CHEMO- AND ENANTIOSELECTIVE
HETEROGENEOUS CATALYTIC
HYDROGENATION OF EXOCYCLIC
$\alpha,\beta$-UNSATURATED KETONES

Ph.D. theses

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In the latest decades the demand for optically pure compounds rapidly increased, for that reason the synthesis of optically active compounds became very important. Asymmetric synthesis has great importance on the one hand, because the raw material demand of the chemical production can be decreased, on the other hand the not effective stereoisomer of a chiral compound often has harmful effect to the living organisms.

Most bioactive compounds are chiral. In some cases the effect of the enantiomers is the same, in other cases one is effective, the other harmless, and the worst case is, when the non-wanted isomer is harmful. In the sixties a tranquillizer, Thalidomid, as racemic mixture was given in the initial period of the pregnancy. The $R$ enantiomer of the racemic drug was tranquillizer, but the $S$ enantiomer had teratogenic effect, therefore more thousand deformed babies were born. Recently it turned out that this compound is able to racemise therefore it can’t be used by no means as a medicine. The pharmaceutical industry tries to decrease the use of racemic drugs, since the unwanted isomer is considered to be an impurity nevertheless in most cases its influence is not dangerous for the human body.

The heterogeneously catalysed enantioselective reactions have been studied more intensively in the last decades. This type of the asymmetric reactions is the most simple, for example a prochiral molecule could be hydrogenated enatioselectively if a chiral molecule was put into the reaction mixture or given to the catalyst. However in the practice these enantioselective heterogeneous catalytic reactions - similarly to the homogenous, or enzyme catalysed systems – are very specific with respect to the reactant. Even the best performing chiral modifier-catalyst system is effective only for a relatively small group of substrates. From the technological point of view the heterogeneous catalysts are much more advantageous than the homogeneous ones, first of all for their easier treatment and separation.

The research group at the Chemical Technology Department of BUTE has been working since about 20 years on asymmetric, first of all on enantioselective heterogeneous catalytic hydrogenations.

Joining to this work I studied the conditions of the chemo- and enantioselective hydrogenation of exocyclic $\alpha,\beta$-unsaturated ketones based on recent analogies (for example: izophorone, $\alpha$-phenyl-cinnamic acid). The model compounds $(E)$-2-benzylidene-1-indanone, $(E)$-2-benzylidene-1-tetralone and $(E)$-2-benzylidene-1-benzosuberone contain two reducible functional groups (C=C and C=O). The objective of my work was the selective saturation of C=C double bond accompanied by producing an optically active product too.
The first step of the study was the determination of the conditions of the chemoselectivity, as beside the C=C double bond the carbonyl-group in α-position is also reducible under the same conditions.

In an enantioselective catalytic hydrogenation the chiral effect can be produced with different methods: a chiral auxiliary is added in stoichiometric amount to the reaction mixture, or a chiral modifier is added in catalytic amount.

The effect of different amino acids, among others that of (S)-proline, as chiral auxiliaries, was tested. As chiral modifiers, different alkaloids (cinchona, ephedrin, vinca), and as the most effective, cinchonidine, were tested.

Both the chemo- and enantioselectivity can be influenced by changing the reaction conditions, I studied the effect of different solvents, achiral additives and different catalysts also.

An additional task was the determination of the absolute configuration of 2-benzyl-1-benzosuberone enantiomers, which was not published in the literature.
1. The exocyclic $\alpha,\beta$-unsaturated ketones, the $(E)$-2-benzylidene-1-indanone (1), the $(E)$-2-benzylidene-1-tetralone (3) and the $(E)$-2-benzylidene-1-benzosuberone (5) can take up three mole hydrogen, the saturation of the $C=C$ and the $C=O$ bonds and the hydrogenolysis of the $C-OH$ bond can occur. The catalytic hydrogenation of the $C=C$ double bond could be performed with complete chemoselectivity. Solvent properties have influence on selectivity, toluene proved to be the best with respect to chemoselectivity. Adding pyridine to the reaction mixture improved selectivity the most. Among the different noble metals the most selective catalyst was the Ru/C, however its activity was very low. Under different conditions the hydrogenation of $(E)$-2-benzylidene-1-benzosuberone afforded the best chemoselectivity ($>90\%$). The different behaviour of the model compounds can be explained with the different flexibility of the 5-7 member rings and with the different conformation of the compounds to be hydrogenated.

2. The absolute configuration of the 2-benzyl-1-benzosuberone enantiomers was determined from NMR and CD data.

3. The hydrogenation of the model compounds in the presence of stoichiometric amount of $(S)$-proline over Pd/C catalyst resulted in high chemoselectivity ($90\%$) and measurable enantioselectivity ($10\%$). In the presence of stoichiometric amount of $(S)$-proline and sodium-methylate optically active products with complete chemoselectivity ($100\%$) were formed, the best enantiomeric excesses in acetonitrile were 13,8\% (1), 10\% (3), 20,1\% (5) respectively. $(S)$-proline favoured the formation of the products with the absolute configuration $R$. The configuration of the enantiomer formed in excess was explained by molecular modelling, regarding its interaction with the catalyst surface and the formed covalent bond between substrate and chiral auxiliary. The initial reaction rate of the reaction with $(S)$-proline is equal with those of without it.

4. The enantioselective hydrogenation of $(E)$-2-benzylidene-1-benzosuberone in the presence of stoichiometric amount of amino acids and sodium-methylate over Pd/C catalyst resulted in optically active product with complete chemoselectivity (with $(S)$-phenyl-alanine $12\%$ ee). The $S$-amino acids favour the formation of product with $R$ configuration, the $R$-amino acids favour the product with $S$ configuration.
5. Cinchona alkaloid chiral modifiers induced significant enantiomeric excess beside complete chemoselectivity. The modifier concentration influences enantioselectivity, the most favourable was the 100:5 catalyst/modifier mass ratio. The highest value in the case of \((E)-2\text{-benzylidene-1-benzosuberone}\) was achieved in the presence of cinchonidine over Pd black catalyst in absolute toluene (\(S\) enantiomer was formed with 53.7% optical purity). The initial reaction rate with cinchonidine was one fifth of the one without the modifier.

6. The different cinchona alkaloids afforded different enantiomeric excesses and configurations, with \((E)-2\text{-benzylidene-1-benzosuberone}\) cinchonine and the quinine resulted in the \(R\) enantiomer with 36% optical purity whilst cinchonidine and quinine in the \(S\) enantiomer with 54% optical purity. \((E)-2\text{-benzylidene-1-indanone}\) gave with cinchonidine over Pd black catalyst in methanol the \(S\)-enantiomer with 9.6% optical purity. \((E)-2\text{-benzylidene-1-tetralone}\) gave with cinchonidine over Pd/TiO\(_2\) catalyst in acetonitrile the \(R\) enantiomer with 9.1% optical purity.

7. Other modifiers, (-)-dihidroapovincaminic acid-ethylester (11.3%), the (-)-pseudo-ephedrin (8.8%) and the \((R,R)-(\pm)\text{-O,O’-dibenzoyl-tartaric acid}\) (11.1%) afforded also measurable enantiomeric excesses in the hydrogenation of the \((E)-2\text{-benzylidene-1-benzosuberone}\).

8. A model based on the linkage between the tertiary nitrogen of the alkaloid and the keto group of the substrate and the steric hindrance in this transitional komplex was proposed for the enantiodifferentiating interaction of cinchonidine and \((E)-2\text{-benzylidene-1-benzosuberone}\).
Publications:


Conferences:


