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ENANTIOSELECTIVE HETEROGENEOUS CATALYTIC HYDROGENATIONS

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Introduction

In 1848 Louis Pasteur discovered that two tartaric acid molecules of otherwise identical properties differed in the sign of their optical rotation. This fundamental discovery was the basis for the development of stereochemistry with far-reaching implications in organic and biochemistry. Soon it was also realized that the biological activity of the two enantiomers can differ considerably, e.g. natural L-asparagine is bitter, whereas artificial D-asparagine is sweet.

Today, pharmaceuticals and vitamins, agrochemicals, flavors and fragrances are increasingly produced as enantiomerically pure compounds. This trend has made the economical enantioselective synthesis of chiral performance chemicals a very important topic.

Four general approaches for producing enantiopure (e.e.>99%) or enantioenriched compunds have evolved:

(i) separation of enantiomers via classical resolution, i.e. crystallization of diastereomeric adducts;

(ii) the chiral pool approach, i.e. the use of chiral building blocks originating from natural products for the construction of the final molecule;

(iii) use of enzymatic and microbial transformations;

(iv) enantioselective syntheses with help of chiral auxiliaries that are not incorporated in the target molecule. The most attractive variant of this approach is of course the enantioselective chemical catalysis where the expensive chiral auxiliary is used in catalytic amounts.

In our research group the asymmetric heterogeneous catalytic hydrogenations have been investigated for many years. During my PhD work I have studied two enantioselective reactions, the enantioselective hydrogenation of the carbonyl group of ethyl pyruvate and that of the carbon-carbon double bond of isophorone. In these reactions a chiral compound, named chiral modifier is added to the reaction mixtures in catalytic amount which induces the enantioselection. The aim of my work was to use novel chiral modifiers beside the known ones in model reactions in order to broaden the scope of the chiral modifiers and to understand the enantiodifferentiation by using modifiers with different structures.

Only a small group of chiral compounds can be used as chiral modifier. As result of the extensive work with modified reactions it turned out that the chiral modifier has to fulfil some structural requirements, i.e. it has to be capable of anchoring on the catalyst surface (condensed aromatic ring) and of interacting with the substrate (e.g. basic amine function). Whereas the *(S)*-α,α-diphenil-2-pyrrolidinemethanol fills all these requirements, it was tested as modifier in the hydrogenation of isophorone and ethyl pyruvate. This molecule has already been used as ligand in homogeneous enantioselective catalytic reduction of prochiral ketons. There were also synthesized the derivatives of this compound, the *(S)*-α,α-dinaphthyl-2-pyrrolidinemethanol and the *(2S)*-2(diphenylmethyl)pyrrolidine.

It was found previously in the hydrogenation of isophorone that the *(S)*-proline is a good chiral auxiliary (e.e. up to 60 %). The chiral auxiliary was added in stoichiometric amount to the solution of the reactant. The hydrogenation reaction itself proved to be diastereoselective as an oxazolidine type intermediate was formed in condensation reaction between isophorone and (*S*)-proline. Based on this study it was supposed that the esterification or amide formation of the (*S)*-proline with condensed aromatic ring containing molecules could result effective chiral modifiers in the asymmetric heterogeneous hydrogenation of isophorone and ethyl pyruvate. Thus the *(S)*-proline 2-napthyl ester, *(S)*-proline 2-(2-napthyl)-ethyl ester, *(S)*-proline 3-ethyl-indole ester and *(S)*-proline-3-ethyl-indolamide were synthesized. *(S)*-proline-2-naphthylamide hydrochloride was also used, which was commercially available. All these compounds were tested in the hydrogenation of isophorone and ethyl pyruvate.

In the enantioselective reactions the effect of the parameters was studied, which are important for the catalytic performance: solvent nature, concentration of the reactant, the modifiers and the catalyst.

It has been found previously in the enantioselective hydrogenation of isophorone in the presence of (-)-dihydroapovincaminic acid ethyl ester that the presence of the chiral modifier and the substrate during the reduction of the oxide layer on the catalyst surface is beneficial for the enantioselectivity. This phenomenon was investigated in more detail in the presence of various effective chiral modifiers using different pretreatment.

Summary

It was investigated the asymmetric effect of pyrrolidine methanol derivatives and (*S*)-proline esters and amides in the hydrogenation of C=C bond of isophorone and C=O bond of ethyl pyruvate. The common features of the used synthetic chiral compounds were the basic amine function in a rigid chiral environment and an aromatic ring system. It can be assumed that the basic secondary nitrogen atom is responsible for interaction with the reactant, while the aromatic ring might be the anchoring part.

Among the pyrrolidine methanol derivatives the *(S)*-α,α-diphenyl-2-pyrrolidinemethanol (DPPM) gave the best e.e., for isophorone 42%, for ethyl pyruvate 25%. It was supposed that the modifier *(S)*-α,α-dinaphthyl-2-pyrrolidinemethanol (DNPM) with two naphthyl groups had stronger anchoring effect, but it gave lower optical purity. We think that the two naphthyl groups on the same carbon atom make the molecule too bulky, weakens the interaction of the modifier with the catalyst surface. The *(2S)*-2(diphenylmethyl)pyrrolidine (DPMP) gave lower optical purity. As the only difference between the structure of DPPM and DPMP is the hydroxyl group, the absence of this group should be responsible for lower e.e., which besides N, probably helps the interaction with the substrate.

