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Nonlinear Effects in Asymmetric Amino Acid Catalysis by Multiple Interconnected Stereoselective Catalytic Networks

Ramon Rios,[a] Patric Schyman,[b, c, e] Henrik Sundén,[a] Gui-Ling Zhao,[a, c] Farman Ullah,[a] Li-Jun Chen,[b, c] Aatto Laaksonen,[b, c] and Armando Córdova*[a, c, d]

The generation of positive nonlinear effects in asymmetric amino acid catalysis by creation of a multiple interconnected stereoselective catalytic network is presented. Density functional theory calculations together with experimental results establish a dynamic model for the enantioselective catalytic network of amino acid catalysis that may have implications for the origins of homochirality (asymmetric amplification).

The origin of homochirality has intrigued scientists ever since Pasteur's discovery of optical activity of biomolecules, such as L-amino acids and D-sugars.[1] Several theories of the origins and evolution of homochirality and its importance for the origins of life have been proposed.[2] In pioneering work, Kagan reported the possibility of achieving asymmetric amplification of products obtained by asymmetric catalysis (positive nonlinear effects).[3] Preceding this seminal work a linear relationship between the *ee* of the chiral catalyst or auxiliary and the extent of the asymmetric synthesis was assumed. For a reaction exhibiting this behavior with scalemic mixtures of catalyst (<0–$100\,\%$ *ee*) plotting the catalyst *ee* along the *x* axis and the corresponding product *ee* along the *y* axis will result in a line. According to Kagan deviations from the straight line can be considered as a nonlinear effect. For example, if the *ee* values of the products exceeded the calculated values for a linear correlation based on the *ee* values of the catalyst, the deviation from the linear correlation was a positive nonlinear effect. This discovery has inspired researchers to investigate the presence of nonlinear effects in asymmetric catalysis and its importance for the origins of homochirality. In this context, Soai demonstrated a remarkable asymmetric amplification of pyrimidyl alkanols generated by asymmetric Zn autocatalysis.[4] These impressive results could be explained by the Frank model involving a combination of autocatalytic and inhibition processes.[2d] In asymmetric amino acid catalysis, nonlinear effects were first observed by Kagan and co-workers during their investigation of the Hajos–Parrish reaction.[3,5] However, they were "re-discovered" by Hanessian in proline-catalyzed conjugate additions as late as 2000.[6] In 2004, Blackmond and co-workers reported nonlinear effects in proline-catalyzed α-aminooxylation of propionaldehyde in $CHCl_3$ under heterogeneous conditions.[7] Notably, performing the same α-aminoxylation reaction in DMSO under homogeneous conditions gives a linear line when plotting the *ee* of product against the *ee* of proline.[7,8] These early examples of nonlinear effects in proline catalysis were independently explained by Hayashi[9] and Blackmond,[10] to be due to the solid–liquid equilibrium of the amino acid catalyst.[11] In 2005, our group discovered the first asymmetric amplification of sugars generated by asymmetric amino acid catalysis under homogeneous conditions.[12] Shortly after, we reported several cases of positive nonlinear effects in proline-catalyzed C–C bond-forming reactions such as the aldol[13] and the Mannich reaction under homogeneous conditions.[14] Moreover, we found that racemic proline can catalyze asym-

[a] Dr. R. Rios, Dr. H. Sundén, Dr. G.-L. Zhao, Dr. F. Ullah, Prof. Dr. A. Córdova
Department of Organic Chemistry
The Arrhenius Laboratory, Stockholm University
106 91 Stockholm (Sweden)
Fax: (+46) 8-154908
E-mail: acordova@organ.su.se
armando.cordova@miun.se

[b] Dr. P. Schyman, Dr. L.-J. Chen, Prof. Dr. A. Laaksonen
Division of Physical Chemistry
The Arrhenius Laboratory, Stockholm University
106 91 Stockholm (Sweden)

