Stereocontrol in asymmetric aldol reactions catalyzed by L-amino acid derivatives and immobilized oligopeptides

Summary of Ph.D. Thesis

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1. INTRODUCTION AND AIMS

The effect of enantiomers of chiral drug molecules on biological targets may be very different. In some cases this difference means “only” difference in activity, but often one of the enantiomers is health-giving, while the other one can be inactive or even toxic. Therefore, in the last decades enantioselective synthesis became an invaluable tool of drug design both in academic research and pharmaceutical industry.

One of the mostly applied stereoselective C-C-bond-formation reactions in asymmetric synthesis is the enantioselective aldol reaction. The first intermolecular asymmetric aldol reaction catalyzed by a small organic molecule (organocatalyst) was described by List and co-workers in 2000. After this breakthrough, major research efforts have been focused on this system to study the effect of reaction parameters and to clarify the mechanism of the reaction. According to this, the nature and the structure of organocatalyst, the reaction media, the reaction conditions and the effect of additives have been studied. Parallel efforts have also clarified the mechanism of the amino acid- or amino acid derivative-catalyzed intermolecular aldol reaction: the accepted mechanism is the enamine mechanism involving enamine formation or carbonyl addition as rate-limiting step. As a consequence of extensive investigations, asymmetric organocatalysis and especially the enantioselective aldol reaction have become a reliably applicable tool in the field of asymmetric syntheses.

The selective production of both enantiomers of a chiral molecule is not an easy challenge because traditionally most of the asymmetric approaches to the synthesis of enantiopure compounds are restricted to only one enantiomer. This limitation could be overcome when both enantiomers of the chiral catalysts are available. In most cases a given enantiomer is produced with a well-designed synthetic chiral catalyst, while obtaining the other enantiomer requires the synthesis of the catalyst with opposite chirality. This latter process can be laborious and expensive, especially for the catalysts with complex structure.

To avoid the selective production of each enantiomer of chiral catalyst, in the last years using catalysts from a single chiral source to access both enantiomers of a product in an enantiodivergent fashion with changing only achiral parameters (e.g. type of solvent, temperature, achiral additives, etc.) has become a major concept.

In the classical organic synthesis water was traditionally considered as a contaminant from a point of view of reaction propagation, therefore the first step was to dry the reagents, solvents and glassware thoroughly. Despite the fact that from the early 1980’s significant progress has been made in the field of organic chemistry in aqueous media, up to now in the field of chiral syntheses organic solvents are used as a reaction media in most cases. At the same time, with respect to environmental concerns, safety and cost, water can be considered as an ideal solvent. Furthermore, water as a component can influence the reaction outcome depending on its concentration and on the nature of the used chiral catalyst (through hydrogen bonds and other polar interactions between catalyst, reagents and additives). Because of these beneficial properties the use of water as a solvent and additive is increasingly considered. Therefore, the use of water in

asymmetric organocatalysis and especially in the field of asymmetric aldol reactions has great actuality.

Asymmetric syntheses using chiral organocatalysts often lead to the formation of important building blocks with high optical purity, which can be used in pharmaceutical industry in the production of active drugs. A disadvantage of these catalysts is their low efficiency, therefore, relatively high amount of catalyst (10-30 mol %) is needed to obtain reasonable yields. Hence, from the point of view of industrial feasibility of chiral synthesis and catalyst reusability, the application of heterogeneous catalysts in a continuous-flow operating mode is seriously considered in industrial context.

Taking into account the fundamental challenges in the field of organocatalysis, my aims were:

- to realize stereocontrol in the asymmetric aldol reactions catalyzed by L-amino acid derivatives in aqueous media by varying only achiral components;
- to study the asymmetric aldol reactions catalyzed by polystyrene resin supported immobilized L-proline, proline and other amino acid containing di- and tripeptides in a continuous-flow fixed-bed reactor system, to investigate the effect of achiral additives on stereochemistry of aldol products;
- to clarify the mechanism of inversion of enantioselectivity observed in the asymmetric aldol reactions catalyzed by L-amino acid derivatives and immobilized oligopeptides.

2. APPLIED MATERIALS AND METHODS

In my work asymmetric aldol reactions between acetone and different aldehydes have been studied (Figure 1).

