Tetrahedron 67 (2011) 7050–7056

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The role of Zn^{2+} in enhancing the rate and stereoselectivity of the aldol reactions catalyzed by the simple prolinamide model

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ARTICLE INFO

Article history:
Received 15 April 2011
Received in revised form 27 June 2011
Accepted 6 July 2011
Available online 14 July 2011

Keywords:
Aldol reaction
Lewis acid
Stereoselectivity
Zinc–prolinamide

ABSTRACT

The aldol reaction between acetone and 4-nitrobenzaldehyde catalyzed by single L-prolinamide and its zinc complexes has been studied. An increase in the rate and the stereoselectivity of the reaction has been shown by using zinc derivatives. A mechanistic proposal, based on NMR and ESI studies, has been put forward to explain the experimental data: zinc–prolinamide complexes catalyze the reaction following the general mechanism of stereoselective enamine nucleophilic addition to the acceptor aldehyde. Zn^{2+} prevents the nonspecific base-catalyzed reaction by diminishing the basicity of the amine nitrogen of prolinamide.

1. Introduction

The stereoselective aldol reaction is considered as one of the most important carbon–carbon bond-forming reactions in organic synthesis, and is a way to obtain chiral β-hydroxy carbonyl compounds.[1]

From the green chemistry viewpoint, it is desirable to perform reactions with a minimum environmental impact, using water as a reaction solvent and safety catalyst.[2] Unfortunately this is not easy, although nature itself provides a model to be imitated: enzymes that catalyze reactions in water under mild conditions with high efficiency and stereoselectivity. Thus, aldolases are nature's catalysts of aldol condensation. According to the mechanism, two different types of aldolases have been identified and classified. The first (class I) contains a Lysine residue in the active site, which is involved in nucleophilic enamine intermediate formation. This activated donor adds stereoselectively to the aldehyde acceptor. The second aldolases type (class II) contains a Zn(II) cofactor at the active site, which is coordinated to His residues. This cation acts by coordinating to the carbonyl oxygen of the ketone donor, and facilitates enolate formation. In both types of aldolases, stereoselectivity is controlled by the enzyme and does not depend on the substrate's structure or stereochemistry, which allows for highly predictable products.[3]

Given the difficulty in using enzymes in a large-scale synthesis, it is desirable to develop simple chemical systems that mimic the action of enzymes by performing highly efficient reactions in water. In this way, L-proline and its derivatives have been employed in recent years in a wide range of asymmetric organic transformations, especially aldol addition.[4] These kinds of catalysts are known to operate via an enamine mechanism (class I aldolase mimics).[5] However in many cases, high enantioselectivities have been achieved only in organic solvents, while the presence of water lowers enantioselectivity.[6] Few examples of efficient organocatalytic asymmetric aldol reactions in water have been described.[7]

Most of the proline derivatives used to date are prolinamides. Some general facts have made these derivatives useful: their synthesis is easy, the presence of a robust amide linkage provides very stable compounds, and the acidity of the hydrogen of an NH moiety is enough to activate electrophiles by hydrogen bonding.[8] Prolinamide itself can catalyze aldol condensation though with little enantioselectivity.[9] But the simplicity of this compound makes it a good model to be used in the optimization of reaction conditions, that might be improved using more sophisticated derivatives. Therefore, it was used in our experiments.

Some years ago, Darbre et al. described how the $Zn(Pro)_2$ complex, as well as $Zn(Arg)_2$ and $Zn(Lys)_2$, are able to catalyze the intermolecular reaction between aldehydes and ketones in water with moderate enantioselectivity. These systems are also active in the self-condensation of glycoaldehyde to form carbohydrates.[10] These authors found that the $Zn(Pro)_2$ complex, prepared under basic conditions, was more effective than proline itself in an aqueous medium, in terms of both yield and stereoselectivity.

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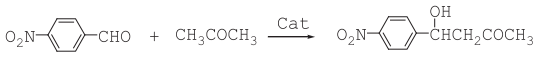
doi:10.1016/j.tet.2011.07.013

Interestingly, different enantiomers were found in excess under both conditions.[10a] This complex can act as a good class II aldolases model. Recently, Penhoat et al. performed a broad screening of different alternative water-compatible Lewis acids cocatalysts with proline in a neutral medium. They obtained the best results in stereoselectivity and conversion using zinc chloride.[11]

Besides, Mlynarsky et al. showed that the addition of $Zn(OTf)_2$ notably improved yield and stereoselectivity in the condensation between different aldehydes and ketones catalyzed by bis(prolinamides). This model assumes the formation of an enamine stabilized in water by coordination to zinc at the active site. Zinc coordinates with both the amide group of the catalyst and the carbonyl group of the aldehyde, thus enabling condensation in the chiral surrounding.[12]

2. Results and discussion

In our work, we used the aldol reaction between acetone and *p*-nitrobenzaldehyde catalyzed by L-prolinamide (Pde from now onward) as a benchmark, and as the simplest model for the proline derivatives of the prolinamide type (Scheme 1). We considered that this simple model would also be a good approximation to natural aldolases, even when stereoselection was always modest, as it contains both the pyrrolidine ring moiety of proline and the amide function present in all enzymes. The addition of Zn^{2+} (zinc acetate) under neutral conditions and the study of its effect may provide an easier understanding of how both types of natural aldolases work. In fact, metalloenzymes also contain a metal at their active site, which is present on the protein surface with at least one free coordination site on the metal ion. The substrate is activated by the coordination to it.[13] The prolinamide geometry with the pyrrolidine nitrogen and the amide function fits the coordination sphere of Zn^{2+}, forming a five-member ring. This coordination sphere can be completed with another prolinamide molecule or other donor species present in the solution.



