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Proline derivatives as organocatalysts for the aldol reaction in conventional and non-conventional reaction media

Abstract: Different L-proline derivatives were investigated as organocatalysts for the aldol condensation reaction between acetone and 4-nitrobenzaldehyde, in a conventional organic solvent (DMSO), in supercritical carbon dioxide, and in mixtures of this solvent and 1-allyl-3-alkylimidazolium chlorides ionic liquids. The catalysts evaluated were: (S)-pyrrolidine-2-carboxylic acid (L-proline), (R)-thiazolidine-4-carboxylic acid (L-thioprolin), (2S,4R)-4-[dimethyl(phenyl)silyl]oxy-pyrrolidine-2-carboxylic acid (dimethylphenylsilyloxy-L-proline), (2S,4R)-4-(tert-butyldimethylsilyl)oxy-pyrrolidine-2-carboxylic acid (butyldimethylsilyloxy-L-proline), and (2S,3R,4R,5S,6R)-6-(acetoxymethyl)-3-[(S)-pyrrolidine-2-carboxamido]-tetrahydro-2H-pyran-2,4,5-triyl triacetate (peracetylated glucosamine-L-proline). One of the catalysts tested, the tert-butyldimethylsilyloxy-L-proline, was very effective, allowing lower reaction times, resulting in better yields and enantiomeric excesses than L-proline itself, both in organic solvent (DMSO) and in sc-CO₂ or a mixture of sc-CO₂ and ionic liquids. The use of the ionic liquid resulted in better yields and enantiomeric excesses in sc-CO₂. The other catalysts tested were not as effective, resulting in yields and enantiomeric excesses similar or inferior to the ones obtained with L-proline.

Keywords: aldol condensation; ionic liquids; L-proline derivatives; organocatalysis; supercritical carbon dioxide.

1 Introduction

The aldol condensation is one of the most widely used reactions employed to form a new carbon-carbon bond. The development of new asymmetric methodologies for this reaction, has contributed to increasing scope and applications even further [1, 2]. In general, these methodologies belong to one of the following categories: (a) use of a chiral inductor (chiral auxiliary) in stoichiometric quantities or in catalytic amounts (as is the case for organocatalysis); (b) use of chiral Lewis acid- or base-catalysts; (c) use of a chiral heterobimetallic catalyst; and (d) use of enzymes of the aldolase type as catalysts [2–4].

Organocatalysis has become a field of central importance for organic synthesis, by employing small chiral organic compounds free of metals as catalysts [5] for the asymmetric synthesis of desired molecules [6, 7]. New methods and the use of alternative techniques, such as microwave irradiation, sonication and non-conventional reaction media (water, ionic liquids and supercritical carbon dioxide), are increasing the scope and possibilities of this kind of asymmetric catalysis [5]. Chiral amino acids, especially L-proline and its derivatives, have been successfully employed as organocatalysts for the aldol reaction, leading to high yields with high stereoselectivity [3, 4, 8, 9].

There are, however, certain disadvantages in the aldol reaction: low selectivity and the use of stoichiometric amounts of aqueous base that needs to be neutralized and separated from the product after the completion of the reaction, leading to a high E factor (a high waste/product ratio) [10, 11]. Evaluation of new reaction media, which could lead to an increase in selectivity and reduce the waste generated in the reaction, is therefore essential [10].

Supercritical carbon dioxide (sc-CO₂) is an environmentally benign solvent with an accessible critical point (T_c=304.2 K, P_c=7.38 MPa) and unique properties, that make it an interesting reaction media [12–15]. Its association with ionic liquids, forming a polar gas expanded

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Scheme 1 Model aldol reaction: (1) propan-2-one; (2) 4-nitrobenzaldehyde; (3) 4-hydroxy-4-(4-nitrophenyl)butan-2-one; (4) (E)-4-(4-nitrophenyl)but-3-en-2-one.

phase, increases even further its possible applications [16]. There are, however, only a few reports in the literature regarding the use of these reaction media for the aldol reaction [1, 11, 17].

