DOI: 10.1002/ejoc.200500352

A Selective Direct Aldol Reaction in Aqueous Media Catalyzed by Zinc–Proline

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Keywords: Aldol reactions / Green chemistry / Aqueous catalysis / Proline / Zinc

The Zn–proline complex is shown to catalyze the aldol reaction of acetone and a wide range of arenecarbaldehydes in aqueous media, accepting even deactivated arenecarbaldehydes such as methoxybenzaldehydes in good yields. Enantiomeric excesses of up to 56 % could be obtained with 5 mol-% of the catalyst at room temperature, and up to 66 % at –15 °C. The aldol reaction is regio- and stereoselective with hydroxyacetone (moderate yields) and dihydroxyacetone (excellent donor, 80–90 % yields with 5 mmol-equiv.). Plausible mechanisms for the reaction are discussed.

Introduction

The aldol reaction is of central importance for the construction of C–C bonds in organic chemistry. Consequently, a large number of catalysts and reagents have been developed in order to achieve efficient addition with high diastereomeric and enantiomeric selectivity.[1] The direct aldol reaction is an attractive method since it avoids the pre-formation of silyl enol ethers or other enol derivatives, and therefore methods to achieve addition with high yields and enantioselectivities are desired. Two strategies have been employed in order to catalyze the asymmetric direct aldol reaction: 1) organocatalysts, including proline[2] and small peptides,[3] which give good yields and impressive enantioselectivities and 2) metal-catalyzed direct aldol reactions with transition metals, particularly zinc complexes.[4,5] Anhydrous organic solvents are often required for high selectivities.

In contrast to the above-described transformations, direct aldol reactions in water have been studied to a lesser extent. This reaction can be accomplished with aldolase enzymes[6] and catalytic antibodies,[7] and an aqueous aldol reaction catalyzed by proline[8] or nornicotine[9] to give racemic products appeared recently. Enantioselective direct aldol reactions of aldehydes with hydroxyacetone (HA) catalyzed by small peptides in mixed solvents have also been reported.[10] Recently, addition of water to organic solvents has been shown to accelerate the proline[11] or tetrazole-pyrrolidine[12] catalyzed aldol reaction. Lewis acid catalysis in water has been investigated with silyl enol ethers and rare-earth metal triflates, as well as other metals.[13] Enantioselectivity has been achieved, although the silyl ether substrate requires a substantial amount of organic solvent due to its poor stability in water. It is surprising that, in general, asymmetric reactions in water, especially formation of carbon–carbon bonds, have not been developed in an extensive manner in spite of the advantages offered by water as a solvent.[14]

We have already reported the aldol reaction of acetone and 4-nitrobenzaldehyde catalyzed by Zn–proline [Zn-$(Pro)_2$] and other Zn–amino acid complexes in the presence of water.[15] This method has been further extended to the aldolization of glycolaldehyde to give tetroses and the cross-aldolization of glycolaldehyde and glyceraldehydes to give pentoses.[16] Here we describe the scope of the $Zn(Pro)_2$-catalyzed reaction with a variety of aromatic aldehydes and ketones. The aldol reaction was also extended to HA and dihydroxyacetone (DHA) as donors.

Results and Discussion

Zn–Amino Acid Complexes as Water-Compatible Catalysts

The reactivity of metal complexes in water is limited because water can compete with the substrate for metal coordination. Criteria for water-compatible Lewis acids have been developed based on a correlation between the catalyst activity and two parameters, namely the hydrolysis constant and water-exchange rate constant.[17] Among several metals that can be considered as suitable for catalysis in water, zinc looked the most appealing to us as it is not redox-active, it can accommodate several coordination geometries, it forms stable complexes with nitrogen-containing ligands, and it is abundant in nature. Zinc is also present in the active site of Class II aldolases, making the $Zn(Pro)_2$ approach aldolase mimics. Therefore we have developed zinc–amino acid com-

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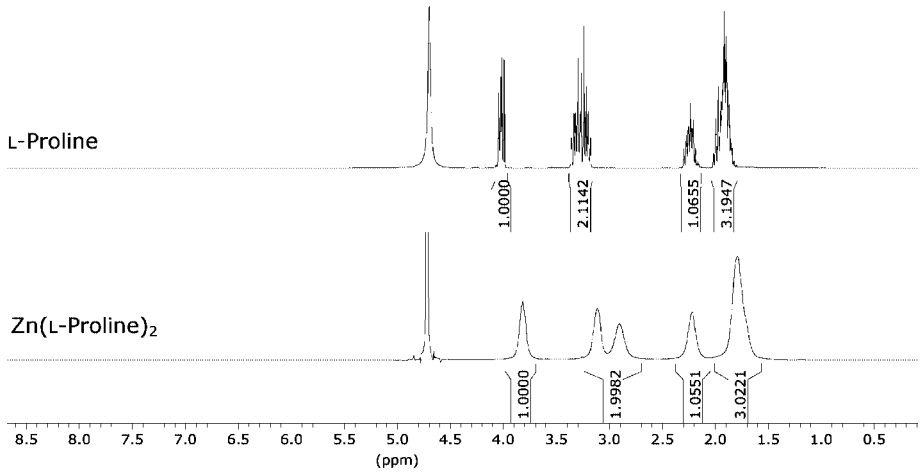


Figure 1. ^{1}H NMR spectrum of $Zn(Pro)_2$ in D_2O compared with the spectrum of L-proline.

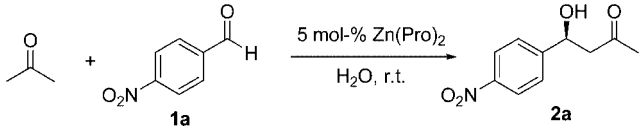
plexes as catalysts for aldol recations in water, and further studied the zinc–proline-catalyzed direct aldol reaction.

Indeed, the $Zn(Pro)_2$ complex can be readily prepared in methanol from proline and zinc acetate in the presence of triethylamine. The complex is stable in water, as shown by the ^{1}H NMR spectrum (Figure 1), and is easily isolated by filtration.

According to the same procedure, a series of Zn–amino acid complexes containing Lys, Arg, His, Glu, Ser, Ile, and *t*-Leu were prepared in good to moderate yields (30–80%). The yields were not optimized and correspond to the amount of product precipitated from the reaction mixture. The complexes were characterized by ^{1}H and ^{13}C NMR spectroscopy.[11]

The $Zn(Pro)_2$-Catalyzed Aldol Reaction of Acetone and Aromatic Aldehydes

The ability of $Zn(Pro)_2$ to act as a catalyst for the aldol reaction in water was first explored with 4-nitrobenzaldehyde and acetone. When 4-nitrobenzaldehyde (**1a**) was stirred in the presence of $Zn(Pro)_2$ (10 mol-%) in acetone/H_2O (2:1) for 24 h, product **2a** was obtained in quantitative yield (Scheme 1). When proline was the catalyst, in acetone/H_2O (2:1), the yield of **2a** after 24 h was 6% and the enantiomeric excess (*ee*) 21%. The zinc complex gave the (*S*) enantiomer in excess (32%), whereas with proline alone the (*R*) enantiomer predominates. We did not observe the formation of **2a** in the presence of zinc acetate or in the absence of the zinc salt or proline (Table 1). Unsaturated ketones derived from water elimination were not detected by ^{1}H NMR spectroscopy in the crude product.



