DOI: 10.1002/adsc.201100143

Diastereo- and Enantioselective Direct Aldol Reactions in Aqueous Medium: A New Highly Efficient Proline-Sugar Chimeric Catalyst

Silvana Pedatella,[a] Mauro De Nisco,[a,*] Domenico Mastroianni,[b] Daniele Naviglio,[a] Ada Nucci,[c] and Romualdo Caputo[a,*]

[a] Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, Via Cintia 4, I-80126 Napoli, Italy
Fax: (+39)-081-674-393; phone: (+39)-081-674-118; e-mail: denisco@unina.it or rocaputo@unina.it
[b] Tecnogen SpA, Località la Fagianeria, Piana di Monte Verna, I-81015 Caserta, Italy
[c] Istituto di Scienze degli Alimenti e della Nutrizione, Università Cattolica del Sacro Cuore, Via Emilia Parmense 84, I-29122 Piacenza, Italy

Received: February 27, 2011; Published online: June 16, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adcs.201100143.

Abstract: A new synthetic catalyst, capable of acting like an enzyme in the accomplishment of direct aldol reactions, is presented. Excellent results, in terms of chemical yields and diastereo-/enantiomeric ratios, are reported for the catalyzed additions of cyclohexanone to variously substituted benzaldehydes.

Keywords: aldol reaction; asymmetric synthesis; green chemistry; L-proline catalyst; organocatalysis

The ability of simple organic molecules from the "chiral pool" to act like an enzyme represents a remarkable synthetic alternative to many established asymmetric transformations. Among the various enantiomerically pure small organic molecules, amino acids and peptides are extremely interesting asymmetric organocatalysts leading to useful levels of enantioselectivity in a wide range of transformations.[1]

In particular, the natural amino acid L-proline acts as an enzyme mimic of the class I aldolase,[2] catalyzing an important organic asymmetric transformation, the aldol reaction.[3] The proline-catalyzed asymmetric aldol addition is well established to proceed *via* the "enamine mechanism" where the proline amino group converts the aldol donor to an enamine and the carboxylic acid group provides a hydrogen bond to the acceptor.[4]

Although the proposed mechanism is based on the class I aldolase mechanism, proline has not been demonstrated to act as an efficient catalyst in aqueous medium.[5] On the other hand it is known[6] that water alters enantioselectivities by interrupting the hydrogen bonds that are crucial for stabilizing the transition states of the asymmetric catalytic reactions, and this may be the reason for the poor enantioselectivity[7] of the proline-catalyzed aldol reactions in water.

Either the use of cosolvents[6] or, *vice versa*, attempts to enhance the hydrophilic nature of proline by grafting on it polyhydroxylated auxiliaries,[8] did not lead to significantly improved results.

Indeed, another non-secondary aspect of the enamine mechanism is that the reactions occurring in the aldolase antibodies are considered to be accomplished in a hydrophobic active site,[9] whereas the amino functionality of lysine and the hydroxy group of tyrosine seem to be also involved in the catalytic cycle.

In fact, small organic catalysts bearing hydrophobic groups were designed with the purpose of matching the hydrophobic nature of the active site in antibodies. The results, in this case, were quite encouraging and some examples of such catalysts are available from the current literature.[10]

Under such circumstances we were stimulated to design a new catalyst that, in our opinion, should have overcome the above-mentioned limits of other reported proline-based catalysts. Therefore, within our current interest in the chemistry of carbohydrates[11] and peptides as organocatalysts,[12] we have synthesized an unprecedented L-prolinamide **1** that, as highlighted in Figure 1, displays three different domains, namely a hydrophobic one, represented by the cumbersome TBDPS protecting group at the anomeric hydroxy position of β-glucosamine, a hydrophilic one, consisting of the sugar moiety with its three free hydroxy groups, and finally the functional domain represented by L-proline nucleus.

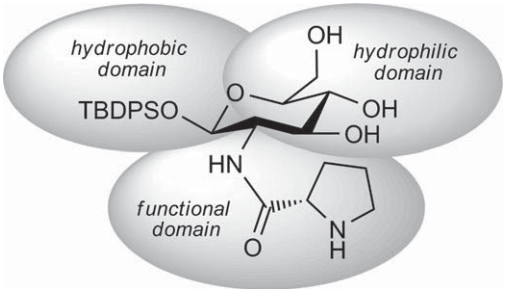


Figure 1. (2*S*)-Pyrrolidine-2-carboxamide (**1**).

