Heterogeneous enantioselective hydrogenation of ketones in presence of cinkona alkaloids

Ph.D. Dissertation Thesis

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1. Introduction

The enantiomers of chiral compounds can act differently in biological system. Accordingly, severe requirements were imposed to the pharmaceutical and agrochemical industry to investigate and use them in optically pure form. Enormous effort has been made to solve the synthesis of the required enantiomers in economically and environmental friendly way.

Among the possibilities the asymmetric catalytic processes are the most convient, because in these it is possible to use less then stochiomeric amount of pure chiral starting material. An important representation of the field is the so-called Orito reaction: the hydrogenation of activated ketones over cinkona alkaloid modified platinum catalysts.

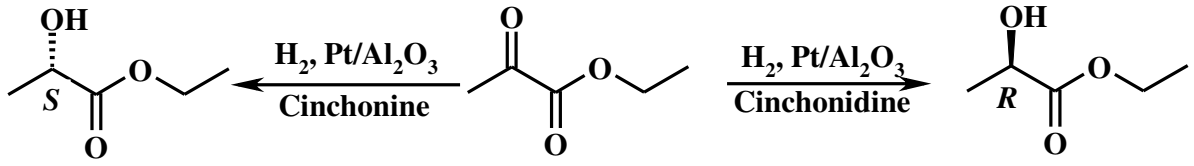
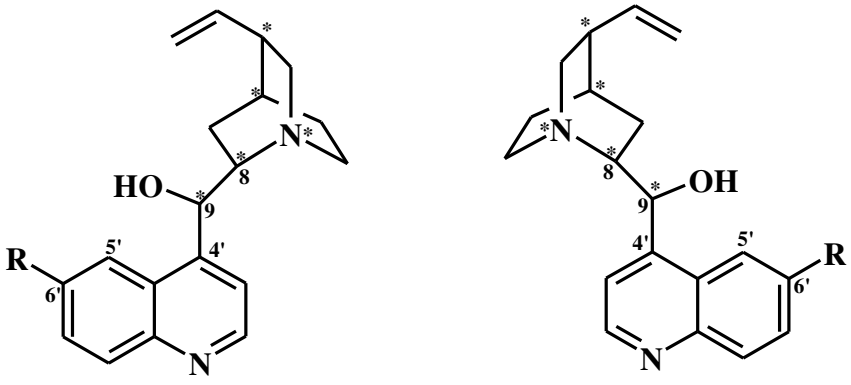


Fig. 1. *The Orito reaction*



Cinchonine: R=H 8(*R*),9(*S*) **Cinchonidine: R=H 8(*S*),9(*R*)**

Quinidine: R=MeO 8(*R*),9(*S*) **Quinine: R=MeO 8(*S*),9(*R*)**

Fig. 2. *The structure of the cinchona alkaloids*

Although, Orito have shown that the reaction can be used for the hydrogenation of a wider range of α-ketoesters, the only substrate examined for a long time was ethyl pyruvate. Our goal was to find new substrates to widen the scope of this reaction, and hopefully help us to understand the reaction mechanism.

2. Experimental

A part of the substrates used in our experiments were commercially available, the others were prepared according to processes published previously. The hydrogenation reactions were carried out in glass reactor under atmospheric pressure, and in a stainless steel autoclave with glass liner under higher pressure. After charging the appropriate quantity of catalyst and solvent into the reactor, the mixture was prehydrogenated for 30 min. Finally, the modifier and the reactant were added into the reactor. The reaction was stirred magnetically, and the hydrogen uptake was followed by a gas burette or a pressure recorder. Samples was withdrawn at the given time, and after the specified reaction time the reactipon was stopped and the catalyst was removed by filtration. The products were identified by mass spectrometry and NMR measurements. The configuration of the products were identified using optical rotation measurements or by comparison with sample with known configuration. The quantitative analysis, i.e. conversions and enantiomeric excesses were determined using chiral chromatography, the enantiomeric and diastereomeric excesses were calculated as ee (*R*) = 100·([R]-[S])/([R]+[S]), de (*threo*) = 100·([threo]-[erythro])/([threo]+[erythro])