Scheme 1.

The catalytic ability of other Zn–L-amino acid complexes [5 mol-% of catalyst, H_2O/acetone (1:2)] was also investigated. While Zn–lysine and Zn–arginine proved to be efficient catalysts, Zn–serine, Zn–histidine, and Zn–cysteine failed to provide significant amounts of **2a** at room temp. after 24 h. Lysine can act as a 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 **2a** was obtained in 74% yield and 6% *ee* with the (*R*)-**2a** enantiomer in excess (Table 1).

Table 1. Conversion yields and *ee* values for the reaction of nitrobenzaldehyde (**1a**) with acetone in H_2O (2:1) to give **2a**, with zinc acetate and amino acids as catalysts at room temp.

Entry	Catalyst	Time [h]	Conv.	*ee*
1	$Zn(CH_3COO)_2$ (5%)	24	0%	–
2	$Zn(CH_3COO)_2$ (5%)	96	6%	–
3	L-proline (10%)	24	6%	21% (*R*)
4	L-lysine (5%)	24	74%	6% (*R*)

When the $Zn(Pro)_2$-catalyzed aldol reaction was carried out with different amounts of water, the *ee* obtained decreased with a corresponding decrease in the water content (Figure 2). A higher enantioselectivity was obtained for **2a** with 66 vol.-% of water [the $Zn(Pro)_2$ complex is not soluble in less then 5% water]. The studies described in this paper were consequently performed with a 1:2 ratio of acetone and water.

The Cu–proline complex also catalyzes the aldol reaction, although in much lower yield. The reaction with acetone and 4-nitrobenzaldehyde gave **2a** with 10% conversion after 96 h.

The scope of the reaction was further investigated with a series of aldehydes and acetone in the presence of $Zn(Pro)_2$ as catalyst. The results are summarized in Table 2.

The results indicate that not only activated arenecarbaldehydes bearing electron-withdrawing groups but also benzaldehyde as well as aldehydes with methoxy substituents undergo the aldol reaction with very good yields and moderate *ee* values. Although the methoxy group should reduce the conversion, we observed a 75% conversion after 36 h in the case of the *ortho* isomer (Entry 10, Table 2). We assume

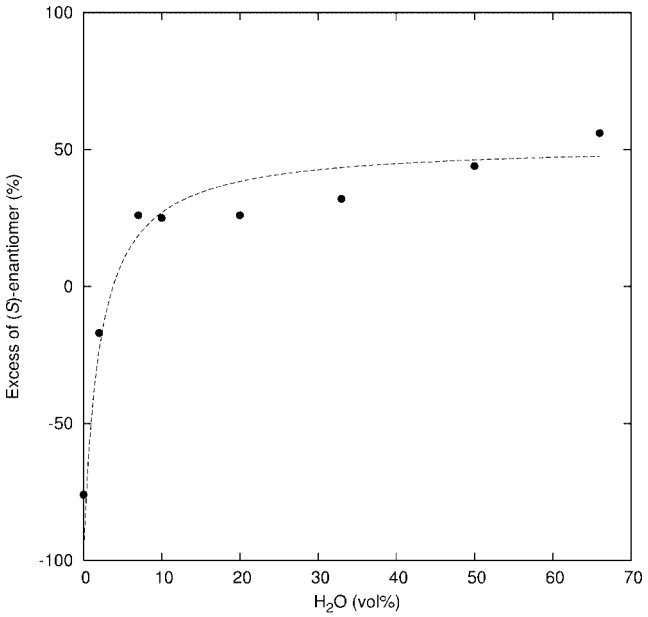
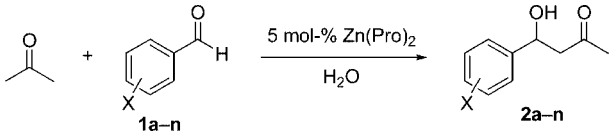


Figure 2. Excess of (*S*) enantiomer of **2a** vs. H_2O (vol%).

that coordination of the OMe group to Zn^{2+} facilitates the reaction. The *ee* of the reaction was not higher than with the other two isomers. The *ortho*-substituted aldehydes **1b** and **1i**, in contrast, gave lower *ee* values than the corre-

Table 2. Direct aqueous aldol reaction of aromatic aldehydes and acetone in water (66 vol.-%) catalyzed by $Zn(Pro)_2$.



Entry	Aldehyde	Aldol product	X	Time [h]	Conv. [%][a]	*ee*[b]
1	**1a**	**2a**	4-NO_2	18	>95	56%
2	**1b**	**2b**	2-NO_2	18	94	<5%
3	**1c**	**2c**	2-Br	18	89	30%
4	**1d**	**2d**	4-F	36	>95	37%
5	**1e**	**2e**	4-CN	22	91	27%
6	**1f**	**2f**	H	48	32	<5%
7	**1g**	**2g**	2-CH_3	72	25	<5%
8	**1h**	**2h**	2-Cl	36	>95	<5%
9	**1i**	**2i**	4-Cl	36	>95	24%
10	**1j**	**2j**	2-OCH_3	36	75	32%
11	**1k**	**2k**	3-OCH_3	36	40	22%
12	**1l**	**2l**	4-OCH_3	36	48	38%
13	**1m**	**2m**	4-CF_3	48	93	35%
14	**1n**	**2n**	naphthyl	45	75	31%

[a] Determined by ^1H NMR spectroscopy. [b] The *ee* was determined by chiral HPLC with a Daicel Chiralpak AS. Conditions: aldehyde (0.75 mmol), acetone (5 mL), $Zn(Pro)_2$ (10 mg), water (10 mL), room temperature.