Simple D-glucosamine has been already demonstrated[13] to exert a catalytic role on the direct aldol reaction of ketones and aromatic aldehydes, although affording moderate yields and poor enantiomeric excess of the aldol product. Also poor, and even worse, results were obtained[14] using D-glucosamine-L-prolinamide as catalyst for the same kind of reactions in water. On the contrary, small proline-based molecules bearing hydrophobic groups were reported[10d] to act as good organocatalysts for aldol reactions. Therefore, we combined all this information in the same molecule that, as expected, turned out to be an excellent organocatalyst to accomplish direct aldol reaction of cyclohexanone and aromatic aldehydes. Experimental details of the synthesis of **1**, which is handily prepared from both commercial D-glucosamine and L-proline, are reported as Supporting Information along with its full spectroscopic characterization.

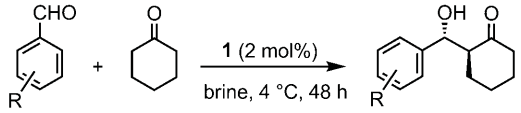
The new catalyst was extensively tested in the direct aldol addition of cyclohexanone to variously substituted benzaldehydes, under standardized conditions (2 mol% loading in brine, 4 °C, 48 h) obtaining rather impressive results (Table 1).

Some other miscellaneous experiments, carried out using different catalyst loadings/solvents/temperatures/reaction times, are reported in Table 2.

All the results show unambiguously that **1** is an efficient catalyst working in aqueous medium (see the poor results of the reactions carried out in THF, Table 2) at low temperature. It is also noteworthy the very low catalyst loading (down to 0.1 mol%, Table 2) that can be utilized, as well as the significant catalyst recovery (72–89%) and its reuse (see Supporting Information).

The compound **1** was also tested in the addition of acetone and 4-nitrobenzaldehyde (Table 3). The reaction with acetone was carried out both in the presence and in the absence of water. In the first case we obtained the aldol product in acceptable yield (42–54%) and low enantioselectivity (66–70%) (entries 1 and 2). When the reaction was carried out without water (entries 4 and 5) the aldol product was obtained in lower yield (10–12%) and better enantioselectivity (72–82%). No reversed configuration of the aldol product was observed.[15] In our opinion the presence of water increases the activity of the catalyst because the more hydrophilic medium enhances the affinity of the hydrophobic aldehyde to the hydrophobic moiety of the catalyst. When water is absent (THF), the aldehyde is well dissolved in the organic solvent and this causes a lower yield. These results, however, are mostly paralleling those reported by various authors for the aldol

Table 1. Cyclohexanone/miscellaneous benzaldehydes aldol additions in brine, 4 °C, 48 h, catalyzed by **1** (2 mol%).



R	Yield [%][a]	*dr* (*anti*:*syn*)[b]	*ee* [%][c]
3-chloro	99	96:4	96
4-chloro	99	97:3	98
3-cyano	86	98:2	96
4-cyano	>99	97:3	96
3-fluoro	98	96:4	96
4-fluoro	99	96:4	98
2-methoxy	95	88:12	83
3-methoxy	>99	92:8	94
4-methoxy	96	87:13	82
3-methyl	99	95:5	94
4-methyl	98	92:8	87
2-nitro	96	98:2	>99
3-nitro	>99	97:3	98
4-nitro	98	97:3	96
4-isopropyl	98	91:9	92

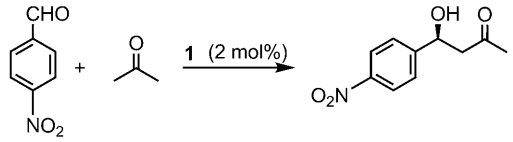
[a] After chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC on chiral column.

Table 2. Aldol additions as in Table 1, catalyzed by **1**, carried out under various reaction conditions.

R	Mol [%]	*T* [°C]	Time	Yield [%][a]	*dr* (*anti*:*syn*)[b]	*ee* [%][c]
4-cyano	2	25	48 h	99	95:5	87
4-cyano	2	−16	48 h	99	99:1	98
4-cyano	0.1	25	4 d	92	90:10	85
4-cyano	0.1	−16	4 d	82	99:1	99
4-cyano (in THF)	2	4	48 h	57	82:18	62
4-nitro	10	−16	48 h	94	97:3	98
4-nitro	2	25	48 h	98	93:7	89
4-nitro	2	−16	48 h	96	96:4	98
4-nitro	0.1	25	4 d	90	89:11	82
4-nitro	0.1	−16	4 d	84	99:1	96
4-nitro (in THF)	2	4	48 h	52	90:10	70

[a] After chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC on chiral column.