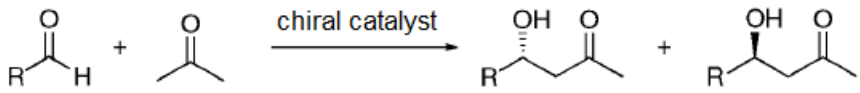
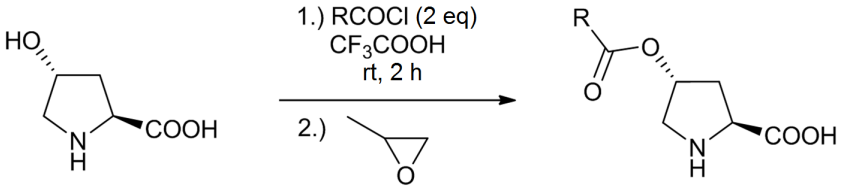


Figure 1

Asymmetric aldol reactions between acetone and different aldehydes catalyzed by hydroxyproline derivatives in organic and aqueous media were carried out in batch reactor. In the reactions that are conducted in aqueous media the acidic conditions were provided by ammonium chloride solution, while the basic conditions were reached using alkali metal- or quaternary ammonium carboxylate salts.

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-esther, *O*-benzyl-Hyp) were used. The hydroxyproline derivatives were synthesized by the following method (Figure 2):



R = 4-tBu-Ph (**1**); Ph (**2**); n-Pent (**3**); n-tridecyl (**4**); 4-n-Hex-Ph (**5**); 1-Naph (**6**); 2-Naph (**7**); 1-Naph-Me (**8**); 4-tBu-Bn (**9**)

Figure 2

The identification and purity control of the synthesized hydroxyproline derivative catalysts were carried out by melting point measurement and on the basis of ^{1}H NMR, ^{13}C NMR and ESI-MS spectra.

The ethyl acetate extract of the aldol reaction product was placed into a GC-vial and quantitatiely analysed (determination of conversion, selectivity and enantioselectivity (ee (%) = 100 x ([A]-[B])/([A]+[B]), where [A] – the concentration of enantiomer which is in excess and [B] - the concentration of the other enantiomer)) using chiral gas chromatography. The residual part of the extract was purified by flash column chromatography (SiO_2, hexanes/EtOAc 7:3) after removing the solvent under reduced pressure. The purity control of the aldol product was carried out on the basis of GC- and NMR analyses. The absolute configuration was determined on the basis of optical rotation measurements and by comparison with values reported in the literature.

The heterogeneous asymmetric aldol reactions catalyzed by immobilized oligopeptides were carried out under flow conditions using fixed-bed reactor (Figure 3).

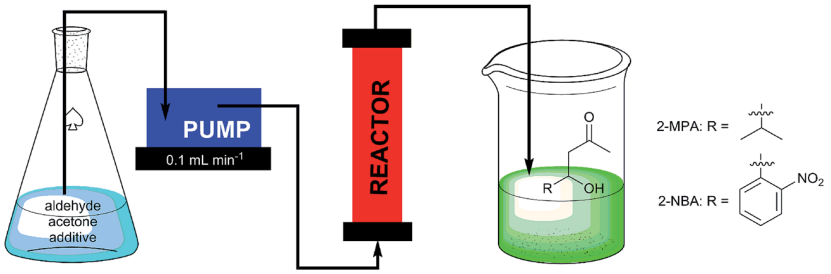


Figure 3

In the heterogeneous asymmetric aldol reactions the catalysts were H-Pro-MBHA-PS (**P**-MBHA-PS), H-Pro-Pro-MBHA-PS (**PP**-MBHA-PS), H-Pro-Pro-Pro-MBHA-PS (**PPP**-MBHA-PS), H-Pro-Asp(OH)-MBHA-PS (**PD**-MBHA-PS), H-Pro-Pro-Asp(OH)-MBHA-PS (**PPD**-MBHA-PS), H-Pro-Glu(OH)-MBHA-PS (**PE**-MBHA-PS), H-Pro-Pro-Glu(OH)-MBHA-PS (**PPE**-MBHA-PS), H-Val-Glu(OH)-MBHA-PS (**VE**-MBHA-PS), H-Val-Val-Glu(OH)-MBHA-PS (**VVE**-MBHA-PS), H-Ser-Glu(OH)-MBHA-PS (**SE**-MBHA-PS), H-Ser-Ser-Glu(OH)-MBHA-PS (**SSE**-MBHA-PS), synthesized in the Department of Medical Chemistry (University of Szeged, Faculty of Medicine) by a solid-phase technique using Fmoc-strategy (Figure 4).

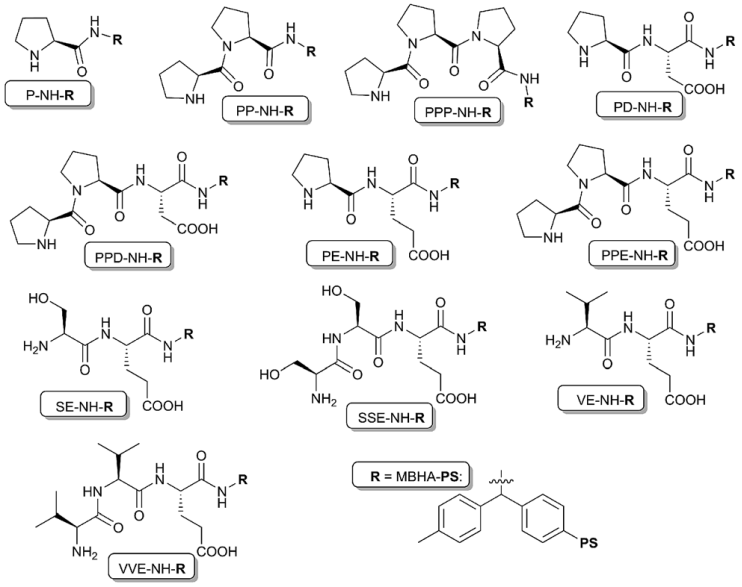


Figure 4

The immobilized oligopeptides were characterized by FT-IR spectroscopy in diffuse reflectance mode (DRIFT), the catalyst loading was calculated from CHN-analysis.

In the process of analysis of the aldol reaction products, a small sample of the crude reaction mixture was analyzed by GC without further purification, and the main part of the crude mixture, after vacuum evaporation of the volatiles, was purified by flash column chromatography using hexanes/EtOAc 7:3 mixture as eluent in the case of 2-nitrobenzaldehyde and hexanes/EtOAc 3:1 mixture in the case of isobutyraldehyde. The purity control of the product was carried out on the basis of GC- and NMR analyses. The absolute configuration was also determined by comparison of the measured optical rotation values with data reported in the literature.

3. NEW SCIENTIFIC RESULTS

3.1. Asymmetric aldol reactions between acetone and different aldehydes catalyzed by hydroxyproline derivatives in organic and aqueous media

1. Studying the known and the newly synthesized amphiphilic L-hydroxyproline derivative catalysts used in the asymmetric aldol reactions between acetone and different aldehydes in organic and aqueous media, 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 (hydrophobic aldehyde and hydrophilic acetone) and the hydrophilic active center of amino acid derivative catalyst getting close to each other. To suit these conditions it is required to establish a proper interface which is supported by the amphiphilic character of the amino acid derivative catalyst. Moreover, for improving the efficiency of the 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.

2. During the optimization of the reactions carried out in aqueous media it was shown that the nature and quantity of the salt additives used for water activity reduction to increase the catalyst efficiency, the reagent aldehyde structure, and the addition of nonionic surfactant to the reaction mixture have significant effect on the reaction outcome.

3. During the course of our research 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 carboxylate, 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.

4. 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 is explained below with different structures of micelle-stabilized transition state described as a metal-free version of the Zimmermann-Traxler model with inclusion of a water molecule.

4.a Under acidic conditions 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 forms in excess, as in organic media) (Figure 5).

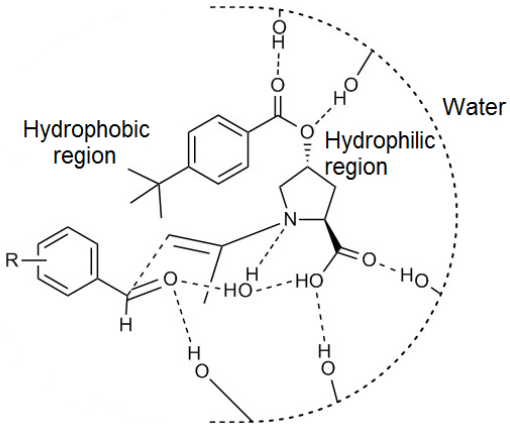


Figure 5

As a result, in the asymmetric aldol reaction between acetone and different aldehydes carried out in the solution of acidic salt (ammonium chloride) in all cases the (*R*) product forms in excess according to the following reaction mechanism (Figure 6):

