NATURAL CHIRAL CATALYSTS ON SOLID SURFACES USED IN MICHAEL ADDITION TO MALEIMIDES

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Abstract

As the most important molecules in living organisms are chiral, the selective production of the optical isomers of substances designed to interact with them, such as drugs, is of paramount importance. In addition, from an environmental point of view, it is also desirable to carry out the asymmetric syntheses as efficiently as possible, thus minimising waste production. Asymmetric catalytic syntheses are one of the best methods for producing enantiomerically pure compounds, whereby the heterogenization of the chiral catalysts can allow their reuse. A simple method to heterogenize chiral catalysts is the adsorption of optically pure material on a solid surface. Some examples of the use of heterogeneous chiral catalysts that can be readily prepared by adsorption are known, however, solids of this type have not yet been used in reactions of maleimides.

Based on these, we set out to explore the combined catalytic effect of natural amino acids and various inorganic oxides in Michael additions between maleimides and aldehydes. The investigation of a variety of starting materials provides an opportunity to study the activity, stereoselectivity and the applicability of these simple chiral catalysts. Our studies have shown that while natural amino acids have only negligible catalytic activity, adsorption on different oxide surfaces (alumina, bentonite or laponite) gave succinimide derivatives with excellent conversions and enantioselectivities. In conclusion, our research has led to the development of a novel chiral heterogeneous catalytic system that can be used to produce valuable optically pure intermediates for use in the pharmaceutical industry.

Introduction

Nowadays, asymmetric organocatalysis is one of the most dynamically developing area of the synthetic chemistry. Inexpensive, readily available natural chiral compounds, such as alkaloids, tartaric acid, and amino acids, are often used to prepare common asymmetric organocatalysts [1]. A major disadvantage of catalysts soluble in the reaction media is that they are difficult to recover, thus the possibility of reusability is lost in many cases.

So-called atom-economic and sustainable processes are also becoming important in the fine chemical industry. In the field of organocatalysis, reactions with asymmetric heterogeneous catalysts are of increasing importance, in which the solid source of chirality can be mechanically separated from the reaction mixture, thus allowing its reusability [2-4]. One of the simplest ways of heterogenization is to attach the homogeneous chiral catalyst to a support that is not soluble in the reaction mixture. Natural amino acids are inexpensive, readily available chiral organocatalysts, but only few catalytic systems are known in which they have been immobilized by adsorption or hydrogen bonding despite this may improve their activity and stereoselectivity in asymmetric reactions [5].

The organocatalysts have various applications in asymmetric C-C coupling reactions, such as the synthetically important Michael addition reactions. The diversity of the starting materials allows the synthesis of a wide range of products of practical interest. Among the Michael acceptors used, maleimide derivatives are outstanding because the succinimides formed can be

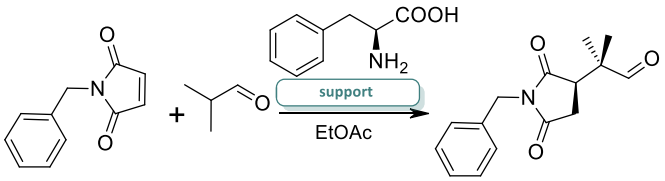
used as valuable intermediates in the pharmaceutical industry [6,7]. There are many succinimide derivatives in the literature that have been applied for the treatment of cancer, epilepsy, the HIV virus infection and degenerative diseases [8,9].
One of the simplest ways to bind the chiral material to the surface of the support is by simple adsorption. An amino acid-hydrotalcite hybrid catalyst has recently been prepared by high-speed ball milling, which afforded excellent results in the Michael addition of maleimides and aldehydes [10]. A major advantage of heterogeneous catalysts created by second-order interactions is that they do not need to be attached to the insoluble support in a preliminary step, as they self-assemble *in situ*. We aimed to use natural amino acids adsorbed on inorganic oxide surfaces as chiral catalysts in Michael additions between maleimides and aldehydes. Our plan was to study the effect of the structure of the α-amino acid and the influence of the applied inorganic oxide on the outcome of the C-C coupling in a selected test reaction, *i.e.* the addition of isobutyraldehyde to *N*-benzylmaleimide, which we have previously investigated using bifunctional homogeneous organocatalysts [11]. Our goal is to develop an environmentally friendly catalytic system in which a new, efficient and reusable catalyst is applied.