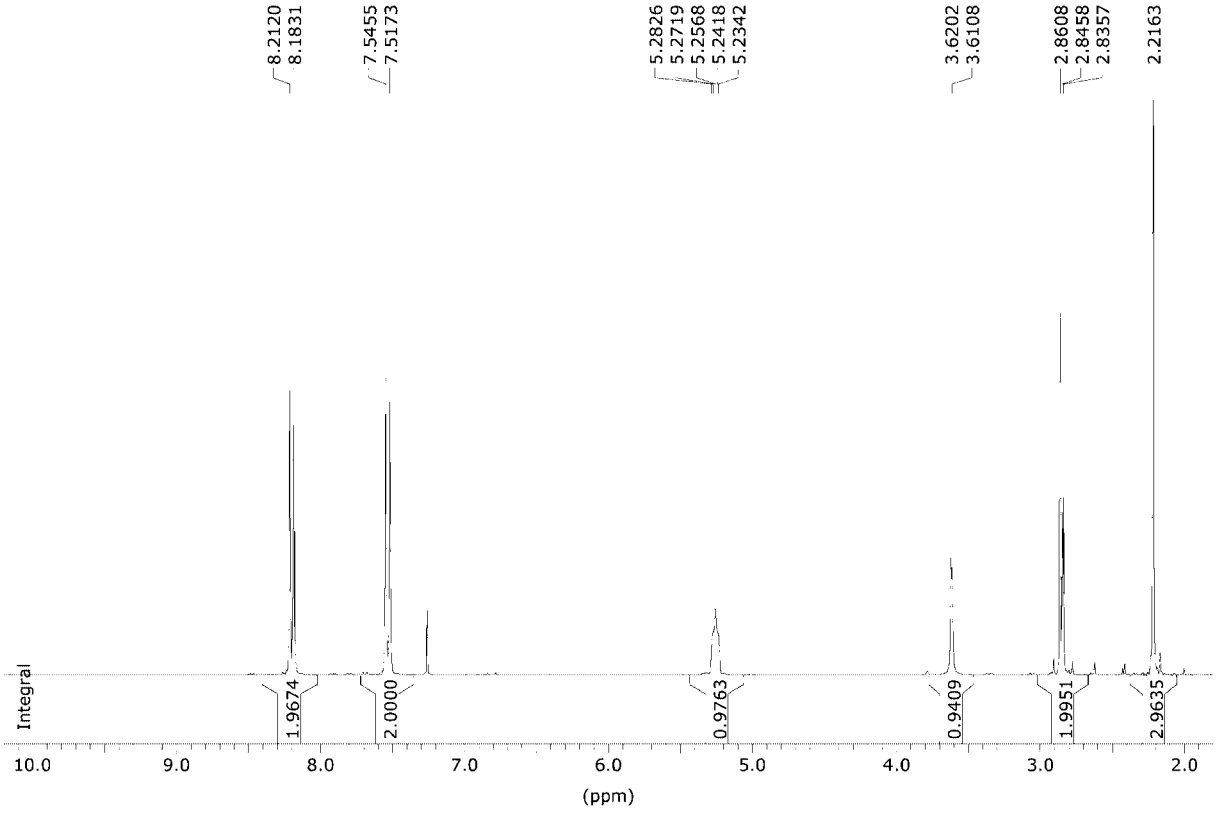


Figure 3. ^1H NMR spectrum (300 MHz, $CDCl_3$) of the crude product **2a** from the aldol reaction of acetone and **1a** after removal of the catalyst by filtration.

sponding *para* isomers. When the reaction of 2-nitrobenzaldehyde (**1b**) was run at –15 °C, the *ee* increased from < 5% to 27%. For the reaction with activated aldehydes (**1a**, **1d**, **1h**, **1i**), no chromatography with organic solvents was necessary, and, after lyophilization, the catalyst was removed by addition of methanol or ethyl acetate and filtration to give only the corresponding aldol products (Figure 3 for **2a**). It is therefore possible to obtain pure aldol products without employing an organic solvent either for preparation of the reagents or purification of the products.

Variation of the Aldehyde and the Ketone Components

Heterocyclic aldehydes were also found to be suitable substrates for the aldol reaction with acetone, as shown in Figure 4. Furfuraldehyde gave the aldol product in quantitative yield after 6 h, and at –15 °C full conversion occurred with 63% *ee* in 22 h. Cinnamaldehyde acts as an electrophile in the reaction.

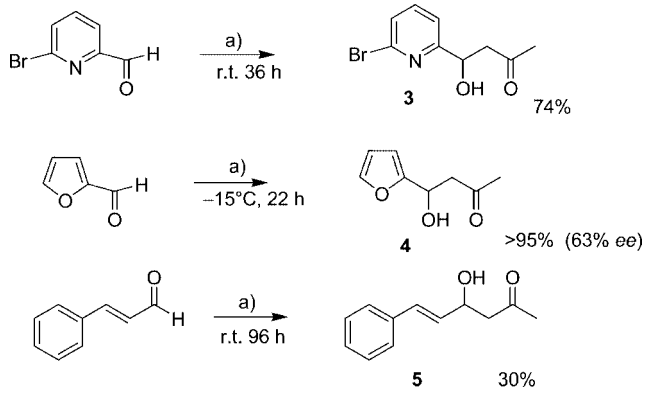


Figure 4. a): $Zn(Pro)_2$ (5 mol-%.), aldehyde (0.75 mmol), acetone (5 mL), water (10 mL).

Variations in the ketone component were also made, and quantitative yields were obtained with cyclopentanone, with a *syn*/*anti* ratio of 3:1, after 18 h. The stereochemistry of the aldol product is rather labile and isomerization can be easily achieved, even during column chromatography,[18] so that the ratio obtained may not correspond to that of the reaction product.[19] Cyclohexanone and 2-butanone underwent aldol reaction with **1a** (Figure 5). The reaction with 2-butanone is regioselective, with only the linear product **8** being detected by ^1H NMR spectroscopy.

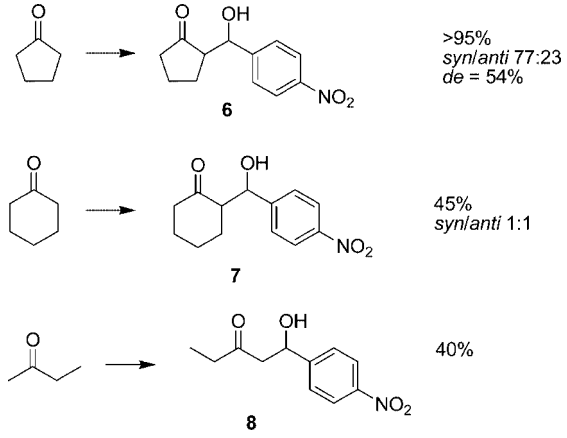
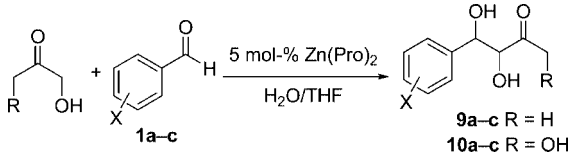


Figure 5. Aldol reaction with **1a** catalyzed by $Zn(Pro)_2$. Conditions: **1a** (1 mmol), ketone (4 mmol), $Zn(Pro)_2$ (5mol-%), THF (8 mL), water (8 mL), room temperature for 48 h.

Reaction with Hydroxyacetone and Dihydroxyacetone

The zinc–proline-catalyzed reaction was extended to HA and DHA. The reaction was first investigated with 5 equiv. of ketone and tetrahydrofuran as co-solvent. The results obtained are shown in Table 3. The reaction of HA gave regioselective formation of the more stable enolate; the linear regioisomer could not be detected by ^1H NMR spectroscopy. The *syn* selectivities observed contrast with the results obtained with proline[2b] but are consistent with the results with the catalytic antibody 38C2[20] and the Lewis acid catalyzed reactions in organic solvents.[4c,5c] DHA is a much better donor than DH, giving aldol products in excellent yields with a preference for the *syn* stereoisomer (Table 3).

