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Dual Proline/Water Compatible Lewis Acid Activation: a Biomimetic Approach for Direct Asymmetric Aldol Reaction

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Abstract. A novel approach based on combinations of various water compatible Lewis acids and *L*-proline co-catalysts has been evaluated for the direct asymmetric aldol reaction. From this screening zinc (II) chloride salts lead to the highest stereoselectivities. Optimized catalytic conditions (Catalytic system : *L*-proline : 20% / $ZnCl_2$: 10% - Solvent mixture : DMSO/H_2O – 8 : 2) give *anti* aldol product with improved enantioselectivity (>99% e.e.) compared to a moderately stereoselective procedure based on proline activation only.

Introduction:

The asymmetric aldol reaction is an important carbon–carbon bond-forming reaction that results in the formation of either one or two vicinal stereocenters.[1] This process can be observed in many different enzymatic transformations for the synthesis of complex biomolecules. For a long time chemists tried to simplify and stereochemically control this reaction using small chiral organic molecules. Mukaiyama aldol reaction of silyl enol ethers with aldehydes catalyzed by Lewis acid transition metals and main group elements chiral complexes can be considered as the first efficient approach in this field.[2] As a disadvantage, compared with biocatalytic pathways based on direct aldol reaction between a ketone and an aldehyde, this strategy require the pretransformation of the ketone into a more active silyl enol ether. More recently, new metal-free organocatalysts deriving from *L*-proline have been reported to activate direct aldol reaction in some cases with exceptional levels of stereoselectivity.[3] Since Barbas III and coworkers initial work on enamine processes,[4] a wide variety of small organic molecules have been successfully envisaged as organocatalysts and most of them are the result of many chemical transformations. For such reason and due to its low cost and natural abundance, *L*-proline is one of the most attractive of these organocatalysts.

Nevertheless numerous drawbacks are still remaining when using proline as the catalyst, including moderate stereoselectivities and finally dehydration (**2**) and 1-oxapyrrolizidine formation (**3**) side-reactions have been currently observed in the presence of aromatic aldehydes (Figure 1).[5]

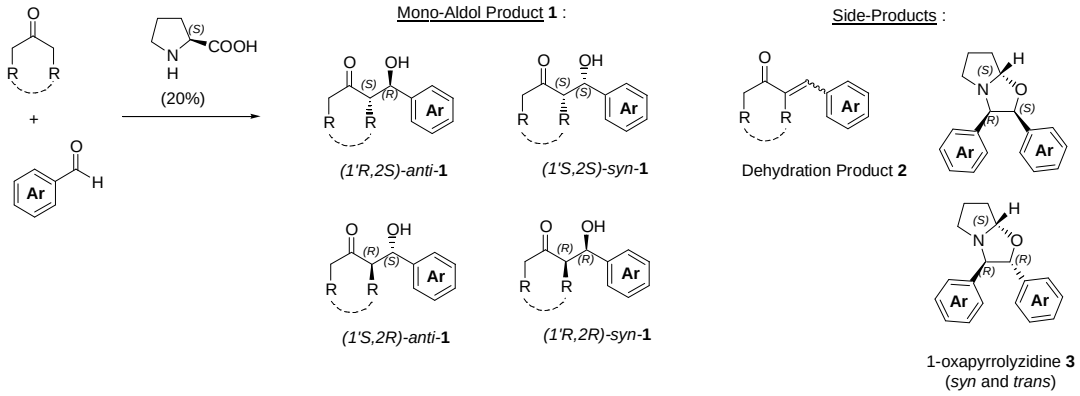


Figure 1. Direct aldol reaction catalyzed by *L*-proline.

Along the last few years, different groups reported asymmetric aldol reactions catalyzed by proline in the presence of a large excess of water.[6] In every cases, water addition leads to important improvements of enantio- and diastereoselectivities. If under such "wet" conditions the aldol reaction is slower, dehydration (**2**) or 1-oxapyrrolizidine formation (**3**) side reactions have been completely suppressed.

As an artless hypothesis, we considered dual water compatible Lewis acid/proline activation as a simple and combined alternative strategy to increase yields and stereoselectivities. Considering a possible interaction between the added Lewis acid, the *L*-proline and the aldehyde the catalytic system could be more organized. Interestingly, both Lewis acid and organocatalytic activations are largely inspired from enzymatic mechanisms encountered in nature.[7] The enamine pathway in *L*-proline catalysis is analogous to the one observed in class I aldolases and Lewis acid activation is done by class II aldolases in the presence of a zinc (II) cofactor (Figure 2).

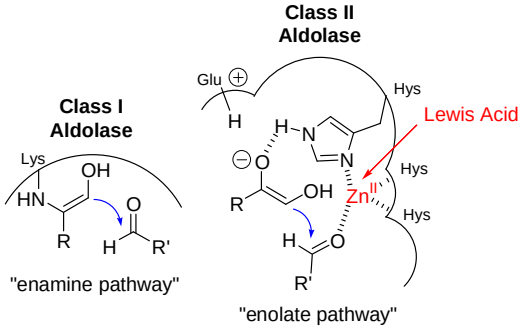


Figure 2. Class I and Class II aldolases active sites schematic representations.[7a]

To our knowledge only few work have been done in this way[8] and the most relevant to this approach has been described by Darbre *and coworkers* with a $Zn(Pro)_2$ complex prepared under basic conditions [8a] and by Mlynarski *and coworkers* with bis(prolinamide)-zinc (II) complexes[8e]. Aldol reaction catalyzed by $Zn(Pro)_2$ is moderatly stereoselective (e.e. up to 56% and d.e. up to 54%). bis(Prolinamide)-zinc (II) complexes demonstrated to be one of the more stereoselective catalytic systems for direct aldol reaction. In both cases, the use of water as a cosolvent is required in order to obtain a complete solubilisation of the complex. However, authors did not evaluate any combination of zinc (II)/*L*-proline or by extension Lewis acid/*L*-proline combinations by simple mixing. This alternative, offering a rapid screening of the Lewis acid and avoiding preformation of the *L*-proline/Lewis acid complexe prior to use, convinced us to focus our efforts in that direction.

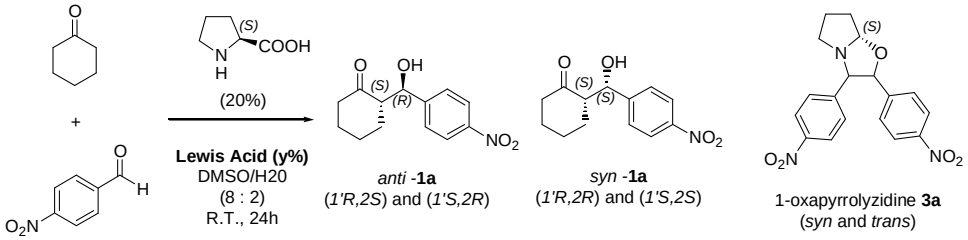
Results and discussion:

Lewis acid catalysis in the presence of water is not trivial, since most of them are decomposed under aqueous conditions. Although, some examples of water-tolerant Lewis acids have been previously reported by Kobayashi and others.[9] Furthermore, Lewis acids in aqueous media are known to coordinate to a molecule of water to generate metallo-hydroxonium species with a nearly neutral range of pKa values.[10] In the presence of ligands, those metallo-hydroxonium species are able to dissociate and equilibrate with different ligand-metal complexes. Such dynamic behaviour is the one observed in metallo-enzymes. *L*-Proline in our case could activate the ketone *via* an enamine intermediate and in the same time act as a ligand and interact with various metal to later activate the aldehyde partner. Furthermore, the nature of the metal could have important effects on stereoselectivities.

In order to evaluate this approach we first decided to screen known water compatible Lewis acids ($ZnCl_2$, $FeCl_3$, $HgCl_2$, $CuCl_2$, $MgCl_2$, $YbCl_3$) in the model reaction between cyclohexanone and *p*-nitrobenzaldehyde catalyzed by *L*-proline (20% mol.) in a 2:8 - water/DMSO solvent mixture (Table

1). These reaction conditions are suitable to evaluate the different effects of Lewis acids on both stereoselectivities and the rate of the reaction by comparison with more standard conditions based on proline alone (entry 1). Without any Lewis acid, a reaction time of 18 hours has been found to be optimal for a complete conversion. Even if conversion is complete, as a drawback compared to Hayashi's similar best result under *L*-proline organocatalysis,[6e] increasing the reaction time to completion and decreasing the amount of catalyst resulted in lower stereoselectivities (40% e.e instead of 96% e.e after 2h – *L*-proline 30% mol. Ref. 6a), suggesting that a thermodynamic equilibrium could be responsible of a partial racemisation of the product along the time. As scheduled, no 1-oxapyrrolizidines (**3a**) has been observed even after 18 hours confirming a crucial effect of water on the chemical selectivity. As a primary observation, addition of Lewis acids to the reaction medium has no effect on the chemical selectivity; in every case we never observe 1-oxapyrrolizidines (**3a**) side products. However, Lewis acids have important effects on the stereoselectivity and the rate of the reaction. It is interesting to note that with or without Lewis acid the same enantiomer *(1'R, 2S)-anti-***1a** is observed in excess in every experiments. Interestingly, $ZnCl_2$, $FeCl_3$, $HgCl_2$, and $YbCl_3$ have a positive effect on the enantioselectivity of the major *anti*-diasteromer (up to 96%, entries 2 and 4).

