Final report

The most challenging task of the modern organic chemistry is to satisfy the increased demand of high value-added fine chemicals keeping in sight the strict environmental requirements and the sustainability problems in an economically competitive manner. Asymmetric catalysis may provide convenient methods for producing optically pure compounds used as chiral building blocks in the pharmaceutical, flavor, fragrance and agrochemical industries, to manufacture products designed to interact with biological systems. Recovery and recycling of the chiral catalysts could be a significant advancement both as concerns the environmental impact of the processes as well as the production costs of the expensive intermediates.

We set as the main goal of our studies the development of novel heterogeneous catalytic systems designed for convenient preparation of organic fine chemicals, with special focus on using heterogeneous catalysts in asymmetric synthesis of optically enriched chiral building blocks. Besides the practical importance of the novel catalysts, procedures and reactions we also intended to study in detail the steps and intermediates through which the reactions occur, to understand the driving force of the selective transformations and the stereodiscrimination, in order to gather information, which may be used to the development of more efficient selective catalytic systems. Among the organic reactions studied were C-C, C-N coupling reactions and hydrogenations, reactions catalyzed by organocatalysts and by metal catalysts.

From the beginning of the present century the asymmetric organocatalytic reactions developed in explosive manner. Design of complex, finely tuned and highly efficient organocatalysts made necessary the recovery and reuse of these compounds. Our investigation aimed at the development of catalytic systems using simple chiral organocatalysts and the possibility of obtaining heterogeneous variants which may be used in several runs or applied in continuous flow systems.

Asymmetric aldol additions are among the most studied organocatalytic reactions, thus continuing our previous studies we used as model reactions the addition of ketones to various aldehydes, as exemplified in *Figure 1*.

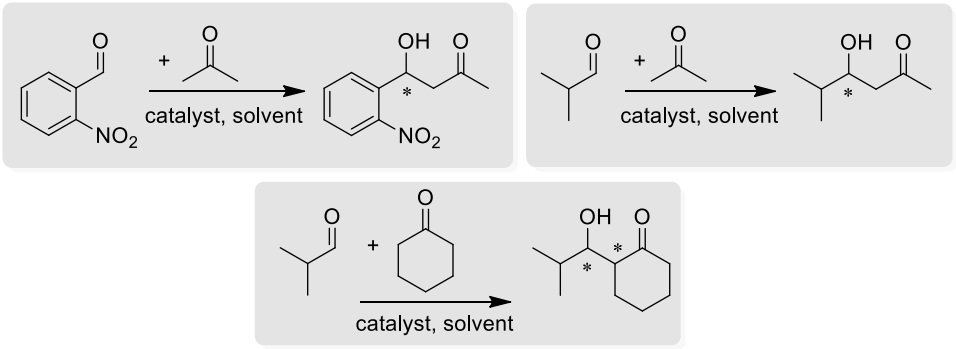

Figure 1.

We have prepared polystyrene resin-supported di- and tripeptides and used these materials as heterogeneous chiral catalysts in asymmetric aldol additions. In the reactions catalyzed by the L-proline terminal materials (*Figure 2.*, **a**), an inversion of the sense of the enantioselectivity was observed when the length of the amino acid sequence increased from two to three, both in batch and flow systems [1]. This interesting inversion of the enantioselectivity was explained by the conformational behavior of the immobilized oligopeptides and the intermediate adducts, which could be evidenced by quantum chemical calculations and by ESI-MS identification of the intermediates' structure. We have shown that during aldol additions catalyzed by L-proline the addition of γ-alumina to the reaction mixture results in the formation of an organic-inorganic hybrid material by adsorption of the amino acid on the surface of the oxide (*Figure 2.*, **b**), which catalyzed the addition to excess formation of the opposite adduct enantiomer as compared with the soluble L-proline [2]. It was shown that the enamine intermediate adsorbed on the solid surface changes the preferential direction of the nucleophilic attack, which eventually leads to the formation of the opposite enantiomer. Chiral catalysts were also prepared by

impregnation of L-proline on graphite oxide, graphene oxide and their sulfated variants and were used as catalysts in enantioselective aldol addition. A stronger interaction of the amino acid with the sulfated carbonaceous materials led to a recyclable heterogeneous organocatalyst [3].