In this work, the use of L-proline derivatives as organocatalysts for the aldol condensation reaction between acetone and 4-nitrobenzaldehyde (Scheme 1), in *sc*-CO₂ and in biphasic systems containing *sc*-CO₂ and ionic liquids derived from imidazole (1-allyl-3-alkyl-imidazolium chlorides) was investigated. L-Proline was used as a control, in order to compare the results of this work with those reported previously in the literature [17].

The influence of pressure, temperature, presence of ionic liquid, and type of catalyst on the yield and enantiomeric composition of the addition product (a β -hydroxy ketone) and on the yield of the elimination product (a α,β -unsaturated ketone) was evaluated.

Two ionic liquids were evaluated for the biphasic systems; 1-allyl-3-methyl-imidazolium chloride [IL1, compound (5)] and 1-allyl-3-hexyl-imidazolium chloride [IL2, compound (6)] (Scheme 2).

2 Experimental section

All chemicals were obtained from commercial sources (Sigma-Aldrich, St. Louis, MO, USA and Merck KGaA, Darmstadt, Germany), except the two ionic liquids which were a gift from Professor Omar A. El Seoud (IQ-USP). Compound purification was carried out by column chromatography over silica gel (230–400 mesh).

Enantiomeric excesses (*e.e.*) were determined by HPLC on a CBM-10A (Shimadzu Corporation Kyoto, Japan) chromatograph, equipped with a AS-H Chiralpak chiral column. The mobile phase was hexane/isopropanol (9:1),

Scheme 2 Ionic liquids: (5) 1-allyl-3-methylimidazolium chloride; (6) 1-allyl-3-hexylimidazolium chloride.

with a 1 h run time at 1 ml/min. Detection was performed by UV-Vis at a wavelength of 254 nm. The peak positions of the R and S enantiomers were determined using an authentic sample of the R-enantiomer. The *e.e.* refers to the excess of this enantiomer (R).

¹H and ¹³C NMR spectra were measured on a Bruker Avance 3 spectrometer (Bruker BioSpin, Billerica, MA, USA) (200 MHz for proton) with samples dissolved in CDCl₃. Chemical shifts are presented in ppm using tetramethylsilane (TMS) as reference.

All of the reactions in *sc*-CO₂ were performed in a 25 ml stainless steel micro reaction apparatus (Parr Instrument Company model 4591, Moline, IL, USA), equipped with a heating jacket, a magnetic drive stirrer and a PID control unit (Parr Instrument Company model 4848). This unit has a type J thermocouple, a tachometer and a pressure transducer, to measure/control temperature (within $\pm 0.3^\circ\text{C}$) and rotation speed (within ± 5 rpm) and to measure pressure (within ± 5 psi).

Supercritical CO₂ was delivered to the reactor at the desired pressure using a syringe pump (Teledyne ISCO model 260D, Lincoln, NE, USA) and the appropriate valves and connections (HIP).

The IUPAC names were obtained using the ChemBioDraw Ultra 12.0.1 software package (PerkinElmer, Cambridge, MA, USA).

2.1 General procedure for the aldol condensation reaction in organic solvents

4-Nitrobenzaldehyde (0.075 g, 0.50 mmol) and catalyst (20–30 mol%) were added to a solution of acetone (1.0 ml) in DMSO (4.0 ml) and the resulting mixture was stirred at room temperature for 4–72 h. The reaction mixture was treated with a saturated ammonium chloride aqueous solution and extracted several times with ethyl acetate. The organic extracts were combined, dried with anhydrous MgSO₄ and the solvent was removed on a rotary evaporator. The pure aldol products were obtained by flash column chromatography on silica gel, eluted with a mixture of hexane/ethyl acetate 2:1 [3].

Scheme 3 Aldol product: (3) 4-hydroxy-4-(4-nitrophenyl)butan-2-one.

Addition product: 4-hydroxy-4-(4-nitrophenyl)butan-2-one (Scheme 3).

^1H NMR: (200 MHz, CDCl_3 , ppm), δ : 2.23 (s, 3H); 2.86 (d, $J=6$ Hz, 2H); 3.72 (s, 1H); 5.27 (t, $J=6$ Hz, 1H); 7.54 (m, 2H); 8.2 (m, 2H).

Elimination product: (E)-4-(4-nitrophenyl)but-3-en-2-one (no Z-isomer was observed) (Scheme 4).