Table 1. Lewis acid screening.



Entry [a]	Lewis acid (20 %)	Conv. (%) [b]	Ratio **1a**/**3a** [b]	d.r. *anti*/*syn* [b]	e.e. *anti*-**1a** (%) [c]
1	-	100	100 : 0	2.5 : 1	40
2	**$ZnCl_2$**	100	100 : 0	9 : 1	96
3	$FeCl_3$	100	100 : 0	7 : 1	85
4	**$HgCl_2$**	100	100 : 0	16 : 1	96
5	$CuCl_2$	<5	n.d.	n.d.	n.d.
6	$MgCl_2$	100	100 : 0	2.5 : 1	9
7	$YbCl_3$	100	100 : 0	2.5 : 1	61

a) General procedure: to a solution of cyclohexanone (5 mmol) and *p*-nitrobenzaldehyde (1 mmol) in a mixture of DMSO/H_2O – 8:2 (3 mL) is added L-proline (0.2 mmol) and Lewis acid (0.2 mmol). The reaction is then stirred at room temperature for 24 h.

b) Determined by ^1H NMR on the crude material.

c) Determined by chiral HPLC (Chiralpack IB) based on the major *(1'R, 2S)-anti-* **1a** enantiomer.

By oppositionin the presence of $MgCl_2$ (entry 6), if conversion is still complete, enantioselectivity is much lower. Surprisingly, when $CuCl_2$ is used as the cocatalyst (entry 5) conversion is extremely low (less than 5%). Furthermore, depending on the nature of the Lewis acid, diastereoselectivity varies considerably, and important positive effects in favor of the *anti*-diastereomer are observed in the case of $ZnCl_2$, $FeCl_3$, $HgCl_2$.

For ecotoxycological considerations,[11] we next turned our efforts on *L*-proline/zinc (II) couple that gave promising results during the screening step. In order to optimise the conditions (table 2), we first envisaged to modify the solvent mixture composition by varying the amount of water. As

expected, when DMSO is used alone as the solvent (entry 2), the chemical selectivity dramatically decreases and large amounts 1-oxapyrrolizidines (**3a**) by-products are generated along the reaction and strongly affect the mono-aldol (**1a**) isolated yield. Such result confirm the important effect of water on the chemical selectivity of the reaction. In the same time, stereoselectivity drops as well. When the reaction is done "in water" (entry 3), the conversion is extremely low, confirming the importance of the organic solvent. In order to acquire more informations concerning the behaviour and the reactivity of the Lewis acid, we then decided to evaluate the catalytic efficiency of $ZnCl_2$ without proline (entry 4) and also to replace the chloride counterions by triflate anions in order to increase Lewis acidity (entry 5). As previously described by Darbre and others no reaction occur in the presence of the Lewis acid only (entry 4).[8d] Replacement of chloride anions by triflate counterions resulted in lower stereoselectivities (entry 5). Best results, in term of conversion (100%) and stereoselectivities (d.r. = 16 : 1 ; e.e. > 99%), were obtained with a 2:1 ratio of *L*-proline/$ZnCl_2$ (respectively 20/10 mol. %) suggesting that the active catalytic system could be based on a [(*L*-Pro)$_2$$ZnCl_2$] complex (entry 6). To our knowledge, these conditions are the best obtained so far under *L*-proline catalysis. Attempt to decrease amounts of both co-catalysts (*L*-proline - 10%, $ZnCl_2$ - 5%) lead to lower conversion, diastereoselectivity and enantioselectivity (entry 7).

Table 2. Optimisation.

