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Organocatalytic Properties of 3,4-Dihydroxyprolines †

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Abstract: The synthesis and organocatalytic properties of (2*S*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylic acid are reported. Using the aldol condensation of cyclohexanone with *p*-nitrobenzaldehyde as a model, a yield of 86%, an enantiomeric excess of 99% and a diastereomeric excess of 25:1 were achieved.

Keywords: organocatalysis; prolines; aldol condensation

1. Introduction

Asymmetric synthesis is the most powerful tool available to organic chemists for synthesizing molecules of high functional and stereochemical complexity as it allows stereoselective introduction of stereogenic centers.

Among the available strategies, catalytic methods are particularly attractive as they avoid having to use stoichiometric amounts of expensive chiral reagents. In addition to enzymes and transition metals, the use of organocatalysts has shown enormous potential, having allowed access to natural products by efficient, economical and environmentally benign procedures. Their tolerance to moisture and oxygen, as well as their compatibility with mild reaction conditions and low toxicity, is particularly attractive.

The use of small organic molecules as organocatalysts was first described independently by Eder [1] and by Hajos [2]. However, it was only recently, following the contributions of List and Barbas III [3] and the seminal work of McMillan [4], that the high potential of organocatalysis was rediscovered, leading to an intensive study of its synthetic possibilities which continues today.

The asymmetric aldol condensation reaction is an attractive method of forming carbon–carbon bonds by the enantioselective production of aldols. A wide range of organocatalysts have been developed that have allowed excellent results to be achieved in the asymmetric version of this and other organic reactions [5], and two main mechanisms of organocatalytic processes have been proposed: enamine catalysis [4] and iminium catalysis [5]. While iminium catalysis makes use of chiral imidazolium salts to activate aldehydes by reversible formation of an iminium ion, enamine catalysis uses amino acids (or derivatives), of particular interest being L-proline, whose conformational rigidity favors selectivity. L-proline and similar catalysts act via an enamine intermediate, with the catalyst performing two specific functions: it first activates the nucleophile through the formation of an enamine, and then activates the electrophile to which it coordinates via its carboxyl group. All this leads to a transition state that explains the high selectivity of the reaction [6].

Although the existing organocatalysts have achieved excellent results, there are problems that have not yet been satisfactorily solved: the use of organic solvents is required and, in addition, a fairly high catalyst load is usually necessary.

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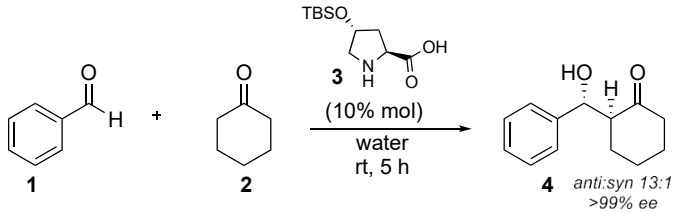
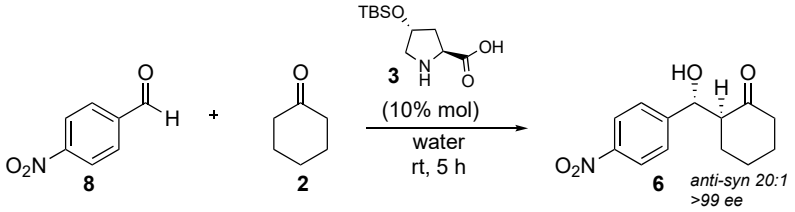
The most recent efforts in this field are directed towards the use of water as a solvent as it is a safe and environmentally friendly medium, avoiding the contamination problems inherent to organic solvents.

The first case of the use of proline as organocatalysts in an aqueous medium for the aldol reaction is shown in Scheme 1, corresponding to the reaction of benzaldehyde with cyclohexanone, catalyzed by (4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-L-proline (**3**), which gave the adduct **4** with a diastereoisomeric ratio of 13:1 and an enantiomeric excess of 99% [7].



Scheme 1. Aldol reaction catalyzed by proline **3**, in an aqueous medium.

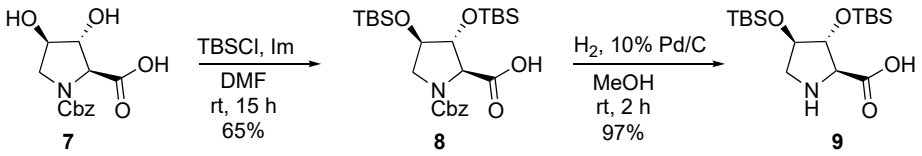
An ulterior similar contribution involved the aldol condensation of *p*-nitrobenzaldehyde with cyclohexanone, catalyzed by (2S,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-L-proline (**3**), providing adduct **9** with a 20:1 diastereoisomeric ratio and an enantiomeric excess of 99% (Scheme 2) [8]. This reaction was used as a model for a similar organocatalytic with 3,4-dihydroxyproline, as reported by studies.