Scheme 1.

In the preliminary experiments, we compared yield and stereoselectivity in the reactions catalyzed by L-prolinamide and its isolated complexes with Zn^{2+} (Zn/Pde 0.5:1, or 1:1) and Cu^{2+} (Cu/Pde 0.5:1), prepared as described in the Experimental section. We used these isolated complexes in most experiments. However, we observed that the results were exactly the same as in the 'in situ' preparation of the complexes by adding the stoichiometric amounts of the metal salt and L-prolinamide to the reaction mixture, as described in Mlynarsky et al.[12]

Fig. 1 compares the results obtained with Pde, Zn/Pde (0.5:1) or Cu/Pde (0.5:1) under different solvent conditions. In all cases, excess enantiomer had an *R* configuration, which is the stereoisomer obtained in the proline enamine catalysis, as described in the literature.[8b,c,14] The reactions catalyzed by the Zn–Pde complex (0.5:1) were faster than those of the Cu–Pde complex (0.5:1) or Pde itself. Larger amounts of these must be used for the same conversion, and the stereoselectivity obtained for free Pde was worse. The best results obtained with the complexes were accomplished in the presence of 5% distilled water, this being the minimal amount required to solubilize the complexes. Pde provided the best results when water was not present at all, but the reaction was very slow under these conditions. As usually observed, addition of water was detrimental to stereoselectivity,[6] and this is also true when using the complexes as catalysts, but to a lower extent. Similar results were obtained when other protic solvents, like methanol, were considered.

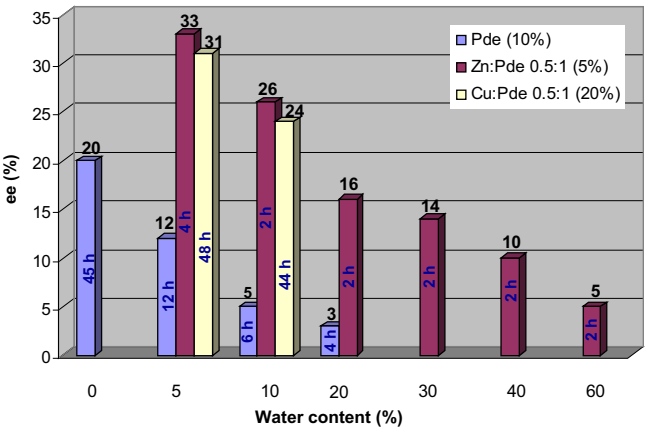


Fig. 1. Effect of water content on the stereoselectivity of Pde and its complexes. Reactions were carried out in acetone as the main solvent and at room temperature until completion.

Table 1 presents the results obtained when different Zn^{2+}/Pde ratios were used. Identical stereoselectivities were reached with the 1:1 and 0.5:1 stoichiometry (compare entries 4–8, 6–10, and 7–12). No reaction was observed in the absence of Pde or when zinc acetate was used as the sole catalyst.

Table 1
Effect of the amount of Zn^{2+}/Cu^{2+}, temperature, and TFA as an additive

Entry	Conditions[a]	% Cat	Time (h)	Yield[b]	% ee[c]
1	Pde, rt	10	12	100	12
2	Pde, 0 °C	10	12	100	12
3	Pde/TFA 1:1, rt	10	48	18	37
4	Zn/Pde 1:1, rt	5	7	100	33
5	Zn/Pde/TFA 1:1:1, rt	5	24	100	40
6	Zn/Pde 1:1, 0 °C	5	8	100	33
7	Zn/Pde 1:1, −20 °C	5	45	80	30
8	Zn/Pde 0.5:1, rt	5	3	100	33
9	Zn/Pde/TFA 0.5:1:1, rt	5	20	100	42
10	Zn/Pde 0.5:1, 0 °C	5	5	100	33
11	Zn/Pde/TFA 0.5:1:1, 0 °C	5	30	100	44
12	Zn/Pde 0.5:1, −20 °C	5	24	100	30
13	Zn/Pde/TFA 0.5:1:1,−20 °C	5	96	50	37
14	Cu/Pde 0.5:1, TA	20	48	87	31
15	Cu/Pde 0.5:1, 0 °C	20	65	80	30
16	Cu/Pde 0.5:1, −20 °C	20	96	25	19

[a] Reactions in acetone with 5% distilled water. Complexes prepared using zinc acetate or copper(II) sulfate were used as a catalyst.
[b] Determined by NMR.
[c] HPLC (IC, Hex/^{i}proh 94/6, 1 ml/min). See the Experimental section for an absolute configuration of the main enantiomer.