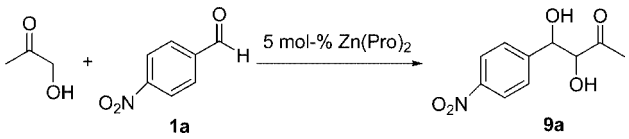
Table 3. Aldol reaction of HA and DHA with aromatic aldehydes catalyzed by $Zn(Pro)_2$.



Aldol product	R	X	Time [h]	Co-solvent	Conv.[a] [%]	*dr* (*syn*/*anti*)[b]
9a	H	4-NO_2	96	20% THF	25	2:1
			66	50% HA	45	1:8
9b	H	2-NO_2	48	none	16	3:2
9c	H	2-Br	96	10% THF	35	5:1
10a	OH	4-NO_2	48	20% THF	80	1:1
10b	OH	2-NO_2	66	5% THF	88	1:1
10c	OH	2-Br	48	10% THF	90	3:1

[a] Determined by ^1H NMR spectroscopy; *dr* = diastereomeric ratio. Conditions: 5 mol-equiv. of HA or DHA, room temp. [b] Determined by ^1H NMR spectroscopy.

Table 4. Aldol reaction of HA and 4-nitrobenzaldehyde.



Entry	Co-solvent [vol.-%]	HA [mol-equiv.]	Co-solvent	Conversion [%][a]
1	40	4	THF	23
2	30	10	THF	60
3	50	4	MeOH	35
4	50	10	MeOH	53

[a] Determined by ^{1}H NMR spectroscopy. Reactions at room temp.

The reaction of HA and 4-nitrobenzaldehyde was investigated with 4 and 10 equiv. of the ketone component and different co-solvents. The results presented in Table 4 show that the reaction takes place in good yield with 10 equiv. of HA. Methanol or tetrahydrofuran as co-solvents gave similar results. We also observed inversion and increase in the diastereomeric selectivity, with *dr* = 1:8 (*syn*/*anti*) when the reaction was run with a 1:1 mixture of HA and water (Table 3). The reaction was further investigated with only 5 mol-equiv. of HA or DHA.

Mechanistic Considerations

The new catalyst developed incorporates a metal that can act as a Lewis acid in water, and in this respect $Zn(Pro)_2$ can be seen as mimic of class II aldolases. On the other hand, the proline could also form an enamine, reacting according to a mechanism similar to class I aldolases. If the metal is acting as a Lewis acid, we can assume that the Zn^{2+} ion coordinates to the ketone in order to facilitate the enolate formation while the proline ligand provides the chiral environment for enantioselectivity (Figure 6). The carbon–carbon bond formation takes place with concomitant coordination of the carbonyl group of the aldehyde or with noncoordinated aldehyde. We have, however, observed that zinc acetate does not catalyze the aldol reaction, which indicates that both zinc and proline are necessary for catalysis. The fact that proline alone does not act as a catalyst here indicates that the enamine formation should be unfavorable under our reaction conditions.[21] Moreover, the (*S*) enantiomer of **2a** was formed in excess with $Zn(Pro)_2$, whereas the (*R*) enantiomer was favored with proline. We can, however, postulate a mechanism involving a zinc-assisted enamine, where zinc complexation stabilizes the enamine intermediate. In this case, zinc dissociation from the amine group provides a nucleophile for addition to the carbonyl group. Coordination to zinc stabilizes the enamine in water, making the condensation with the aldehyde possible (proposed intermediates shown in Figure 7).[22] Further studies of the reaction mechanism are still necessary and currently underway.

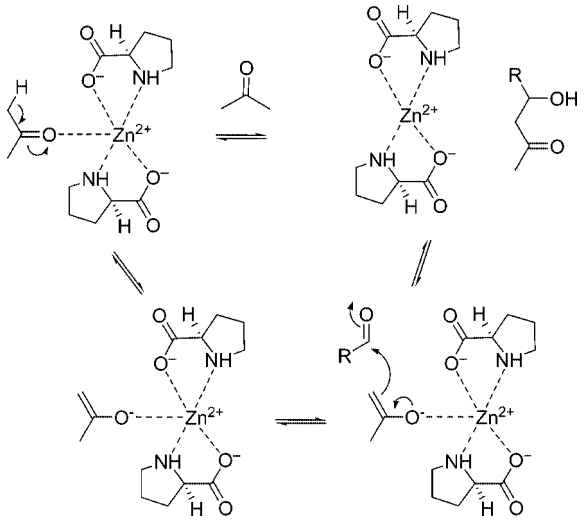


Figure 6. Proposed mechanism of the zinc–proline-catalyzed aldol reaction with zinc acting as Lewis acid.

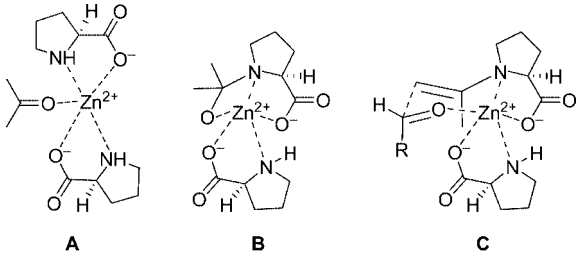


Figure 7. Proposed intermediates for the zinc-assisted enamine mechanism of the zinc–proline-catalyzed aldol reaction.

Conclusions

The direct aldol reaction catalyzed by $Zn(Pro)_2$ complex in aqueous media has been investigated with respect to the structure of the aldehyde and the ketone donor. The reaction takes place at room temperature and is complete, in some cases, after only 6 h. HA and DHA proved to be suitable partners for the reaction with aromatic aldehydes. The enantioselectivity can be improved by running the reaction at –15 °C. Although the *ee* values obtained are low to moderate, it is remarkable that any enantioselectivity can be attained in water and mostly at ambient temperature. To date, these are the best results reported for the direct aldol reaction catalyzed by small metal complexes in water.

In the case of activated aldehydes, quantitative yields and pure products were obtained without the need for chromatographic separation with organic solvents, thus making the $Zn(Pro)_2$-catalyzed aldol reaction a truly green method. A mechanistic pathway involving formation of a zinc-stabilized enamine in water is proposed for the new reaction.

Experimental Section

General: Chemicals and solvents were purchased of the best possible quality from commercial suppliers. For thin-layer chromatography (TLC), Merck 60 F254 silica-gel plates were used and compounds were visualized by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), concd. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating. Flash chromatography was performed using Merck 60 silica gel (particle size 0.040–0.063 mm). Solvents were distilled before use. ^{1}H NMR spectra were recorded with a Bruker AVANCE300 (300 MHz) or Bruker DRX500 (500 MHz). Chemical shifts are given in ppm relative to solvent residual peak. Coupling constants (*J*) are reported in Hz. Preparative RP-HPLC was performed with HPLC-grade acetonitrile and MilliQ deionized water in Waters prepak cartridge 500 g (RP-C18 20 mm, 300 Å pore size) installed on a Waters Prep LC4000 system from Millipore. The compounds were eluted from the column starting from 90% A and 10% D with a gradient of 1% D min^{-1} [eluent A: H_2O with 0.1% TFA; eluent D: CH_3CN/H_2O (60:40) with 0.1% TFA] with a flow rate of 100 mL min^{-1} and UV detection (214 or 254nm). Chiral HPLC was performed with a Waters 600E System Controller and a Waters 996 Photodiode Array Detector operating a Chiralpak AS column from Daicel Chemical Industries Ltd., eluting with *n*-hexane and 2-propanol. Analytical HPLC was performed with the same system as above on a Chromolith Performance column and eluting with A and D. Melting points were determined with a Büchi 510 apparatus and are not corrected. Mass spectra were recorded by the MS service (University of Bern, Switzerland).

