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Inhibition of imidazolidinone intermediate formation in the aldol reactions catalyzed by zinc–prolinamide complexes

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ABSTRACT

The use of zinc salts as cocatalysts in aldol condensations catalyzed by single prolinamide (and in the extension by other more complex prolinamides) can prevent the formation of the parasitic intermediate imidazolidinone, with faster and also more stereoselective reactions than those catalyzed by the free amine. This new finding, together with this ion's already known properties, make zinc salts highly suitable additives for aldol reactions catalyzed for prolinamide derivatives.

1. Introduction

L-Proline (Pro) and its derivatives have been employed in recent years as simple chemical systems that mimic the action of enzymes in a wide range of asymmetric organic transformations, especially aldol addition.[1] This kind of catalysts is known to operate via an enamine mechanism (class I aldolase mimics).[2]

Stability of prolinamides, their easy preparation, and the presence of an NH moiety in their structure, whose acidity is sufficient to activate electrophiles by hydrogen bonding, imply that these proline derivatives have been the most widely used to date.[3] Prolinamide (Pde from now onward) is a simple compound that can catalyze aldol condensation, although with slight stereoselectivity.[4] This compound can be used as a model to optimize basic reaction conditions, which can then be extended to more sophisticated derivatives. For this reason, it has been used in our experiments.

The mechanistic studies performed in the aldol reaction using Pro as a catalyst[2,5a] have shown the presence of different kinds of intermediates of varying stability (Scheme 1). The first is an iminium carboxylate, derived from a hemiaminal between proline and the ketone after dehydration. Iminium is in equilibrium with either oxazolidinone or an enamine, the key intermediate in the addition to the acceptor aldehyde.[2] Oxazolidinone has traditionally been considered a parasitic species that does not appear to play any productive role in the catalysis, but removes catalytic loading from the actual reaction.[2c] However, some groups now agree that this cyclic intermediate plays a more active role, even as actual organocatalysts.[5]

To date, very few mechanistic analyses of aldol reaction use prolinamide derivatives. The studies of Gryko and Morán using L-prolinethioamides and aromatic prolinamides, respectively, have shown the formation of a stable cyclic imidazolidinone as the main intermediate.[6]

Zinc salts have been used as cocatalysts in aldol reactions. Darbre et al. described the use of the $Zn(Pro)_2$ complex to catalyze the intermolecular reaction between aldehydes and ketones, which was more effective than proline itself in an aqueous medium in terms of both yield and stereoselectivity.[7] After performing a broad screening of different alternative water-compatible Lewis acids cocatalysts with proline in a neutral medium, Penhoat et al. obtained excellent results using zinc chloride in both, stereoselectivity and conversion.[8] Mlynarsky notably improved yield and stereoselectivity in condensation between different aldehydes and ketones catalyzed by bis(prolinamides) by the addition of $Zn(OTf)_2$. They proposed a model in which the enamine intermediate is stabilized in water by coordination to zinc. The ion coordinates with both the amide group of the catalyst and the carbonyl group of the aldehyde, thus enabling condensation in a chiral enviroment.[9]

In a previous work, we studied the role of zinc ion in enhancing the rate and stereoselectivity of the aldol condensations catalyzed by the simple Pde model. We concluded that this catalyzes the reaction following the general mechanism of enamine nucleophilic

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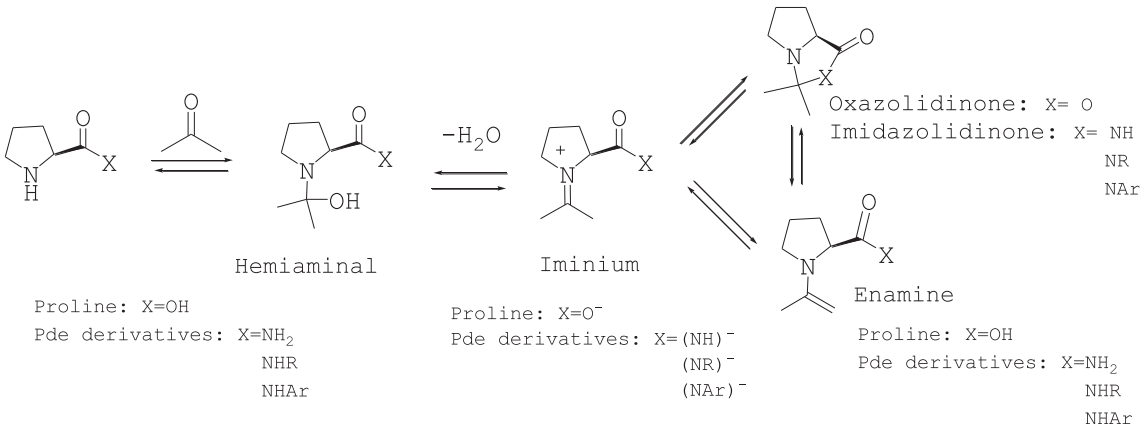


