Enantioselective hydrogenation of aliphatic α,β-unsaturated acids over cinchona-modified Pd catalyst

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Ph.D. Dissertation Thesis

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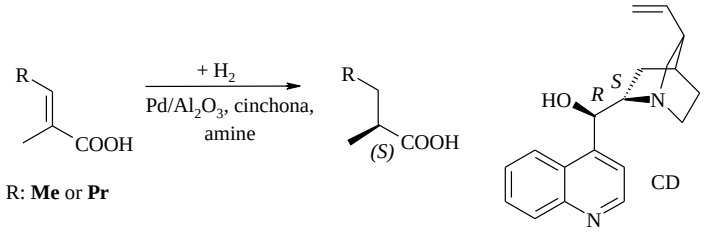
1. Introduction

Enantioselective hydrogenations are among the most useful catalytic methods for preparing optically pure chiral intermediates. A large variety of chiral metal complexes have been developed and applied in the asymmetric hydrogenation of a wide range of substrates. Promotion of green and environmental benign processes initiated the development of heterogeneous catalytic systems as alternatives of chiral complexes. A simple approach to obtain catalytically active chiral materials for hydrogenation is the modification of metal surfaces with adsorbed optically pure organics.

Supported Pd catalysts modified by cinchona alkaloids were found to provide high enantioselectivities in the hydrogenation of prochiral olefins. Excellent enantiomeric excesses (ee) were obtained in reactions of *(E)*-2,3-diphenylpropenoic acids. The use of an achiral amine additive, such as benzylamine increased the enantioselectivity in these hydrogenations.



Scheme Enantioselective hydrogenation of *(E)*-2-methyl-2-butenoic acid (TG) and *(E)*-2-methyl-2-hexenoic acid (MHA) over cinchonidine modified Pd/Al_2O_3

Lower enantioselectivities could be attained in the hydrogenation of aliphatic α,β-unsaturated carboxylic acids. Recently, it was found that the use of benzylamine additive also increases the ee in the

hydrogenation of aliphatic carboxylic acids (see scheme). However, the effect of the structure of the achiral amine additive was studied only in the hydrogenation of (E)-2,3-diphenylpropenoic acid and itaconic acid.

Here I disclose the results of my study on the effect of the achiral amine additive structure on the enantioselective hydrogenation of (E)-2-methyl-2-butenoic acid and *(E)*-2-methyl-2-hexenoic acid (see Scheme 1) over cinchona alkaloid modified Pd catalyst.

2. Experimental

Substrates used in our experiments were commercially. Hydrogenations were carried out in stainless steel autoclaves equipped with a pressure transmitter (P40, PMA GmbH) and with glass liner.

Under typical conditions 15 mg 5% Pd/Al_2O_3, 10 cm^3 solvent, 0.05 mmol cinchona, 1 mmol acid and 1 mmol amine additive were loaded into reactor, the autoclave was flushed with H_2, filled to 5 MPa H_2 and the reaction was commenced by stirring the slurry using magnetic agitation (1000 rpm) at room temperature (295 K). Initial H_2 uptake rates (R_{Hi}) were calculated from the recorded pressure drops up to 40±5% conversions corrected with the uptake registered in the absence of the acid. After the given time (t) the H_2 was released, the slurry was filtered, the solution was treated with 10% HCl aq solution, dried over $NaSO_4$ and analyzed.

Products were identified by mass spectrometry. The quantitative analysis, i.e. conversions and enantiomeric excesses were determined using chiral chromatography.

3. Novel Scientific Results

Effect of amine additives [1,2]

I. It was ascertained that the addition of one equivalent of primary amine increases the enantioselectivity in the enantioselective hydrogenation of TIG and MHS over cinchonidine modified Pd catalyst. A variety of amines were found effective in increasing the ee, always accompanied by a decrease in the initial rate.

II. We have found that secondary amines are similarly or even more effective in increasing the enantioselectivity as primary ones. It was shown that the basic strength of the additive may be varied in relatively wide range (from pKa 9.5 to 11.5). However, the amines beside the right basicity must also fulfil steric requirements in order to provide high enantioselectivities.

III. The most efficient amine additives were found benzylamine (BA) and the newly found N-methylbenzylamine (NMBA).

IV. An increase in the chain length of the aliphatic amines decreased the initial rate, accompanied by moderate increase in the enantioselectivity.

Hydrogenation temperature [1,2]

V. Decreasing the hydrogenation temperature to 273 K increased more the ee in the presence of amines when compared with amine free hydrogenations. In consequence *(S)*-2-methylhexanoic acid could be prepared in up to 71% optical purity, unprecedented in enantioselective hydrogenations of aliphatic unsaturated carboxylic acids over chirally modified heterogeneous catalyst..

Effect of the achiral amine amount [2]

VI. Using less then 1 equivalent (eq., as compared with the acid) of either amines the ee increased continuously by increasing the amine amount, the maxima in the presence of BA was obtained at 1 eq. of amine, whereas with NMBA the ee increased up to 1.5 eq. in the hydrogenation of both acids (TIG, MHA).

The catalyst amount dependence [2]

VII. The use of various catalyst amounts indicated kinetically controlled reaction under the typical conditions. Based on the decrease in the number of active sites in presence of amines we assumed that these take part in the formation of the surface intermediate.

Effect of solvent dependence [3]

VIII. The solvent dependence of the ee in the presence of amines indicated that these additives are involved in the rate determinant step of the reaction.

IX. Dilution effects were in agreement with the participation of acid dimers in reactions carried out in aprotic solvents, whereas protic solvents interfere in the modifier–acid interaction.

Effect of the modifier concentration and structure [3]

X. The influence of amines on the effect of modifier concentration showed the involvement of the adsorbed additive in the reaction possibly by participating in the formation of the intermediate responsible for the enantioselection.

XI. These suggestions were confirmed by ees obtained over catalyst modified by cinchona alkaloid derivatives and deviations from the linear behavior obtained using modifier 1/1 mixtures.

XII. Based on these results combined with published data, i.e. the effect of the amine amount and the structure of the intermediate in the absence of amine additives, we suggest structures shown in Fig. as possible surface intermediate complexes formed in the presence of amine additives in aprotic solvents.

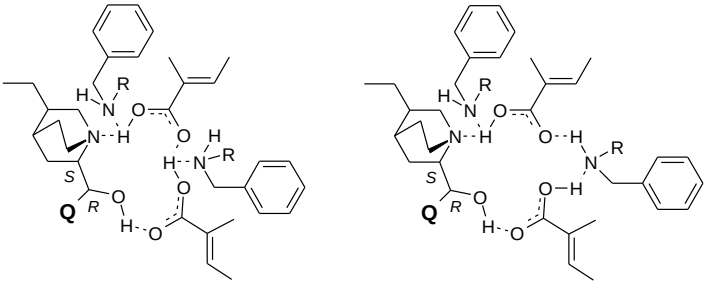


Fig. Possible surface intermediate complexes formed in the presence of amine additives in aprotic solvents

4. Publications Related to the Subject of the Dissertation

[1] Gy. Szőllősi, Zs. Makra, M. Bartók: Enantioselective hydrogenation of *(E)*-2-methyl-2-butenoic acid over cinchonidine modified pd catalyst. Effect of the structure of achiral amine additives

React. Kinet. Mech. Catal. **96** (2009) 319.

IF.: 0.557

[2] Zs. Makra, Gy. Szőllősi, M. Bartók: Achiral amine additives in the enantioselective hydrogenation of aliphatic α,β-unsaturated acids over cinchonidine-modified Pd/Al_2O_3 catalyst

Catal. Today **181** (2012) 56.

IF.: 2.980

[3] Zs. Makra, Gy. Szőllősi: Hydrogenation of *(E)*-2-methyl-2-butenoic acid over cinchona-modified Pd catalyst in the presence of achiral amines: Solvent and modifier effect

Catal. Commun. **46** (2014) 113.

IF.: 2.915

5. Lectures and Posters Related to the Dissertation

1. Makra Zs.: Amin adalékok hatása alifás α,β-telítetlen karbonsavak heterogén enantioszelektív hidrogénezésére

XXXI. Kémiai Előadói Napok, Szeged, **2008.**

2. Szőllősi Gy., Makra Zs.: Effect of amine additives on the heterogeneous enantioselective hydrogenations of aliphatic α,β-unsaturated carboxylic acids

Tenth International Syposium on Heterogeneous Catalysis, Varna, Bulgaria, **2008.**

3. Makra Zs.: Amin adalékok hatása alifás α,β-telítetlen karbonsavak heterogén katalitikus enantioszelektív hidrogénezésére

A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 9. tudományos előadóülése, Szeged, **2009.**

4. Makra Zs.: Telítetlen karbonsavak enantioszelektív hidrogénezése heterogén katalizátoron

XXXII. Kémiai Előadói Napok, Szeged, **2009.**

5. Makra Zs., Szőllősi Gy., Bartók M.: Telítetlen karbonsavak enantioszelektív hidrogénezése heterogén katalizátoron amin adalékok jelenlétében

MKE 1. Nemzeti Konferencia, Sopron, **2011.**

6. Makra Zs.: Alifás α,β-telítetlen karbonsavak enantioszelektív hidrogénezése módosított Pd-katalizátoron

Katalízis Munkabizottság, Budapest, **2013.**

6. Further Publications

[1] Gy. Szőllősi, Zs. Makra, F. Fülöp, M. Bartók: The first case of competitive heterogeneously catalyzed hydrogenation using continuous-flow fixed-bed reactor system: hydrogenation of binary mixtures of activated ketones on Pt-alumina and on Pt-alumina-cinchonidine Catalysts, *Catal Lett.* **141** (2011) 1616.

IF.: 2.242

[2] Gy. Szőllősi, Zs. Makra, M. Fekete, F. Fülöp, M. Bartók: Heterogeneous enantioselective hydrogenation in a continuousflow fixed-bed reactor system: hydrogenation of activated ketones and their binary mixtures on Pt–alumina–cinchona alkaloid catalysts, *Catal Lett.* **142** (2012) 889.

IF.: 2.244

[3] Gy. Szőllősi, Zs. Makra, L. Kovács, F. Fülöp, M. Bartók: Preparation of optically enriched 3-hydroxy-3,4-dihydroquinolin-2(1H)-ones by heterogeneous catalytic cascade reaction over supported platinum catalyst, *Adv. Synth. Catal.* **355** (2013) 1623.

IF.: 5.535

7. Further Lectures and Posters

1. Makra Zs.: Aktivált ketonok kompetitív hidrogénezése átáramlásos rendszerben

XXXIV. Kémiai Előadói Napok, Szeged, **2011.**

2. Zs. Makra, Gy. Szőllősi, M. Bartók: Heterogeneous enantioselective hydrogenations in a continuous-flow fixed-bed reactor system

11th Pannonian International Symposium on Catalysis, Obergurgl, Austria, **2012.**

8. Summarized Impact factors

Sum of the impact factors of the publications related to the dissertation: **6,452**

Sum of the impact factors of the other publications: **10,021**

Sum of the impact factors of all publications: **16,473**

Sum of the citations (MTMT, 2014.05.24): **36**

Sum of the citations without selfcitations: **24**