General Procedure for the Preparation of Aldol Products from Aldehydes and Acetone: In a typical experiment, a mixture of aldehyde (0.75 mmol), acetone (5 mL), and $Zn(Pro)_2$ (10 mol-%, 25 mg) was dissolved in water (10 mL). The reaction mixture was stirred for 48 h, filtered, and water was added. The final product was extracted with ethyl acetate (3 × 50 mL), and the combined extracts were dried with $MgSO_4$. The solvent was removed in vacuo to give the resulting oily or solid products. The conversion was determined from the ^{1}H NMR spectrun of the crude product. For identification, the products were isolated by flash chromatography (ethyl acetate/hexane mixtures) and the spectroscopic data compared with the literature values.

4-Hydroxy-4-(4-nitrophenyl)butan-2-one (2a):[2f] According to the general procedure and starting from **1a** (113 mg, 0.75 mmol), **2a** was isolated in quantitative yield (152 mg, >95%) after solvent evaporation and catalyst precipitation with ethyl acetate. ^{1}H NMR ($CDCl_3$): δ = 8.20 (d, *J* = 8.5 Hz, 1 H), 7.55 (d, *J* = 8.5 Hz, 1 H), 5.25 (m, 1 H), 3.56 (d, *J* = 3.2 Hz, 1 H), 2.85 (m, 2 H), 2.25 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 208.51, 150.04, 147.22, 126.37, 123.71, 123.57, 68.94, 51.43, 30.67 ppm. *ee* = 56%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 2.0 mL min^{-1}]: t_R(minor) = 8.47 min; t_R(major) = 10.02 min.

4-Hydroxy-4-(2-nitrophenyl)butan-2-one (2b):[2f] According to the general procedure and starting from **1b** (76 mg, 0.50 mmol), **2b** could be isolated (98 mg, 94%). ^{1}H NMR ($CDCl_3$): δ = 8.00 (d, *J* = 8.2 Hz, 1 H), 7.93 (d, *J* = 8.3 Hz, 1 H), 7.70 (t, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 5.71 (d, *J* = 4.6 Hz, 1 H), 3.76 (s, 1 H), 3.17 (d, *J* = 4.9 Hz, 1 H), 2.81 (dd, *J* = 4.9, 2.6 Hz, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.56, 139.11, 134.56, 128.94, 125.20, 66.40, 51.79, 31.19 ppm.

4-(2-Bromophenyl)-4-hydroxybutan-2-one (2c):[23] According to the general procedure and starting from **1c** (93 mg, 0.50 mmol), **2c** could be isolated after column chromatography (74 mg, 61%). ^{1}H NMR ($CDCl_3$): δ = 7.54–7.35 (m, 4 H), 5.47 (d, *J* = 5.2 Hz, 1 H), 3.60 (s, 1 H), 3.03 (d, *J* = 5.4 Hz, 1 H), 2.72–2.62 (dd, *J* = 5.2, 2.7 Hz, 1 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.74, 142.38, 133.36, 129.71, 128.61, 128.10, 121.93, 69.58, 50.84, 31.33 ppm. *ee* = 30%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 2.0 mL min^{-1}]: t_R(major) = 2.50 min and t_R(minor) = 3.32 min.

4-(4-Fluorophenyl)-4-hydroxybutan-2-one (2d):[2f] According to the general procedure and starting from **1d** (106 mg, 0.85 mmol), **2d** could be isolated (154 mg, 91%). ^{1}H NMR ($CDCl_3$): δ = 7.38–7.33 (m, 2 H), 7.09–7.03 (m, 2 H), 5.16 (d, *J* = 4.6 Hz, 1 H), 3.35 (s, 1 H), 2.87 (t, *J* = 5.5 Hz, 2 H), 2.23 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 208.93, 162.23 (d, $J_{C,F}$ = 245.26 Hz), 138.50 (d, $J_{C,F}$ = 3.12 Hz), 127.32 (d, $J_{C,F}$ = 8.11 Hz), 115.36 (d, $J_{C,F}$ = 21.22 Hz), 69.24, 51.93, 30.73 ppm. *ee* = 37%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 2.0 mL min^{-1}]: t_R(minor) = 2.13 min; t_R(major) = 2.78 min.

4-(4-Cyanophenyl)-4-hydroxybutan-2-one (2e):[3b] According to the general procedure and starting from **1e** (39 mg, 0.30 mmol), **2e** could be isolated after column chromatography (52 mg, 91%). ^{1}H NMR ($CDCl_3$): δ = 7.68 (d, *J* = 8.2 Hz, 2 H), 7.51 (d, *J* = 8.2 Hz, 2 H), 5.23 (s, 1 H), 3.55 (s, 1 H), 2.86 (t, *J* = 5.1 Hz, 2 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.25, 148.71, 133.12, 127.07, 69.83, 52.25, 31.45 ppm. *ee* = 27%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 2.0 mL min^{-1}]: t_R(major) = 5.12 min; t_R(minor) = 8.17 min.

4-Hydroxy-4-phenylbutan-2-one (2f):[3a] According to the general procedure and starting from **1f** (106 mg, 1.0 mmol), **2f** could be isolated after column chromatography (54 mg, 32%). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.20 (m, 4 H), 5.20 (d, *J* = 4.9 Hz, 1 H), 3.48 (s, 1 H), 2.82 (t, *J* = 5.1 Hz, 2 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.79, 129.28, 128.43, 126.37, 70.61, 52.71, 31.50 ppm.

4-Hydroxy-4-(*o*-tolyl)butan-2-one (2g):[24] According to the general procedure and starting from **1g** (84 mg, 0.70 mmol), **2g** could be isolated after column chromatography (13 mg, 11%). ^{1}H NMR ($CDCl_3$): δ = 7.28–7.17 (m, 4 H), 5.41 (d, *J* = 5.2 Hz, 1 H), 2.85 (t, *J* = 5.5 Hz, 1 H), 2.73 (d, *J* = 5.4 Hz, 1 H), (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 210.74, 131.62, 129.39, 128.88, 128.23, 127.18, 125.98, 69.79, 51.69, 28.54, 20.52 ppm.

4-(2-Chlorophenyl)-4-hydroxybutan-2-one (2h):[2a] According to the general procedure and starting from **1h** (63 mg, 0.45 mmol), **2h** could be isolated in quantitative yield (89 mg, >95%). ^{1}H NMR ($CDCl_3$): δ = 7.34 (m, 4 H), 5.13 (t, *J* = 4.9 Hz, 1 H), 3.39 (s, 1 H), 2.88 (dd, *J* = 4.9, 2.5 Hz, 2 H), 2.22 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.62, 141.96, 134.12, 129.43, 127.78, 69.95, 52.55, 31.50 ppm.

