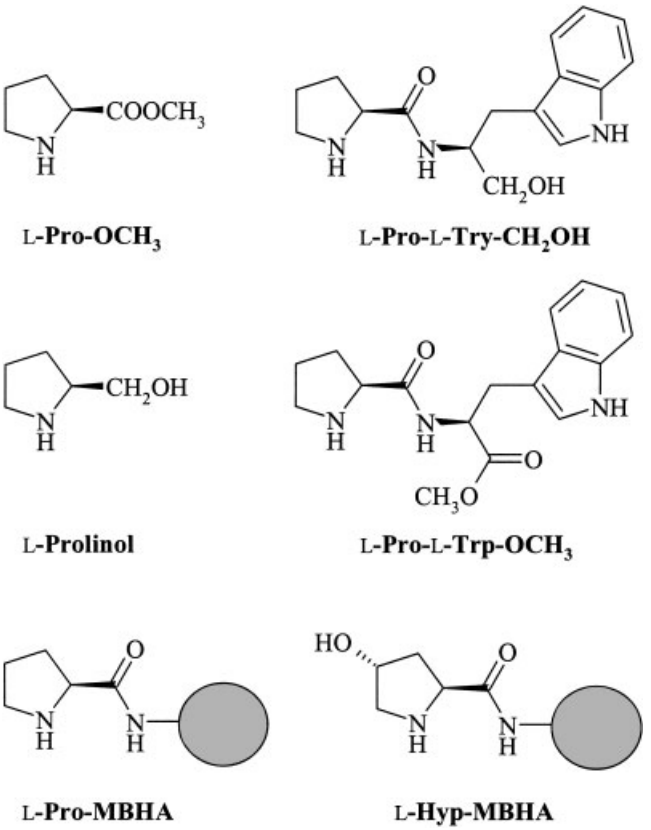


Fig. 4. L-Proline derivatives tested as catalysts.

products were formed in poor yields. Although 2-pyrrolidine carboxamide was inefficient in catalyzing the direct aldol addition, the peptide derivative L-Pro-L-Try-CH_2OH was found to be an unexpectedly good catalyst. The results obtained using this compound as catalyst are listed in Table 2.

In these reactions the aldol addition took place at a lower rate compared with that catalyzed by L-proline, yet only 10 mol% of catalysts (due to the lower solubility of this compound) were used in these experiments (compared to 20 mol% of L-proline). The ee's obtained were only slightly lower (by 10–20%), whereas the selectivities of the β-hydroxyketones increased or remained unchanged.

Since the presence of a peptide bond instead of a free carboxylic acid group also led to good results, a catalyst prepared by coupling L-proline on a H_2N-terminal polystyrene resin could also be efficient. However, the role of the primary hydroxyl group and the effect of the chiral center derived from tryptophan in L-Pro-L-Try-CH_2OH were unknown. To reveal the potential role of the hydroxyl group and the possible effect of the second chiral center, L-Pro-L-Trp-OCH_3 and L-prolinol (Fig. 4) were tested as catalysts. The dipeptide ester was found to be an even better catalyst than the reduced derivative (L-Pro-L-Try-CH_2OH) in the aldol addition of acetone to (**8**) (after 24 h reaction 70% conversion, β-hydroxyketone selectivity 65%, ee 86% *R*). Accordingly, the presence of the primary hydroxyl group is not necessary for obtaining good ee's. By using L-prolinol, low aldehyde conversions and low β-hydroxyketone selectivities were obtained after a 48-h reaction (β-hydroxyketone selectivities: 25% (**1**); 16% (**3**); 20% (**5**); 35% (**6**); 22% (**7**); 32% (**8**); 20% (**9**); 36% (**10**)). Asymmetric induction was observed in the reactions of aldehydes with long or bulky carbon chains (ee's: 5% (**1**); 5% (**3**); 22% (**5**); 74% (**6**); 44% (**7**); 74% (**8**); 31% (**9**); 54% (**10**); the configuration of the exceeding enantiomer was always *R*). These results allowed us the conclude that the presence of a hydroxyl group or of a second chiral center is not needed for asymmetric catalysis. Besides the secondary amino group, a peptide bond is sufficient for inducing ee's, the value of which is influenced much more by the structure of the aldehyde and the catalyst molecule via the possibilities of their spatial arrangement.

Encouraged by these results, two resin-bonded catalysts were prepared, having L-proline (L-Pro-MBHA) or L-4-

TABLE 2. Direct asymmetric aldol addition of acetone to aliphatic aldehydes catalyzed by L-Pro-L-Try-CH_2OH[a]

Substrate	R	Reaction time h	Conversion %[b]	Selectivity %[c]	Ee[d] %
(1)	$CH_2CH_2CH_3$	24	60	65	62
		48	97	64	61
(2)	$CH(CH_3)_2$	48	100	90	73
(3)	$CH_2(CH_2)_2CH_3$	24	48	55	60
		48	65	57	59
(4)	$CH(CH_3)CH_2CH_3$	48	90	86	dr*:60/40; 89; 85
(5)	$CH_2CH(CH_3)_2$	24	75	52	68
		48	95	55	68
(6)	$C(CH_3)_3$	48	93	75	80
(7)	$CH_2(CH_2)_3CH_3$	48	52	70	61
(8)	$CH(CH_2CH_3)_2$	48	88	85	74
(10)	$CH_2(CH_2)_5CH_3$	48	78	68	60

[a]Reaction conditions: 5 mL acetone (68 mmol), 1 mmol aldehyde, 0.1 mmol catalyst, 10 μL n-tetradecane, 25°C.
[b]Conversion of the aldehyde (GC).
[c]Selectivity of the cross-aldol addition product (β-hydroxyketone).
[d]Ee values determined by chiral capillary GC. The configuration of the exceeding enantiomer was (*R*) in all cases.
*dr: diastereomeric ratio.