Scheme 1. Intermediates proposed for proline and prolinamide derivatives in catalyzed asymmetric aldol condensation.

addition to the acceptor aldehyde. Zn^{2+} acts by preventing the base-catalyzed reaction, by diminishing the basicity of the amine nitrogen of Pde, and by also favoring enamine formation in an aqueous medium. The prolinamide geometry with the pyrrolidine nitrogen and the amide function fits the coordination sphere of Zn^{2+} to form a five-member ring. This coordination sphere can be completed with either another prolinamide molecule or another donor species present in the solution to afford very stable complexes.[10]

Based on our previous results and those described in the literature,[2,6] we decided to study the possible role of Zn^{2+} in inhibiting the formation of the above-described parasitic intermediate imidazolidinone to hence, contribute to an increase in both the yield and the stereoselectivity of the reaction.

2. Results and discussion

2.1. Imidazolidinone formation kinetics

First of all, we studied the formation of the imidazolidinone intermediate between Pde and acetone (**1**) by NMR under different conditions. For this purpose, we recorded the ^{1}H NMR spectra of Pde, $ZnPde_2$ (prepared in situ by mixing 0.5 equiv of zinc acetate and 1 equiv of Pde), Pde/TFA (1:1) and $ZnPde_2$/TFA (0.5:1:1) at different times using an acetone/water mixture (85/15) as the deuterated solvent. We employed this solvent because zinc complexes are not soluble in the amounts required to perform the spectrum, when using less water. Fig. 1 shows the kinetics of cyclic imidazolidinone formation in all cases. Free Pde was completely converted into imidazolidinone after 12 h. On the other hand, when Pde was complexed with the Lewis acid Zn^{2+}, the cyclic intermediate formed much more slowly. Protonation of Pde or its zinc complex ($ZnPde_2$) by Brönsted acid TFA practically inhibited the formation of this intermediate (Spectra in Supplementary data).

Previously, Gryko et al. described that the use of protonated L-prolinethioamide catalysts, instead of the free base, for the direct aldol condensation between 4-nitrobenzaldehyde and acetone could improve both the yield and the stereoselectivity of the reaction. These authors studied different acids to protonate the catalyst to find a relationship among the pKa of the acid, the amount of imidazolidinone intermediate formed, and the yield and stereoselectivity of the aldol product. The best results were achieved in cases in which fewer cyclic intermediate levels were detected.[6b]

We also carried out the study of imidazolidinone formation (**1**) by NMR using methanol and chloroform as solvents. In these cases, 1.5 equiv of acetone in relation to Pde were added and the spectra were recorded at different times. Imidazolidinone completely

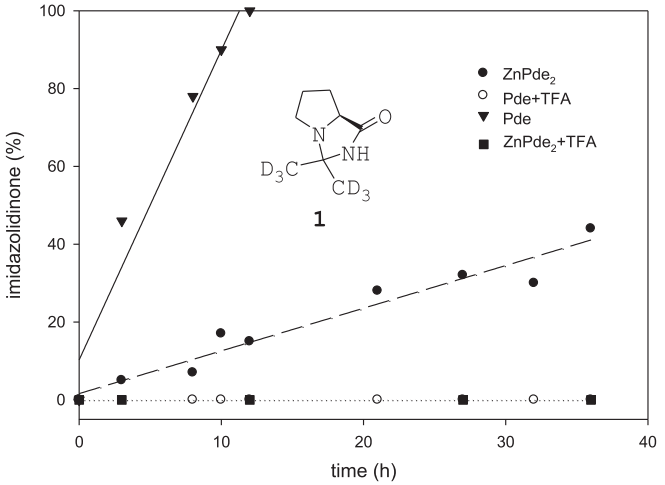


Fig. 1. Imidazolidinone **1** formation kinetics at rt in the absence of additives and in the presence of zinc acetate or/and trifluoroacetic acid.