Our studies were also extended on using hydroxyl-functionalized 4-hydroxy-proline derivatives in asymmetric aldol addition in aqueous solvent [4,5]. The stereochemical outcome of the addition of acetone to various aromatic aldehydes could be tuned by the addition of achiral salts, ammonium chloride afforded the (*R*)-product, whereas under basic conditions, using sodium acetate the (*S*)-enantiomer formed in excess. A crucial role was attributed to the apolar *tert*-butyl group found in the proline derivative (*Figure 2.*, **c**), which facilitated the formation of a micellar biphasic system. Accordingly, a catalyst structure that contains the necessary amino acid moiety on one hand and a hydrophobic 'tail' that contributes to the stabilization of the aqueous/organic interface on the other hand had to be present in the catalyst. A systematic study on the hydroxyproline derived catalyst structure showed that both an aromatic ring and an alkyl chain are necessary for a working catalyst. Furthermore, the rigidity of the catalyst structure was also found to be an important factor. Using the same series of proline-derived chiral catalyst the α-amination reaction between diethyl azodicarboxylate and propanal was also investigated [6]. Although, we have detected in water similar inversion of the enantioselectivity sense as in the aldol additions, the values obtained were low due to racemization of the product under the reaction conditions.

During these studies on the asymmetric aldol additions and related reactions several comprehensive reviews were compiled with recent advancements in this field of the organic chemistry, such as those surveying aldol reactions proceeding under aqueous or neat conditions [7], reactions catalyzed by immobilized organocatalysts [8] and asymmetric procedures in which dual stereocontrol was observed [9].

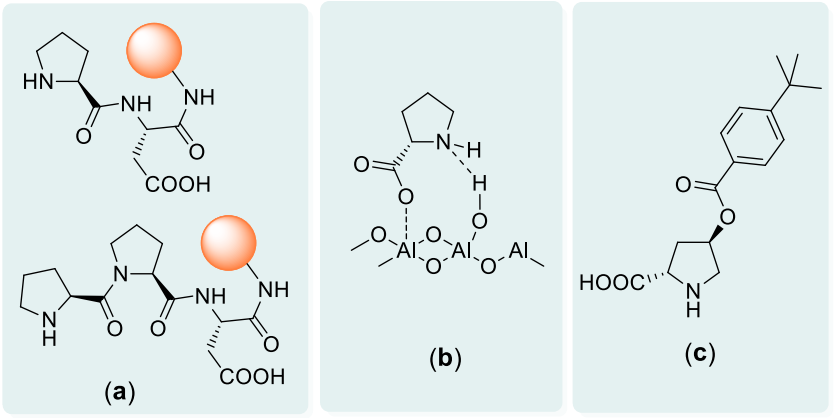

Figure 2.

Among the synthetically most useful asymmetric transformations are also the stereoselective Michael additions, which due to the employed large variety of donors and acceptors may provide valuable, complex chiral building blocks for the preparation of optically pure target compounds. Due to the high price of the chiral organic bases used as catalysts in these reactions, development of immobilized organocatalysts or applying simple, natural materials in these reactions is of paramount importance. During our studies we have investigated the stereoselective additions of aldehydes and a fluorine substituted β-ketoester to β-nitrostyrene derivatives and the addition of isobutyraldehyde to *N*-substituted maleimides (*Figure 3.*).

The asymmetric Michael addition of the fluorine containing carbon nucleophile to β-nitrostyrene was carried out with an easily obtainable cinchona alkaloid derivative, i.e. β-isocupreidine, which provides high stereoselectivities in homogeneous reaction, and could be easily immobilized over inorganic materials. Anchoring the deprotonated alkaloid molecule over the particle surface of an anion-exchanger layered double hydroxide resulted in inorganic–organic hybrid material (*Figure 4.*, **a**), with catalytic performance approaching that of the soluble organocatalysts, which could be reused in case the reactions were carried out in apolar media. Based on characterization data of the chiral solid

and catalytic results bonding possibilities of the cinchona derivative to the surface of the layered double hydroxide by electrostatic interactions and hydrogen bonding was suggested [10].

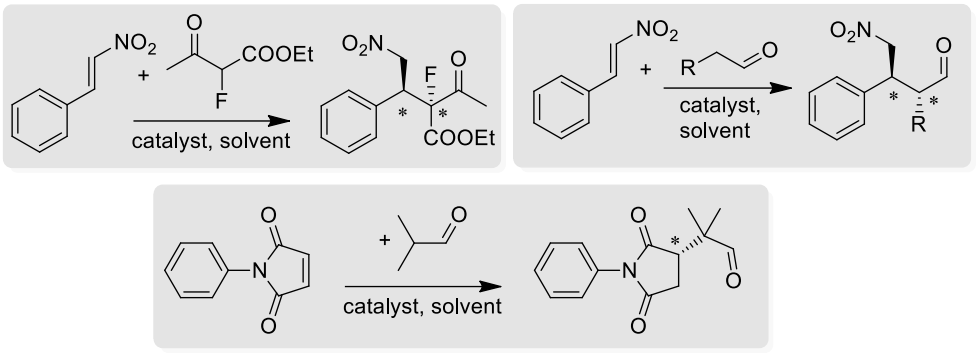

Figure 3.

An unprecedented enantioselectivity increase was observed in the presence of inorganic oxides such as laponite in the asymmetric Michael addition of aldehydes to β-nitrostyrene derivatives catalyzed by amino acids. This stereoselective reaction was catalyzed by the organic-inorganic hybrid material formed *in situ* by adsorption of L-proline on the solid surface (*Figure 4.*, **b**), which could be recycled several times with maintained stereoselectivities. Characterization of the chiral hybrid material by FT-IR spectroscopy and powder XRD measurements indicated anchoring of the proline on the surface of the laponite particles with the involvement of both the carboxylic acid and the amino group. Linear natural amino acids became also active in the asymmetric Michael addition following adsorption on laponite and provided the opposite enantiomer in excess as compared with L-proline. Based on our detailed study a plausible reaction pathway occurring on the surface was proposed [11].

Chiral solid materials were prepared by covalent bonding of optically pure 1,2-diamines on sulfonyl chloride functionalized supports. The heterogeneous catalyst prepared by bonding 1,2-diphenylethane-1,2-diamine to polystyrene (*Figure 4.*, **c**) was highly enantioselective in the asymmetric Michael addition of isobutyraldehyde to maleimides, giving results approaching those obtained using soluble mono-sulfonamide derivatives. The anchored catalyst was recyclable few times keeping its activity and still providing high, up to 97%, enantiomeric excesses. These materials were among the first efficient recyclable catalysts used in the enantioselective Michael addition of aldehydes to maleimides [12].

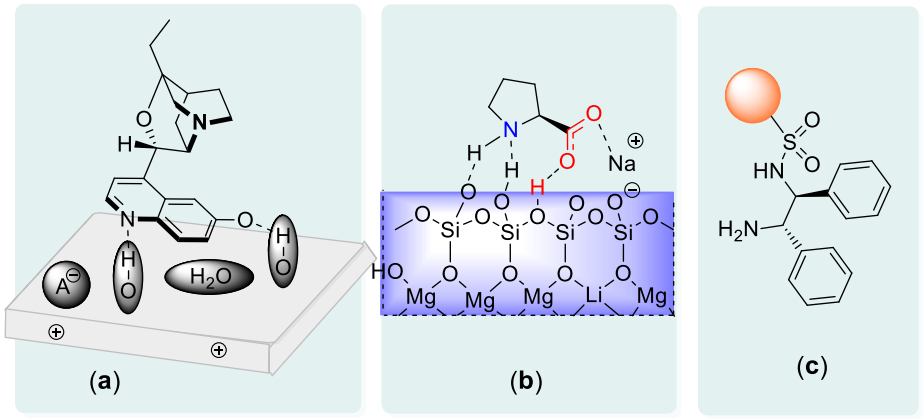

Figure 4.