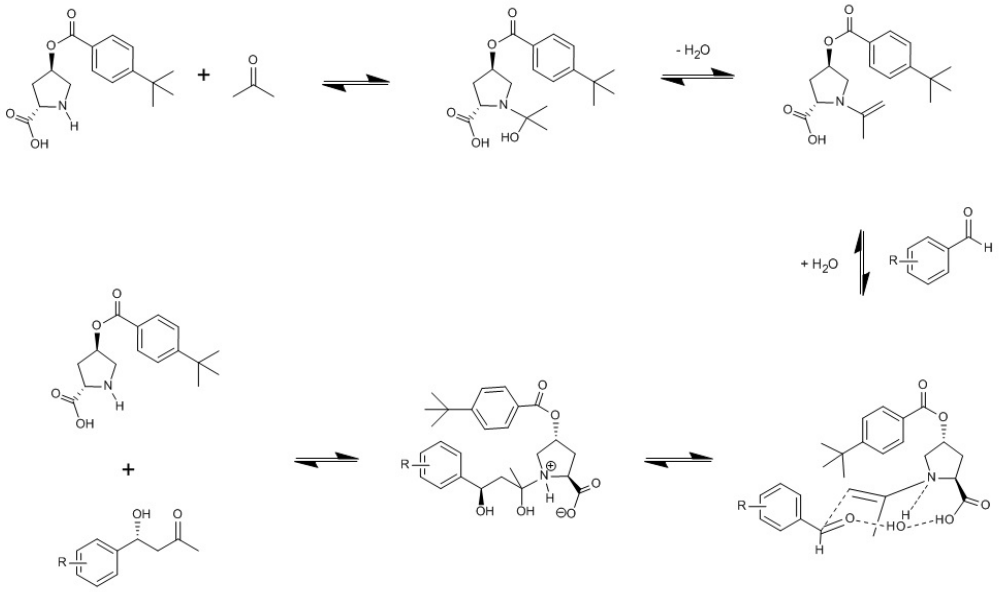


Figure 6

4.b In the solution of basic salts (alkali metal carboxylates, quaternary ammonium carboxylate), 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 forms in excess) (Figure 7).

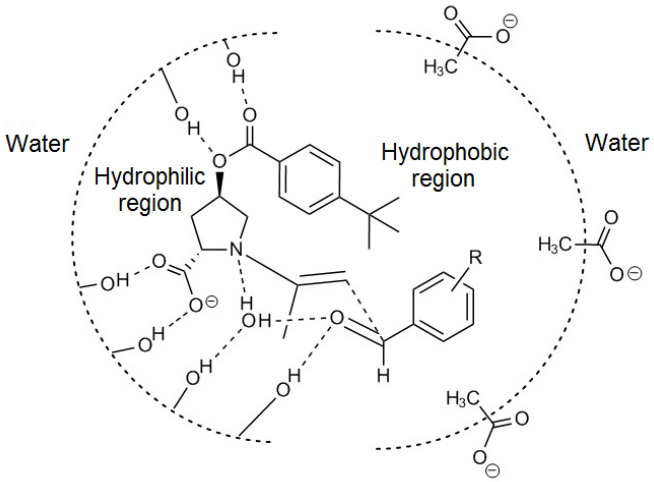


Figure 7

Thus, in the asymmetric aldol reaction between acetone and different aldehydes under basic conditions the formation of the (*S*) product is preferred according to the following reaction mechanism (Figure 8):