While no significant differences in stereoselectivity were observed with temperature, the reaction rate dropped at lower temperatures. Moreover in the reaction catalyzed by CuPde (0.5:1), a reduction in ee took place at the lowest temperature, which is probably due to poor complex solubility (entries 14–16).

Protonated chiral prolinamide derivatives are usually more effective than the free base for stereoselective aldol additions since protonation diminishes the basic strength of the amine catalyst, favoring iminium ion catalysis.[15] In our case, we made similar observations. Table 1 and Fig. 2 show the results when 1 equiv of trifluoroacetic acid, relative to prolinamide, was added under standard conditions (5% water) at different temperatures. In all

cases, the use of protonated prolinamide resulted in slower reactions, but better stereoselectivity (entries 1–5, and 8–13). Thus, the greatest increase occurred when prolinamide trifluoroacetate salt was used instead of free Pde.

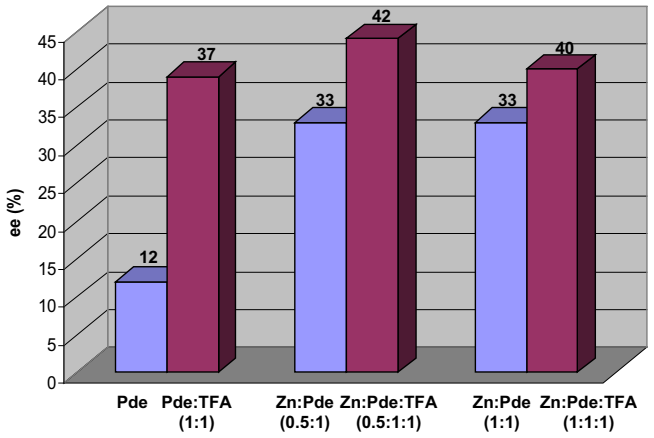


Fig. 2. Effect of TFA on stereoselectivity.

Regarding yield and ee, the same trend for 4-nitrobenzaldehyde was observed for the 2- and 3-regioisomers used as substrates in the aldol condensation with acetone (Fig. 3). Reactions with the trifluoroacetate salts of the complexes were the most stereoselective. The greatest ee increase was also observed when comparing free prolinamide and its trifluoroacetate salt.

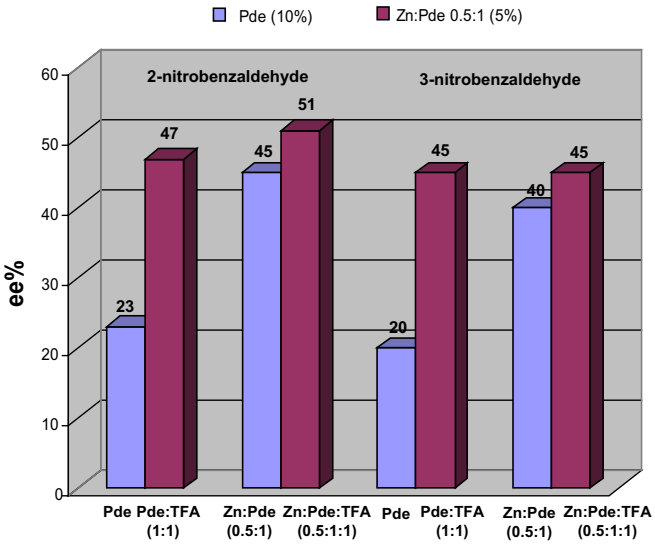


Fig. 3. Reaction with 2 and 3-nitrobenzaldehyde (in acetone with 5% water).

2.1. NMR and ESI-MS measurements

The above results show that Zn^{2+} plays a role in the mechanism of the reaction being produced, this being faster and more stereoselective in almost all cases, even when adding increased amounts of water. It would be very interesting to know the catalytic complex structure but, unfortunately, suitable crystals for an X-ray analysis could not be obtained for either zinc complex (Zn/Pde 0.5:1, Zn/Pde 1:1), or for the copper complex (Cu/Pde 0.5:1).

The complex between zinc oxide and L-proline, prepared under basic conditions (Bis(L-prolinato-N,O)zinc(II)), was previously described to show two prolines, trans in relation to each other, and coordinated to the Zn atom via their nitrogen and carboxylic oxygen atoms. A fifth coordination site of the Zn atom is occupied by a symmetry-related O atom of a neighboring proline molecule, generating an infinite polymeric chain.[16a] Moreover, the complex between zinc chloride and D,L-proline, prepared under neutral conditions (Dichlorobis(DL-proline-κO)zinc(II)), shows Zn^{2+} ion tetrahedrally coordinated with two halogenides and two O atoms of two negatively charged carboxylates as donors. Hydrogen bonding links the molecule in linear chains. Halogenides and carbonyl oxygens act as acceptors of hydrogen bonds, which are donated by the positively charged ammonium groups.[16b]

Although knowledge of the complex structure in the solid state is of interest, knowledge of the nature of the species in solution under the reaction conditions could be even more interesting. The analysis of the complexes by ^{1}H NMR indicates new species formation.

