DOI: 10.1002/adsc.200700110

Asymmetric Amplification in the Amino Acid-Catalyzed Synthesis of Amino Acid Derivatives

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Received: February 27, 2007

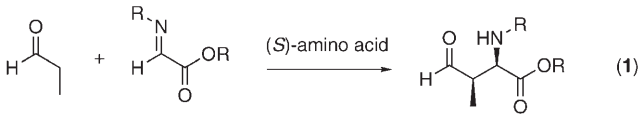
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The origins of biological homochirality have intrigued researchers since Pasteur's discovery of the optical activity of biomolecules. Herein, we present the first example of asymmetric amplification in the amino acid-catalyzed enantioselective synthesis of amino acid derivatives that provides support for a synergistic model for the evolution of homochirality by amino acid catalysis.

Keywords: amino acids; asymmetric amplification; homochirality; kinetic resolution

The origins of biological homochirality have fascinated researchers since Pasteur's discovery of the optical activity of biomolecules.[1] Frank proposed that evolution of high asymmetry from a small imbalance of enantiomers could be achieved by a combination of autocatalytic and inhibition processes.[2] In this context, Soai and co-workers were first able to demonstrate experimentally that a product of certain chirality is generated faster because of a non-linear forward reaction step in zinc-promoted additions.[3] Recently, significant non-linear effects have been observed in purely organocatalytic reactions involving amino acids or peptides as catalysts.[4,5] The works of Hayashi et al.,[6a] Blackmond et al.[6b,c] and Breslow[6e] imply the disproportionation of enantiomers between solution phase and solid phase without overall amplification of *ee*.[6] These phase transition effects are not related to chemical reactions, but rather to solubility equilibria. Moreover, asymmetric amplification is present in the amino acid-catalyzed formation of sugars under homogeneous reaction conditions.[5d,e] These results have led to speculations of amino acid catalysis as a route to the origins of homochirality.

The Mannich reaction is an important reaction in organic synthesis.[7] In this context, the direct catalytic Mannich-type reaction is a very useful transformation for the asymmetric synthesis of functional amino acid derivatives with high stereoselectivity.[7f,8] One of these reactions is the amino acid-catalyzed asymmetric synthesis of amino acid derivatives [Eq. (1)].[8d]



(1)

Herein, we show the first example of asymmetric amplification in the amino acid-catalyzed enantioselective synthesis of amino acid derivatives giving precedence for amino acid catalysis as a route for the origins of homochirality.

During our studies of the amino acid-catalyzed reaction between propionaldehyde **1a** and *N*-*p*-methoxyphenyl (PMP) protected α-imino glyoxylate **2** using different levels of enantioenriched (*S*)-proline as the catalyst, we found a significant asymmetric amplification of the enantiomeric excess in the formation of the corresponding amino acid derivative **3a** [Eq. (2), Figure 1].

(2)

To the best of our knowledge this is the first report of a positive non-linear effect in an amino acid-catalyzed Mannich-type reaction. We have now investigated[5e] whether the enantioenriched amino acid prod-