Experimental

Natural amino acids were purchased from Sigma-Aldrich and used as received. Isobutyraldehyde and a few *N*-substituted maleimides were commercial products and were used without purification. Solvents, reagents and inorganic additives of analytical grades were used in all reactions. To prepare new maleimides we purchased analytical grade primary amines and maleic anhydride. Maleimides were synthesized using sodium acetate and acetic anhydride in one day at 70°C. The crude products were purified by flash chromatography. The hybrid catalyst was prepared *in situ* in the reaction mixture.
Catalytic Michael additions were performed in vials with magnetic stirring. The chiral catalyst and the inorganic oxide were suspended in the given solvent, followed by the addition of a maleimide derivative and four equivalents of isobutyraldehyde. The mixture was stirred at the indicated temperature. After the given time, the products were separated by centrifugation and analysed by GC-MSD and GC-FID using chiral capillary columns. Larger scale experiments were also carried out and the resulted products were purified by flash chromatography for determination of the isolated yields. The pure compounds were characterized by ^{1}H- and ^{13}C-NMR spectroscopy. The chiral hybrid materials were investigated by FT-IR and Raman spectroscopy, XRD measurements and scanning electron microscopy.

Results and discussion

Due to the prominent importance of succinimides, our primary goal was to develop a sustainable catalytic system for the C-C coupling reaction of maleimides and aldehydes in an enantioselective manner. Our research group has already investigated a similar catalytic system in other Michael additions [5], which provided a good starting point for the design of our catalytic system. L-phenylalanine was selected as chirality source on the basis of literature results and applied in our test reaction by *in situ* adsorption on different oxide supports (Scheme 1.) [7,10].



Scheme 1. Michael additions using L-Phe on inorganic supports.

In the first step, we investigated the effect of inorganic oxide quality in the Michael addition of *N*-benzylmaleimide and isobutyraldehyde using L-Phe natural amino acid (Figure 1). It can be seen on the figure that the reaction proceeds with minimal transformation without solid support. Using acidic oxides the conversion of succinimide is low, similar with the reaction carried out without additive. Al_2O_3 with a slightly basic surface and the cation-exchanger clays Laponite (Lap-RD) or Bentonite (Ben-H) with layered structures provided excellent conversions and high enantioselectivities.

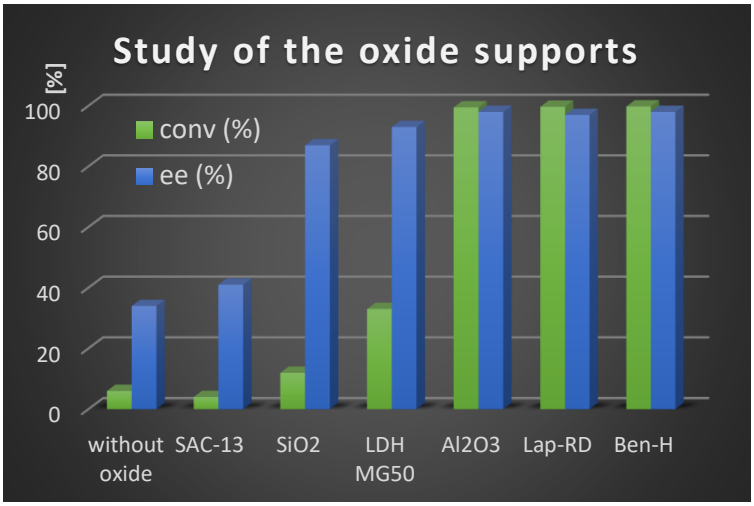


Figure 1. Testing the quality of inorganic oxide supports.