Scheme 2. Aldol reaction catalyzed by proline **3** in an aqueous medium.

2. Result and Discussion

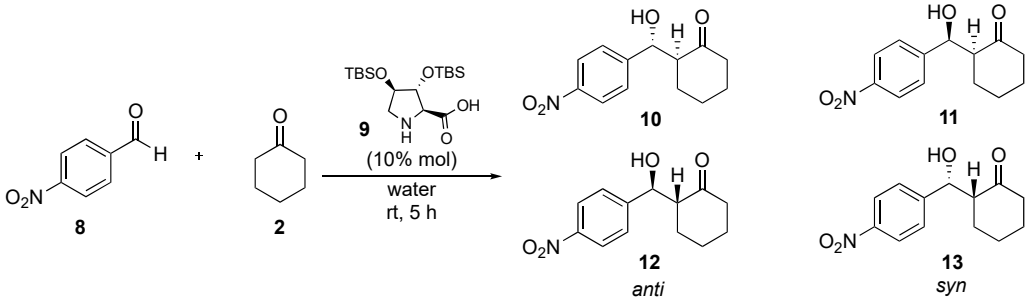
Proline **9** was prepared from the known proline **7**, according to the protocol shown in Scheme 3.



Scheme 3. Synthesis of proline **9**.

Next, proceeding as depicted in Scheme 4, to a solution of *p*-nitrobenzaldehyde (1.0 eq) and cyclohexanone (5.0 eq) in water the catalyst **8** (0.1 eq) was added and the mixture was stirred at room temperature for 5 hours, stopping the reaction by neutralizing with a phosphate-buffered solution pH 7. The elaboration of the reaction mixture was followed by purification by column chromatography [AcOEt/Hex 1:4]. The mixture of aldols **10**, **11**, **12** and **13** was isolated with a yield of 86%.

From its ^{1}H NMR spectrum (Figure 1), the diastereomeric relationship between the *anti* and *syn* enantiomer pairs could be easily established. For the *anti* enantiomers, the signal due to the proton at position 4 (at α to the hydroxyl group) appears as a doublet of doublets located at 4.89 ppm, whereas in the case of the *syn* enantiomers this signal appears as a triplet at 5.48 ppm. Relative integration of the two signals gave an approximate diastereomeric ratio of 1 (*syn*):25 (*anti*) (Figure 2).



Scheme 4. Aldol reaction catalyzed by proline **9**, in an aqueous medium.

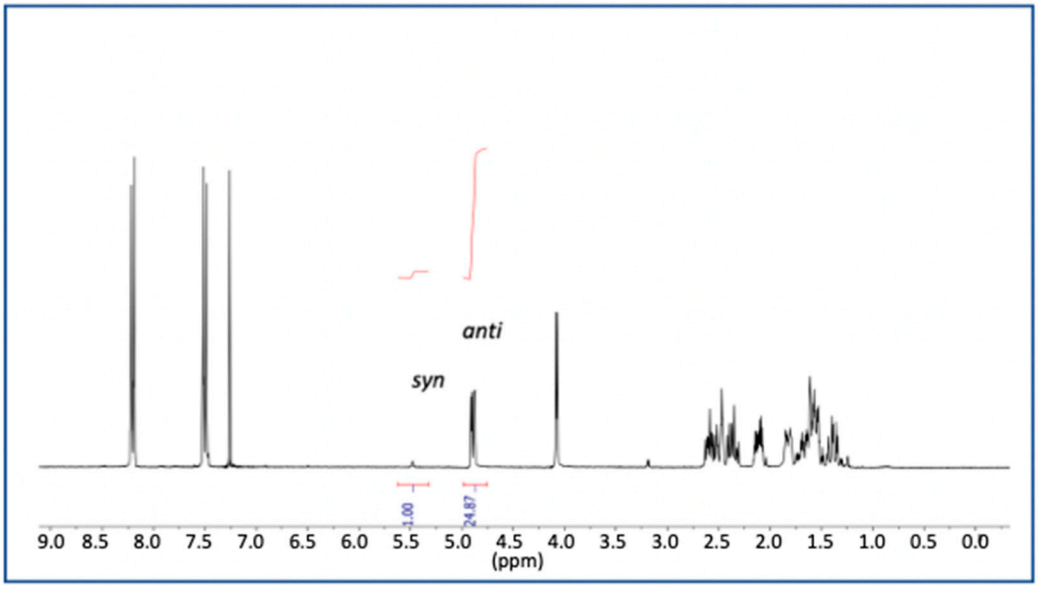
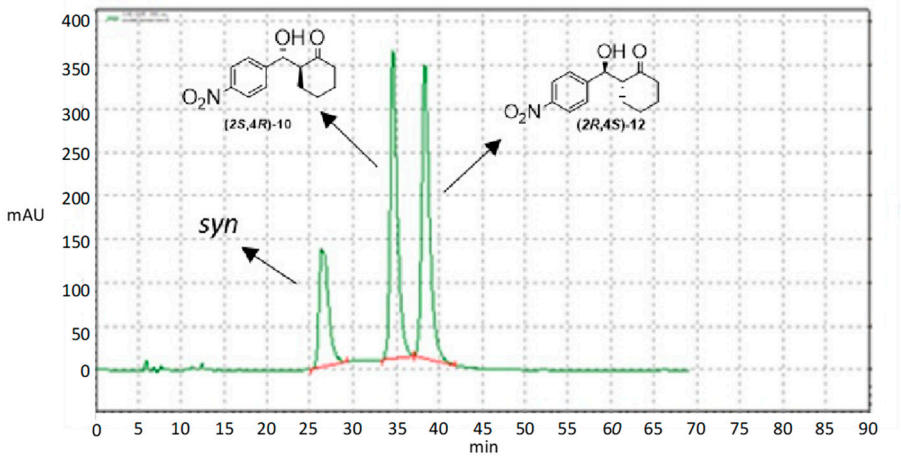