[c] Dr. P. Schyman, Dr. G.-L. Zhao, Dr. L.-J. Chen, Prof. Dr. A. Laaksonen, Prof. Dr. A. Córdova
Berzelii Center EXSELENT on Porous Materials
The Arrhenius Laboratory, Stockholm University
106 91 Stockholm (Sweden)

[d] Prof. Dr. A. Córdova
Department of Natural Sciences, Engineering and Mathematics
Mid Sweden University, SE-851 70 Sundsvall (Sweden)

[e] Dr. P. Schyman
Current address: Institute of Chemistry and
The Lise Meitner-Minerva Center for
Computational Quantum Chemistry
The Hebrew University of Jerusalem, 91940, Jerusalem (Israel)

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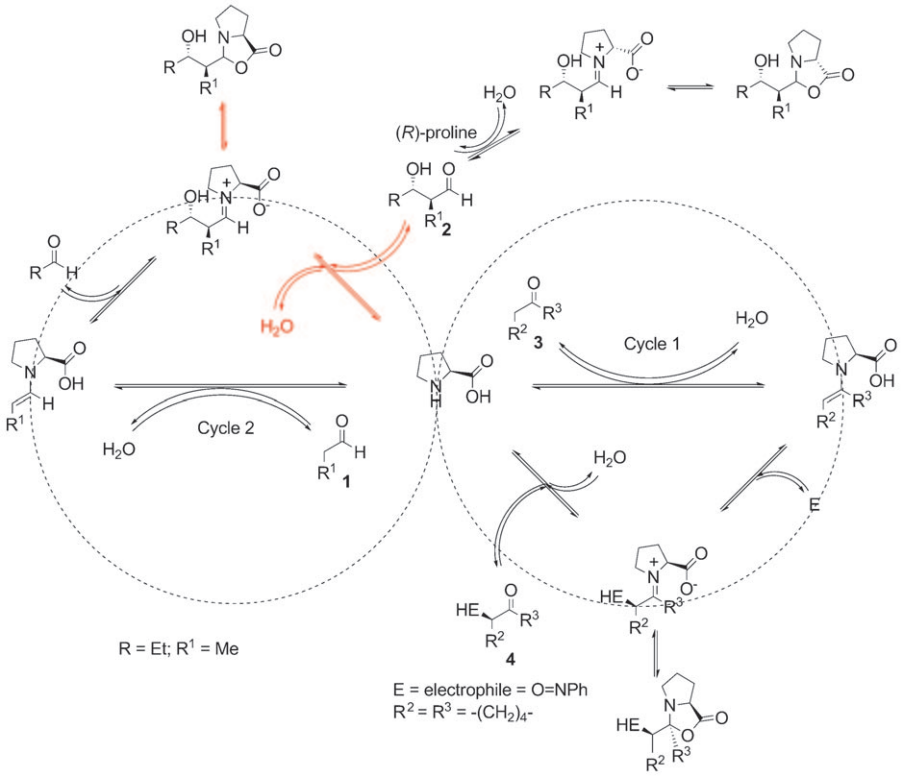
metric reactions by the addition of optically active β-hydroxy aldehydes (>95% *ee*) such as naturally occurring C-3 and C-4 sugars. This is due to sugar-assisted kinetic resolution of the amino acid catalysts by forming covalent oxazolidinone intermediates.[13] Recently, Tsogoeva and Mauksch reported asymmetric amplification due to recycling by denucleation and nonlinear autocatalytic crystal growth[2o] of an amino acid derivative under heterogeneous conditions.[15]

Based on the importance of nonlinear effects in asymmetric catalysis and its relevance to the origins of homochirality, we became curious if it is possible to generate them by creating a dynamic catalytic network[16] of an amino acid catalyst (Scheme 1). In fact, a dynamic catalytic network such as the one displayed in Scheme 1 may also be considered in investigations of nonlinear effects in proline-catalyzed asymmetric transformations under homogeneous conditions (cycle 1), in which, for example, self-aldolization of the donor aldehyde may be present (cycle 2). Herein, we report the generation of significant positive nonlinear effects in asymmetric amino acid catalysis under homogeneous conditions, which can be explained by the model for cooperative catalytic stereoselective pathways.