4-(4-Chlorophenyl)-4-hydroxybutan-2-one (2i):[3b] According to the general procedure and starting from **1i** (73 mg, 0.50 mmol), **2i** could be isolated in quantitative yield (104 mg, >95%). ^{1}H NMR ($CDCl_3$): δ = 7.36–7.32 (m, 4 H), 5.51 (d, *J* = 4.4 Hz, 1 H), 3.56 (s, 1 H), 3.00 (d, *J* = 5.5 Hz, 1 H), 2.69 (dd, *J* = 5.5, 4.2 Hz, 1 H),

2.23 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.96, 140.83, 131.88, 130.09, 127.99, 67.37, 50.74, 31.34 ppm. *ee* = 24%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 1.5 mL min^{-1}]: t_R(minor) = 4.68 min; t_R(major) = 5.15 min.

4-Hydroxy-4-(2-methoxyphenyl)butan-2-one (2j):[25] According to the general procedure and starting from **1j** (68 mg, 0.50 mmol), **2j** could be isolated after column chromatography (68 mg, 70%). ^{1}H NMR ($CDCl_3$): δ = 7.46 (d, *J* = 8.2 Hz, 1 H), 7.28 (d, *J* = 8.3 Hz, 1 H), 7.06 (t, *J* = 8.0 Hz, 2 H), 5.43 (t, *J* = 4.9 Hz, 1 H), 3.86 (s, 3 H), 3.43 (s, 1 H), 2.96 (d, *J* = 4.9 Hz, 1 H), 2.82 (dd, *J* = 4.9, 2.5 Hz, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.94, 158.76, 134.58, 128.71, 126.90, 66.02, 55.95, 50.41, 30.61 ppm. *ee* = 32%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 1.5 mL min^{-1}]: t_R(minor) = 8.05 min; t_R(major) = 8.63 min.

4-Hydroxy-4-(3-methoxyphenyl)butan-2-one (2k):[26] According to the general procedure and starting from **1k** (68 mg, 0.50 mmol), **2k** could be isolated after column chromatography (39 mg, 40%). ^{1}H NMR ($CDCl_3$): δ = 7.47 (d, *J* = 8.3 Hz, 1 H), 7.39 (s, 1 H), 7.28 (t, *J* = 5.3 Hz, 1 H), 7.06 (d, *J* = 8.3 Hz, 2 H), 5.15 (t, *J* = 4.9 Hz, 1 H), 3.82 (s, 3 H), 3.49 (s, 1 H), 2.83 (t, *J* = 4.8 Hz, 2 H), 2.21 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.06, 160.61, 130.35, 113.99, 111.89, 70.55, 56.00, 52.71, 31.51 ppm. *ee* = 37%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 1.5 mL min^{-1}]: t_R(minor) = 6.81 min; t_R(major) = 7.32 min.

4-Hydroxy-4-(4-methoxyphenyl)butan-2-one (2l):[25] According to the general procedure and starting from **1l** (136 mg, 1.0 mmol), **2l** could be isolated after column chromatography (80 mg, 41%). ^{1}H NMR ($CDCl_3$): δ = 7.47 (d, *J* = 8.3 Hz, 1 H), 7.39 (s, 1 H), 7.27 (t, *J* = 5.3 Hz, 1 H), 7.06 (d, *J* = 8.3 Hz, 2 H), 5.15 (t, *J* = 4.9 Hz, 1 H), 3.82 (s, 3 H), 3.49 (s, 1 H), 2.83 (t, *J* = 4.8 Hz, 2 H), 2.21 (s, 3 H) ppm.

4-Hydroxy-4-[4-(trifluoromethyl)phenyl]butan-2-one (2m):[25] According to the general procedure and starting from **1m** (134 μL, 1.0 mmol), **2m** could be isolated after column chromatography (220 mg, 93%). ^{1}H NMR ($CDCl_3$): δ = 7.77 (d, *J* = 8.3 Hz, 2 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 5.30 (q, *J* = 4.4 Hz, 1 H), 2.90 (d, *J* = 4.9 Hz, 2 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 208.65, 146.91, 129.72 (q, $J_{C,F}$ = 32.45 Hz), 34, 125.94, 125.41 (q, $J_{C,F}$ = 3.74 Hz), 124.12 (q, $J_{C,F}$ = 272.10 Hz), 69.15, 51.74, 30.61 ppm. *ee* = 35%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 2.0 mL min^{-1}]: t_R(minor) = 2.02 min; t_R(major) = 2.95 min.

4-Hydroxy-4-(2-naphthyl)butan-2-one (2n):[2a] According to the general procedure and starting from **1n** (200 mg, 1.3 mmol), **2n** could be isolated after column chromatography (149 mg, 53%). ^{1}H NMR ($CDCl_3$): δ = 8.37 (s, 1 H), 7.97–7.49 (m, 6 H), 5.34 (d, *J* = 5.4 Hz, 1 H), 3.43 (s, 1 H), 3.00 (t, *J* = 5.5 Hz, 2 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.77, 130.28, 129.85, 129.12, 128.42, 127.95, 127.22, 126.98, 125.86, 125.11, 124.47, 70.75, 52.66, 31.55 ppm. *ee* = 31%, determined by HPLC [Daicel Chiralpak AS, *i*PrOH/hexane (20:80), UV 254 nm, flow rate 2.0 mL min^{-1}]: t_R(minor) = 3.56 min; t_R(major) = 4.46 min.

4-(6-Bromopyridin-3-yl)-4-hydroxybutan-2-one (3): According to the general procedure and starting from 6-bromopyridine-2-carbaldehyde (95 mg, 0.50 mmol), **3** could be isolated after column chromatography as a yellow oil (91 mg, 74%). IR (neat): $\tilde{\nu}$ = 3386, 2918, 2848, 2360, 1680, 1203, 1203, 1138, 725, 631 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.62–7.48 (m, 3 H), 5.17 (d, *J* = 5.4 Hz, 1 H), 3.88 (br. s, 1 H), 3.18 (d, *J* = 5.3 Hz, 1 H), 2.92 (dd, *J* = 5.4, 3.2 Hz, 1 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.96, 163.95, 141.80, 139.94, 127.42, 119.92, 70.53, 50.55, 31.55 ppm. MS (EI): *m*/*z* (%) = 245 (20) [M$^+$], 243 (20) [M$^+$], 210 (70), 212 (70), 200 (100), 202 (100), 188 (85), 186 (95), 158 (55), 106 (45), 104 (60), 78 (100), 51 (45), 43 (65). HR ESI MS(+): calcd. for $C_9H_{10}BrNNaO_2$ 265.9792; found 265.9786.