^1H RMN: (200 MHz, CDCl_3 , ppm), δ : 2.43 (s, 3H); 6.82 (d, $J=16$ Hz, 1H); 7.54 (d, $J=16$ Hz, 1H); 7.7 (m, 2H); 8.27 (m, 2H).

2.2 General procedure for the aldol condensation reaction in sc-CO_2 or in biphasic systems containing ionic liquids

The 25 ml stainless steel Parr reaction apparatus was charged with acetone (1.0 ml), 4-nitrobenzaldehyde (0.075 g, 0.50 mmol) and the appropriate amount of one of the catalysts evaluated (20–30 mol%): L-proline, 0.034 g; L-thioprolin, 0.026 g; dimethylphenylsilyloxy-L-proline, 0.053 g; butyldimethylsilyloxy-L-proline, 0.049 g; and peracetylated glucosamine-L-proline, 0.048 g. In some experiments, an ionic liquid (1.0 ml) or a base (TEA, 0.07 ml) were also added. The reactor temperature was set to the desired value at the control unit, while the reactor was gently purged with a very small flow of CO_2 for 1 min. It was then charged with CO_2 at the desired pressure using the Teledyne syringe pump. The stirrer speed was set to 500 rpm (verified with the tachometer) and the reactor

Scheme 4 Dehydration product: (4) (E)-4-(4-nitrophenyl)but-3-en-2-one.

was kept at the set conditions for the desired time. The reactor was then slowly depressurized. All the CO_2 exiting the reactor was passed through a glass trap containing 20 ml of ethyl acetate, in order to collect any material that might have been carried out by the gas. The reactor was then thoroughly washed with ethyl acetate twice (each time with approximately 20 ml of solvent), to ensure that no material remained attached to the walls, or other parts of the vessel. All of the ethyl acetate fractions were combined and the solvent was removed under reduced pressure in a rotary evaporator. In the experiments where an ionic liquid was used, the washing of the reactor was performed with acetone in the same way as described before. The acetone was removed under reduced pressure and the resulting ionic liquid was extracted three times with ethyl acetate (around 10 ml each time), the fractions were combined and the solvent removed under reduced pressure in a rotary evaporator.

The organic fraction obtained after the solvent removal, was submitted to flash column chromatography in silica gel, eluted with hexane:ethyl acetate (2:1), in order to separate products from unreacted reagents. The recovered 4-nitrobenzaldehyde was weighed and used to determine the conversion. The isolated product obtained was weighed and used to determine the yield.

2.3 Catalyst preparation

2.3.1 (R)-thiazolidine-4-carboxylic acid (thio-L-proline) (Scheme 5)

The procedure was based on that described by Kaupp et al. [18]. Cysteine (0.48 g, 4 mmol) and p-formaldehyde (0.12 g, 4 mmol) were mixed in a scintillation vial and the mixture was stirred for 4 h at room temperature. The system was then kept under vacuum at 80°C for another 30 min. The product was purified by column chromatography. ^1H NMR (200 MHz, CDCl_3 , ppm), δ : 2.31 (dd, $J=6$ Hz, 2H); 4.29 (q, $J=10$ Hz, 2H); 4.61 (dd, $J=6$ Hz, 1H). ^{13}C NMR (50 MHz, D_2O , ppm), δ : 32.0, 48.4, 62.2, 169.7.

Scheme 5 Catalyst (7) (R)-thiazolidine-4-carboxylic acid.

Scheme 6 Catalyst **(8)** (2S,4R)-4-((dimethyl(phenyl)silyloxy)-pyrrolidine-2-carboxylic acid.

2.3.2 (2S,4R)-4-(dimethyl(phenyl)silyloxy)-pyrrolidine-2-carboxylic acid (dimethylphenylsilyloxy-L-proline) (Scheme 6)