The planned and synthesized chiral molecules induced an e.e. in the hydrogenation of isophorone (e.e. 4-23%) and ethyl pyruvate (e.e. 4-5%). In the hydrogenation of ethyl pyruvate the e.e. values were low, corresponding to our expectations, that the *(S)*-proline as additive in the same reaction gave low optical purity too.

However the e.e. values obtained in the presence of novel chiral modifers are moderate (<50%), these compounds increase the narrow choice of chiral molecules that could be used as modifiers. Furthermore the new findings improve our knowledge about the structural parts needed for asymmetric induction, how to design the appropriate chiral modifiers for heterogeneous hydrogenation. These findings represent steps in the right direction to understand the enantiodifferentiation. It is also useful to produce enantioenriched compounds, because the resolution of them is easier than that of the racemates.

Theses

1. The synthetic *(S)*-α,α-diphenyl-2-pyrrolidinemethanol (DPPM), *(S)*-α,α-dinaphthyl-2-pyrrolidinemethanol (DNPM) and *(2S)*-2(diphenylmethyl)pyrrolidine (DPMP) can be used as chiral modifiers in the enantioselective hydrogenation of C=C bond of isophorone and that of C=O bond of ethyl pyruvate. In their presence the hydrogenation of the reactants resulted in an excess of (*S*)-(+)-dihydro isophorone and (*S*)-(-)-ethyl lactate.
2. The condensed aromatic rings are responsible for the adsorption of chiral modifier on the catalyst surface. The DPPM modifier containing two phenyl groups gave the best e.e., for isophorone 42%, for ethyl pyruvate 25%. The DNPM modifier with two naphthyl groups afforded lower e.e. (isophorone: e.e.~25%, ethyl pyruvate: e.e.~5%), because the two naphthyl groups on the same carbon atom make the molecule too bulky weakening the interaction of the modifier with the catalyst surface. The synthesis of compound containing only one naphthyl group have not been achieved yet.
3. The DPMP resulted in about half the optical purity observed in the presence of DPPM in the hydrogenation of isophorone. As the only difference between the structure of DPPM and DPMP is the hydroxyl group, the absence of this group should be responsible for lower e.e. value. It is supposed that the hydroxyl group plays a crucial role with the basic N atom in the enantiodifferentiation forming a double interaction with the substrate.
4. The interaction between isophorone and the DNPM chiral modifier in solution was detected by circular dichroism spectroscopy.
5. Esterification or amide formation of (*S)*-proline with condensed aromatic ring containing molecules resulted in effective chiral modifiers in the asymmetric heterogeneous hydrogenation of isophorone and ethyl pyruvate. In the hydrogenation of ethyl pyruvate the e.e. values were low (e.e. 4-5%), corresponding to our expectations as the *(S)*-proline as additive in the same reaction gave low optical purity too. In the case of isophorone the results were better (ee~4-23%). The spacer between the anchoring group and the chiral entity was advantageous for optical purity.

6. The polar solvents and solvent mixtures are advantageous for enantioselectivity in the presence of pyrrolidine methanol derivatives and (*S*)-proline esters and amides. In the hydrogenation of isophorone with *(S)*-α,α-diphenyl-2-pyrrolidinemethanol modified palladium the systematic investigation of the effect of solvents contributed to a significant improvement in the enantioselectivity. Using the mixture of equal quantity of water and methanol the optical purity increased by 20 absolute % compared to the reaction made in pure methanol. Acidic and basic additives decreased the enantioselectivity.
7. The e.e. was strongly depended on the type of the catalyst both in the hydrogenation of isophorone and ethyl pyruvate. The Pd black catalyst served the best optical purity in the enantioselective hydrogenation of isophorone, for ethyl pyruvate it was the 5% Pt/Al_2O_3 Janssen catalyst.
8. The enantioselectivity increased with ascending concentration of the chiral modifiers and reached a limit. Increasing the modifier concentration above this value seems to have no significant influence on the optical purity.
9. The presence of the chiral modifier and the substrate during the reduction of the catalyst is beneficial for the enantioselectivity. It can be explained by two argumentations. The one is that during reduction of the catalysts in the presence of the modifier and the substrate new surface sites are forming. There is still no direct experimental proof available for the nature of this beneficial surface restructuring of the catalyst in the presence of the chiral modifier-substrate complex. We assume, that this restructured site forming ability depends on, besides the substrate-modifier-catalyst interaction, the properties of catalyst, like its dispersion, mode of preparation and the support material used. The hydrogenation of a prochiral substrate on appropriate restructured site presumably gives the enantiomeric product in higher excess. On the other hand we should also consider that the effects observed in the present study can be explained with the decreased adsorption of the chiral modifier and the substrate because of the enhanced hydrogen adsorption occurred during the preliminary reduction of the catalyst.

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