3. Novel Scientific Results

Investigation of the effect of α-oxocarboxylic acid esters structure on the enantioselectivity [1,2]

I. The hydrogenation of pyruvic acid methyl, ethyl, isopropyl, isobutytl, *terc*-butyl and neopentyl esters and the ethyl esters of 3-methyl-2-oxobutanoic acid, 4-methyl-2-oxopentanoic acid, phenylglyoxylic acid and 4-phenyl-2-oxobutanoic acid was investigated. Under identical reaction conditions when the size of the ester group was increased the enantioselectivity and the reaction rate decreased lesser then when the size of the alkyl groups of the carboxylic acid was increased.

II. When the ester group was increased, the corresponding (*R*) alcohols could be prepared in over 90 % ee in the presence of cinchonidine, whereas the (*S*) alcohols can be obtained in around 90% ee when cinhonine used as modifier. High enaniomeric excess could also be obtain with the expanded carboxylic parts, but under different the reaction conditions. The 2-oxo-3,3-dimethyl-butanoic acid ethyl ester could be reduced only in 80% e.e.

III. As these results shown, the Orito reaction is a general method for the enantioselective hydrogenation of the α-ketoesters. However the reaction conditions have to be optimized for each substrate separately.

Hydrogenation of esters of phenylglyoxylic acid [3]

IV. The hydrogenation of phenylglyoxylic acid methyl, cyclohexyl, adamantyl, 1- and 2-naphtyl, and 2-decahydronaphthyl esters was investigated in toluene and acetic acid. Under identical conditions the reaction rate of the hydrogenation was higher in toluene then in acetic acid. The enantiomeric excess was around 80%, the only exception was

found to be the reaction of 2-naphthyl ester. As the results showed, these bulky groups do not disturb the interaction of the modifier with the substrates.

V. In the enantioselective hydrogenation of these compounds in presence of β-isocinchonine in toluene inversion of enantioselectivity occurred. (*R*) alcohols formed in excess, while cinchonine and its derivatives gave excess of (*S*) alcohols. Consequently, this inversion phenomena is a general feature of the α-oxocarboxylic acid esters hydrogenation and it is not limited to ethyl pyruvate.

Hydrogenation of α-oxocarboxylic acid derivatives bearing a steroid skeleton [4]

VI. The hydrogenation of 5α-cholestan-3β-yl pyruvate, 5α-cholestan-3β-yl phenylglyoxylate, 3-phenylglyoxyloxy-lithocholic acid methyl ester, methyl 3α-acetoxy-23-oxo-5β-cholan-24-oate was investigated. In the absence of modifier racemic hydrogenation takes place, in spite of the chiral centers present in the substrates. In presence of modifier the diastereoselectivities and the reaction rates of the hydrogenations altered in the same way. In most cases the enantioselectivity was in the range 40-60%, only 3-phenylglyoxyloxy-lithocholic acid methyl ester gave lower ee (14%), presumably because the conformation of the steroid skeleton obstruct the adsorption of the reactant molecule on the metal surface.

Hydrogenation of 2-oxoglutaric acid [5]

VII. 5-oxotetrahydrofuran-2-carboxylic acid is a useful reagent in asymmetric synthesis. Although its multi step synthesis was solved, the hydrogenation of 2-ketoglutaric acid seemed to be a much simpler way to prepare it. In this case the cyclization was spontaneous, and both reactions occured in one step.

VIII. Under the optimized conditions the desired (*R*)-5-oxotetrahydrofuran-2-carboxylic acid was formed in 92% ee in water. This result was significant not only because of the highest ee value obtained in the hydrogenation of ketoacids, but also because the solvent is environmental friendly and economic.