In our further studies Bentonite was chosen from these inorganic supports, because it is one of the cheapest, easily obtainable clay mineral. In the next step, we investigated the effect of the amount of this oxide, which is shown in Figure 2. Very small amounts of the oxide support are sufficient to form close to optically pure succinimide by complete transformation of the maleimide. It can also be seen that the amount of oxide has no effect on the enantioselectivity but it has an effect on the reaction rate.

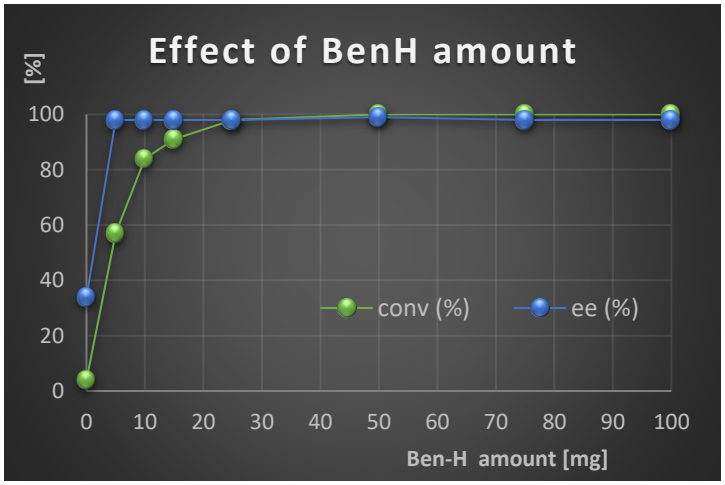
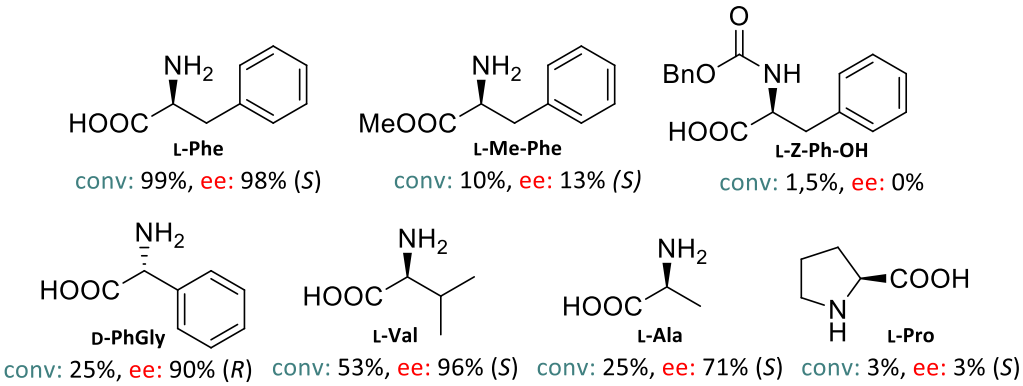


Figure 2. Effect of the amount of bentonite in the test reaction.

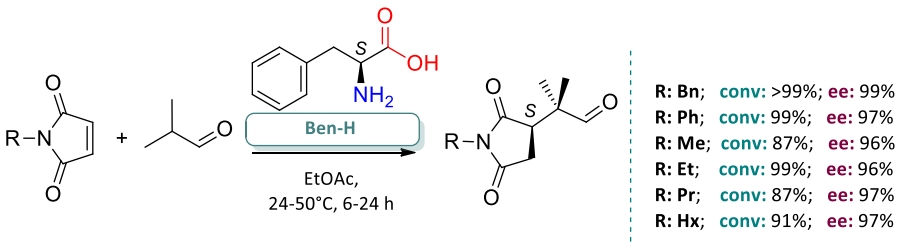
The effect of amino acid structure was also investigated (Scheme 2.). The results show that both the carboxylic acid group and the amino group play a key role in the catalysis. When other

open-chain primary amino acids were used, only moderate conversion values and low enantioselectivities were obtained, so that in comparison with phenylalanine, it appears that carbon chain quality plays a significant role in steric hindrance. The amino acid with a ring structure (L-Pro) is not properly involved in the catalysis.