Table 3. Acetone/4-nitrobenzaldehyde aldol additions, catalyzed by **1** (2 mol%), carried out under various reaction conditions.



Solvent	*T* [°C]	Time	Yield [%][a]	*ee* [%][b]
brine	25	48 h	42	66
brine	4	48 h	54	70
brine	−16	4 d	21	75
THF	25	48 h	10	72
THF	4	48 h	12	82

[a] After chromatography.
[b] Determined by HPLC on chiral column.

addition of acetone and aromatic aldehydes in the presence of water.[2e,4d,5,10b,15,16]

The performances of the catalyst **1** can be accounted for by considering that in water (even more in brine, due to the salting-out effect[17]) the catalyst molecules may undergo molecular aggregation, much like surfactants, creating a local hydrophobic microenvironment in which reactions can take place. In other words, in the transition state the organic non-polar reactants would be buried in the hydrophobic environment[18] whereas the entire system would be kept in water by a hydrophilic surface. After accomplishment of the reaction, the moderately polar aldol molecules would be squeezed out of the hydrophobic environment and locate themselves closer to the polar surface of the catalyst.[19]

As a matter of fact, the only significant variable in the use of catalyst **1** in aqueous medium seems to be the temperature: in our opinion this is in line with the proposed transition state (Figure 2) insofar as low temperature could reduce the molecular freedom and, consequently, contribute to the aggregation that creates a hydrophobic environment to hold the non-polar reactants.

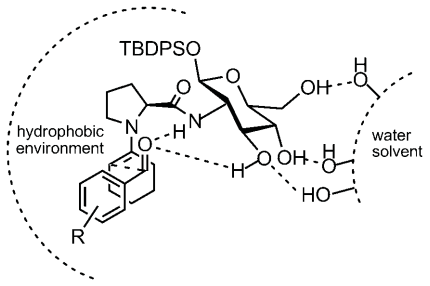


Figure 2. Proposed transition state for aldol reactions catalyzed by **1**.

Our results show that the synthetic catalyst **1** works "in the presence of water"[10d,20] without organic solvent, much like an enzyme accomplishing aldol reactions with very high enantioselectivity in most cases. It can be regarded as a first example of and a lead for a new family of enzyme-like organocatalysts carrying different sugars and/or hydrophobic moieties to be investigated for other C–C bond forming reactions.

Experimental Section

General Procedure for Cyclohexanone/Miscellaneous Benzaldehydes Aldol Reactions Catalyzed by 1

Into an 8-mL Wheaton clear glass, screw-cap vial, solid **1** (7.7 mg, 1.5×10^{-2} mmol) suspended in brine (or THF) (1 mL), cyclohexanone (3.0 mmol), and the aldehyde under investigation (0.75 mmol) were charged in sequence. The mixture was vigorously stirred in the stoppered vial at the chosen temperature/time (*cf.* Table 1 and Table 2). After quenching by 20% aqueous NH_4Cl (4 mL) and extraction with Et_2O (3×5 mL), the organic layers were washed with brine and dried (Na_2SO_4). The combined water extracts containing salts and most of the recovered catalyst were freeze-dried and put aside. Evaporation of the solvents under reduced pressure gave a crude residue that was adsorbed on a preparative layer plate eluting twice with hexane:EtOAc (7:3) to get residual starting aldehyde and *anti* plus *syn* couples. The *anti*:*syn* ratio was determined by 500 MHz ^{1}H NMR. The *anti ee* was determined by HPLC on a chiral column (Daicel, Chiralpak, IC). The solid coming from the freeze-dried water extracts was worked up as reported in the Supporting Information to recover the residual catalyst. Recovery range: 72–89% (when 2 mol% used). All the experiments were duplicated.

Acknowledgements

The authors thankfully acknowledge the skilful collaboration of Semiha Bektaş (ERASMUS fellow, 2009). ^{1}H and ^{13}C NMR spectra were performed at Centro Interdipartimentale di Metodologie Chimico-Fisiche, Università di Napoli Federico II. The Varian Inova 500 MHz NMR instrument is the property of Consorzio INCA.

References

[1] a) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812–816; b) A. Córdova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, *Chem. Eur. J.* **2006**, *12*, 5383–5397.

[2] a) N. Mase, C. F. Barbas III, *Org. Biomol. Chem.* **2010**, *8*, 4043–4050; b) S. Takayama, G. J. McGarvey, C.-H. Wong, *Chem. Soc. Rev.* **1997**, *26*, 407–415; c) W.-D. Fessner, in: *Stereoselective Biocatalysis*, (Ed: R. N. Patel), M. Dekker, New York, **2000**, pp 239–265; d) K. N. Rankin, J. W. Gauld, R. J. Boyd, *J. Phys.*

Chem. A **2002**, *106*, 5155–5159; e) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024–3025.