Scheme 1. Possible stereoselective catalytic networks of (*S*)-proline catalysis under homogeneous reaction conditions. The green pathway is possible when scalemic proline is used as catalyst.

The generally postulated catalytic mechanism for the (*S*)-proline-catalyzed enantioselective additions of ketones or aldehydes to different electrophiles involves iminium, enamine and oxazolidinone intermediates (Scheme 1, cycle 1).[17] The main consensus is that the enantioselective C–C or C–X (X = hetero atom) bond-forming step occurs via a metal-free six-membered transition state according to the List–Houk model involving one proline-derived enamine intermediate.[17,18] Seebach and Eschenmoser has challenged this theory by proposing a transition state involving the oxazolidinone intermediate, which can be formed between the amino acid molecule and the donor carbonyl during the initial enamine formation.[19] We envisioned that the addition of an achiral aldehyde **1** to the general catalytic cycle 1 would initiate and link catalytic cycle 2 to it (Scheme 1).[20,21] Simultaneously, the dynamic catalytic pathway involving the formation of stereoselective oxazolidinone intermediates between the catalyst and the chiral β-hydroxy aldehyde **2** from cycle 2 would be created (Scheme 1, red and green pathways).[13,22] Thus, the simple addition of an achiral aldehyde **1** would generate a dynamic interconnected catalytic stereoselective network. It should also be possible to determine whether this catalytic network can generate nonlinear effects in asymmetric amino acid catalysis. We decided to investigate the (*S*)-proline-catalyzed α-aminooxylation of cyclohexanone **3a** as the model reaction for the general catalytic cycle 1 using nitrosobenzene as the electrophile. The advantage of this transformation is that the C–O bond formation is fast and the reaction does not exhibit nonlinear effects under homogeneous conditions (Figure 1).[8] This is be-

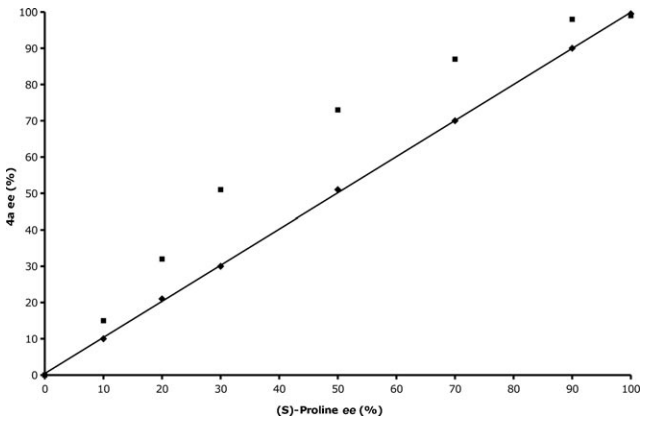
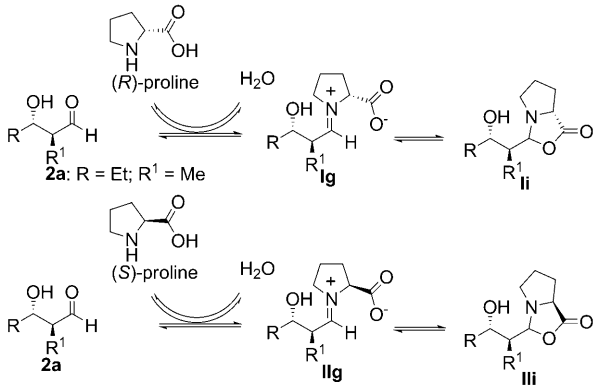
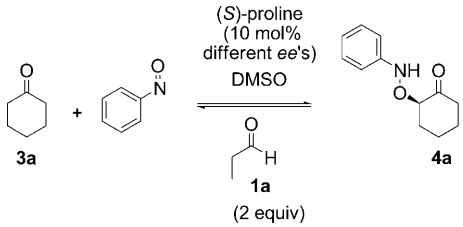


Figure 1. Relation between the enantiomeric excess of (*S*)-proline and that of the newly formed chiral ketone **4a** in the catalytic asymmetric aminooxylation of cyclohexanone **3a**. ■: Addition of aldehyde **2a**. ◆: no additive. The standard deviation for the *ee* values is ±0.5% and based on three separate experiments.