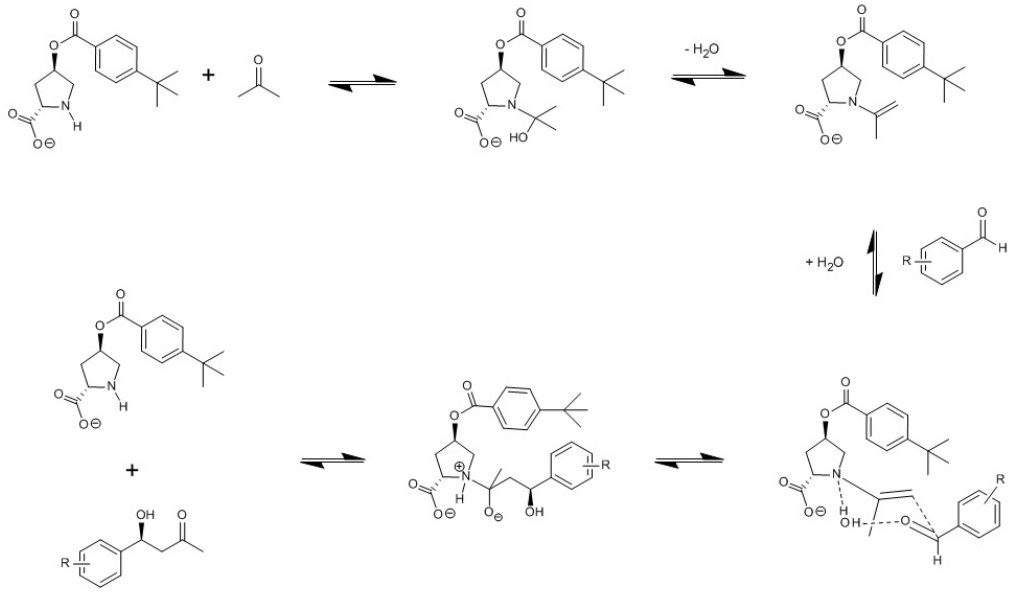


Figure 8

3.2. Heterogeneous asymmetric aldol reactions between acetone and different aldehydes catalyzed by immobilized oligopeptides in continuous-flow system

To exploit the advantages of heterogeneous catalysis in industrially relevant scenarios, we explored the asymmetric aldol reactions of acetone with 2-nitrobenzaldehyde and isobutyraldehyde under continuous-flow conditions in a fixed-bed reactor using polystyrene resin supported immobilized oligopeptides for stereocontrol. The following results were obtained:

5. Studying the stability of the catalysts in the asymmetric aldol reaction of acetone with 2-nitrobenzaldehyde as a model reaction catalyzed by **PD**-NH-MBHA-PS and **PPD**-NH-MBHA-PS under flow conditions for 8 hours, it was determined that both catalysts showed good stability. This finding confirmed the applicability of immobilized oligopeptide catalysts under continuous-flow conditions as well (Figure 9):

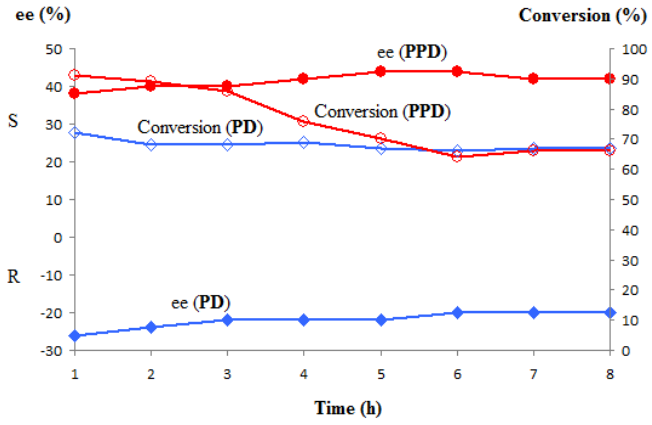


Figure 9

6. The linear correlation between enantioselectivity and composition of the immobilized catalyst mixture of L-**P**-NH-MBHA-PS and D-**P**-NH-MBHA-PS in different proportions in the reaction of acetone and 2-nitrobenzaldehyde proved the heterogeneous character of the reaction (Figure 10):

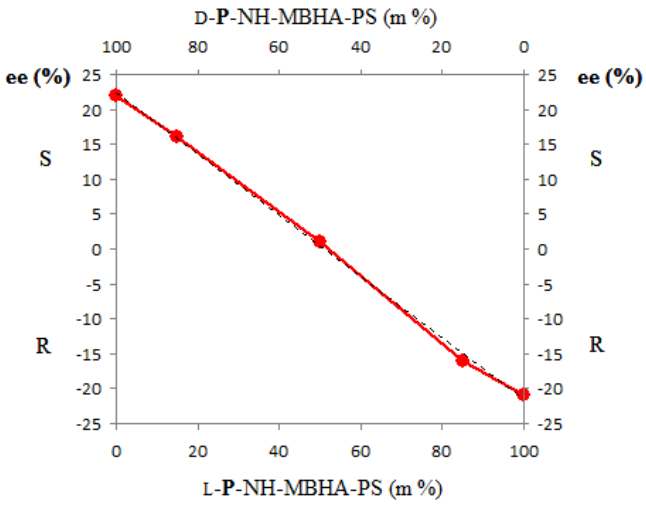


Figure 10

7. By using polystyrene bound L-proline or di- and tripeptides composed of only L-proline as catalysts under continuous-flow conditions the reactions yielded the aldol-addition product with (*R*) configuration in excess. These catalysts showed acceptable catalytic activities and delivered moderate enantioselectivities. When **PD**-NH-MBHA-PS and **PE**-NH-MBHA-PS immobilized dipeptide catalysts were used, the (*R*) product was formed in excess. On the other hand, **PPD**-NH-MBHA-PS and **PPE**-NH-MBHA-PS immobilized tripeptide catalysts led to the formation of the (*S*) products in excess (inversion of enantioselectivity occurred) both in case of aromatic and aliphatic aldehydes (high catalyst activity and moderate enantioselectivity for aromatic aldehyde, whereas low catalyst activity and relatively high enantioselectivity for aliphatic aldehyde).