[3] a) M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904–1905; b) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; c) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

[4] a) M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem. Int. Ed.* **2010**, *49*, 4997–5003; b) X. Zhu, F. Tanaka, R. A. Lerner, C. F. Barbas III, I. A. Wilson, *J. Am. Chem. Soc.* **2009**, *131*, 18206–18207; c) B. Wang, G.-H. Chen, L.-Y. Liu, W.-X. Chang, J. Li, *Adv. Synth. Catal.* **2009**, *351*, 2441–2448; d) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; e) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425–471; f) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem.* **2006**, *118*, 5653–5655; *Angew. Chem. Int. Ed.* **2006**, *45*, 5527–5529; g) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570–579; h) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591.

[5] a) S. Singh Chimni, D. Mahajana, V. V. S. Babub, *Tetrahedron Lett.* **2005**, *46*, 5617–5619; b) Y.-S. Wu, W.-Y. Shao, C.-Q. Zheng, Z.-L. Huang, J. Cai, Q.-Y. Deng, *Helv. Chim. Acta* **2004**, *87*, 1377–1384; c) Y.-Y. Yi-Yuan Peng, O.-P. Ding, Z. Li, P. G. Wang, J.-P. Cheng, *Tetrahedron Lett.* **2003**, *44*, 3871–3875; d) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024–3025.

[6] a) R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010**, *110*, 6302–6337; b) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772.

[7] a) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33–57; b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171.

[8] a) A. Lu, P. Gao, Y. Wu, Y. Wang, Z. Zhou, C. Tang, *Org. Biomol. Chem.* **2009**, *7*, 3141–3147; b) A. Tsutsui, H. Takeda, M. Kimura, T. Fujimoto, T. Machinami, *Tetrahedron Lett.* **2007**, *48*, 5213–5217.

[9] X. Zhu, F. Tanaka, Y. Hu, A. Heine, R. Fuller, G. Zhong, A. J. Olson, R. A. Lerner, C. F. Barbas III, I. A. Wilson, *J. Mol. Biol.* **2004**, *343*, 1269–1280, and references cited therein.

[10] a) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812–816; b) V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 2593–2595; c) S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246–10256; d) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972–975; *Angew. Chem. Int. Ed.* **2006**, *45*, 958–961; e) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735.

[11] S. Pedatella, M. De Nisco, B. Ernst, A. Guaragna, B. Wagner, R. J. Woods, G. Palumbo, *Carbohydr. Res.* **2008**, *343*, 31–38.

[12] M. De Nisco, S. Pedatella, H. Ullah, J. H. Zaidi, D. Naviglio, O. Ozdamar, R. Caputo, *J. Org. Chem.* **2009**, *74*, 9562–9565.

[13] N. Singh, J. Pandey, R. P. Tripathi, *Catal. Commun.* **2008**, *9*, 743–746.

[14] A. Tsutsui, H. Takeda, M. Kimura, T. Fujimoto, T. Machinami, *Tetrahedron Lett.* **2007**, *48*, 5213–5217.

[15] F. Giacalone, M. Gruttadauria, P. Lo Meo, S. Riela, R. Noto, *Adv. Synth. Catal.* **2008**, *350*, 2747–2760.

[16] a) M. Raja, V. K. Singh, *Chem. Commun.* **2009**, 6687–6703; b) D. Almaşi, D. A. Alonso, A.-N. Balaguer, C. Nájera, *Adv. Synth. Catal.* **2009**, *351*, 1123–1131.

[17] a) N. Ni, M. M. El-Sayed, T. Sanghvi, S. H. Yalkowsky, *J. Pharm. Sci.* **2000**, *89*, 1620–1625; b) R. Breslow, *Acc. Chem. Res.* **2004**, *37*, 471–478.

[18] a) D. Font, S. Sayalero, A. Bastero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2008**, *10*, 337–340; b) D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653–4655.

[19] In our opinion, this might explain the absolute lack of racemization of the aldol species even under critical reaction conditions (e.g., 48 h, 2 mol%, 25 °C) (see Supporting Information).

[20] a) J. Paradowska, M. Stodulski, M. Jacek, *Angew. Chem.* **2009**, *121*, 4352–4362; *Angew. Chem. Int. Ed.* **2009**, *48*, 4288–4297; b) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278–8280; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102; c) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281–8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104.