The procedure was based on that described by Opalka et al. [19]. Dimethylphenyl silane (1.86 g) was added to a solution of (E)-4-hydroxy-L-proline (1.39 g) in acetonitrile (6 ml), in a round bottom flask. This mixture was cooled to 0°C, and DBU (1.95 ml) was added. The reaction was allowed to warm to room temperature and stirred for 24 h and then extracted three times with pentane. The pentane extracts were combined and concentrated. Methanol (32 ml), tetrahydrofuran (THF) (16 ml), water (16 ml), and a 2 M NaOH aqueous solution (24 ml) were added to the resulting oil. The mixture was stirred at room temperature for 90 min and then the pH was adjusted to 6, using an aqueous 1 M HCl solution. The solvents were then removed under reduced pressure, leaving a yellow clear liquid. ¹H NMR (200 MHz, DMSO-d₆, ppm), δ: 2.37 (s, 3H); 0.29 (s, 6H); 1.15 (t, J=14 Hz, 1H); 1.96 (s, 1H); 4.01 (q, J=22 Hz, 1H); 7.42 (m, 7H). ¹³C NMR (50 MHz, DMSO-d₆, ppm), δ: 0.53, 0.73, 14.03, 20.68, 59.71, 127.73, 128.96, 129.37, 132.69, 132.90, 139.05, 170.24.

2.3.3 (2S,4R)-4-(tert-butyl(dimethyl)silyloxy)pyrrolidine-2-carboxylic acid (t-butyl-dimethylsilyloxy-L-proline) (Scheme 7)

The procedure was based on that described by Opalka et al. [19]. Tert-butyl dimethyl silane (1.86 g) was added to a solution of (E)-4-hydroxy-L-proline (1.39 g) in acetonitrile (6 ml), in a round bottom flask. This mixture was cooled to 0°C, and DBU (1.95 ml) was added. The reaction was allowed to warm to room temperature and stirred for 24 h and then extracted three times with pentane. The

Scheme 7 Catalyst **(9)** (2S,4R)-4-((tert-butyl(dimethyl)silyloxy)-pyrrolidine-2-carboxylic acid.

pentane extracts were combined and concentrated. Methanol (32 ml), THF (16 ml), water (16 ml), and a 2 M NaOH aqueous solution (24 ml) were added to the resulting oil. The mixture was stirred at room temperature for 90 min and then the pH was adjusted to 6 using an aqueous 1 M HCl solution. The solvents were then removed under reduced pressure until a white precipitate just began to form. At this point, water was added until all the precipitate went into solution. The solution was then allowed to sit until crystals formed. The crystals were filtered and washed with diethyl ether to afford white crystals [19]. ¹H NMR (200 MHz, MeOD, ppm), δ: 0.14, 0.15 (s, 3H); 0.93 (s, 8H); 2.07 (m, 1H); 2.35 (m, 1H); 3.16 (m, 1H); 3.42 (m, 1H); 4.17 (q, J=18 Hz); 4.66 (m, 1H).

2.3.4 (2R,3R,4R,5R,6S)-2-(acetoxymethyl)-6-(pyrrolidine-2-carboxamido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (peracetyl-glucosamine-L-proline) (Scheme 8)

The procedure was based on the method described by Chandrasekhar et al. [8]. N-benzyloxycarbonyl-protected proline (2 g, 7.9 mmol) was dissolved in dry dichloromethane (10 ml). HOBt (1.28 g, 9.48 mmol) was added and the reaction mixture was stirred for 15 min. The solution was cooled to 0°C and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) (3.02 g, 15.8 mmol) was added, followed by a solution of peracetylated glucosamine (2.55 g, 7.9 mmol) and diisopropylethylamine (DIEPA) (7.9 mmol, 1.10 ml) in dry dichloromethane (10 ml). The mixture was stirred overnight at room temperature. After completion of the reaction (monitored by TLC), water (20 ml) was added, and the two layers were separated. The organic layer was washed with aqueous ammonium chloride (10 ml) and then aqueous sodium bicarbonate (15 ml), dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography. The deprotection of the compound was carried out by hydrogenation with 20%

Scheme 8 Catalyst **(10)** (2S,3R,4R,5S,6R)-6-(acetoxymethyl)-3-[(S)-pyrrolidine-2-carboxamido]tetrahydro-2H-pyran-2,4,5-triyl triacetate.

$\text{Pd}(\text{OH})_2/\text{C}$ (50 mg) [8]. ^1H NMR (200 MHz, CDCl_3 , ppm), δ : 2.03 (m, 17H); 3.53 (m, 1H); 3.84 (m, 1H); 4.18 (m, 1H); 5.20 (m, 2H); 5.95 (d, $J=10$ Hz, 1H); 7.50 (m, 5H).