8. In case of the immobilized di- and tripeptide catalysts were lacking the proline moiety (**SE**-NH-MBHA-PS, **VE**-NH-MBHA-PS, **SSE**-NH-MBHA-PS and **VVE**-NH-MBHA-PS), inversion of enantioselectivity was not observed (product with (*R*) configuration was formed in excess).

9. The presence of benzoic acid, as an achiral additive, resulted in significant increase of the conversion in the reaction of acetone and 2-nitrobenzaldehyde when polystyrene bound L-proline or di- and tripeptides composed of only L-proline were used as catalysts. However, as an original finding, it is even more important that in the presence of benzoic acid with **P**-NH-MBHA-PS catalyst the (*R*) product was formed in excess**,** while with **PP**-NH-MBHA-PS and **PPP**-NH-MBHA-PS catalysts the (*S*) product was formed in excess (inversion of enantioselectivity occurred).

10. The reason for the non-trivial effect observed upon using benzoic acid additive is suggested to be that the protonation of the more flexible di- and tripeptides caused by benzoic acid (compared to L-proline) results in a change in catalyst conformation. This change is then affecting the structure of the transition state in the aldol reaction of acetone and 2-nitrobenzaldehyde which will lead to the formation of product with (*S*) configuration in excess. This effect gives us the possibility to control the stereoselectivity of the asymmetric aldol reactions by achiral additives.

4. PAPERS RELATED TO THE THESIS

[1] A. Gurka, I. Bucsi, L. Kovács, G. Szőllősi and M. Bartók
Reversal of the enantioselectivity in aldol addition over immobilized di- and tripeptides: studies under continuous flow conditions
RSC Adv., **4**, 61611-61618 (2014) IF: 3.840

[2] A. A. Gurka, K. Szőri, G. Szőllősi, M. Bartók and G. London
Tuning the sense of product stereochemistry in aldol reactions of acetone and aromatic aldehydes in the presence of water with a single chiral catalyst
Tetrahedron Lett., **56**, 7201-7205 (2015) IF: 2.379

[3] A. A. Gurka, K. Szőri, M. Bartók and G. London
Dual stereocontrol in aldol reactions catalysed by hydroxyproline derivatives in the presence of a large amount of water
Tetrahedron: Asymm., **27**, 936-942 (2016) IF: 2.108

[4] A. A. Gurka and G. London
Dual stereocontrol in enantioselective aldol reactions
Org. Prep. Proc. Int., (2017) (Accepted) IF: 1.750

Summarized impact factors of the publications related to the thesis: 10.077

5. OTHER PAPERS

[1] G. Szőllősi, M. Fekete, A. A. Gurka and M. Bartók
Reversal of Enantioselectivity in Aldol Reaction: New Data on Proline/γ-Alumina Organic-Inorganic Hybrid Catalysts
Catal. Lett., **144**, 478-486 (2014) IF: 2.291

[2] A. A. Gurka, K. Szőri, M. Szőri, M. Bartók and G. London
Application of hydroxyproline derivatives in enantioselective α-amination reactions in organic and aqueous environments: a structure-activity relationship study
Struct. Chem., **28**, 415-421 (2017) IF: 1.854

Summarized impact factors of the other publications: 4.145

6. SCIENTIFIC LECTURES RELATED TO THE THESIS

[1] Gurka András, Szőllősi György, Bartók Mihály
Immobilizált oligopeptidekkel katalizált folyamatos áramú enantioszelektív aldol addíciós reakciók
MKE 2. nemzeti konferencia
Hajdúszoboszló, 2015. augusztus 31-szeptember 2.

[2] András Gurka, György Szőllősi, Mihály Bartók
Continuous flow enantioselective aldol additions over immobilized oligopeptides

Eleventh International Symposium on Heterogeneous Catalysis
Varna, Bulgaria, 6-9 September 2015

[3] London Gábor, Gurka András
Kettős sztereokontroll vizes közegű aldol reakciókban
Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése
Balatonszemes, 2016. május 18-20.