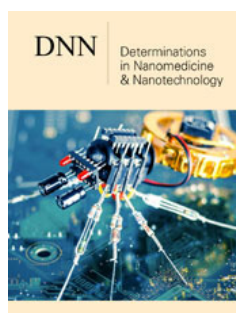


# Micelle-Stabilized Transition State in the Aqueous Asymmetric Organocatalysis

András A Gurka\*

Department of Organic Chemistry, Hungary



## Abstract

Micelle-stabilized transition state with direct participation of a water molecule is proposed to explain the explored dual stereocontrol in the asymmetric aldol reactions of acetone with different aldehydes catalyzed by amphiphilic proline derivatives in aqueous media. According to the proposed model a water molecule stimulates the concerted bond reorganization in the transition state. The proposed mechanism has universal character, and it is applicable to all enamine-based asymmetric organocatalytic reactions carried out not only in aqueous, but in organic media as well.

**Keywords:** Micelle; Amphiphilic proline derivative; Six-membered ring; Dual stereocontrol; Enantioselectivity

## Results and Discussion

To realize dual stereocontrol by varying only achiral components, asymmetric aldol reactions between acetone and different aldehydes catalyzed by amphiphilic hydroxyproline derivatives in organic and aqueous media were carried out. In the reactions commercially available catalysts (L-proline, L-hydroxyproline, O-benzyl-Hyp-HCl) and catalysts newly synthesized by methods known from the literature (O-(4-tert-butylbenzoyl)-Hyp, O-benzoyl-Hyp, O-caproyl-Hyp, O-myristoyl-Hyp, O-(4-hexylbenzoyl)-Hyp, O-1-naphthoyl-Hyp, O-2-naphthoyl-Hyp, O-(1-naphthylacetyl)-Hyp, O-(4-tert-butylphenylacetyl)-Hyp, O-1-naphthoyl-Hyp-methyl-ester, O-benzyl-Hyp) were used. The hydroxyproline derivatives were synthesized by the following method (Figure 1); [1]. The identification and purity control of the synthesized hydroxyproline derivative catalysts were carried out by melting point measurement and on the basis of <sup>1</sup>H NMR, <sup>13</sup>C NMR and ESI-MS spectra. Studying the known and the newly synthesized amphiphilic L-hydroxyproline derivative catalysts used in the asymmetric aldol reactions between acetone and different aldehydes, it was shown that for prevention of the phase separation in aqueous media it is required to provide such conditions where reagents with different water affinity and the hydrophilic active center of amino acid derivative catalyst getting close to each other. To suit these conditions, it is needed to establish a proper interface by micelle formation, which is supported by the amphiphilic character of the amino acid derivative catalyst. Moreover, for improving the efficiency of the micelle-forming catalyst it is important to reduce the water activity using brine with adequate salt concentration, thus stabilizing the interface in case of addition of micelle-forming nonionic surfactant, as well [1]. As a result, it was found that in the solution of an acidic salt (ammonium chloride) in all cases the (R) aldol products were formed in excess, similar to that in organic solvents, with high selectivities and enantioselectivities and moderate conversions. Contrary to this, in the solution of basic salts (alkali metal carboxylates, quaternary ammonium carboxylate) in most of the aldol-reactions the (S) products were formed in excess with excellent conversions and selectivities and with low to moderate enantioselectivities [1,2].

\*Corresponding author: András A Gurka, Department of Organic Chemistry, Hungary

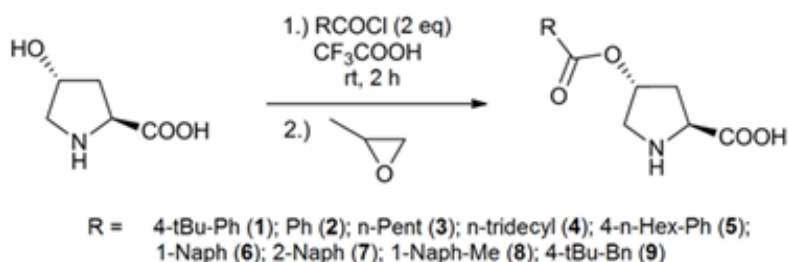
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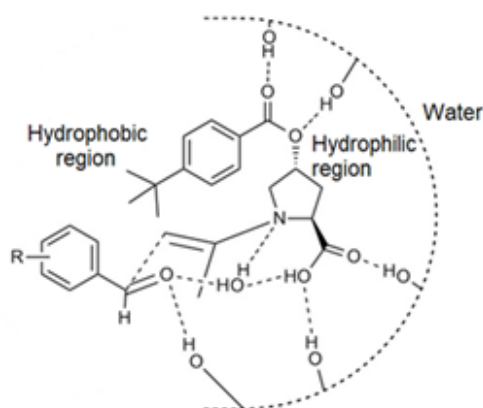
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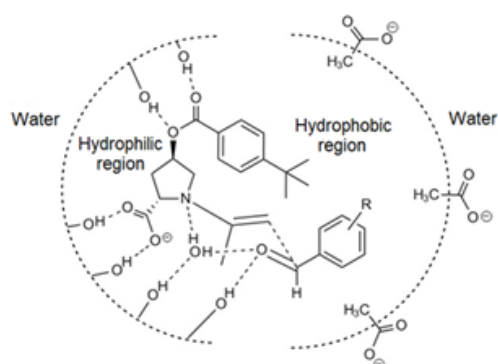
**Figure 1:** Method of synthesis of L-hydroxyproline derivative catalysts.

The explored phenomenon is giving the possibility to control the stereoselectivity of asymmetric aldol reactions catalyzed by L-amino acid derivatives in aqueous media and it was explained with different structures of micelle-stabilized transition state described as a metal-free version of the Zimmerman-Traxler model with explicit participation of a water molecule [1]:

- i. Under acidic conditions, as in organic media the carboxylic proton spatially directs the aldehyde through H-bonding so that the re-face of the aldehyde is attacked by the enamine, thus providing stereocontrol for the reaction ((R) product is formed in excess) (Figure 2).



**Figure 2:** Transition state of asymmetric aldol reaction carried out in the solution of acidic salt.



**Figure 3:** Transition state of asymmetric aldol reaction carried out in the solution of basic salt.

- ii. In the solution of basic salts, when the catalyst is lacking the acidic proton and when the carboxylate group of the amino acid, together with the carboxylate of salt, acts mainly as a micelle stabilizer, the Si-face of the aldehyde may be more easily attacked by the enamine, resulting in formation of the opposite enantiomer ((S) product is formed in excess) (Figure 3); [1,2].

Under neutral conditions, where the proline (derivative) catalyst is predominantly zwitterionic, the lone electron pair of the explicit water molecule is attached by the ammonium proton, and only one proton of water molecule will be transferred in the transition state [3]. Being suitable to explain dual stereocontrol, the proposed mechanism has universal character and can be applied to all enamine-based asymmetric organocatalytic reactions carried out not only in aqueous, but in organic media as well, because the initial step of catalytic cycle, which involves the formation of an enamine from the carbonyl compound and proline (derivative), liberates one water molecule [4]. The evidence of the universal character of the proposed mechanism and its applicability to all enamine-based asymmetric organocatalytic reactions is the observed inversion of enantioselectivity in the L-hydroxyproline derivative-catalyzed asymmetric  $\alpha$ -amination reaction stimulated by changing the pH of aqueous solution [5], where the different transition states and therefore the stereochemical outcome of the reaction can be easily explained with the proposed mechanism.

## References

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3. In the concentrated solution of neutral salt (NaCl) (S) product is formed in excess.
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