1-(Furan-2-yl)-1-hydroxypropan-2-one (4):[27] According to the general procedure and starting from furan-2-carbaldehyde (192 mg, 2.0 mmol), **4** could be isolated after column chromatography (166 mg, 56%). ^{1}H NMR ($CDCl_3$): δ = 7.36 (d, *J* = 8.3 Hz, 1 H), 6.59 (t, *J* = 8.0 Hz, 1 H), 6.32 (d, *J* = 8.3 Hz, 1 H), 5.20 (d, *J* = 5.2 Hz, 1 H), 3.26 (s, 1 H), 3.12 (dd, *J* = 5.4, 2.9 Hz, 1 H), 3.99 (d, *J* = 5.5 Hz, 1 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.47, 155.63, 142.89, 111.04, 107.05, 64.54, 52.66, 31.44 ppm.

(*E*)-4-Hydroxy-6-phenylhex-5-en-2-one (5):[28] According to the general procedure and starting from cinnamaldehyde (238 mg, 1.8 mmol), **5** could be isolated after column chromatography (83 mg, 30%). ^{1}H NMR ($CDCl_3$): δ = 7.49–7.33 (m, 5 H), 7.96 (dd, *J* = 6.9 Hz, 1 H), 6.30 (d, *J* = 7.5 Hz, 1 H) 4.79 (d, *J* = 5.4 Hz, 1 H), 3.11 (s, 1 H), 2.77 (d, *J* = 5.2 Hz, 2 H), 2.24 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.72, 164.24, 144.28, 131.24, 129.33, 128.51, 127.24, 69.22, 50.68, 31.58 ppm.

General Procedure for the Preparation of Aldol Products from Aldehydes and Hydroxy Ketones or Ketones: In a typical experiment, a mixture of aldehyde (1 mmol), THF (2 mL), ketone or hydroxy ketone (5 mmol), and $Zn(Pro)_2$ (5 mol-%, 10 mg) was dissolved in water (10 mL). The reaction mixture was stirred for 48 h, filtered and water was added. The product was extracted with ethyl acetate (3 × 50 mL), and the combined extracts were dried with $MgSO_4$. After solvent removal, the residue was purified by medium pressure chromatography (elution with 20–40% ethyl acetate/hexane), and the solvent was removed in vacuo to give the resulting oily or solid products.

2-[Hydroxy(4-nitrophenyl)methyl]cyclopentanone (6):[2f] According to the general procedure and starting from **1a** (91 mg, 0.60 mmol) and cyclopentanone (169 mg, 2.0 mmol), **6** could be isolated after column chromatography (139 mg, >95%). ^{1}H NMR (CD_3OD): δ = 8.19 (d, *J* = 8.6 Hz, 2 H), 7.59 (d, *J* = 8.6 Hz, 2 H), 5.31 (s, 1 H), 5.08 (d, *J* = 7.0 Hz, 1 H), 2.65–1.70 (m, 6 H) ppm. ^{13}C NMR (CD_3OD): δ = 220.78, 128.65, 128.18, 127.77, 127.17, 124.04, 70.76, 56.65, 42.79, 39.69, 25.10, 22.85 ppm.

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (7):[2f] According to the general procedure and starting from **1a** (453 mg, 3.0 mmol) and cyclohexanone (588 mg, 6.0 mmol), **7** could be isolated after column chromatography (300 mg, 45%). ^{1}H NMR ($CDCl_3$): δ = 8.26 (d, *J* = 8.3 Hz, 2 H), 7.51 (d, *J* = 8.3 Hz, 2 H), 5.48 (s, 1 H), 4.91 (d, *J* = 6.9 Hz, 1 H), 2.56–1.33 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 221.22, 128.35, 128.64, 127.65, 125.84, 124.78, 124.19, 70.86, 56.45, 42.45, 40.76, 35.46, 27.46, 25.73 ppm.

1-Hydroxy-1-(4-nitrophenyl)pentan-3-one (8):[2f] According to the general procedure and starting from **1a** (193 mg, 1.3 mmol) and 2-butanone (368 mg, 5.1 mmol), **8** could be isolated after column chromatography (115 mg, 40%). ^{1}H NMR ($CDCl_3$): δ = 8.24 (d, *J* = 8.6 Hz, 2 H), 7.57 (d, *J* = 8.6 Hz, 2 H), 5.28 (s, 1 H), 3.68 (s, 1 H), 2.87 (dd, *J* = 6.4, 2.4 Hz, 1 H), 2.83 (dd, *J* = 6.4, 2.4 Hz, 1 H), 2.46 (q, *J* = 7.1 Hz, 2 H), 1.11 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 211.68, 128.23, 127.46, 127.16, 124.46, 124.28, 76.19, 69.83, 54.01, 14.87 ppm.

3,4-Dihydroxy-4-(4-nitrophenyl)butan-2-one (9a) as a *synlanti* Mixture:[8] According to the general procedure and starting from **1a**

(151 mg, 1.0 mmol) and HA (370 mg, 5.0 mmol), **9a** could be isolated after column chromatography (47 mg, 21%). ^{1}H NMR ($CDCl_3$): δ = 8.25 (d, J = 8.3 Hz, 3 H), 7.67 (d, J = 8.3 Hz, 3 H), 5.24 (d, J = 2.6 Hz, 1 H), 5.12 (d, 0.5 H, J = 4.7 Hz), 4.50 (d, 0.5 H, J = 4.7 Hz), 4.44 (d, J = 2.6 Hz, 1 H), 3.01 (br. s, 0.5 H), 2.83 (br. s, 1 H), 2.39 (s, 3 H), 2.00 (s, 1.5 H) ppm. ^{13}C NMR (CD_3OD): δ = 211.53, 129.27, 128.69, 124.05, 82.01, 74.53, 27.60, 26.00 ppm.

3,4-Dihydroxy-4-(2-nitrophenyl)butan-2-one (9b) as a *syn*/*anti* Mixture: According to the general procedure and starting from **1a** (151 mg, 1.0 mmol) and HA (370 mg, 5.0 mmol), **9b** could be isolated in low yield after column chromatography (8 mg, 4%) in a *syn*/*anti* ratio of 1:0.6. ^{1}H NMR ($CDCl_3$): δ = 8.15–7.51 (several signals, 6.4 H), 5.92 (d, J = 1.3 Hz, 1 H), 5.56 (d, J = 6.2, 0.6 H), 4.59 (s, J = 1.3 Hz, 1 H), 4.47 (d, J = 6.2 Hz, 0.6 H), 2.54 (s, 3 H), 2.20 (s, 1.8 H) ppm.

