

**HETEROGENEOUS ASYMMETRIC MICHAEL ADDITIONS USING
ENVIRONMENTALLY FRIENDLY CATALYSIS:
APPLICATION OF CHIRAL INORGANIC-ORGANIC HYBRID MATERIALS**

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Abstract

In the last few decades, the development of environmentally benign, sustainable processes for the preparation of optically pure intermediates used in the pharmaceutical, food and agrochemical industries received increasing attention. Processes applying recyclable, chiral heterogeneous catalysts based on readily available, natural, optically pure compounds may be convenient alternatives of the classical asymmetric synthetic methods. During our studies, we have attempted the development of novel heterogeneous catalysts by adsorption of natural amino acids on the surface of inorganic oxides. These materials formed either *in-situ* during reactions or prepared *ex-situ* were tested in various asymmetric Michael additions. Amino acids adsorbed on laponite were found the most efficient in catalyzing the addition of aldehydes or ketones to nitrostyrene derivatives. In these reactions occurring via enamine catalysis, the material obtained by adsorption of proline was found to be a highly active and stereoselective catalyst, although proline afforded low enantioselectivities. In the Michael addition of nitroalkanes or β -keto esters to unsaturated ketones, both laponite and alumina were efficient in increasing the enantioselectivities. In these reactions, which take place through iminium catalysis, only moderate enantioselectivities could be reached. The chiral inorganic-organic hybrid materials were characterized by infrared spectroscopy and powder X-ray diffractometry, evidencing bonding of the amino acids on the surface of the oxides. Our results demonstrated that an inorganic surface on which a chiral organocatalyst is immobilized by simple adsorption may have beneficial effect on the asymmetric reaction catalyzed by the chiral material, due to surface improved asymmetric induction. In conclusion, these hybrid materials are promising candidates for future application in environmentally friendly processes.

Introduction and aims

Asymmetric catalytic methods are convenient procedures for preparing optically pure organic chemicals [1]. Recent requirements to decrease the environmental impact and improve the sustainability of fine chemicals production motivated the use of heterogeneous, easily separable, recyclable chiral catalysts in these processes. From practical reasons is advantageous the attachment of chiral soluble catalysts to solid supports by noncovalent bonding. Noncovalent immobilizations of optically pure organocatalysts were seldom reported [2,3]. Natural amino acids are cheap, readily available chiral organocatalysts. However, only few catalytic systems are known in which these catalysts were immobilized on supports by simple adsorption or hydrogen bonding and provided improved activity and/or stereoselectivity [4,5]. It is also important that anchoring of organocatalysts on supports by simple adsorption may be carried out *in-situ*, without pre-preparation of the solid catalyst.

Michael additions are among the most studied C–C bond-forming organocatalytic asymmetric reactions, due to the easy preparation of complex organic molecules via these transformations [6]. In our previous studies we have observed the remarkable effect of inorganic oxide additives on the proline catalyzed asymmetric aldol reactions [5] and the Michael addition of aldehydes on β -nitrostyrene derivatives [7]. In the present work, our aim was to study the applicability of the proline-inorganic oxide hybrid catalyst in various asymmetric Michael additions. The effect of addition of oxide additives on the asymmetric addition of aldehydes or ketones to nitrostyrene will be compared with that obtained in other Michael additions. Among the reactions studied using proline catalyst both without and with inorganic additives are reactions of α,β -unsaturated ketones with nitroalkanes or β -ketoesters.

Experimental

Inorganic oxides used in this study were commercially available materials. Amino acids used as catalysts and reactants: *trans*- β -nitrostyrene, aldehydes, ketones, α,β -unsaturated ketones, nitroalkanes, β -ketoesters and solvents were of analytical grade and used as provided by suppliers.

In a typical reaction, the given amount of amino acid and inorganic oxide were introduced into a glass vial followed by the addition of the solvent and the reactants. The slurry was stirred magnetically for the given reaction time, diluted with the solvent and centrifuged. The supernatant solution was analysed by GC-MSD for identification of the products and by GC-FID to determine the conversions and stereoselectivities. The addition products were purified by flash chromatography for determination of the yields. The purity of the products was checked by ^1H and ^{13}C NMR spectroscopy. The inorganic-organic hybrid materials were examined by infrared spectroscopy, powder X-ray diffractometry and scanning electron microscopy.

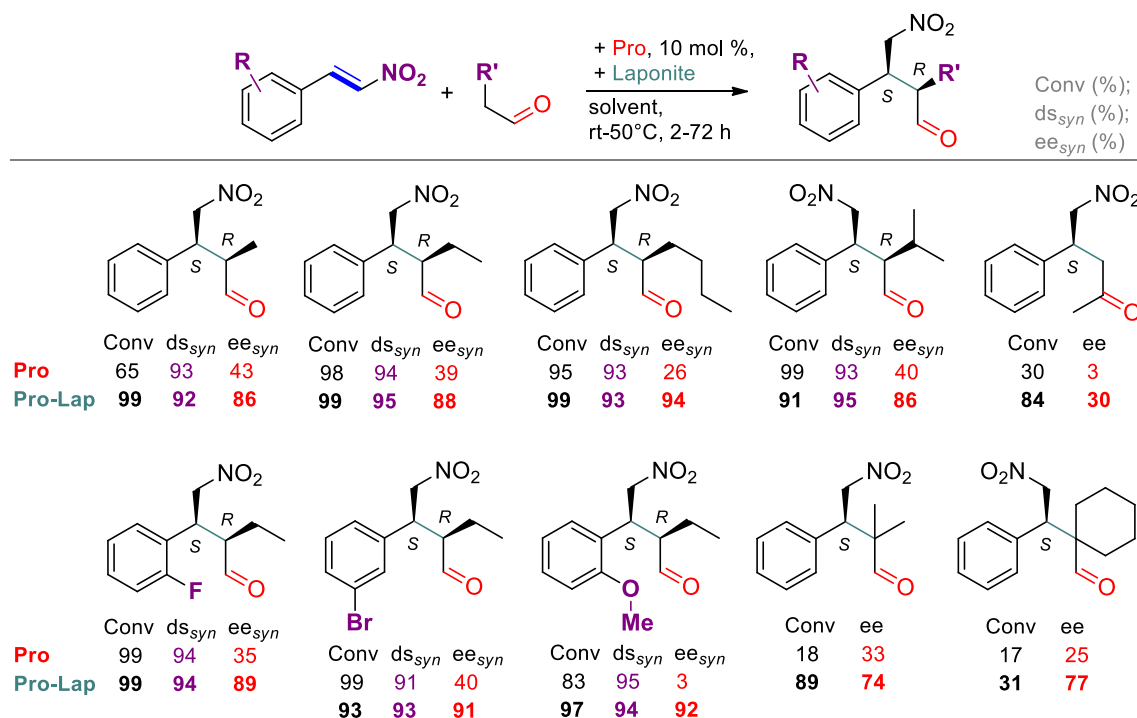
Results and discussion

In our initial investigation, we examined the scope of the proline catalyzed Michael addition of aldehydes to β -nitrostyrenes, a reaction occurring through enamine activation, similarly as the organocatalytic asymmetric aldol addition of ketones to aldehydes. In the latter reactions, inversion of the sense of the enantioselectivity was observed by addition of γ -alumina, explained by the involvement of the solid surface in the stereoselective step [5]. During an initial screening, various oxide additives were tested. As compared with the reaction using solely the L-proline (Pro) as catalyst, the enantioselectivity of the reaction increased significantly in the presence of $\gamma\text{-Al}_2\text{O}_3$, montmorillonite, bentonite and laponite (Lap). The latter material gave the best values in the addition of butanal to β -nitrostyrene. The scope of the reaction was found to be broad; in the reaction of several linear aldehydes high enantiomeric excesses (ee) were obtained (Figure 1). Substituents on the phenyl ring had small effects on the enantioselectivities. In the addition of α -branched aldehydes also increased both the conversions and the enantiomeric excesses in the presence of laponite, however lower values were obtained as compared with reactions of the linear aldehydes. The reactions of ketones was also accelerated and improved enantioselectivities were obtained, although, in these reactions the ee values remained low.

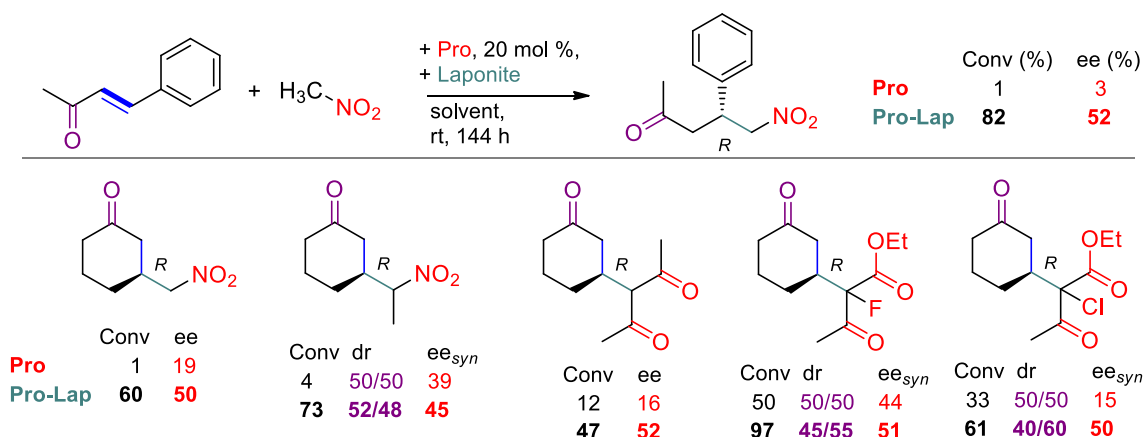
The adsorption of Pro on laponite with the involvement of the surface silanol groups, i.e. by hydrogen-bonding, was demonstrated by infrared spectroscopy. To determine the location of the amino acid attached to the Lap particles X-ray diffractometric investigations were carried out, which indicated the adsorption of Pro on the surface of Lap particles. This may explain the relatively easy partial desorption of the amino acid during reaction upon recycling. However, the recovered solid hybrid material could be recycled several times with only a small decrease in its activity. Results obtained with pyrrolidine derivatives used instead of