Scheme 2. Testing different amino acids on bentonite in the test reaction.

The best performing catalyst, natural L-Phe on bentonite, was used to optimize the reaction conditions. The effects of temperature, reaction time, solvent and reactant quantity and quality were studied to achieve full conversion of the maleimides and isolation of the corresponding products with high enantioselectivity. Several promising maleimide derivatives, which are not commercially available, were identified as potential candidates for reaction and were prepared and purified. The results in Scheme 3. show that maleimides containing aliphatic groups at the *N*-position also gave good results, but did not reach the values obtained in the presence of the aromatic system. Thus, we could extend of the applicability of the reaction in Michael additions with isobutyraldehyde in the catalytic system described above, which opened a favorable route to the preparation of optically pure succinimides with diverse structures.



Scheme 3. Using L-Phe and BenH hybrid heterogenous catalyt in the test reaction.

Accordingly, we have succeeded in developing heterogeneous catalysts using inexpensive natural amino acids and readily available inorganic oxides that retain their activity after repeated use, rivalling the results of catalysts used in the homogeneous system. This represents a major step forward towards environmentally friendly heterogeneous catalytic methods as opposed to the use of expensive chiral organocatalysts.

Conclusion

In our research, we have developed a catalytic system that has the potential to produce valuable optically pure intermediates for the pharmaceutical industry. We have succeeded in developing low-cost, solid, reusable chiral catalysts with natural amino acids and inorganic oxides, which can be used to achieve similar or better results than the soluble chiral catalysts used to date. The

applicability of the organic–inorganic hybrid catalysts were investigated in several asymmetric conjugate additions to various maleimides. With this organocatalyst, high conversions and enantioselectivities can be achieved in Michael additions of aldehydes, thus provided and environmentally benign method for the preparation of optically pure succinimides. This represents a major step forward in the application of heterogeneous catalysis in the pharmaceutical industry for the environmentally friendly and sustainable production of optically pure intermediates.

Acknowledgements
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References

[1] B. List (Ed.), Science of Synthesis: Asymmetric Organocatalysis 1, Lewis Base and Acid Catalysts, Thieme, Stuttgart, 2012.
[2] *Chiral Catalyst Immobilization and Recycling*, D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs (Eds), Wiley- VCH, Weinheim, **2000**.
[3] *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques and Applications*, M. Gruttadauria, F. Giacalone, (Eds.), John Wiley & Sons, Hoboken, NJ, **2011**.
[4] *Enantioselective Homogeneous Supported Catalysis*, R. Sebesta (Ed.), RSC Green Chemistry No. 15, RSC Publ., Cambridge, 2012.
[5] Gy. Szőllősi, D. Gombkötő, A. Zs. Mogyorós, F. Fülöp, *Adv. Synth. Catal.* **2018**, *360*, 1992-2004.
[6] *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Toll for the Stereocontrolled Synthesis of Complex Molecules,* J. L. Vicario, D. Badía, L. Carrillo, E. Reyes (Eds.), RSC Publ., RSC Catalysis Series No. 5, Cambridge, **2010**.
[7] C. G. Kokotos, *Org. Lett.* **2013**, *15*, 2406–2409.
[8] C. Freiberg, H. P. Fischer, N. A. Brunner, *Antimicrob. Agents Chemother.* **2005**, *49*, 749–759.
[9] S. E. Michalak, S. Nam, D. M. Kwon, D. A. Horne, C. D. Vanderwal, *J. Am. Chem. Soc.* **2019**, *141*, 9202–9206.
[10] J. M. Landeros, C. Cruz-Hernández, E. Juaristi, *Eur. J. Org. Chem.* **2021**, 5117-5126.
[11] Kozma, F. Fülöp, Gy. Szőllősi, *Adv. Synth. Catal.* **2020**, *362*, 2444-2458.