Enantioselective hydrogenations and transfer hydrogenations of prochiral compounds are very convenient and simple methods to introduce asymmetry in organic molecules. Chiral modification of catalytically active metal surfaces is the simplest way to obtain heterogeneous asymmetric catalysts highly efficient in enantioselective hydrogenations of specific types of compounds, such as α-ketoesters. Based on our extensive experience on the enantioselective hydrogenations over cinchona alkaloid-modified metal surfaces, reviewed recently [13], we have developed a novel heterogeneous

catalytic cascade reaction for the preparation of optically enriched 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones, which occurs via successive enantioselective hydrogenation of the ketone group, reduction of the nitro group and cyclization of the resulting intermediate by intramolecular amidation (*Figure 5*.). Results of studies on the effect of the amount of acetic acid and catalyst, nature of the Pt support, kinetic examinations, effect of H_2 pressure, and modifier and substrate concentrations showed that all three steps of this catalytic cascade take place on the Pt surface and the final intramolecular amidation was preceded by desorption of the aminoalcohol after complete reduction of the substrate and re-adsorption of this intermediate [14]. This asymmetric heterogeneous catalytic cascade reaction has also been investigated over platinum modified by cinchonidine in continuous-flow system using a fixed-bed reactor. Results obtained in the flow apparatus contributed to the understanding of the reaction pathway through which the quinolone is formed. It was shown that, at low conversions, the intermediate aminohydroxyester desorbs preferentially and is further transformed by readsorption and cyclization to the quinolone derivative after close to complete disappearance of the 2-nitrophenylpyruvate. However, at high conversion, the formation of the quinolone may also occur instantaneously on the Pt surface following the two competitive reduction steps [15].

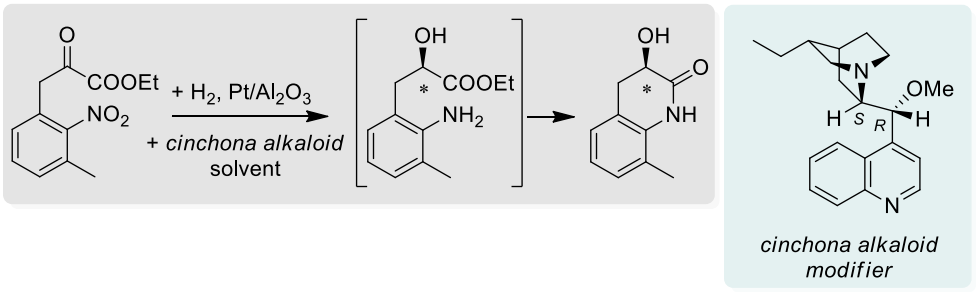

Figure 5.

Our studies were extended on the transfer hydrogenation of pharmaceutically relevant molecules. The Noyori-type ruthenium catalysts formed using *N*-(para-tosyl)-1,2-diphenylethylene-1,2-diamine ligands have been found efficient in the regiospecific transfer hydrogenation of 16-hydroxymethylidene-13α-estra-1,3,5(10)-trien-17-one derivatives. Further reduction of the isolated products yielded the corresponding diol isomers in almost equal amounts without protection-deprotection protocols [16]. We have developed a convenient, environmentally benign method for the enantioselective transfer hydrogenation of aromatic ketones using chitosan, a biocompatible, biodegradable chiral ligand of natural origin in aqueous solvent mixture. In this catalytic system the transformation of heterocyclic ketones occurred with exceptional enantioselectivities (*Figure 6.*). Based on spectroscopic studies the structure of the chiral complex formed with chitosan and the possible interactions responsible for the stereo-discrimination were also suggested [17].