The ^{1}H NMR spectra of the complex in methanol presented a downfield displacement in the signals of the pyrrolidine ring hydrogens. The shift of protons more closely to the nitrogen atom was particularly significant, especially the double doublet signal corresponding to H–Cα (Fig. 4). No significant differences in Pde signals were observed in the spectra when a ratio of Zn/Pde 0.5:1 or 1:1 was used, which did not allow us to determine the nature and stoichiometry of the formed species.

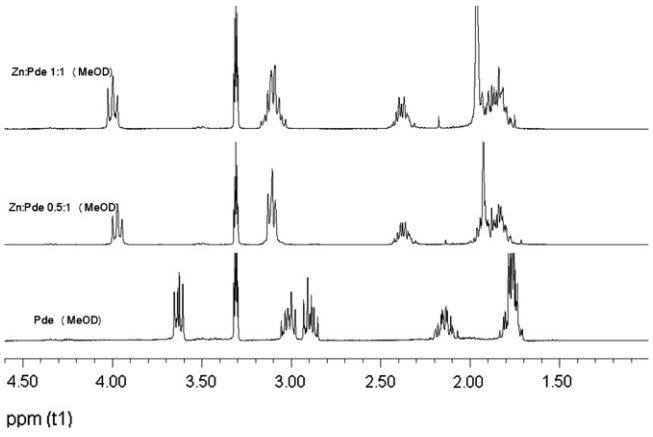


Fig. 4. ^{1}H NMR in methanol of Pde and its complexes with 0.5 or 1 equiv of zinc acetate dihydrate.

The similar stereoselectivity obtained when using the trifluoroacetate salt of prolinamide ($PdeH^+$) and the trifluoroacetate salts of the zinc complexes (Table 1) may indicate that complexes are not formed when the nitrogen of the amine is protonated by the acid, being in these cases protonated prolinamide the catalytic species. To confirm this hypothesis, the spectra of Pde/TFA and Zn/Pde/TFA were recorded in methanol and in DMSO-d_6. Both species exhibited a downfield displacement in the pyrrolidine moiety signals in relation to prolinamide, especially for the former (Fig. 5). The changes in the amide/ammonium area in the spectra recorded in DMSO were highly significant: signal at 3.1 ppm (N–H) disappeared in the protonated prolinamide, and two new signals appeared at 8.3 and 9.4 ppm (N–H ammonium). These signals were erased after the addition of zinc acetate, and a new broad signal increased again at 3.1 ppm (N–H and water from the zinc acetate dihydrate). These observations allow us to conclude that, in the presence of Zn^{2+}, N of pyrrolidine coordinates to it, and that the equilibrium among protonated Pde, free Pde, and Pde coordinated to the ion must be displaced mostly to the later species. Similar

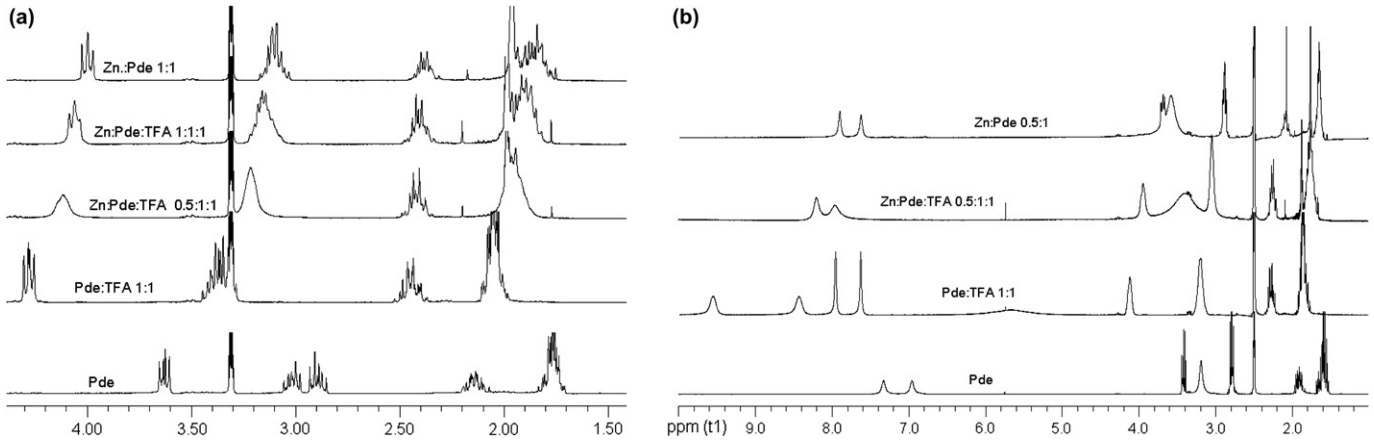


Fig. 5. (a) ^{1}H NMR in methanol and (b) in DMSO-d_6 of Pde, Pde with 1 equiv of trifluoroacetic acid, Pde with 1 equiv of both trifluoroacetic acid and 0.5/1 equiv of zinc acetate, and Pde with zinc acetate.

behavior was observed in the experiments carried out in methanol when studying the signal corresponding to Hα.