Figure 1. ^{1}H NMR of the aldolic mixture **10-13**.



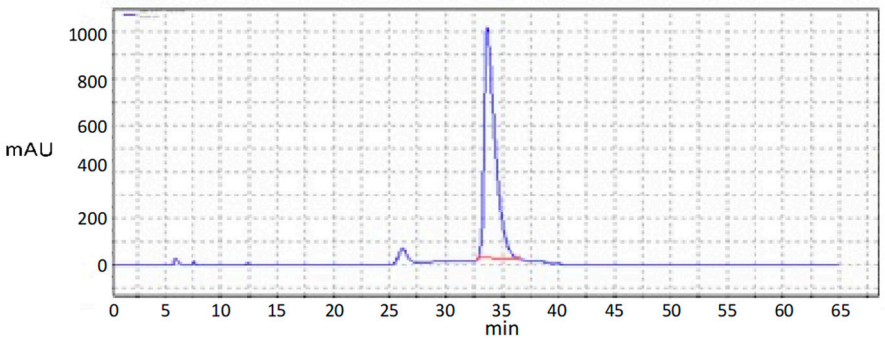
DAD-CH2 266 nm Results

Retention Time	Area	Area %
26,340	41687078	19.97
54,593	81460999	39.02
38,327	85631545	41.02

Figure 2. Chromatogram of racemic mixtures of the aldols **10**–**13**.

The enantiomeric excess was determined by HPLC-UV. To establish the optimal separation conditions for the *anti* enantiomers, a sample of the racemic mixtures without and anti, obtained when the standard reaction was carried out using pyrrolidine as catalyst, was first prepared. Optimum separation conditions were obtained when an OD-H column was used in a hexane/isopropanol mixture (8:2) and a flow rate of 0.5 mL/min, as indicated in the chromatogram shown in Figure 2, for 3 min, corresponding to the mixture of enantiomers of the aldols, a peak at 34.6 min due to aldol (2*S*-4*R*)-10 and a peak at 38.3 min due to aldol (2*R*-4*S*)-**12**. Peak assignments were carried out by comparison with the literature [9].

Using these separation conditions, the chromatogram obtained for the reaction mixture resulting from carrying out the standard reaction with organocatalyst **9** showed that the major product of the reaction was aldol (2S,4R)-**10**, obtained with an enantiomeric excess greater than 99% (Figure 3). In addition, the optical rotation value obtained [+10.4° (c 4.95, $CHCl_3$)] for the mixture also showed that the major compound corresponded to the dextrorotatory aldol (2S,4R)-**10**.



DAD-CH2 254 nm Restults

Retention Time	Area	Area %
33,660	264729032	100

Figure 3. Chromatogram of the aldol mixture of the standard reaction with catalyst **9**.

3. Conclusions

Therefore, if we compare the results obtained with our catalyst **9** with those obtained with proline **3** reported in the literature, it can be observed that the yield (86%) and the enantiomeric excess (>99%) are identical, with a diastereomeric ratio of 25:1 versus 20:1 (Table 1). This allows us to establish that the presence of an additional substituent at the C-3 position of proline or the opposite configuration at C-4 does not have a major influence on this reaction, beyond slightly increasing the diastereoselectivity.

Table 1. Results obtained for catalyst **3** and **9**.

Catalyst	Overall Yield	e.e.	*Anti*/*syn* Ratio	Major Reaction Product
3	86%	>99%	20:1	**10**
9	86%	>99%	25:1	**10**

Comparison of the results for compounds **3** and **9**.

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