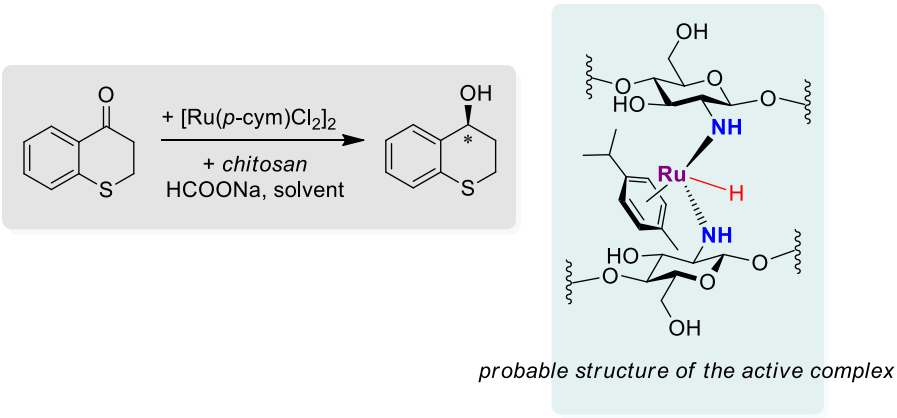

Figure 6.

Reviews on cascade reactions using heterogeneous catalysts [18,19] and on continuous flow processes were published [20]. Based on our experiences on the application of heterogeneous catalysts in asymmetric synthesis a book chapter was also compiled summarizing reactions in which both heterogenized organocatalysts and immobilized metal catalysts were used [21].

Due to the practical importance of reactions catalyzed by palladium catalysts our studies were also extended on the use of novel supported palladium catalysts, as versatile tools to obtain structurally very divers organic compounds. Coupling reactions and transfer hydrogenations of nitro compounds and ketones catalyzed palladium catalysts are among the most useful reactions to obtain valuable complex organic molecules (*Figure 7.*).

We have investigated the Heck coupling reaction of styrene and bromobenzene using various supported Pd catalysts such as Pd/C, $Pd/BaSO_4$, Pd-EnCat. We have optimized the experimental conditions by using different bases in the presence of quaternary ammonium salts. It was found that the examined catalysts work as a reservoir of the catalytically active Pd species during the reaction. The Pd-EnCat catalyst displayed the highest activity and selectivity [22]. Silica-supported Pd catalysts with extremely low Pd loadings were synthesized in the presence of the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate. Raman spectra indicated the presence of the ionic liquid in the Pd-silica samples. These materials were found to be excellent catalysts in the Heck coupling reactions of methyl acrylate and styrene with substituted bromoarenes and chloroarenes, the latter could be efficiently transformed without applying harsh reaction conditions [23]. We have also reported the application of Pd-polydopamine and magnetic Fe_3O_4@Pd-polydopamine catalysts in catalytic transfer hydrogenations and Heck coupling reactions. The reduction of a wide range of aromatic nitro-compounds to the corresponding anilines could be efficiently performed, while the reduction of carbonyl compounds was found to be less general. The magnetic Fe_3O_4@Pd-polydopamine system facilitated catalyst recovery and reuse without considerable loss of activity in nitro-group reduction. The efficiency of the catalyst in Heck couplings was comparable to that in transfer hydrogenation, however, no catalytic activity was observed upon reuse in this case, likely due to metal leaching. We also explored tandem Heck reaction/catalytic transfer hydrogenation sequences, however, the two reactions showed limited compatibility under the applied conditions [24]. The effect of catalyst restructuring on the polydopamine-supported Pd catalyzed transfer hydrogenation of ethyl 4-nitrobenzoate and the catalytic hydrogenation of (*E*)-2-methyl-2-butenoic acid was also studied. In the transfer hydrogenation reaction aggregation was primarily dependent on the H-source used, while in the catalytic hydrogenation additives in combination with the reductive environment led to extensive Pd aggregation and thus decreased catalytic activity. The enantioselective hydrogenation of (*E*)-2-methyl-2-butenoic acid showed increased enantioselectivity and decreased conversion with increased particle size [25].