Electrospray ionization mass spectrometry (ESI-MS) has proved to be a useful tool in the qualitative study of a solution at equilibrium.[17] Application of the positive ion mode (ESI^{+}) allowed us to detect all the participating species. Stoichiometry could be determined directly from their *m*/*z* values and the isotopic pattern of peaks. Each peak's relative intensity should not be considered quantitatively if we believe that the sensitivity of this technique to detect different species depends on its ability to undergo ionization.

The ESI-MS spectrum corresponding to the relation Zn/Pde 1:1 in methanol shows an equilibrium of different complexes between prolinamide and Zn^{2+} (Supplementary data). A peak at *m*/*z* 237 corresponding to a Zn–prolinamide complex (1:1) with one acetate equivalent, and the peaks at *m*/*z* 291, and the most intense one at 351, were, respectively, expected for those complexes with one Zn and two prolinamides (0.5:1), and with one additional acetate ion in the second case. The ESI-MS spectrum corresponding to a Zn/Pde 0.5:1 ratio in methanol solution was very similar, but the peak at *m*/*z* 237 appeared with very low intensity. Even though this is a qualitative technique, the behavior of all these species must be similar under ionization conditions. The fact that the peak at *m*/*z* 351, was the most intense one in all cases indicates that the stoichiometry for the most stable complex is two molecules of Pde and one of zinc ion ($ZnPde_2$).

The ESI-MS corresponding to Zn/Pde/TFA 1:1:1 shows the presence of some 1:1 (*m*/*z* 195, 237,) and 1:2 (*m*/*z* 291, 323, 351) complexes between Zn and Pde. These data agree with the NMR experiments shown in Fig. 5, indicating the major preference of the N of pyrrolidine to be coordinated by zinc (Scheme 2).

and ^{13}C NMR spectra of Pde showed the presence of two species, but only the signals corresponding to one of them remained several hours later (Fig. 6).

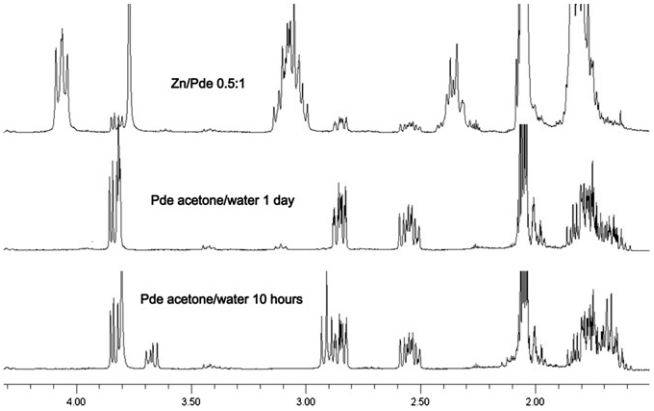
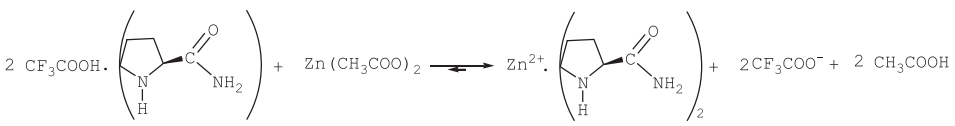


Fig. 6. ^{1}H NMR in acetone/water (85:15) of Pde (at different times) and Zn/Pde 0.5:1.

In order to clarify the identity of this species, we must consider all the possible intermediates that might form between Pde and acetone. Most mechanistic studies performed in the aldol reaction use Pro as catalyst.[5,18] To date very few use prolinamide derivatives.[19] In all cases, an enamine-based mechanism is accepted if compared with the reactions catalyzed by Class I aldolase enzymes (Scheme 3). The addition of proline to acetone provides different kinds of intermediates whose stability depends on the reaction

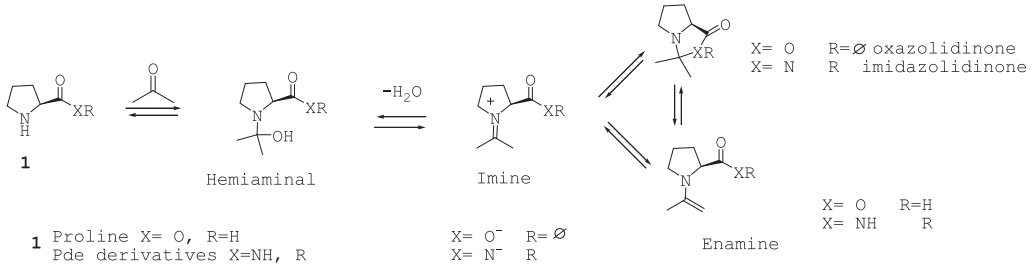


Scheme 2.

A series of similar experiments was carried out using deuterated acetone as a solvent. The zinc complexes of prolinamide were insoluble in pure acetone, and could not be dissolved in the solvents mixture used in our reactions containing 5% water, at least at the concentration required for the analysis by ^{13}C NMR. Therefore, a mixture of 85:15 acetone/water had to be used. Initially, the ^{1}H

conditions. The first intermediate is a hemiaminal that affords an iminium carboxylate after dehydratation, which is in equilibrium with an oxazolidinone or an enamine, considered the key intermediate in the addition to the acceptor aldehyde.[5] The enamine had never been detected in situ in different NMR studies before Gschwind et al. described it as an intermediate in the self-

aldolization of propionaldehyde catalyzed by proline in DMSO (water content less than 15%).[20] In fact, theoretical studies done in both the gas phase and solution have shown a lack of stability for this intermediate.[18] Oxazolidinone, considered a parasitic[5c,18] species in the asymmetric aldol reaction, is usually described as the main compound when using aprotic solvents. Equilibrium shifts to the iminium intermediate in the presence of protic solvents.[18a] On the other hand, the studies carried out by Gryko and Morán using L-prolinethioamides and aromatic prolinamides, respectively, have shown the formation of a cyclic imidazolidinone as the main intermediate, which is stable under different conditions, and even has been isolated and fully characterized (Scheme 3).[19]



Scheme 3. Intermediates proposed for proline (1, XR=OH) and prolinamine derivatives (1, XR=NHR) catalyzed asymmetric aldol condensation.

The ^{13}C NMR spectra of Pde in the mixture used (acetone/water 85:15) shows a signal at 76 ppm, corresponding to a quaternary carbon bonded to oxygen and nitrogen atoms. This product, and in analogy to the studies described before, has been identified as the imidazolidinone derived from the condensation between prolinamide and acetone (Supplementary data). Those signals corresponding to methyl-d_3 carbons could not be observed in acetone-d_6 due to D–C coupling. Therefore, in order to fully characterize this intermediate, it was synthesized in a flask by dissolving in acetone (acetone-h_6) Pde for 20 h. Evaporation of the solvent yielded a white solid whose spectrum recorded in $CDCl_3$ showed two clear singlets corresponding to the diastereotopic CH_3 signals.

The ^1H and ^{13}C NMR spectra of the Zn^{2+}–Pde complex in acetone-d_6 (Fig. 6) indicate the absence of the imidazolidinone intermediate and a downfield displacement of those signals corresponding to Pde.

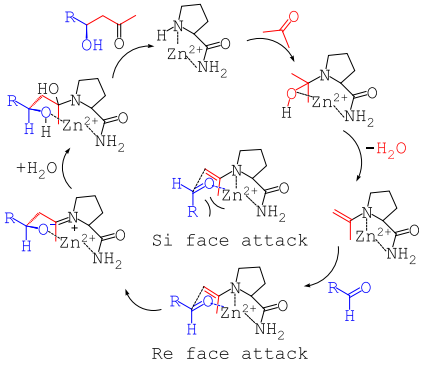
The ESI-MS spectra in acetone solution were also recorded. The base peak at m/z 155 corresponds to one of the imine/enamine or imidazolidinone intermediates. Peaks at m/z 237 and m/z 291 were also present in those samples corresponding to the complexes.

2.2. Mechanistic considerations

The results observed in our study are consistent with Darbre's experiments using $Zn(Pro)_2$.[10] For Pde, the NMR and ESI-MS experiments indicate the formation of complexes whose majority stoichiometry Zn/Pde in solution is 0.5:1 ($ZnPde_2$). To check if the reaction catalyzed by the complex occurs through the formation of an imine–enamine type intermediate, a solution of $ZnPde_2$ and 1.5 equiv of acetone in methanol was treated with $NaBH_4$.[10e] The isolation of *N*-isopropyl prolinamide allowed us to test this hypothesis (Supplementary data). Therefore, we can conclude that the catalyst acts as Class I aldolase.

Reactions with free Pde proved to be slower and less stereoselective than those with the zinc complexes. This fact indicates that Zn^{2+} plays a role in the reaction rate and in stereoselection, and that the model is also analogous to Class II aldolases.[11] Zn^{2+} may accelerate the process by acting as a Lewis acid because it coordinates the ketone, approaches the N of the pyrrolidine ring and makes hemiaminal formation easier (Scheme 4). The dehydration of this species is faster too with the complex because zinc, acting as a Lewis acid, could coordinate to the O of the hydroxyl group of the hemiaminal, thus favoring its dehydration and nucleophilic enamine formation. Zn^{2+} coordination to the O of the acceptor aldehyde makes it more electrophilic and also increases the reaction rate. Moreover, this interaction fixes aldehyde in such a way that the nucleophilic *Re* attack is favored for steric considerations. Although less effective, the interaction with aldehyde could also be performed by hydrogen bonds forming with the amide hydrogens when using Pde as a catalyst. When the concentration of water (or of any other protic solvent) in the reaction medium increases, it competes with Zn^{2+} or with the hydrogens of the amide group in the ZnPde or Pde catalyzed reactions, respectively, by breaking down the chiral environment for enantioselective addition.