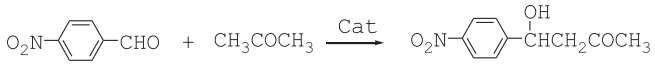
formed in methanol in less than 1 h, even when an almost stoichiometric amount of acetone was used. In contrast, the reaction in chloroform was very slow, and imidazolidinone and Pde were present in the solution after 9 days (80:20 ratio). This observation is consistent if one considers that the cyclic intermediate is formed from charged iminium, which is stabilized and forms more quickly in polar solvents.

The formation of the cyclic intermediate from the zinc complex or from the trifluoroacetate salt was studied in methanol. Behavior was very similar to that observed in the acetone/water mixture explained above. As the complex was not soluble in chloroform, this solvent could not be used.

2.2. Comparison of catalytic activity

As mentioned in the Introduction, Zn^{2+} has been used by different groups to improve aldol condensation reactions.[7–10] In order to determine the relationship between improved performance when using zinc and inhibition in the intermediate formation, we synthesized this compound and checked its activity as a catalyst. We used the aldol reaction between acetone and *p*-nitrobenzaldehyde as a benchmark (Scheme 2). In all cases, excess enantiomer had an *R* configuration.[3b,c,11]

Table 1 and Fig. 2 show the results obtained for the various catalysts used. The fastest reaction was catalyzed by the $ZnPde_2$ complex (100% after 3 h). In agreement with the results described



Scheme 2. Aldol reactions studied in this work.

Table 1
Results for the aldol reaction between acetone and *p*-nitrobenzaldehyde catalyzed by the studied catalysts

Catalyst[a]	Time (h)	Yield[b]	% ee[c]
Pde	12	100	14
(Pde−acetone)imidazolidinone	72	15	14
Pde+TFA	48	18	44
ZnPde2	3	100	33
ZnPde2+TFA	24	90	44

[a] Reactions in acetone with 5% distilled water. Complexes were prepared in situ using zinc acetate as salt.
[b] Determined by NMR.
[c] HPLC (IC, Hex/i-proh 94/6, 1 ml/min).

seem to contribute are faster imidazolidinone formation from Pde (Fig. 1) and the poor catalytic activity shown by the cyclic species.

When Pde was protonated by the Brönsted acid TFA, no imidazolidinone was formed. However, the reaction catalyzed by the TFA salt was only slightly faster than that catalyzed by imidazolidinone. Indeed protonation of pyrrolidine nitrogen helps diminish its nucleophilic capacity, which prevents not only imidazolidinone formation, but also the formation of the active enamine species. When TFA was added to the $ZnPde_2$ complex, an intermediate rate was obtained somewhere between that observed in the reaction catalyzed by $ZnPde_2$ and that found when the trifluoroacetate salt of Pde was the catalyst, and was closer to the former. Under these conditions, pyrrolidine nitrogen can be protonated or complexed by the zinc ion, and is the second most important species, as we have previously reported (Scheme 3).[10]

These results indicate that Zn^{2+}, as a Lewis acid, plays a similar role to that of Brönsted acid, and that it also acts by inhibiting the formation of the parasitic cyclic intermediate. The high stability of the $ZnPde_2$ complex results from the coordination of Zn2+ to both

