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Zn-Proline catalyzed direct aldol reaction in aqueous media†

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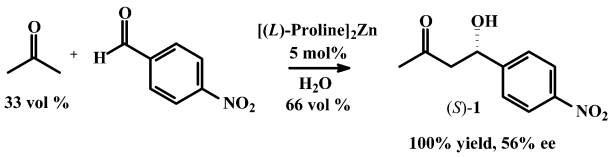
Zn complexes of proline, lysine and arginine are efficient catalysts for the aldol addition of p-nitrobenzaldehyde and acetone in aqueous medium, giving quantitative yields and enantiomeric excesses up to 56% with 5 mol% of the catalysts at room temperature.

The aldol reaction is one of the most important reactions in organic synthesis for the formation of C–C bonds. It is therefore not surprising that a large number of methods have been developed in order to achieve this goal.[1] The direct aldol reaction is an attractive method since it avoids the pre-formation of silyl enol ethers and consequently, considerable efforts have been made in order to develop methods for the direct aldol reaction with high yields and enantioselectivity. In spite of that, only few methods have been reported;[2] recently, proline and chiral zinc complexes have been shown to act as enantioselective catalysts for aldol reactions. Thus, L-proline catalyzes the direct aldol addition of acetone and a variety of aldehydes,[3] with formation of an iminium ion which is converted to the corresponding enamine nucleophile, mimicking the class I aldolases. The methods utilizing Lewis acids rely on the catalysis of metal complexes bearing chiral ligands, such as the heterobimetallic $LaLi_3$tris(binaphthoxide) and the Zn-BINOL homobimetallic catalysts developed by Shibasaki[4] as well as Trost's Zn^{II}-semi crown ether.[5] The reactions described above have been carried out under anhydrous conditions in organic solvents and the metal complexes were reported to be water sensitive. Direct aldol reactions in water with high enantioselectivity can be accomplished with aldolase enzymes[6] and catalytic antibodies.[7] Methods with small molecule catalysts are however reported to give racemates. The aqueous aldol catalyzed by nornicotine appeared recently[8] and the proline catalysed reaction has been extended to buffered aqueous media.[9] Lanthanides and lead triflates have been used as catalysts for the aldol reaction of aldehydes and silyl enol ethers in EtOH–water 9 : 1.[10–12] However, chiral Lewis acids that efficiently catalyze direct aldol reactions in aqueous media have not been investigated to the same extent although such catalysts would have important advantages related to environmental issues.[13]

We are interested in developing water soluble Lewis acids having unprotected amino acids as chiral ligands and to investigate their activities as catalysts for the direct aldol reaction. Here we report the aldol reaction of acetone and p-nitrobenzaldehyde catalyzed by a Zn–proline complex in the presence of water. The catalytic ability of Zn-complexes bearing other amino acids is also reported.

The Zn–proline complex was prepared by the reaction of zinc acetate (1 eq.) with proline (2 eq.) in methanol and the spectroscopic data[14] indicate the mononuclear $Zn(proline)_2$-complex to be the prevailing species.‡ When 4-nitrobenzaldehyde was stirred in the presence of Zn–proline complex (5 mol %) in acetone–H_2O (1 : 2) for 24 h, product **1** was obtained in quantitative yield and 56 % ee (Scheme 1). When proline (10 mol %) was the catalyst, in acetone–H_2O (2 : 1), the yield of **1** after 24 h was 6% and the ee 21%. It is interesting to note that with the zinc complex the *S* enantiomer was observed in excess whereas with proline alone the *R* enantimer, in agreement with the reported result,[3] was in excess. The former results indicate that the two reactions occur with different mechanisms and that the Zn–proline complex is not dissociated under the reaction conditions. The low yield of conversion in the presence of proline alone is also an indication that the enamine-mechanism does not operate well in aqueous medium. We did not observe the formation of **1** in the presence of zinc acetate or in the absence of zinc salts or proline. Side products like the α,β-unsaturated ketone derived from aldol condensation were not detected by ^1H NMR spectroscopy. In fact, only the aldol product **1** was formed under our reaction conditions. Furthermore, the zinc–proline complex is soluble in water but is not soluble in organic solvents, which allows for simple and quantitative recovery of the catalyst. The aldol reaction was also carried out in H_2O–THF (1 : 2) with only 5 eq. of acetone to give 63% of **1** and 50% ee (*S*-**1**). Benzaldehyde and naphthaldehyde also gave the aldol adduct with acetone, and cyclohexanone, 2-butanone and hydroxyacetone proved to be suitable reaction partners with p-nitrobenzaldehyde to give the aldol product in good to moderate yields. These preliminary results show that the aldol reaction can be used with non-activated aldehydes and different ketones.§



Scheme 1

The effect of water–acetone ratio on the reaction rate and on the enantiomeric excess of product **1** was also investigated (Table 1). The lower reaction rates with decreasing percentage

Table 1 The effect of water in the yield and ee for the zinc–proline catalyzed aldol reaction of acetone with 4-nitrobenzaldehyde to give **1**

Entry	% H_2O	Time/h	Yield[a]	ee[b]	Enantiomer in excess in product **1**
1	66	24	100%	56%	*S*
2	50	24	100%	44%	*S*
3	33	24	100%	32%	*S*
4	20	20	56%	26%	*S*
5	10	20	6%	—	—
6	10	96	100%	25%	*S*
7	7	20	5%	—	—
8	7	96	81%	26%	*S*
9	2	20	2.5%	—	—
10	2	96	15%	17%	*R*
11	0	20	3%	—	—
12	0	96	8%	56%	*R*

[a] The yields were determined by ^1H NMR spectroscopy. [b] The ee was determined by chiral HPLC analysis (Waters 600 system using a Chiralpak AS from Dancel Chemical Industries, Ltd). Complex solubility decreases from entry 1 (completely soluble) to entries 9–12 (insoluble).