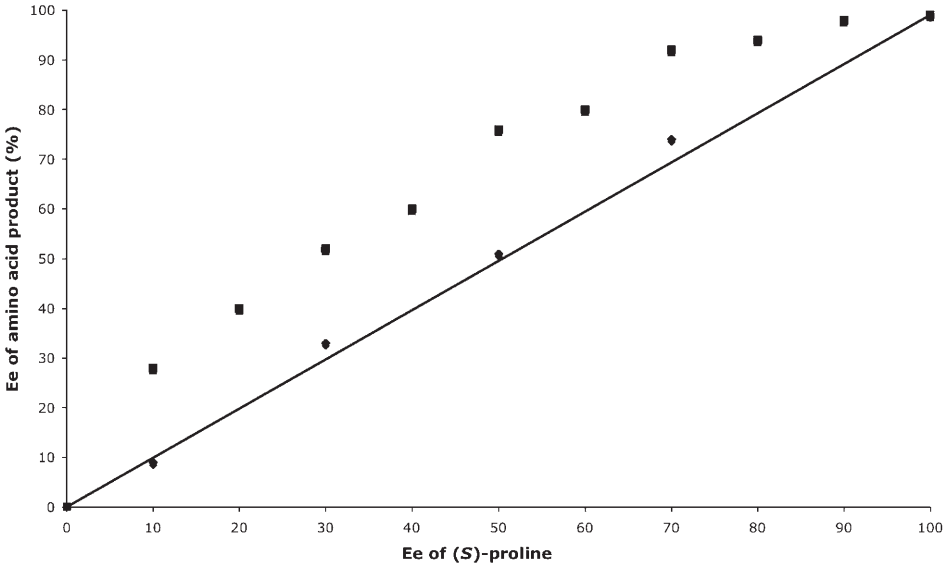


Figure 1. Relation between the enantiomeric excess of (*S*)-proline and that of the newly formed amino acid derivative **3a** (■) and **3b** (◆) in the catalytic asymmetric amino acid synthesis using propionaldehyde **1a** and cyclohexanone **1b** as donors, respectively. The standard deviation for the *ee* values is ±0.5% and based on three separate experiments.

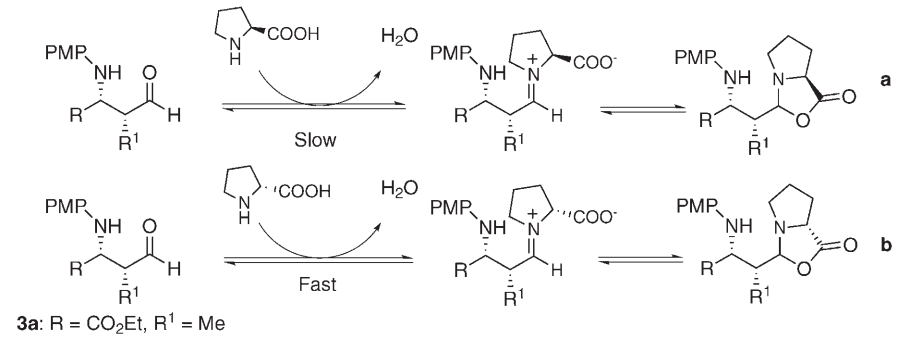
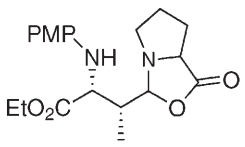


Figure 2. Oxazolidinone formation between **3a** and (*S*)-proline (**a**) and (*R*)-proline (**b**), respectively.

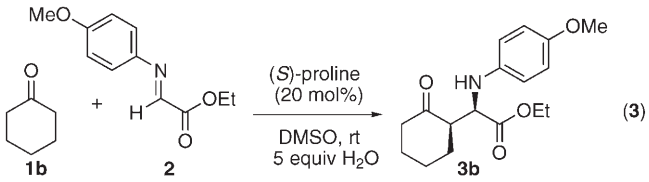
uct **3a** was involved in the mechanism of the asymmetric amplification.

According to this scenario, the amino acid derivative **3a** derived by amino acid catalysis would react at different rates with the (*S*)- or (*R*)-amino acid and consequently "auto"-kinetically resolve the amino acid catalyst by forming covalent intermediates such as oxazolidinones giving rise to amplification of the enantiomeric excess in the next catalytic cycle (Figure 2). This would also be in line with the supposition that a single proline molecule takes part in the formation of the amino acid derivative **3a** according to the proposed mechanisms and transition states of previously reported proline-catalyzed enantioselective Mannich reactions.[9] Moreover, Seebach and Eschenmoser recently proposed in an elegant study that the oxazolidinones formed in proline-catalyzed reactions may also have a pivotal role during the catalytic cycle and not only be "dead ends".[10] This novel mechanistic suggestion additionally supports our theory that the difference in reactivity due to diastereoselective interactions between the (*S*)- and (*R*)-amino acid with the chiral (*S*)-amino acid product **3a** in the formation of covalent chiral product intermediates such as oxazolidinones gives rise to amplification of the enantiomeric excess. In order to support our hypothesis, we performed a series of experiments. High-resolution mass spectroscopic analyses of the proline-catalyzed reactions between **1a** and **2** established the formation of an oxazolidinone intermediate **I** between the amino acid product **3a** and the proline catalysts (Eq. [2]).[11]



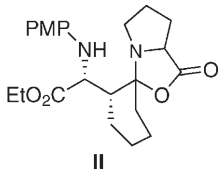
I

We also investigated the relation between the enantiomeric excess of (*S*)-proline and that of the newly formed amino acid derivative **3b** in the catalytic asymmetric Mannich-type reaction between cyclohexanone **1b** and **2** [Eq. (3), Figure 1].