Hydrogenation of ethyl 2-fluoro-3-oxobutanoate [6]

IX. With cinchonidine as modifier, the (*S*) enantiomer of the reactant reacted much faster then the (*R*), and since the rate of racemization was higher then the hydrogenation rate, the product of this reaction was mainly (2*S*,3*R*)-2-fluoro-3-hydroxy butanoic acid ethyl ester. This novel method for producing optically enriched α-flouro-β-hydroxy esters is the first example of spontaneous dynamic kinetic resolution of a racemic fluorinated compound over modified heterogeneous catalyst. Under optimal reaction condition 82% ee was obtained with 95% chemoselectivity and 98% diastereomeric excess in a solvent mixture acetic acid: tetrahydrofurane 5:1 mixture.

X. Accordingly to these results one α fluorine substituent is able to activate ketones for obtaining high ee in their hydrogenation over cinchona modified Pt.

Hydrogenation of 2-fluorocyclohexanone [7]

XI. In the hydrogenation of ethyl-2-fluoro-3-oxobutanoate the ester group can also interact with the modifier and may influence the enantioselective hydrogenation. In order to prove that only one α fluorine substituent can activate a ketone for the Orito reaction, the hydrogenation of 2-fluorocyclohexanone was also investigated. The faster hydrogenation of the (*S*) enantiomer was also observed and the (1*R*,2*S*)-2-fluorocyclohexanol was formed in good selectivity in acidic solvent. In this solvent the racemization rate is small, fast racemization may be obtained using basic catalyst.

Hence only kinetic resolution was attained. Under optimized conditions 59% ee and nearly 80% de were achieved in solvent mixture tetrahydofurane: acetic acid 1:1.

XII. Based on these results we pointed out the one α fluorine substituent can activate ketones for the Orito reaction.

4. Publications Related to the Subject of the Dissertation

1 **Szőri K.**, Sutyinszki M., Felföldi K., Bartók M.: Heterogeneous asymmetric reactions Part 28. Efficient and practical method for the preparation of (*R*)- and (*S*)-α−hydroxy esters by the enantioselective heterogeneous catalytic hydrogenation of α -ketoesters *Appl. Catal. A Gen.* **237** (2002) 275–280.

IF.: 1.915

2 **Szőri K.**, Török B., Felföldi K., Bartók M.: Enantioselective Hydrogenation of α -ketoesters over a Pt/Al_2O_3 catalyst. Effect of steric constraints on the Enantio-selection. *Catalysis of Organic Reactions* (Ed. M.E. Ford), 2000, Marcel Dekker, Inc., Basel, p.489-495.

IF.: -

3 **Szőri K.**, Balázsik K., Felföldi K., Bartók M.: Study of enantioselective hydrogenation of bulky esters of phenylglyoxylic acid on Pt-CD and Pt-β-ICN chiral catalysts: Steric effect of ester groups and inversion of enantioselectivity *J. Catal.* **241** (2006) 149–154.

IF.:4.533

4 **Szőri K.**, Balázsik K., Felföldi K., Bucsi I., Cserényi Sz., Szőllősi Gy, Vass E., Hollósi M., Bartók M.: New data on the effect of steric constraints on the chiral induction in the Orito reaction: Hydrogenation of activated steroid ketones *J. Mol. Catal. A* **294** (2008) 14-19.

IF.: 2.814

5 Felföldi K., **Szőri K.**, Bartók M.: Heterogeneous asymmetric reaction Part 35. Enantioselective hydrogenation of 2-oxoglutaric acid over cinchona modified Pt/Al_2O_3 catalysts *Appl. Catal. A Gen.* **251** (2003) 457–460.

IF.: 2.825

6 **Szőri K.**, Szőllősi Gy., Bartók M.: Dynamic Kinetic Resolution over *Cinchona*-Modified Platinum Catalyst: Hydrogenation of Racemic Ethyl 2-Fluoroacetoacetate *Adv. Synth. Catal*. **348** (2006) 515–522.

IF.: 4.762

7 **Szőri K.**, Szőllősi Gy., Bartók M.: Asymmetric hydrogenation of racemic 2-fluorocyclohexanone over cinchona modified Pt/Al_2O_3 catalyst *J. Catal.* **244** (2006) 255–259.