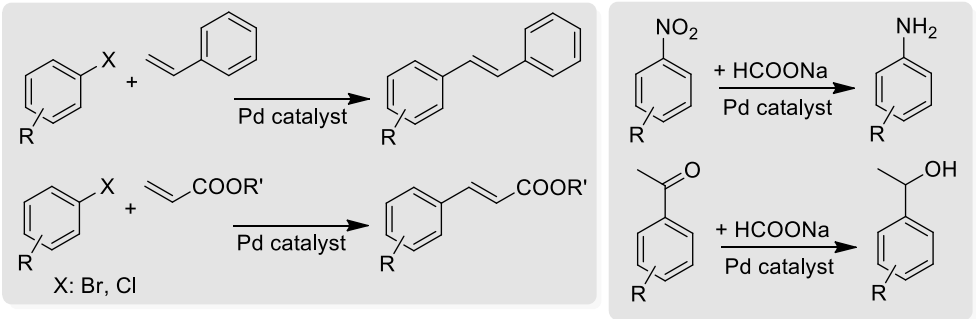

Figure 7.

We have applied supported palladium catalyst in allyl alcohol isomerization and subsequent aldol condensation and heterocyclization reactions (*Figure 8.*). The activity of Pd/Al_2O_3 in these transformations is suggested to be due to the participation of the Lewis acidic sites of the support in the activation of the alcohol towards oxidative dehydrogenation by the metal and subsequent hydride transfer. The resulting enolate/aldehyde could undergo further reactions promoted by the support. In the aldol condensation reactions of the isomerization product, electron poor aromatic aldehydes and

heteroaromatic aldehydes showed the highest activity. 1,2-Disubstituted aromatics gave heterocyclic products in one-pot multistep reaction sequences [26]. In our subsequent study we have exploited the different reactivities present in the catalytic cycle of the Pd/Al_2O_3 catalyzed redox isomerization of allyl alcohol. We showed that the allyl alcohol derived acrolein and enol can be involved in further cascade reactions leading to a diverse set of products. While the oxidation product acrolein can react via Michael and oxa-Michael reactions, the enol formed by isomerization can be readily involved in aldol condensation processes. Salicylaldehydes, that are able to react on their electrophilic carbonyl and nucleophilic hydroxyl groups with allyl alcohol derived enol and acrolein (*Figure 8.*), respectively, were used to explore conditions in order to control the structure of the heterocyclic product [27].

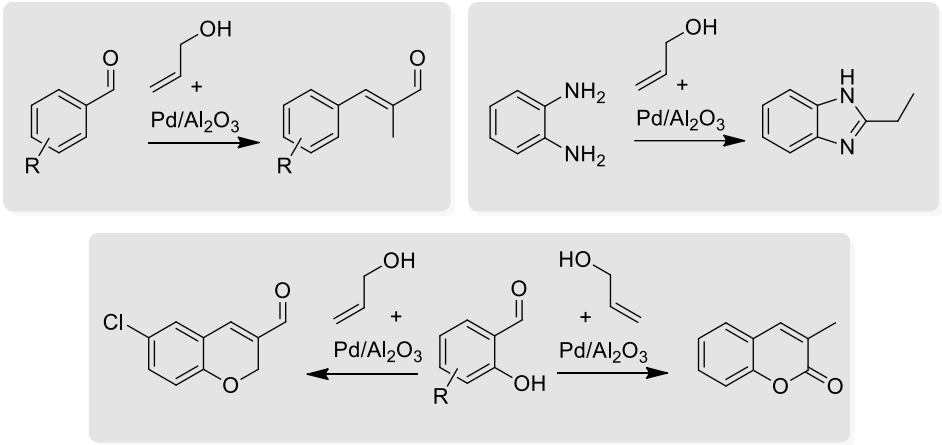

Figure 8.

To sum up the research work carried out according to the plan submitted in the application, we have developed, characterized and explored the limits of the applicability of novel heterogeneous chiral catalysts for asymmetric aldol and Michael additions. We used chirally modified metal surface in enantioselective cascade reactions, chiral metal complexes in asymmetric transfer hydrogenations and heterogeneous palladium catalysts in reductive, oxidative and coupling transformations, including cascade reactions. Our results contributed to the development of efficient catalytic materials, which may be used in sustainable, environmentally benign methods designed for the preparation of organic fine chemicals.