Scheme 2. The "reacted-free" equilibrium between the two enantiomers of proline and β-hydroxy aldehydes **2**. Products **2** can be obtained by (*S*)-proline catalysis.

cause the formation of the bicyclic oxazolidinone intermediate (Scheme 2, the blue pathway) obtained from the corresponding product **4a** and the proline catalyst is not preferred due to steric constrains and therefore cannot affect a reaction performed with a scalemic catalyst.[13,14] Thus, we have performed several α-aminooxylation reactions under homogeneous reaction conditions using (*S*)-proline (50% *ee*) as the catalyst and different achiral aldehydes **1** as additives. We found that the addition of propionaldehyde **1a** resulted in asymmetric amplification of product **4a** [Eq. (1), Figure 1].



(1)

Plotting the product *ee* of **4a** against the *ee* of the proline catalyst gave a significant positive nonlinear relationship (Figure 1).

Thus, the addition of aldehyde **1a** did initiate the formation of a catalytic network that synergistically created the asymmetric amplification of product **4a**, which normally exhibits a linear relationship. We also found that β-hydroxy aldehyde **2a** was formed (Scheme 1, cycle 2). In fact, the proline-catalyzed asymmetric dimerization of aldehyde **1a** exhibited nearly the same asymmetric amplification of **2a** as the one of **4a**. Moreover, high-resolution mass spectrometry and ^{1}H NMR analysis revealed the presence of oxazolidinone intermediates[17g] formed between **2a** and proline by means of the dynamic pathways marked red and green in Scheme 1. Notably, these pathways have the ability to affect the two enantiomers of the amino acid differently due to the inherent diastereomeric interactions with chiral aldehyde **2a** (Scheme 2). We did not observe any reaction between the aldehyde **1a** and nitrosobenzene under our reaction conditions supporting that the nonlinear effect was generated and transferred from catalytic cycle 2 to cycle 1 in Scheme 1.

To shed more light on "reacted-free" equilibrium for both (*R*)- and (*S*)-proline (Scheme 2) and on the origin of the nonlinear effect we performed density functional theory (DFT) calculations (Figure 2). The calculations were per-