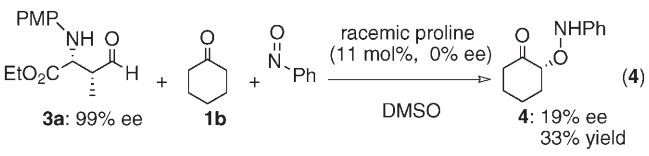


(3)

The reaction showed a linear relationship between the *ee* of (*S*)-proline and the *ee* of the amino acid derivative **3b**. Moreover, high-resolution mass spectroscopic analyses of the reaction between **1a** and **2** did not detect the formation of an oxazolidinone intermediate **II**.



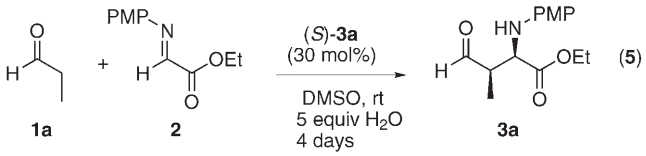
This suggests that the amino acid derivative **3b** with a keto group did not react with the catalyst to form the corresponding bicyclic oxazolidinone **II** due to possible steric constraints. In comparison, amino acid derivative **3a** with a more reactive aldehyde moiety will form the corresponding oxazolidinone **I** with less steric interactions under the set reaction conditions. Moreover, we also investigated the *ee* of (*S*)-proline (6 mg) in wet DMSO (1.09 mL) as function of the *ee* of the initially added solid (*S*)-proline after 16–18 h of stirring and observed a negative non-linear effect and lower enantiomeric excess of the (*S*)-proline in solution (see Supporting Information).[12] Thus, no phase behaviour of the amino acid catalysts was responsible for the positive non-linear effects observed in the amino acid-catalyzed synthesis of amino acid derivatives under our reaction conditions.[6c,12] We also investigated whether the chiral amino acid product **3a** could be used to kinetically resolve proline in a parallel transformation. The racemic proline-catalyzed α-aminoxylation of cyclohexanone **1b** that furnishes the corresponding racemic α-aminoxylated ketone **4** was chosen as the model reaction.[5e] Hence, we added amino acid derivative **3a** with 99% *ee* (0.7 mmol) that had been obtained by (*S*)-proline catalysis, to a mixture of racemic proline (11 mol%) in DMSO (0.4 mL) [Eq. (4)].



(4)

After 24 hour of stirring, cyclohexanone **1b** (0.7 mmol) was added to the homogeneous solution. Next, nitrosobenzene (0.3 mmol) in DMSO (0.4 mL) was slowly added by a syringe pump to the reaction mixture. Notably, product (2*R*)-**4** was isolated in 33% yield with 19% *ee* after 2 h. Moreover, product **4** was not formed without the addition of a catalytic amount of racemic proline under our reaction conditions. The presence of oxazolidinone **I**, formed by the reaction between amino acid **3a** and the proline catalysts, in this reaction was established by high-resolution mass spectroscopic analysis. Consequently, amino acid derivative **3a** can be used for the *in situ* kinetic resolution of racemic proline catalyst according to Figure 2.

The possibility of an autocatalytic asymmetric amplification in the catalytic enantioselective synthesis of amino acid derivatives **3** was also investigated [Eq. (5), Supporting Information].[13,14]