Finally, the results in Table 1 suggest the enhancement of the stereoselectivity by using Brönsted acid (TFA) as additive. This observation can be easily explained by the fact that protonation of the amine prevents its action as Brönsted base in the intermolecular condensation that would lead to the racemic aldol. So, in acidic conditions the enantioselective nucleophilic attack is the mechanism favored.[12a,15] The competitive reaction as Brönsted base seems to be more important when Pde, rather than its zinc complexes, is used as a catalyst, and stereoselectivity increases further by its protonation (Fig. 2). In the zinc complexes, the basicity of nitrogen has already diminished because of ion coordination. Addition of Brönsted acid to Pde allows the attainment of similar ee than with Zn–Pde complexes, although the reaction is faster in the second case.



Scheme 4. Mechanism proposed for the cross aldol reaction between 4-nitrobenzaldehyde and acetone catalyzed by the zinc complex of prolinamide (only one Pde is shown for clarity).

The interesting mechanistic studies conducted by Gryko and Morán with prolinamide derivatives as catalysts for the aldol reaction has allowed them to verify that the imidazolidinone intermediate could be responsible for the reduction in yield and stereoselectivity of the aldol product.[19] They have observed that the

addition of Brönsted acid inhibits their formation, being able to improve the stereochemical results.

The conditions we used (addition of TFA or Zn^{2+} to Pde) could suppress the formation of the imidazolidinone intermediate, and as result lead to an increase of the stereoselectivity and yield in relation to reactions catalyzed with Pde. In fact, as shown in Fig. 6, imidazolidinone intermediate is observed only in the spectrum of Pde in acetone, but not in that of the $ZnPde_2$.

We are currently conducting experiments that allow us to learn more about the role of this intermediate imidazolidinone and the possible inhibition of its formation through the use of complexes of Zn as catalyst.

3. Conclusions

In short, we have studied the possible role of zinc ion in aldol condensations catalyzed by the simple Pde model. We conclude that this catalyzes the reaction following the general mechanism of enamine nucleophilic addition to the acceptor aldehyde. Zn^{2+} not only prevents the base-catalyzed reaction by diminishing the basicity of the amine nitrogen of Pde, but also acts by favoring enamine formation in an aqueous medium. Besides, the Lewis acid character of Zn^{2+} makes the interaction with the acceptor aldehyde more effective. Exclusion of water from the reaction center could also avoid its coordination with ion, thus making it more acidic, and could prevent its coordination to the aldehyde. The stereoselectivity achieved with this model is modest, but can be improved by using other derivatives in which the ion is wrapped in a more hydrophobic environment.

4. Experimental

4.1. General

All the commercially available reagents were purchased from Aldrich. Reactions were monitored by thin layer chromatography (TLC) on Merck silica plates 60 F_{254}. Flash chromatography was performed on Merck silica gel (60-particle size: 0.040–0.063 mm). NMR spectra were recorded with Bruker DRX 300 spectrometers in different deuterated solvents. Chemical shifts are reported in parts per million in relation to the residual solvent peaks. Absolute configurations were determined by comparing with the optical rotations reported in the literature, and these were performed in a Perkin–Elmer 241 Polarimeter using a Na lamp. Electrospray ionization mass (ESI-MS) spectra were recorded in an Ion Trap Esquire 3000+Mass Spectrometer (Bruker), coupled with an HPLC Agilent 1100. Samples were analyzed by direct infusion at 240 μl/h. Positive-ion conditions: ES capillary voltage, 4100 V; Skimmer, 40 V; Cap Exit, 135 V; Trap Drive, 37; Oct RF, 138.6 Vpp; Lens 1, −5 V; Lens 2, −60 V; Nebulizer, 10 psi; Dry Gas, 5 l/min; Dry Ta, 350 °C. Scanning was carried out from 80 to 600 *m*/*z*.

High performance liquid chromatography (HPLC) was performed with a Merck Hitachi Lachrom system. For the analytical work, a Chiralpak IC column (5 μm, 250×4.6 mm ID) was used with the solvent mixture indicated in each case. The wavelength for detection was fixed at 254 nm.

4.2. Isolation of complexes

Complexes Zn^{2+}/prolinamide 1:2 ($ZnPde_2$), 1:1 (ZnPde) and Cu^{2+}/prolinamide 1:2 ($CuPde_2$) were prepared by mixing a solution of neutral Pde (1.75 mmol, 200 mg) in tetrahydrofurane with a solution of either zinc acetate dihydrate (0.87 or 0.435 mmol) or cupper nitrate trihydrate (0.87 mmol) in the minimum amount of this solvent in which these salts are soluble. The mixture was stirred for 30 min, and the white and blue precipitates were, respectively, collected by vacuum filtration and dried (70%, 60% and 96% yields, respectively).