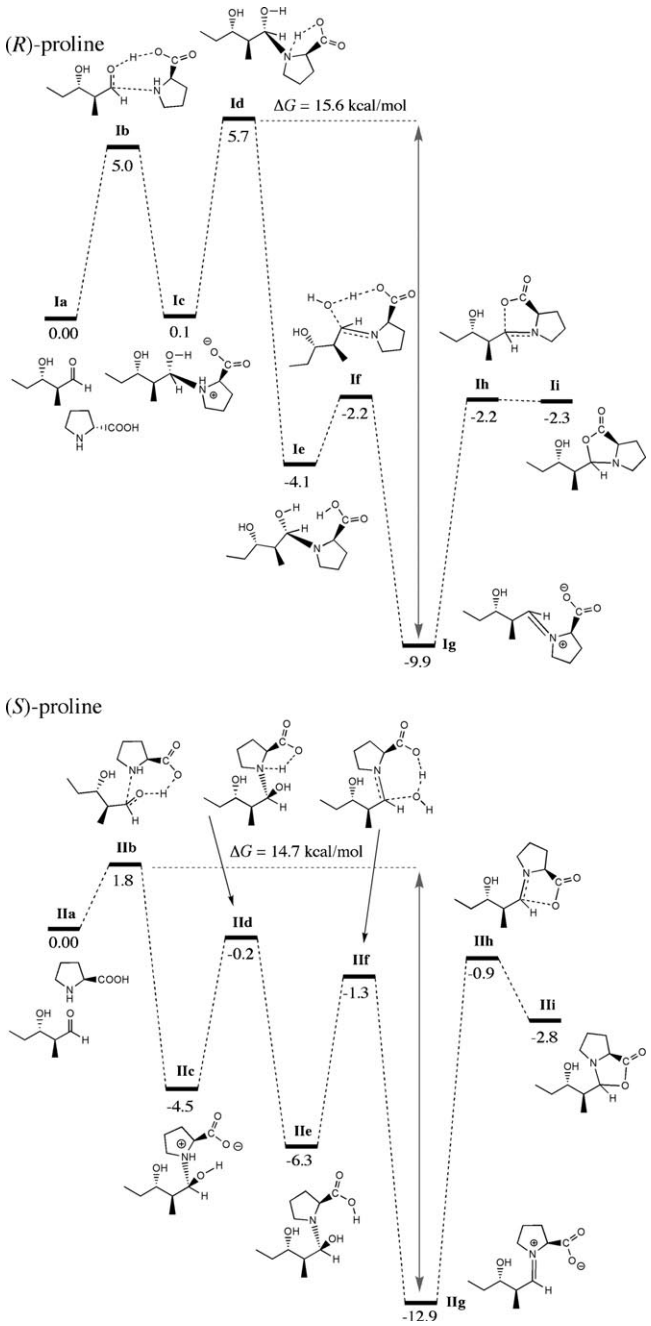
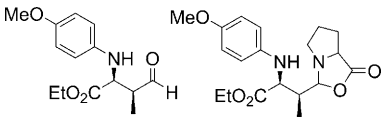


Figure 2. Energy profiles for the parallel reactions. Energies given in the graph are free energies (kcal mol^{-1}) calculated with B3LYP/6-311+G-(2d,2p) in DMSO. The labels on the energy profiles refer to the corresponding structures that can be found in the Supporting Information along with all the stationary structures.