4-(2-Bromophenyl)-3,4-dihydroxybutan-2-one (9c): Starting from **1c** (185 mg, 1.0 mmol) and HA (370 mg, 5.0 mmol), **9c** was obtained according to the general procedure and with the following modifications: the aqueous solution was lyophilized and the crude product purified by preparative RP-HPLC to separate the two diastereoisomers. ***syn*-9c:** Yield: 70 mg (27%); oil. IR (neat): $\tilde{\nu}$ = 3379, 1676, 1437, 1199, 1140, 845 cm^{-1}. ^{1}H NMR (CD_3OD): δ = 7.73 (app. d, 1 H), 7.60 (app. d, 1 H), 7.43 (app. t, 1 H), 7.15–7.25 (m, 1 H), 5.50 (d, J = 1.69 Hz, 1 H), 4.38 (d, J = 1.69 Hz, 1 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (CD_3OD): δ = 210.31, 143.19, 132.85, 130.37, 129.97, 128.36, 122.39, 79.29, 74.29, 29.75 ppm. HR ESI MS(+): calcd. for $C_{10}H_{11}BrNaO_3$ 280.9789; found 280.9784. Anal. RP-HPLC (254 nm, gradient 90% A, 10% D to 50% A, 50% D in 10 min): t_R = 5.161 min. ***anti*-9c:** Yield: 16 mg (6%); white solid, m.p. 85–87 °C. IR (neat): $\tilde{\nu}$ = 3379, 1701, 1462, 1365, 1319, 1234, 1190, 1120, 1086, 1064, 1018, 756, 681 cm^{-1}. ^{1}H NMR (CD_3OD): δ = 7.58–7.68 (m, 2 H), 7.40 (app. t, 1 H), 7.12–25 (m, 1 H), 5.29 (d, J = 4.9 Hz, 1 H), 4.40 (d, J = 4.9 Hz, 1 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (CD_3OD): δ = 210.03, 141.69, 133.91, 132.12, 128.78, 128.62, 126.99, 79.59, 73.85, 26.54 ppm. HR ESI MS(+): calcd. for $C_{10}H_{11}BrNaO_3$ 280.9789; found 280.9783. Anal. HPLC (254 nm; gradient 90% A, 10% D to 50% A, 50% D in 10 min): t_R = 5.585 min.

1,3,4-Trihydroxy-4-(4-nitrophenyl)butan-2-one (10a) as a *syn*/*anti* Mixture:[8] According to the general procedure and starting from **1a** (151 mg, 1.0 mmol) and DHA (450 mg, 5.0 mmol), **10a** could be isolated after column chromatography (185 mg, 77%). ^{1}H NMR (CD_3OD): δ = 8.25 (m, 2 H), 7.7 (m, 2 H), 5.3 (d, J = 2.4 Hz, 0.5 H), 5.05 (d, J = 5.8 Hz, 0.5 H), 4.55 (m, 1 H), 4.40 and 4.30 (2 br. d, 1 H) ppm. ^{13}C NMR (DMSO): δ = 211.76, 146.22, 131.09, 128.63, 128.14, 124.66, 123.26, 79.29, 73.76, 66.83 ppm.

1,3,4-Trihydroxy-4-(2-nitrophenyl)butan-2-one (10b): Starting from **1b** (151 mg, 1.0 mmol) and DHA (450 mg, 5.0 mmol), **10b** was obtained according to the general procedure with the following modifications: the aqueous solution was lyophilized and the crude product purified by preparative RP-HPLC to separate the two diastereoisomers. ***syn*-10b:** Yield: 103 mg (43%); oil. IR (neat): $\tilde{\nu}$ = 3327, 1726, 1523, 1342, 1230, 1053, 717, 631 cm^{-1}. ^{1}H NMR (CD_3OD): δ = 8.0 (m, 2 H), 7.75 (app. t, 1 H), 7.52 (app. t, 1 H), 5.71 (d, J = 2.07 Hz, 1 H), 4.66 (s, 2 H), 4.48 (d, J = 2.07 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 212.61, 149.41, 138.80, 134.38, 132.09, 129.82, 125.45, 79.80, 71.00, 68.24 ppm. HR ESI MS(+): calcd. for $C_{10}H_{11}NNaO_6$ 264.0484; found 264.0486. Anal. HPLC (254 nm; gradient 90% A, 10% D to 50% A, 50% D in 10 min): t_R = 3.096 min. ***anti*-10b:** Yield: 91 mg (38%); yellowish solid, m.p. 58–61 °C. IR (neat): $\tilde{\nu}$ = 3271, 1724, 1529, 1040, 1082, 834, 793, 732 cm^{-1}. ^{1}H NMR (CD_3OD): δ = 7.83 (d, J = 7.16 Hz, 1 H), 7.75 (d, J = 6.6 Hz, 1 H), 7.55 (app. t, 1 H), 7,38 (app. t, 1 H), 5.48 (d, J = 6.22 Hz, 1 H), 4.46 (d, J = 19.4 Hz, 1 H), 4.32 (d, J = 19.4 Hz, 1 H), 4.11 (d, J = 6.22 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 212.35, 138.13, 134.24, 130.65, 129.83, 125.45, 79.79, 71.86, 68.60 ppm. HR ESI MS(+): calcd. for $C_{10}H_{11}NNaO_6$ 264.0484; found 264.0475. Anal. HPLC (254 nm; gradient 90% A, 10% D to 50% A, 50% D in 10 min): t_R = 3.377 min.

4-(2-Bromophenyl)-1,3,4-trihydroxybutan-2-one (10c): Starting from **1c** (185 mg, 1.0 mmol) and DHA (450 mg, 5.00 mmol), **10c** was obtained according to the general procedure with the following modifications: the aqueous solution was lyophilized and the crude product purified by preparative RP-HPLC to separate the two diastereoisomers. ***syn*-10c:** Yield: 170 mg (62%), oil. IR (neat): $\tilde{\nu}$ = 3253, 1734, 1468, 1439, 1103, 1066, 1022, 750, 654 cm^{-1}. ^{1}H NMR (CD_3OD): δ = 7.70 (d, J = 8.3 Hz, 1 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.39 (app. t, 1 H), 7.16–7.21 (m, 1 H), 5.45 (d, J = 2.07 Hz, 1 H), 4.59 (s, 2 H), 4.41 (d, J = 2.07 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 213.31, 142.09, 133.79, 131.35, 130.54, 128.72, 122.67, 79.00, 74.72, 68.44 ppm. HR ESI MS(+): calcd. for $C_{10}H_{11}BrNaO_4$ 296.9738; found 296.9749. Anal. HPLC (254 nm; gradient 90% A, 10% D to 50% A, 50% D in 10 min): t_R = 4.963 min. ***anti*-10c:** Yield: 71 mg (26%), white solid, m.p. 66–69 °C. IR (neat): $\tilde{\nu}$ = 3282, 1722, 1464, 1369, 1323, 1188, 1074, 1018, 737 cm^{-1}. ^{1}H NMR (CD_3OD): δ = 7.50–7.77 (m, 2 H), 7.35 (app. t, 1 H), 7.1–7.2 (m, 1 H), 5.22 (d, J = 4.9 Hz, 1 H), 4.35–4.50 (m, 3 H) ppm. ^{13}C NMR (CD_3OD): δ = 212.17, 141.69, 133.91, 130.66, 130.60, 128.86, 124.16, 79.47, 75.89, 68.79 ppm. HR ESI MS(+): calcd. for $C_{10}H_{11}BrNaO_4$ 296.9738; found 296.9732. Anal. HPLC (254 nm; gradient 90% A, 10% D to 50% A, 50% D in 10 min): t_R = 4.366 min.

Supporting Information (see footnote on the first page of this article): Selected NMR spectra and HPLC traces.

Acknowledgments

This work was supported by the University of Berne and the Swiss National Science Foundation. We thank Sandra Zima for assistance in preparing the aldol products.

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Received: May 17, 2005
Published Online: October 25, 2005