Pro, showed that the carboxylic acid group play role in anchoring the amino acid on the surface. Acceleration of the reaction may be attributed to the presence of the acidic surface silanol groups. As in homogeneous reactions acid additives influenced only the diastereoselectivity of the reaction, while the ee was not affected, the ee increase observed in the surface reactions may be ascribed mostly to steric effects.

Figure 1. Results of the asymmetric Michael addition of carbonyl compounds to β -nitrostyrene derivatives catalyzed by Pro or Pro-Lap hybrid material.



According to the above-described results obtained in Michael additions occurring via enamine mechanism, Pro adsorbed on the surface of an inorganic oxide may increase the activity of the organocatalyst accompanied by a significant increase of the stereoselectivity, if steric constraints allow the approach of the reactants to the chiral centre situated on the surface. Our next goal was to test other Michael additions, which proceed through iminium salt formation in order to attempt further extension of the scope of the developed inorganic-organic chiral hybrid catalyst. Results obtained in the additions of nitromethane or nitroethane to 4-phenyl-3-buten-2-one or 2-cyclohexen-1-one are presented in Figure 2. Minor conversions and low enantioselectivities were obtained when Pro was used as catalyst. The presence of laponite increased significantly the conversions, thus, the corresponding products were obtained in good yields.

Figure 2. Results of the Michael addition of various nucleophiles to α,β -unsaturated ketones using Pro or Pro-Lap catalysts.

The enantiomeric excesses also increased, however, in all three reactions only around 50% ee could be reached. Similarly, in reactions of acetylacetone or α -substituted acetoacetates with 2-cyclohexen-1-one, both the conversions and the ee values increased with Pro-Lap, as compared with Pro. Interestingly, in these transformations also enantiomeric excess values around 50% were reached, although the structure of the Michael donor differed significantly in comparison with the nitroalkanes. However, these results showed without any doubt that in presence of Lap the reactions occur on the surface of the *in-situ* formed chiral hybrid material. According to the above results, we reached to the conclusion that in asymmetric reactions proceeding through iminium activation the structure of the surface species formed by participation of the adsorbed amino acid and the unsaturated ketone will determine the stereochemical outcome of the reactions, whereas the structure of the donor has only marginal effect. Moreover, the similar results obtained with the two unsaturated ketones indicated that the stereochemistry of the surface reaction is influenced mostly by the adsorbed organocatalyst, thus we may anticipate a large substrate scope of this chiral heterogeneous catalytic system.

Conclusions

In summary, during our studies, we have attempted the development of novel heterogeneous catalysts by adsorption of natural amino acids on the surface of inorganic oxides. These materials formed either *in-situ* during reactions or prepared *ex-situ*, were tested in various asymmetric Michael additions occurring both through enamine and iminium activation. Amino acids adsorbed on laponite were found the most efficient in catalyzing the addition of aldehydes or ketones to nitrostyrene. The material obtained by adsorption of proline was found to be a highly active and stereoselective catalyst, comparable with the laboriously prepared synthetic chiral organocatalysts. In the Michael addition of nitroalkanes or β -ketoesters to unsaturated ketones also increased conversions and enantioselectivities were obtained in the presence of oxide additives. In the latter reactions the similar enantiomeric excesses showed that the stereochemical outcome of the additions is influenced mostly by the structure of the oxide and the amino acid, thus a generally applicable asymmetric heterogeneous catalytic system was developed. Our results demonstrated that an inorganic oxide may have beneficial effect on the asymmetric reaction catalyzed by a chiral organocatalyst immobilized on its surface by simple adsorption, due to a surface improved

asymmetric catalytic process. Accordingly, these hybrid materials are promising candidates for future application in environmentally friendly processes.

Acknowledgements

Financial support by the UNKP-19-3-SZTE-153 New National Excellence Program of the Ministry of Human Capacities (V. J. Kolcsár) is appreciated.

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