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b301117h/

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of water reflect, at least in part, the decreasing solubility of the complexes in the reaction medium. The zinc–proline complex becomes insoluble in 2 vol % water–acetone yielding poor conversion and the *R*-enantiomer in excess (entries 9–12). We conclude that in the two latter cases the reaction is catalyzed by proline alone, formed by slow dissociation from zinc.

Examination of the pH rate profile for the Zn–proline catalyzed reaction (H_2O–acetone 1:2) showed that with decreasing pH there was decreased yield and increased ee (*S*-**1**): the reaction was run at pH 9, 8, 7 and 6 and gave yields of **1** of 100%, 96%, 33% and 18% and ee values of 32, 31, 41 and 44%, respectively.

The catalytic ability of other Zn-(*L*)-amino acid complexes (5 mol % of catalyst, H_2O–acetone 1:2) was also investigated (Table 2). The complexes were prepared and isolated as described for Zn—proline and the binary zinc–amino acid complex proved to be the main species by ESI-MS for histidine,[15,16*a*] lysine and serine.[15,16*b*] While Zn–lysine and Zn–arginine proved to be efficient catalysts (Table 2, entries 2,3), Zn–serine, Zn–histidine and Zn–cysteine failed to provide significant amounts of **1** after 24 h at rt.[15,16] Interestingly, after 96 h, Zn–glutamic acid complex gave **1** in 98% yield and ee comparable to the one obtained with Zn–proline (entry 4). Lysine can act as general base catalyst and in fact, when the aldol reaction was run in the presence of 5 mol% of lysine, in the absence of zinc, product **1** was obtained in 74% yield and 6% ee with the *R*-**1** enantiomer in excess. The higher ee values observed with different amino acids, however, require catalysis by a chiral Lewis acid.

In summary, we have shown that zinc-complexes of proline, lysine and arginine are efficient catalysts for the direct aldol reaction of acetone and p-nitrobenzaldehyde. The reaction takes place in aqueous medium, what represents an important development in the search of environment friendly solvents for organic reactions, and the method does not require the pre-formation of silyl enol ethers in organic solvents. Although the enantioselectivity is still moderate, further studies are in progress in order to improve it.

Our results represent the first example of a direct aldol reaction catalyzed by a chiral Lewis acid that takes place in water, at room temperature and shows enantioselectivity. We have also demonstrated that Zn–amino acids complexes are competent catalysts in aqueous medium. Moreover, in order to develop enzyme mimics and to attempt to understand the mechanism of the chemistry of life, catalysts able to act in water are necessary, and, in that respect, zinc coordinated to amino acids represents a good model for the class II aldolases.

Table 2 Yields and ee for the reaction of acetone with 4-nitrobenzaldehyde catalyzed by Zn–amino acid complexes

Entry	L-a.a.[a] in Zn complex	Time (h)	Yield	ee (*S*-**1**)
1	Pro	24	100%	32%
2	Lys	24	100%	24%
3	Arg	24	100%	54%
4	Cys	24	3%	n.d.
5	Cys	96	13%	35%
6	Glu	24	< 1%	n.d.
7	Glu	96	98%	32%
8	His	24	4%	n.d.
9	His	96	45%	27%
10	Ser	24	5%	n.d.
11	Ser	96	24%	20%
12	Ile	24	10%	n.d.
13	Ile	96	36%	45%
14	t-Leu	24	15%	n.d.
15	t-Leu	96	74%	51%

[a] L-amino acid in the Zn-complex; n.d. = not determined, *t*-Leu = L-*tert*-Leucine.

Notes and references

‡ The zinc–amino acid complexes were prepared by adding Et_3N (0.6 ml) to the amino acid (4.34 mmol) in MeOH (10 ml), followed, after 10 min, by zinc acetate (2.17 mmol). After stirring for 45 min a white precipitate was collected by filtration (23–95% yield). Complexes were characterized by ^1H- and ^{13}C- NMR and ESI-MS.

The zinc–proline complex (5 µmol) was stirred in acetone–water (1.5 ml) with 4-nitrobenzaldehyde (0.1 mmol) for the time indicated. The solvent was evaporated and after addition of $CDCl_3$ and filtration of the non-soluble complex, the product was analyzed by ^1H NMR spectroscopy.

§ The aldol reaction was also carried out with hydroxyacetaldehyde in water, without any co-solvent to yield a mixture of tetroses and hexoses.

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