3 Results and discussion

The behavior of the L-proline derivatives as organocatalysts for the aldol condensation of acetone with 4-nitrobenzaldehyde was evaluated using several reaction conditions in different reaction media. The results were reported as conversions (percentage of reagent converted to products), yields of the addition product (percentage of the addition product formed) and enantiomeric excesses of the addition product (excess of the R-enantiomer). The most promising catalysts were explored more thoroughly.

3.1 (S)-pyrrolidine-2-carboxylic acid (L-proline)

Initial tests with L-proline were performed to compare the data of this work with existing literature results [17]. The temperature and pressure were chosen based on the literature, however, the pressure had to be set at a lower value (150 bar), due to equipment limitation.

The results obtained agree with those previously reported on the literature (Entry 1 – Table 1), but with a lower enantiomeric excess. The use of the ionic liquid (IL1) in combination with sc-CO_2 (Entry 2 – Table 1) resulted in slightly higher enantiomeric excess, but also increased the amount of the elimination product (higher conversion for the same yield of the addition product).

3.2 (2S,4R)-4-(dimethyl(phenyl)silyl)-oxy-pyrrolidine-2-carboxylic acid (dimethylphenylsilyloxy-L-proline)

This catalyst was not as effective as L-proline, as can be seen from the results in Table 2. Using exactly the same

Table 2 Results obtained with dimethylsilyl proline.

Entry	Conversion (%)	Yield (%)	e.e. (%)	Solvent	Condition
1	35.3	35.3	55.2	sc-CO_2	24 h/150 bar/40°C
2	10.0	10.0	46.8	sc-CO_2	6 h/150 bar/40°C
3	6.0	6.0	21.8	sc-CO_2	48 h/150 bar/40°C
4	0	0	–	sc-CO_2 +IL1	24 h/150 bar/40°C

reaction conditions resulted in slightly lower yields and enantiomeric excesses with the silyloxy derivative. Reducing the reaction time resulted in lower yields and e.e. (Entry 2 – Table 2). An increase in the reaction time resulted in much lower yields and e.e.s (Entry 3 – Table 2), probably as a result of racemization by a retro-aldol reaction (as evidenced by the reduced e.e.) and catalyst degradation observed for longer reaction times. The use of an ionic liquid (IL1) actually prevented any reaction from proceeding (Entry 4 – Table 2) and thus no further tests with the other ionic (IL2) were performed.

3.3 (R)-thiazolidine-4-carboxylic acid (thio-L-proline)

This catalyst was also not as effective as L-proline, as can be seen by the results in Table 3. Using DMSO as a solvent, the yields were low, even though the e.e.s were higher than the ones obtained with L-proline. In sc-CO_2 , the results were worse, with very low yields, probably because of the very low solubility of the catalyst in sc-CO_2 . The presence of a base (0.07 ml of TEA) made the results even worse.

Table 3 Results obtained with thiazolidine as catalyst.

Entry	Conversion (%)	Yield (%)	e.e. (%)	Solvent	Condition
1	36.0	10.8	0	DMSO+TEA	24 h/RT
2	40.0	14.4	71.6	DMSO	24 h/RT
3	17.3	2.8	47.8	sc-CO_2	24 h/150 bar/40°C
4	13.4	13.4	15.9	sc-CO_2 +TEA	24 h/150 bar/40°C
5	6.6	2.0	70	sc-CO_2 +IL2	24 h/150 bar/40°C

Table 4 Results obtained with proline-glucosamine as catalyst.

Entry	Conversion (%)	Yield (%)	e.e. (%)	Solvent	Condition
1	17.3	11.2	41.4	sc-CO_2	24 h/150 bar/40°C
2	17.3	15.4	21.29	sc-CO_2	6 h/150 bar/40°C
3	37	3	0	sc-CO_2	48 h/150 bar/40°C

Table 1 Results obtained with (S)-pyrrolidine-2-carboxylic acid (L-proline) as catalyst.

Entry	Conversion (%)	Yield (%)	e.e. (%)	Solvent	Condition
1	70.8	36.8	56.5	sc-CO_2	24 h/150 bar/40°C
2	91.6	36.5	60.7	sc-CO_2 +IL1	24 h/150 bar/40°C

Table 5 Results obtained with tert-butyl dimethylsilyl proline as catalyst.