Publications

[1] A. Gurka, I. Bucsi, L. Kovács, Gy. Szőllősi, M. Bartók, *RSC Adv.* **2014**, *4*, 61611-61618.
[2] Gy. Szőllősi, M. Fekete, A. A. Gurka, M. Bartók, *Catal. Lett.* **2014**, *144*, 478-486.
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Selected relevant conference presentations

1. Gy. Szöllősi, L. Kovács: Cinchona Alkaloid Catalysts in the Asymmetric Michael-addition of Fluorinated C-nucleophile to β-Nitrostyrene. Chirality 2014, P-180, 2014, Prága, (Cseh Köztársaság).
2. Gy. Szőllősi, L. Kovács, Zs. Makra, K. Szőri, M. Bartók: Enantioselective cascade reactions catalyzed by chirally modified metal surfaces. 12th Pannonian International Symposium on Catalysis, K2, 2014, Trest, (Cseh Köztársaság).
3. A. Gurka, Gy. Szőllősi, M. Bartók: Immobilizált oligopeptidekkel katalizált folyamatos áramú enantioszelektív aldol addíciós reakciók. Magyar Kémikusok Egyesülete 2. Nemzeti Konferencia, 2015, SZ-P-8, Hajdúszoboszló.
4. L. Kovács, Gy. Szőllősi, M. Bartók: 2-Nitrofenilpiroszőlősav észeterek reakciója cinkonidinnel módosított Pt katalizátoron átáramlásos rendszerben. Magyar Kémikusok Egyesülete 2. Nemzeti Konferencia, 2015, SZ-P-16, Hajdúszoboszló.
5. A. Gurka, Gy. Szőllősi, M. Bartók: Continuous-flow enantioselective aldol additions over immobilized oligopeptides. Eleventh International Symposium on Heterogeneous Catalysis, 2015, P48, Varna, Bulgária.
6. Gy. Szőllősi, L. Kovács, V. Kozma, V. J. Kolcsár: Asymmetric Michael-addition catalyzed by a cinchona alkaloid derivative non-covalently immobilized over layered materials. 13th Pannonian International Symposium on Catalysis, 2016, P40, Siófok.
7. Gy. Szőllősi, D. Gombkötő, A. Mogyorós: Michael-addition of aldehydes to nitroolefins catalyzed by amino acids on metal oxides, a surface-improved asymmetric reaction. 13th Pannonian International Symposium on Catalysis, 2016, P41, Siófok.
8. Gy. Szőllősi, D. Gombkötő, A. Mogyorós, T. Győri: Asymmetric Michael-addition catalyzed by natural amino acids on the surface of inorganic oxides. Europacat 13th European Congress on Catalysis, P3.60, 2017, Firenze, (Olaszország).
9. V. J. Kolcsár, Gy. Szőllősi: Chitosan, a natural ligand for highly enantioselective Ru catalyzed transfer hydrogenation of ketones. Europacat 13th European Congress on Catalysis, P3.64, 2017, Firenze, (Olaszország).
10. V. Kozma, Gy. Szőllősi: Asymmetric Michael-additions using homogeneous and heterogenized chiral 1,2-diamine derivatives. Europacat 13th European Congress on Catalysis, P3.63, 2017, Firenze, (Olaszország).
11. V. J. Kolcsár, Gy. Szőllősi: Chitosan, a natural ligand for highly enantioselective Ru catalyzed transfer hydrogenation of ketones. 14th Pannonian International Symposium on Catalysis, P-1.1, 2018, High Tatras, (Szlovákia).
12. V. Kozma, Gy. Szőllősi: Asymmetric Michael additions using heterogenized chiral 1,2-diamine catalysts. 14th Pannonian International Symposium on Catalysis, P-2.9, 2018, High Tatras, (Szlovákia).
13. Gy. Szőllősi, A. Zs. Mogyorós, D. Gombkötő, B. Fancsali, V. J. Kolcsár, V. Kozma, G. Kőhl: Heterogeneous asymmetric Michael additions catalyzed by proline-inorganic oxide hybride materials. 14th Pannonian International Symposium on Catalysis, P-2.16, 2018, High Tatras, (Szlovákia).