TABLE 3. Direct asymmetric aldol addition of acetone to aliphatic aldehydes catalyzed by L-Pro-MBHA and L-Hyp-MBHA[a]

Substrate	R	Catalyst	Use nr.[b]	Conversion %[c]	Selectivity %[d]	Ee[e] %
(1)	$CH_2CH_2CH_3$	L-Pro-MBHA	1	100	50	54
			2	100	46	53
(2)	$CH(CH_3)_2$	L-Pro-MBHA	1	100	65	70
			2	100	55	65
(3)	$CH_2(CH_2)_2CH_3$	L-Pro-MBHA	1	65	45	48
			2	50	45	50
			3	50	40	49
(5)	$CH_2CH(CH_3)_2$	L-Pro-MBHA	1	84	44	62
			2	64	44	58
			3	55	45	54
(6)	$C(CH_3)_3$	L-Pro-MBHA	1	66	75	86
			2	65	55	81
(7)	$CH_2(CH_2)_3CH_3$	L-Pro-MBHA	1	65	50	54
			2	48	48	54
(8)	$CH(CH_2CH_3)_2$	L-Pro-MBHA	1	55	58	80
		L-Hyp-MBHA	1	85	25	56
(10)	$CH_2(CH_2)_5CH_3$	L-Pro-MBHA	1	70	40	63
			2	40	36	63

[a]Reaction conditions: 5 mL (68 mmol) acetone, 1 mmol aldehyde, 0.2 mmol catalyst, 10 µL n-tetradecane, 25°C, 48 h.
[b]Use number of the catalyst.
[c]Conversion of the aldehyde (GC).
[d]Selectivity of the cross-aldol addition product (β-hydroxyketone).
[e]Ee values determined by chiral capillary GC. The configuration of the exceeding enantiomer was (*R*) in all cases.

hydroxyproline (L-Hyp-MBHA) coupled to amino-resin by their carboxylic groups. The results obtained with these catalysts are presented in Table 3.

The activity of the L-Pro-MBHA catalyst was similar to that of L-Pro-L-Try-CH_2OH; however, the selectivities and the ee's obtained with the immobilized catalyst were in most cases lower. The immobilized catalyst could be removed from the reaction mixture by simple filtration and reused in a second and a third run. In these repeated runs the selectivities and the ee's were only slightly lower compared to those obtained in the first run (Table 3). The use of L-Hyp-MBHA led to significantly increased activity in the reaction of (**8**), accompanied by a substantial decrease in selectivity and ee. This resembled the behavior of L-prolinol, proving that the presence of the hydroxyl group promotes side-reactions.

Thus, by immobilization of L-proline on polystyrene resin we prepared a catalyst which may be reused several times with only a small loss in activity. Furthermore, if L-Pro-HMBA was swelled in 4 mL CH_2Cl_2 and less acetone was used (1 mL, 13.5 mmol) in the reaction of (**5**), similar results were obtained (ee 55%). Although these results are promising, it should be noted that the best results are still obtained by the use of L-proline as catalyst. Further experiments are needed to prepare novel heterogeneous catalysts which ensure improved yields and ee's.

Finally, according to the accepted mechanism, the reaction takes place through the formation of the enamine from acetone and the catalyst. The stereospecific interaction of this enamine with the formyl group leads to a transition state in which, as has been supposed, the acidic proton interacts with both the carbonyl oxygen and the amino group by hydrogen bonding, ensuring a rigidity necessary for asymmetric induction (see Fig. 2).[22,24] Our findings that in the reaction of aliphatic aldehydes enantiodifferentiation could be obtained even in the absence of a free protonic acid led us to the conclusion that other binding possibilities may exist in these cases. It is possible that, in the absence of a free acidic group, the water molecule eliminated during the formation of the enamine plays a role in the transition state. However, this supposition does not explain the striking difference in the behavior of L-proline methyl ester and the peptide derivatives used in our work. Another possibility could be the participation of the amide group, via the -CO-NH-R hydrogen in the binding of substrates. This is supported by the much lower ee's obtained with L-prolinol as catalyst. However, the enantiodifferentiation obtained in the reaction of bulky aldehydes in the presence of this latter compound showed that the effect of the peptide bond may also be of a steric nature. These conclusions urge us to study the reaction in the presence of other simple N-substituted amides and other pyrrolidine derivatives before drawing further conclusions concerning the mechanism of the reaction.

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