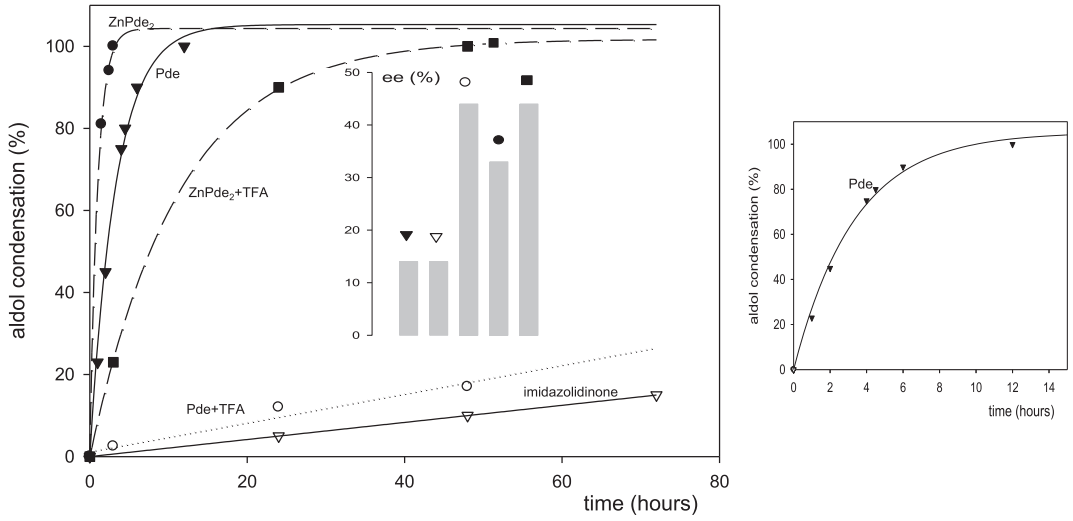


Fig. 2. The reactions at rt in acetone with 5% distilled water. Yield was determined by NMR, and the ee by chiral HPLC.

by Gryko and Morán,[6] cyclic imidazolidinone catalyzed condensation, but the reaction was slower and achieved lower stereoselectivity (only 15% after 72 h).

Initially Pde catalyzes condensation more slowly than its zinc complex, and this tendency becomes greater as the reaction progresses (extension Fig. 2). This fact can be easily explained if we consider the Lewis character of the zinc ion, which coordinates to the O of the acceptor aldehyde; this makes it more electrophilic and favors the addition of the activated donor (Fig. 3).[10] Moreover, and taking into account that the rate of the reaction catalyzed by the free amine progressively decreases over time, the other factors that

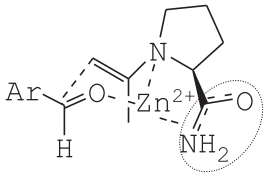


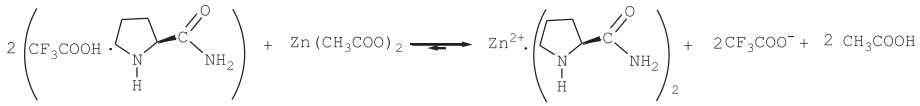
Fig. 3. Coordination of Zn^{2+} to Pde−enamine and to the acceptor aldehyde. *Re* attack was favored to minimize the steric interaction between the aromatic ring (aldehyde) and the CH_3 group (enamine). Only one molecule of Pde is shown in the complex for clarity purposes.

groups: pyrrolidine nitrogen and amide (Scheme 4). The individual affinity of pyrrolidine nitrogen by zinc must be lower than its affinity by the Brönsted acid (H^+), which makes this nitrogen more nucleophile in the complex than in the protonated species, and which also favors its attack on the ketone. On the other hand, coordination of zinc to the amide group in the complex lowers the nucleophilicity of its nitrogen making imidazolidinone formation more difficult when imine is formed, and favoring in this case the formation of the enamine active species.

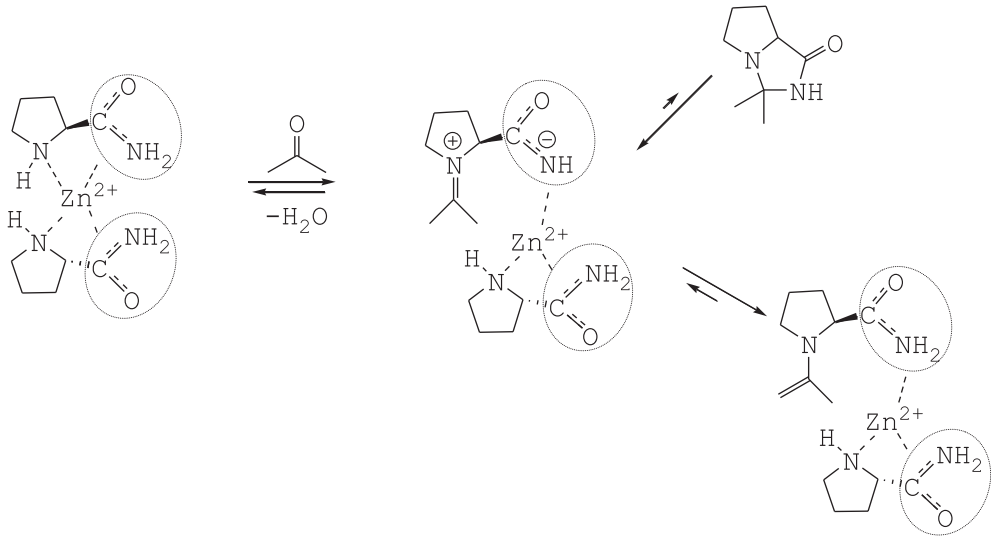
2.3. Characteristics of the imidazolidinone intermediate