4.2.1. Pde. ^{1}H NMR (MeOD): 1.70–1.83 (m, 3H), 2.00–2.20 (m, 1H), 2.89–2.93 (m, 1H), 2.90–3.10 (m, 1H), 3.60–3.70 (m, 1H). ^{13}C NMR (MeOD): 27. 04 (t), 32.33 (t), 48.03 (t), 61.39 (d), 179.89 (s).

4.2.2. Imidazolidinone Pde–acetone. ^{1}H NMR ($CDCl_3$): 1.43 (s, 3H), 1.45 (s, 3H), 1.60–2.02 (m, 3H), 2.06–2.29 (m, 1H), 2.56–2.66 (m, 1H), 2.88–3.02 (m, 1H), 3.92 (1H, dd, 9.76 Hz, 4.75 Hz), 6.67 (1H, br s).^{13}C NMR ($CDCl_3$): 23.63 (q), 25.65 (t), 25.82 (t), 30.72 (q), 48.69 (t), 63.98 (d), 74.84 (s).

HRMS (EI^+) calcd for $C_8H_{14}N_2O$ 154.1106, found 154.1104. Anal. Calcd for $C_8H_{14}N_2O$: C 62.33, H 9.09, N 18.18. Found C 62.20, H 9.16, N 18.10. Mp 140–142 °C.

4.2.3. $ZnPde_2$. ^{1}H NMR (MeOD): 1.75–1.95 (m, 3H), 2.33–2.45 (m, 1H), 3.00–3.20 (m, 2H), 3.95–4.05 (m, 1H). ^{13}C NMR (MeOD): 27.44 (t), 32.36 (t), 48.62 (t), 60.16 (d), 180.27 (s). ESI-MS^+ (MeOD): 351, 291, 236.

4.2.4. $CuPde_2$. ESI-MS^+ (MeOD): 290.

See Supplementary data.

4.3. Typical aldol condensation procedure

The corresponding aldehyde (0.165 mmol, 25 mg) and catalyst (5% of the zinc complex or 10% of Pde) were added to a mixture of acetone–water (2.375–0.125 ml) in a capped vial. The resulting mixture was stirred at the indicated temperature and monitored by TLC. The reaction was quenched by addition of saturated ammonium chloride solution and evaporation of acetone in vacuum. Then, water was extracted with methylene chloride and the organic phase was dried over sodium sulfate. Crude material was employed to determine the yield by NMR and the ee by HPLC using a chiral stationary phase.

Reaction products were purified previously by column chromatography (hexane/ethyl acetate, 4:1) and characterized by NMR and chiral HPLC. Data were consistent with those described in the literature.[8b,c]

4.3.1. 4-Hydroxy-4-(p-nitrophenyl)-butan-2-one. ^{1}H NMR ($CDCl_3$): 2.21 (s, 3H), 2.84 (m, 2H), 3.60 (s, 1H), 5.26 (m, 1H), 7.53 (d, 8.8 Hz, 2H), 8.20 (d, 8.8 Hz, 2H). ee was determined by HPLC with a Chiralpak IC column 94/6 hexane/2-propanol, 254 nm, 1.0 mL/min, t_R=31.6 (minor, *S*), t_R=33.5 min (major, *R*).

4.3.2. 4-Hydroxy-4-(o-nitrophenyl)-butan-2-one. ^{1}H NMR ($CDCl_3$): 2.16 (s, 3H), 2.63 (dd, 17.8 Hz, 9.4 Hz, 1H), 3.09 (dd, 17.8 Hz, 2.0 Hz), 3.90 (s, 1H), 5.60 (m, 1H), 7.40 (m, 1H), 7.61 (m, 1H), 7.86 (m, 1H). ee was determined by HPLC with a Chiralpak IC column 85/15 hexane/2-propanol, 254 nm, 1.0 mL/min, t_R=24.8 (major, *R*), t_R=27.0 min (minor, *S*).

4.3.3. 4-Hydroxy-4-(m-nitrophenyl)-butan-2-one. ^{1}H NMR ($CDCl_3$): 2.23 (s, 3H), 2.90 (m, 2H), 3.59 (s, 1H), 5.30 (m, 1H), 7.53 (m, 1H), 7.70 (m, 1H), 8.24 (m, 1H). ee was determined by HPLC with a Chiralpak IC column 80/20 hexane/2-propanol, 254 nm, 1.0 mL/min, t_R=12.6 min (major, *R*), t_R=13.6 (minor, *S*).

Acknowledgements

This work has been supported by Spanish Dirección General de Investigación Científica y Técnica Consolider Ingenio 2010 (CSD 2007-00006), (CTQ 2007-65720). We gratefully acknowledge SCSIE (Universitat de València) for access to instrumental facilities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.013.

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