Entry	Conversion (%)	Yield (%)	<i>e.e.</i> (%)	Solvent	Condition
1	100.0	88.5	77.9	DMSO	24 h/RT
2	78.8	55.7	57.0	DMSO+TEA	24 h/RT
3	62.0	49.0	77.9	DMSO (25 ml)	24 h/RT
4	69.3	62.5	78.8	DMSO	2 h/RT
5	66.7	50.0	76.7	sc-CO ₂ +DMSO (4 ml)	2 h/150 bar/40°C
6	74.6	41.0	3.4	sc-CO ₂ +TEA	24 h/150 bar/40°C
7	82.0	55.1	0	sc-CO ₂ +TEA	48 h/150 bar/40°C
8	66.7	42.7	0	sc-CO ₂ +TEA	24 h/200 bar/40°C
9	67.3	40.5	8.5	sc-CO ₂ +TEA	6 h/150 bar/40°C
10	87.3	53.4	22.0	sc-CO ₂ +TEA	2 h/150 bar/40°C
11	81.3	60.0	21.4	sc-CO ₂ +TEA+IL1	2 h/150 bar/40°C
12	73.3	46.0	34.8	sc-CO ₂	2 h/150 bar/40°C
13	78.6	54.0	79.0	sc-CO ₂ +IL1	2 h/150 bar/40°C
14	66.7	50.0	76.7	sc-CO ₂ +DMSO (4 ml)	2 h/150 bar/40°C
15	74.6	42.3	63.7	sc-CO ₂ +IL2	2 h/150 bar/40°C

3.4 (2R,3R,4R,5R,6S)-2-(acetoxymethyl)-6-(pyrrolidine-2-carboxamido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (peracetyl-glucosamine-L-proline)

The derivatization of L-proline with a peracetylated sugar (a CO₂-philic group) increased the solubility of the proline derivative in sc-CO₂. However, this had almost no effect on the catalytic properties of the compound, as can be seen from the results in Table 4. The yields and *e.e.s* were low and the catalyst was not as effective as L-proline.

3.5 (2S,4R)-4-(tert-butyldimethylsilyloxy)-pyrrolidine-2-carboxylic acid (t-butyl-dimethylsilyloxy-L-proline)

This catalyst provided the best results. Using DMSO as a solvent resulted in a very good yield, 88.5%, and a good *e.e.*, 77.9% (Entry 1 – Table 5). The presence of a base (TEA) decreased both the yield and the *e.e.* (Entry 2 – Table 5). The reaction time can be reduced to 2 h, with a low decrease in yield and no effect in the *e.e.* (Entry 4 – Table 5). Dilution of the reagents, using the same total volume of the high pressure reactor (25 ml), in order to compare the results with the ones in sc-CO₂, resulted in a significant decrease in yield (49.0%), but no effect on the *e.e.* (Entry 3 – Table 5).

Using sc-CO₂ as a solvent resulted in lower yields and a very low *e.e.* for longer reaction times (Entry 6 – Table 5). Decreasing the reaction time, however, resulted in good

yields, around 46.0%, comparable to those observed for the reaction in diluted conditions in DMSO (same volume as the sc-CO₂ phase, 25 ml) (Entry 12 – Table 5). The *e.e.*, however, was very low.

The best results for sc-CO₂ were obtained in the presence of the ionic liquid (IL1), with a yield of 54.0% and a very good *e.e.* of 79.0% (Entry 13 – Table 5). This is probably the result of the higher polarity of the ionic liquid phase. Our group is currently investigating this issue in detail in order to understand the effect created by the presence of the ionic liquid.

4 Conclusions

One of the catalysts tested, the tert-butyldimethylsilyloxy-L-proline, was very effective, allowing lower reaction times, resulting in better yields and *e.e.* than L-proline itself, both in organic solvent (DMSO) and in sc-CO₂ or a mixture of sc-CO₂ and ionic liquids. The use of the ionic liquid resulted in better yields and *e.e.* in sc-CO₂.

The other catalysts tested were not as effective, resulting in yields and *e.e.s* similar or inferior to the ones obtained with L-proline.

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