Entry[a]	*L*-Proline (x %)	Lewis acid (y %)	Ratio DMSO/H_2O	Conv.[b] (%)	Ratio **1a**/**3a**[b]	d.r. *anti*/*syn*[b]	e.e. *anti*-**1a** (%)[c]
1	20	$ZnCl_2$ (20%)	80 : 20	100	100 : 0	9 : 1	96
2	20	$ZnCl_2$ (20%)	100 : 0	100	81 : 19	1.5 : 1	63
3	20	$ZnCl_2$ (20%)	0 : 100	2	n.d.	n.d.	n.d.
4	-	$ZnCl_2$ (20%)	80 : 20	3	n.d.	n.d.	n.d.
5	20	$Zn(OTf)_2$ (20%)	80 : 20	100	100 : 0	9 : 1	89
6	20	$ZnCl_2$ (10 %)	80 : 20	100 (99[d])	100 : 0	16 : 1	>99
7	10	$ZnCl_2$ (5%)	80 : 20	63	100 : 0	7 : 1	74
8	20	-	100 : 0				

a) General procedure : To a solution of cyclohexanone (5 mmol) and *p*-nitrobenzaldehyde (1 mmol) in a mixture of DMSO/H_2O – 80 : 20 (3 mL) is added *L*-proline (x %) and Lewis acid (y %). The reaction is then stirred at room temperature for 24 h.
b) Determined by ^{1}H NMR on the crude material after extraction and evaporation.
c) Determined by chiral HPLC (Chiralpack IB) based on the major *(1'R, 2S)-anti-* **1a** enantiomer.
d) Isolated yield for the mono aldol product **1**.

Conclusion:

In summary, a biomimetic approach based on a conceptual fusion between Class I and Class II aldolases mechanism has been evaluated for the direct asymmetric aldol reaction. The study of the effect of various water compatible Lewis acids on *L*-proline organocatalysis in the presence of water produced important results. From this screening, $ZnCl_2$ and $HgCl_2$ lead to the highest stereoselectivities and conversions. A solvent mixture DMSO/water (8:2) appears to be optimum for the solubility of the Lewis acid, the control of the diastereoselectivity and for exclusive formation of the mono-aldol product. The optimized catalytic conditions (*L*-proline: 20% - $ZnCl_2$: 10%) give anti-product with improved enantioselectivity (>99% e.e) compared to moderately stereoselective procedure based on proline alone. More than a new and presumably efficient tool in organic chemistry, this procedure appears to be an excellent and readily available biomimetic model analog to Class II aldolases that opens new interrogations concerning the exact nature of the chemical bonds involved in such enzymes. Answer to those questions could argue or explain the choice of nature for zinc (II) cofactor as the Lewis acid active center. Further studies focusing on the full scope of this system are in progress and will be reported in due course.

Experimental Section :

General Information:

All reactions were conducted under air unless otherwise stated. Synthesis grade DMSO, CH_2Cl_2, cyclohexanone and aromatic aldehydes were used as received (Aldrich, France). ^1H NMR, ^{13}C NMR experiments were performed with a Bruker (Wissembourg, France) Avance 300 Ultrashield spectrometer at room temperature in $CDCl_3$ or DMSO-d^6 with calibration on the solvent peak. Chemical shifts are given in δ and coupling constants in Hz. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard Model HP 1100 liquid chromatography (Agilent, Palo Alto, USA) equipped with a UV detector and an autosampler, using Chiralpack IB columns (250 x 4.6 mm i.d.) (Chiral Technologies, France), protected by a guard column and operated at 24°C. Solutions were analyzed by HPLC/UV. Samples were dissolved in isopropanol/CH_2Cl_2 mixture (1:1) to a concentration of 1 mg/mL. The mobile phase composition was hexane/isopropanol-97/3-v/v. The separation was realized in isocratic mode at a flow rate of 1 mL/min. The injected volume was 10 µL. The column eluent was directed to a UV detector at a fixed wavelenght. Data were acquired and integrated with a MassLynx 4.0. (Micromass, Waters, Manchester, United Kingdom). Racemic standard products were prepared using DL-proline as catalyst in order to establish HPLC conditions.