IF.: 4.533

5. Lectures Related to the Dissertation

1. **Szőri K.**: α-oxokarbonsav-észterek enantioszelektív hidrogénezése *XXV. Kémiai Előadói Napok*, **2002.** Program és előadás-összefoglalók

2. **Szőri K.**: Nagy enantiomer tisztaságú *(R)*-5-oxotetrahidrofurán-2-karbonsav és etilészterének előállítása heterogén enantioszelektív hidrogénezéssel *Szegedi Ifjú Kémikusok Támogatásáért Alapítvány tudományos előadóülése*, **2003.**

3. **Szőri K.:** Fluoroketonok heterogén katalitikus enantioszelektív hidrogénezése *MTA Katalízis Munkabizottság,* **2007.**

6. Posters Related to the Dissertation

1. **Szőri K.**, Török B., Felföldi K., Bartók M.: Enantioselective Hydrogenation of α -ketoesters over a Pt/Al_2O_3 catalyst. Effect of steric constraints on the enantioselection *18th Conference on catalysis of organic reactions*, **2000.** USA, *Pre-prints of the conference,* Poster 23.

2. **Szőri K.**, Szöllösi Gy., Bartók M.: Enantioselective heterogeneous catalytic hydrogenation of ethyl 2-fluoroacetoacetate *7th International Symposium on Catalysis Applied to Fine Chemicals*, **2005.** Germany, *Book of Abstract 93*

3. **Szőri K.**, Felföldi K., Bartók M.: Sztereokémiai tényezők szerepe az α -ketoészterek Pt/Al_2O_3-cinkonidin katalizátoron lejátszódó enantioszelektív hidrogénezésben *MKE Vegyészkonferencia*, **2001.** *Előadásvázlatok,* 118.

4. **Szőri K.**, Felföldi K., Bartók M.: Nagy enantiomer tisztaságú (*R*)-5-oxo-tetrahidrofurán-2-karbonsav előállítása heterogén enantioszelektív hidrogénezéssel *MKE Vegyészkonferencia,* **2003.** *Program és Előadásösszefoglalók,* P109

7. Further Publications

1. Felföldi K., **Szőri K.**, Török B., Bartók M.: Sonochemical hydrosylilation of 2-substituted cyclohexanones in the presence of Wilkinson complex. *Ultrasonic Sonochem.,* **7** (2000) 15-17.

IF.: 0.947

2. Balázsik K., **Szőri K.**, Felföldi K., Török B. Bartók M.: Asymmetric synthesis of alkyl 5-oxotetrahydrofuran-2-carboxylates by enantioselective hydrogenation of dialkyl 2-oxoglutarates over cinchona modified Pt/Al_2O_3 catalysts *Chem. Commun.* **2000** 555–556.

IF.: 3.695

3. Sutyinszki M., **Szőri K.**, Felföldi K., Bartók M.: Heterogeneous asymmetric reactions. 29. Enantioselective hydrogenation of ethyl benzoylformate over dihydrocinchonidine- modified platinum-alumina catalyst in acetic acid *Catal. Lett.* **81** (2002) 281-284.

IF.: 1.559

4. Sutyinszki M., **Szőri K.**, Felföldi K., Bartók M.: 98% Enantioselectivity in the asymmetric synthesis of a useful chiral building block by heterogeneous method: Enantioselective hydrogenation of ethyl-benzoylformate over cinchona modified Pt/Al_2O_3 catalysts in the acetic acid *Catal. Commun.* **3** (2002) 125–127.

IF.: 1.890

5. **Szőri K.**, Szőllősi Gy., Felföldi K. Bartók M.: A novel asymmetric heterogeneous catalytic reaction: Hydrogenation of ethyl 2-acetoxyacrylate on cinchonidine modified Pd and Pt catalyst *React. Kinet. Catal. Lett.* **84** (2005) 151-156.