formed by using the Gaussian 03[23] software package and the B3LYP functional.[24,25] Geometries were optimized with the 6-31G(d,p) basis set, and characterized with frequency calculations. Final energies were obtained with the larger basis set 6-311+G(2d,2p). The effect of solvation in DMSO was included by using a polarizable continuum model (IEF-PCM).[26] We have previously proposed that racemic proline is resolved by the dynamic equilibrium shown in Scheme 2 due to that (*R*)-proline reacts faster with **2a** and as a consequence less "free" (*R*)-proline would be accessible. Indeed, our calculations revealed that the initial barrier to form the proline–aldol intermediate **Ic** via concerted transition state **Ib**, in which both simultaneous C–N bond formation and proton transfer occur for (*R*)-proline, is larger relative to the formation of the (*S*)-proline-derived intermediate **IIc** via concerted transition state **IIb** (Figure 2). However, for both *R* and *S* enantiomers, the most stable intermediates **Ig** and **IIg**, respectively, are formed with barriers of 5.7 and 5.0 kcal mol^{-1}, respectively. The pathway of (*R*)-proline is initiated by a *Si*-facial attack on the carbonyl group of aldehyde **2a** via reactant **Ia**. This is opposite to the *Re*-facial attack of (*S*)-proline on the aldehyde group of **2a** via reactant **IIa** (Figure 2). Other attacks were also considered; however, only the most favored are shown here (see Supporting Information). The pathways of (*R*)- and (*S*)-proline are energetically different. For example, when (*R*)-proline attacks the bulky *Si*-face of aldehyde **2a**, the energies are higher relative to the reactant **Ia** during the initial hemiaminal bond formation. This is not the case for the *Re*-facial attack of (*S*)-proline on **2a**, even though the reactants **Ia** and **IIa** are close in energy. These energy differences between (*R*)- and (*S*)-proline result in different energy maxima on their energy profiles. Consequently, for (*R*)-proline the energy maximum **Id** occurs when the proton is transferred from the nitrogen of the proline moiety to its carboxyl group. In the case of (*S*)-proline, the highest energy on the potential energy surface is transition state **IIb**. The lowest energies in both pathways are the iminium intermediates **Ig** and **IIg**, respectively. The energy barriers are relative to the respective reactants **Ia** and **IIa**. However, for the purpose of comparing the reactivity between (*R*)- and (*S*)-proline the rate-determining states of the release of the amino acids are of interest. All intermediates and transition states can be found in the Supporting Information, as well as energies calculated at different levels. When comparing the Gibbs free-energy differences (ΔG) for the two reaction pathways it can be seen that the ΔG for (*R*)-proline is larger compared to (*S*)-proline. Moreover, as described vide supra both enantiomers of the amino acid readily enter their respective pathways. Thus, the major energy difference between the enantiomers of proline in the reaction with **2a** is in the reversible step. Notably, this energy difference $\Delta\Delta G$ between the *R* and *S* enantiomer was 0.9 kcal, which is in accordance with the experimental result obtained for the kinetic resolution of racemic proline by nearly enantiomerically pure **2a** (66% *ee* of (*S*)-proline). Our calculations together with the experimental results show that the positive nonlinear effects created from the catalytic network were due to the unproductive "reacted-free" equilibrium of the enantiomers of the amino acid with chiral aldehyde **2a**, in which (*R*)-proline is present a longer time. As a result an excess of non-bound (*S*)-proline ($ee > ee_{initial}$) was able to catalyze the parallel reaction pathways creating asymmetric amplification of the corresponding products.

Our results show that observation of nonlinear effects in amino acid catalysis can be used for giving mechanistic information on the influence of the different interconnected catalytic pathways during proline-catalyzed stereoselective reactions between aldehydes or ketones and different electrophiles (Scheme 1). For example, it explains the absence of nonlinear effects as for the proline-catalyzed α-aminooxylation of **3a** (Figure 1). In this case, the general cycle 1 in Scheme 1 was the fastest pathway since oxazolidinone formation and self-aldol reactions are very slow due to steric effects. The mechanistic network displayed in Scheme 1 should also be considered for the proline-catalyzed Mannich reaction between propionaldehyde **1a** and *p*-methoxyphenyl (PMP)-protected α-iminoglyoxylate (Scheme 1, **2a**=**3b**: R^3=H; E=PMPNH=CHCO$_2$Et).[14]

In this case, both the "reacted-free" equilibrium between the enantiomers of proline and the chiral aldehyde **2a** or **4b** via oxazolidinone intermediates such as **IIi** and **IIIi**, respectively, must have cooperatively contributed to the asymmetric amplification of the corresponding product **4b** according to Scheme 1 (red, green, and blue pathways).[27] The proline-



4b **IIIi**

catalyzed reaction of propionaldehyde **2a** to other PMP-protected imines does not always exhibit nonlinear effects under homogeneous conditions.[28] This study suggests that for these transformations the catalytic cycle 1 of Scheme 1 must have been the fastest pathway and as a consequence the dynamic "reacted-free" equilibrium between the corresponding chiral products and the amino acid catalyst does not have time to affect the whole network. This is in accordance with kinetic measurements for these reactions, which determined the Mannich reaction to be significantly faster than the aldol reaction.[29]

In summary, the generation of positive nonlinear effects in asymmetric amino acid catalysis by a novel cooperative catalytic network has been demonstrated. The addition of an achiral aldehyde generated the multiple interconnected stereoselective catalytic network. DFT calculations together with experimental results showed that the asymmetric amplification has its origin in the unproductive "reacted-free" equilibrium of the enantiomers of the amino acid with the corresponding chiral aldehyde products, in which (*R*)-proline is present for a longer time as compared to (*S*)-proline.