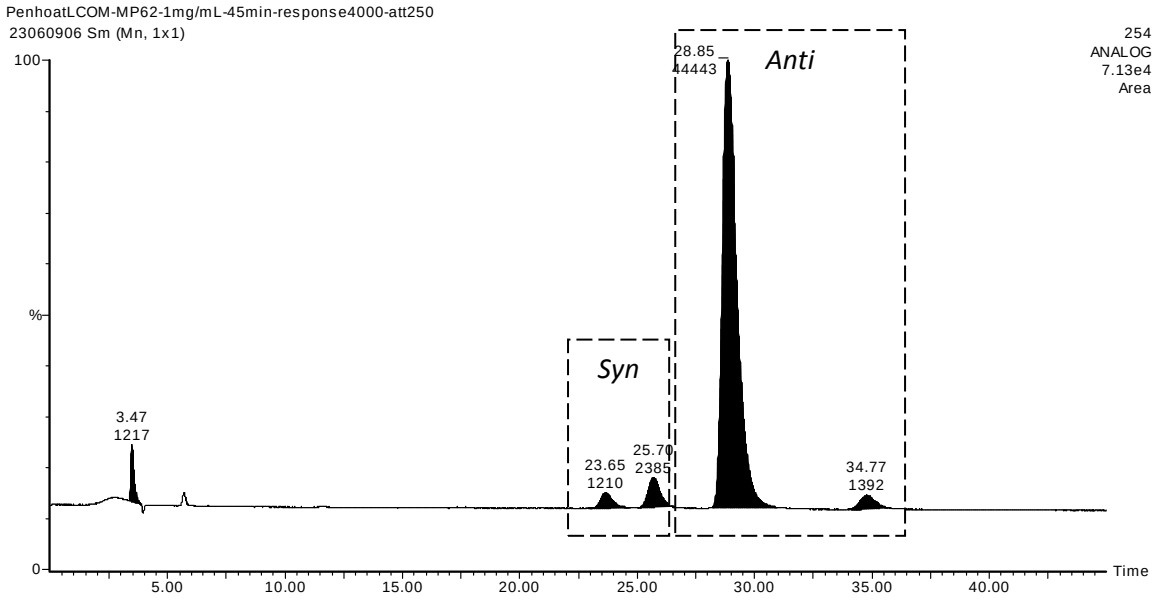
Typical Procedure for the Lewis acid screening:

To a mixture of *L*-proline (23 mg, 0.2 mmol, 20 mol %), Lewis acid (0.2 mmol, 20 mol %) and *p*-nitrobenzaldehyde (1 mmol) are added DMSO (2.2 mL) and water (0.8 mL) at room temperature and the resulted suspension is stirred for 15 min. Cyclohexanone (5 mmol) is added to the mixture and the whole reaction is stirred for 18 h. The reaction mixture is quenched with 10 mL of an ammonium chloride solution (1M) and then extracted with CH_2Cl_2 (2×10 mL). The organic phase is then dried over $MgSO_4$ and evaporated under reduced pressure. The crude material is directly analyzed by ^1H NMR without further purification. Chiral HPLC (Chiralpack IB, hexane-*i*PrOH – 97:3 - flow rate 1 mL.min^{-1}, λ = 254 nm, Retention times: ***Syn*** diastereomer: major enantiomer tr = 23.6 min, minor enantiomer tr = 26.7 min; ***Anti*** diastereomer: major enantiomer tr = 28.8 min, minor enantiomer tr = 34.8 min.) has been realized directly on the crude mixture or after purification by simple trituration in few mL of Na_2CO_3 (1M) solution of the crude yellow solid followed by filtration and drying.

Optimized Procedure with $ZnCl_2$ as the co-catalyst:

To a mixture of *L*-Proline (23 mg, 0.2 mmol, 20 mol %), $ZnCl_2$ (0.1 mmol, 10 mol %) and *p*-nitrobenzaldehyde (1 mmol) are added DMSO (2.2 mL) and water (0.8 mL) at room temperature and the resulted suspension is stirred for 15 min. Cyclohexanone (5 mmol) is added to the mixture and the whole reaction is stirred for 18 h. The reaction mixture is quenched with 10 mL of an ammonium chloride solution (1M) the resulted solid is then triturated in few mL of Na_2CO_3 (1M) solution and filtrated to afford the corresponding (*2S,1'R*)-2-(Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (**1a**) as a yellow solid (m = 246 mg, yield = 99%).

Chiral HPLC :
Column: Chiralpack IB - Eluant: hexane-*i*PrOH – 97:3 - Flow rate: 1 mL.min$^-$1 - Wavelength: λ=254 nm
Retention times:
Syn diastereomer: major enantiomer - tr = 23.6 min, minor enantiomer - tr = 26.7 min
Anti diatereomer: major enantiomer - tr = 28.8 min, minor enantiomer - tr = 34.8 min.



<u>1H NMR</u> :

<u>*Anti*</u> <u>diastereomer</u>:
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.91 (d, *J* = 3.3 Hz, 1H), 4.09 (d, J = 3.3 Hz, 1H), 2.60 (m, 1H), 2.34-2.53 (m, 2H), 1.53-2.15 (m, 6H).

<u>*Syn*</u> <u>diastereomer</u>:
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 5.49 (s, 1H), 3.17 (s, 1H), 2.62-2.31 (m, 3H), 2.08 (m, 1H), 1.85-1.36 (m, 6H).

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