Imidazolidinone (**1**) remained stable in solution for several days, especially in methanol (Supplementary data). In this solvent, a slow and progressive deuteration of the CH_3 groups was observed (75% after 10 days), indicating the existence of an equilibrium between the cyclic species and the imine/enamine intermediates (Scheme 1). The presence of all these species was confirmed by reduction of isolated imidazolidinone with $NaBH_4$ in methanol, which yields, along with the starting material and Pde, *N*-isopropyl prolinamide.[7e]

The high stability of the cyclic intermediate accounts for its poor catalytic activity in aldol condensation, and also the progressive



Scheme 3. The equilibrium between the different species derived from Pde in the presence of TFA and zinc acetate.



Scheme 4. Inhibition by Zn^{2+} of imidazolidinone intermediate formation (in the $ZnPde_2$ complex, only the coordination between the ion and Pde is shown, but other donor species can be present).

slowing noted when Pde is in used. The stereochemical results are very similar with both catalysts (Fig. 2) indicating a great similarity in the active species derived from them.

With any of the catalysts used, *Re* attack was always favored by steric considerations (Fig. 3), and the enantiomer formed had a preferentially *R* configuration. However when zinc was used as the cocatalyst, coordination of the ion to the O of the acceptor aldehyde fixed it more rigidly, thereby improving the stereoselectivity in the addition process.[10]

3. Conclusions

By way of conclusion, zinc–prolinamide complexes catalyze the aldol reaction following the general mechanism of stereoselective enamine nucleophilic addition to the acceptor aldehyde. Zn^{2+} plays a role in preventing the nonspecific base-catalyzed reaction by diminishing the basicity of the amine nitrogen of prolinamide, and by also maintaining the conformation of the acceptor fixed during the addition, and by finally preventing the formation of the parasitic intermediate imidazolidinone. This results in faster reactions that are also more stereoselective than those catalyzed by the free amine. Similar results have been obtained when using Brönsted acids but, in this case, and due to the significant decrease in the nucleophilicity of nitrogen, reactions are much slower.

The stereoselectivity achieved with the simple model under study (Pde) was always modest. However, these conclusions can be applied to more complex models.

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}. NMR spectra were recorded with Bruker DRX 300 spectrometers in the indicated deuterated solvents, and infrared spectra on a Nicolet is10 spectrophotometer provided with an ATR accessory. 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, Hex/i-proh 94/6, 1 ml/min, wavelength for detection fixed at 254 nm) was used.

4.2. Characterization of $ZnPde_2$ complex

Isolated[10] or in situ prepared complex Zn^{2+}–Prolinamide 1:2, prepared by mixing the stoichiometric amounts of Pde and zinc acetate dehydrate, was characterized by NMR, IR and ESI-MS(+).

$ZnPde_2$. ^{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). IR ν_{max} (solid/cm^{-1}): 3345, 3273, 3166, 1668, 1557, 1385. ESI-MS$^+$ (MeOD): 351, 291, 236.

4.3. General procedure for the aldol reaction

Aldehyde (0.165 mmol, 25 mg) and catalyst (5% of the zinc complex, 10% of Pde or 10% of Pde–acetone imidazolidinone) were added to an acetone/water mixture (2.375–0.125 ml) in a capped vial. The resulting mixture was stirred at rt 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 chiral HPLC.

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.[3b,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, J=8.8 Hz, 2H), 8.20 (d, *J*=8.8 Hz, 2H). The 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)).

4.4. Synthesis of the imidazolidinone derived from Pde and acetone

Pde (100mg) was dissolved in a mixture of acetone/methanol (2/1, 3ml). After 5 h, the solvent was evaporated in vacuum to dryness, yielding a solid that was identified as compound (**1**).[10]

4.4.1. Pde–acetone imidazolidinone. ^{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, *J*=9.76, 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.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.025.

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