Moreover, important mechanistic information can be gathered on the amino acid catalyzed networks using nonlinear effects studies. The strategy of addition of achiral aldehydes to amino acid catalyzed transformations can also be synthetically useful for reactions performed without enantiomerically pure amino acid catalysts (asymmetric amplification). The nonlinear effects generated by the possible inherent catalytic network of asymmetric amino acid catalysis may be of relevance for the evolution of homochirality since they provide both a model and mechanism for the asymmetric amplification of organic molecules such as sugars and amino acids.

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[1] a) W. A. Bonner, *Origins Life Evol. Biospheres* **1991**, *21*, 59; b) J. L. Bada, *Nature* **1995**, *374*, 594; c) S. F. Mason, *Nature* **1985**, *314*, 400.

[2] For selected examples see: a) W. A. Bonner, *Origins Life Evol. Biospheres* **1994**, *24*, 63; b) J. L. Bada, *Origins Life Evol. Biospheres* **1996**, *26*, 518; c) N. Lahav, *Biogenesis Theories of Life's Origin*, Oxford University Press, New York: **1999**, p. 257; d) F. C. Frank, *Biochem. Biophys. Acta* **1953**, *11*, 459; e) J. S. Siegel, *Chirality* **1998**, *10*, 24; f) J. S. Siegel, *Nature* **2002**, *419*, 346; g) S. L. Miller, The Origin of Homochirality in Life, Santa Monica, **1995**; h) J. M. Ribó, J. M. Crusats, F. Sagues, J. Claret, R. Rubires, *Science* **2001**, *292*, 2063–2066; i) M. Mauksch, S. B. Tsogoeva, *ChemPhysChem* **2008**, *9*, 2359; j) D. G. Blackmond, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5732; k) J. Cronin, S. Pizzarello, *Science* **1997**, *275*, 95; l) S. Pizzarello, *Acc. Chem. Res.* **2006**, *39*, 231; m) A. Córdova, *AIP Conf. Proc.* **2008**, *979*, 47; n) R. Breslow, Z. L. Cheng, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 9144; o) C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504.

[3] a) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353. For an excellent review see: b) T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem.* **2009**, *121*, 464; *Angew. Chem. Int. Ed.* **2009**, *48*, 456.

[4] a) K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767; b) K. Soai, T. Kawasaki, *Chirality* **2006**, *18*, 469; c) T. Kawasaki, Y. Matsumura, T. Tsutsumi, K. Suzuki, M. Ito, K. Soai, Science 2009, 324, 492.

[5] Z. G. Hajos, D. G. Parrish, *J. Org. Chem.* **1974**, *39*, 1615, and references therein.

[6] S. Hannesian, V. Pham, *Org. Lett.* **2000**, *2*, 3737.

[7] S. P. Mathew, H. Iwamura, D. Blackmond, Angew. Chem. 2004, 116, 3379; Angew. Chem. Int. Ed. 2004, 43, 3317.

[8] A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673.

[9] Y. Hayashi, M. Matsuzawa, J. Yamaguchi, S. Yonehara, Y. Matsumoto, M. Shoji, D. Hashizume, H. Koshino, *Angew. Chem.* **2006**, *118*, 4709; *Angew. Chem. Int. Ed.* **2006**, *45*, 4593.

[10] a) M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells, Jr., U. Pandya, A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*, 621; b) M. Klussmann, A. J. P. White, A. Armstrong, D. G. Blackmond, *Angew. Chem.* **2006**, *118*, 8153; *Angew. Chem. Int. Ed.* **2006**, *45*, 7985.

[11] R. Breslow, M. S. Levine, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 12979.

[12] A. Córdova, M. Engqvist, I. Ibrahem, J. Casas, H. Sundén, *Chem. Commun.* **2005**, 2047.

[13] A. Córdova, H. Sundén, Y. Xu, I. Ibrahem, W. Zou, M. Engqvist, *Chem. Eur. J.* **2006**, *12*, 5446.

[14] I. Ibrahem, H. Sundén, P. Dziedzic, R. Rios, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1868.

[15] a) S. B. Tsogoeva, S. Wei, M. Freund, M. Mauksch, *Angew. Chem.* **2009**, *121*, 598; *Angew. Chem. Int. Ed.* **2009**, *48*, 590. For a review, see: W. L. Noorduin, E. Vlieg, R. M. Kellogg, B. Kaptein *Angew. Chem.* **2009**, *121*, 9778; *Angew. Chem. Int. Ed.* **2009**, *48*, 9600.

[16] For a review on dynamic networks in chemistry, see: a) R. F. Ludlow, S. Otto, *Chem. Soc. Rev.* **2008**, *37*, 101; in prebiotic chemistry, see: b) J. W. Szostak, *Nature* **2009**, *459*, 171.

[17] For selected reviews, see: a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2004**; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; c) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; for selected papers on the enamine formation, see: d) C. Marquez, J. O. Metzger, *Chem. Commun.* **2006**, 1539; e) S. Lakhdar, T. Tokuyasu, H. Mayr, *Angew. Chem.* **2008**, *120*, 8851; *Angew. Chem. Int. Ed.* **2008**, *47*, 8723; f) S. Lakhdar, R. Appel, H. Mayr, *Angew. Chem.* **2009**, *121*, 5134–5137; *Angew. Chem. Int. Ed.* **2009**, *48*, 5034; g) M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem.* **2010**, *122*, 5117–5123; *Angew. Chem. Int. Ed.* **2010**, *49*; h) U. Groselj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Ushimaru, *Helv. Chim. Acta* **2009**, *92*, 1225.

[18] a) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16; b) C. Alleman, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558, and references therein; c) K. N. Rankin, J. W. Gauld, R. J. Boyd, *J. Phys. Chem. A* **2002**, *106*, 5155.

[19] D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurtwala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425.

[20] For a review on the pioneering use of achiral additives or ligands in asymmetric catalysis, see: P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297–3344.

[21] For the first use of additives to improve proline-catalyzed reactions by Hannesian see: reference [6]. See also selected references: a) A. I. Nyberg, A. Usano, P. M. Pihko, *Synlett* **2004**, 1891; b) X. Companyó, G. Valero, L. Crovetto, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 6564; c) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem. Int. Ed.* **2008**, *47*, 10187; d) N. Zotova, A. Moran, A. Armstrong, D. G. Blackmond, *Adv. Synth. Catal.* **2009**, *351*, 2765; e) D. G. Blackmond, A. Moran, M. Hughes, A. Armstrong, *J. Am. Chem. Soc.* **2010**, *132*, 7598; f) I. Ibrahem and A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3363; g) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839; h) D. E. Ward, V. Jheengut, *Tetrahedron Lett.* **2004**, *45*, 8347.

[22] A. Córdova, I. Ibrahem, J. Casas, H. Sundén, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *11*, 4772.

[23] Gaussian 03, Revision D.01. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. Millam, M. S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A.Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski,

B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

[24] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.

[25] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.

[26] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999.

[27] HRMS analysis determined the presence of oxazolidinone intermediates **III i** and **II i**, respectively, to be present in this reaction (see ref. [14]). Moreover, the addition of aldehyde product **4b** (99% *ee*) to the racemic proline-catalyzed α-aminooxylation of ketone **3a** gave **4a** with 19% *ee*. In comparison, the addition of aldehyde **2a** (99% *ee*) enabled racemic proline to catalyze the α-aminooxylation of ketone **3a** to give **4a** with 66% *ee* (see ref. [13]).

[28] A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1957.

[29] Y. Hayashi, T. Urushima, M. Shoji, T. Uchimaru, I. Shiina, *Adv. Synth. Catal.* **2005**, *347*, 1595.

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