IF.: 0.670

6. **Szőri K.**, Szőllősi Gy., Bartók M.: The enantioselective hydrogenation of 5,6-dihydro-2H-pyran-3-carboxylic acid over a cinchona alkaloid-modified palladium catalyst: asymmetric synthesis of a cockroach attractant *New J. Chem.* **32** (2008) 1354–1358.

IF.: 2.942

7. Szőllősi Gy., **Szőri K.**, Bartók M.: Enantioselective hydrogenation of arecaidine over cinchona alkaloid-modified palladium catalyst: A novel route to enantioenriched nipecotic acid derivatives *J. Catal.* **256** (2008) 349–352.

IF.: 5.167

8. **Szőri K.**, Balázsik K., Cserényi Sz., Szőllősi Gy., Bartók M.: Inversion of enantioselectivity in the 2,2,2-trifluoroacetophenone hydrogenation over Pt-alumina catalyst modified by cinchona alkaloids *Appl. Catal. A Gen.* **362** (2009) 178-184.

IF.: 3.564

9. Cserényi Sz., Szöllősi Gy., **Szőri K.**, Fülöp F., Bartók M.: Reversal of the ee in enantioselective hydrogenation of activated ketones in continuous-flow fixed-bed reactor system *Catal. Commun.* **12** (2010) 14-19.

IF.: 3.000

8. Further Lectures

1. Szöllősi Gy., **Szőri K.**, Hermán B., Cserényi Sz., Felföldi K., Fülöp F., Bartók M.: Scope of the Cinchona Alkaloids-Modified Palladium Catalysts in Enantioselective Hydrogenation of Unsaturated Carboxylic Acids. *Europacat VIII, O5-13*, **2007**, Turku/Abo, (Finnország).

9. Further Posters

1. Szöllösi Gy., Török B., Felföldi K., **Szőri K.**, Bartók M.: Application of nonchiral derivatization in the separation of optical isomers of asymmetric hydroxy compounds by chiral gas-chromatography. *International symposium on Advances in Chromatography, Electrophoresis and Related Separation Methods,* **1998.**, Hungary. *Abstracts Vol.1A*.

2. Török B., Balázsik K., Felföldi K., Szöllösi Gy., **Szőri K.**, Bartók M.: Ultrasonics in asymmetric syntheses. Sonochemical enentioselective hydrogenation of prochiral C=O groups over platinum catalysts. *10th.International Symposium on Chiral Discrimination*, **1998**, Austria, *Book of Abstracts,* L-42.

3. Szöllősi Gy., **Szőri K.**, Bartók M.: Stereoselective Hydrogenation of Optically Pure Trifluoroacetyl Compounds *14th International Symposium on Chirality*, **2002.**, Germany, *Programme, Abstracts and List of Participants,* PG14ű

4. Szöllősi Gy., **Szőri K.**, Bartók M.: Asymmetric Michael Addition over Heterogenized Cinchona Alkaloid Catalyst *6th International Symposium on Catalysis Applied to Fine Chemicals*, **2003.**, Netherland, *Book Of Abstracts,* P159

5. Balázsik K., **Szőri K.**, Notheisz F., Bartók M.: Solvent effect and mechanism of Orito-reaction *6th International Symposium on Catalysis Applied to Fine Chemicals*, **2003.**, Netherland, *Book Of Abstracts,* P158

6. **Szőri K.**, Bartók M.: Mechanism of enantioselective heterogeneous catalytic hydrogenation of methyl benzoylformate *7th Pannonian International Symposium on Catalysis*, **2004.** Srni 95

7. Balázsik K., **Szőri K.**, Cserényi Sz., Szöllősi Gy., Bartók M.: Unexpected inversion of selectivity in the Orito reaction: 2,2,2-trifluoroacetophenone hydrogenation *EuropaCat IX Catalysis for a Sustainable World,* P2-89 **2009.** Salamanca

10. Summarized Impact factors

Sum of the impact factors of the publications related to the dissertation:	21.382
Sum of the impact factors of the other publications:	23.434
Sum of the impact factors of all publications:	44.816
Sum of the citations (Web of Knowledge, 2010.09.28.)	201
Sum of the citations without selfcitations	115