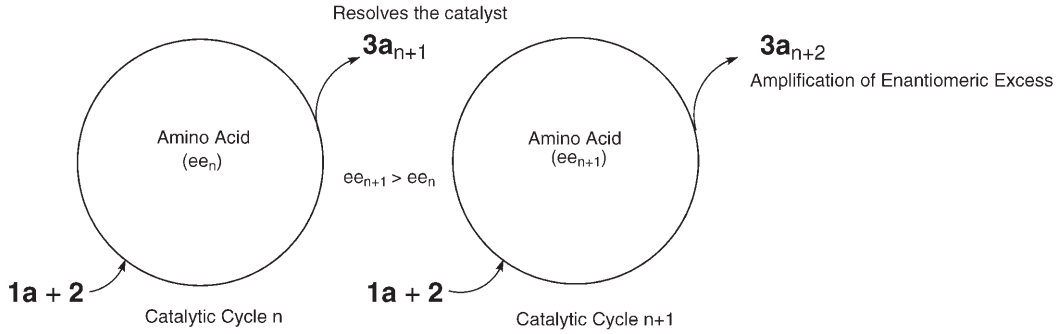


(5)

For instance, propionaldehyde **1a** was reacted with imine **2** in the presence of a catalytic amount (30 mol%, 20 mg) of amino acid derivative **3a** with 52% *ee* in wet DMSO (1.02 mL). The reaction was quenched after 4 days and **3a** was isolated in <1% yield after subtracting the initially added 30 mol% **3a** with an *ee* of 40% (the measured *ee* is for the total isolated product). The control reaction without an initial addition of a catalytic amount of chiral amino acid derivative **3a** gave racemic product **3a** in 6% yield. This product was possibly catalyzed by *p*-anisidine formed from minor hydrolysis of imine **2**. Moreover, product **3a** (20 mg) did not racemize in wet DMSO (1.02 mL) under 4 days of stirring and was recovered in 83% yield with 99% *ee*. Thus, no significant asymmetric amplification or autocatalysis had occurred in the reaction shown in Eq. (5).

Based on our experiments, we propose a synergistic mechanism between the amino acid-derived products and their amino acid catalyst to be due to the asymmetric amplification in the amino acid-catalyzed synthesis of amino acid derivatives (Scheme 1).

Thus, the enantioenriched (*S*)-amino acid product **3a** reacted faster with (*R*)-proline as compared to (*S*)-proline due to plausible different diastereoselective



Scheme 1. The synergistic model for the asymmetric amplification in the amino acid catalyzed asymmetric formation of amino acid derivative **3a**.

interactions between the β-amino group of **3a** and the amino acid, which increased the concentration of free (*S*)-proline in the solution and gave rise to amplification of the enantiomeric excess of **3a** in the next catalytic cycle. This is also in accordance with the origins of asymmetric amplification in the amino acid-catalyzed enantioselective sugar formation where kinetic data clearly show that the (*S*)-proline-derived β-hydroxy aldehyde product reacts faster with (*R*)-proline as compared to (*S*)-proline.[5e] Hence, the intrinsic ability of amino acid-derived products to kinetically resolve their amino acid catalyst, which leads to amplification of the enantiomeric excess in their own formation, provides additional support for our original synergistic model for the evolution of asymmetry of biomolecules by organic catalysis.

In summary, we have shown that product-assisted kinetic resolution of an amino acid catalyst by covalent intermediates is the origin of the significant amplification of enantiomeric excess in the amino acid-catalyzed formation of amino acid derivatives. This is also the first example of observations of non-linear effects in organocatalytic Mannich reactions. The inherent ability of simple amino acid products derived from amino acid catalysis to resolve its amino acid catalyst and thereby giving rise to significant asymmetric amplification gives further support for a possible model for the origins of homochirality *via* amino acid catalysis. Further mechanistic studies investigating the role of the different chiral oxazolidinone intermediates and molecular modelling are ongoing in our laboratory.

Experimental Section

Typical Procedure for the Amino Acid-Catalyzed Addition of Aldehydes to Imine 2

To a round-bottom flask charged with proline with a specific *ee* value (0.05 mmol, 20 mol%) were added DMSO (1 mL), propionaldehyde (0.75 mmol), H_2O (1.25 mmol) and imine **2** (0.25 mmol, 1.0 equiv) sequentially. The reaction was vigorously stirred at room temperature for 18 h. Next, the crude was purified by silica gel column chromatography (toluene:AcOEt, 6:1) to afford the final compound **3a**.

Acknowledgements

We gratefully acknowledge the Swedish National Research Council, Wenner-Gren Foundation, Carl-Trygger Foundation and Lars-Hierta Foundation for financial support. We thank Prof. Jan-E. Bäckvall for valuable discussions.

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