# Enantioselective hidrogenation of activated ketones over heterogen catalyst modified by cinchona alkaloid in continuous-flow system

Ph. D. Dissertation theses

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## 1. Introduction

Nowadays, ensuring high optical purities in asymmetric catalytic synthetic transformation is of increased significance. Various strategies have been pursued to design solid enantioselective catalysts, that is, to combine catalytic activity with a suitable stereochemical control of the reaction. Among this approaches, only modification of the catalytic metal surface by a strongly adsorbing chiral compound, termed as modifier, has as synthetical potential. One of the most intensively studied heterogeneous enantioselective catalytic reaction is the Orito reaction, that is enantioselective hydrogenation of activated ketones on Pt catalyst modified by cinchona alkaloids.

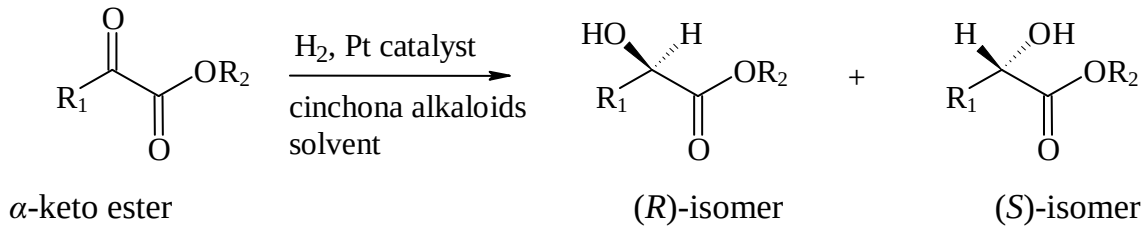


**Fig. 1.** Hydrogenation of $\alpha$-keto esters over supported Pt.

When modifier mixtures are used, the Orito reaction presented a strange and unique behavior so-called nonlinear phenomenon (NLP). The nonlinearity of the Orito reaction gives insight into the dynamics of modifier competition at the metal surface, so one can interpret the different kinds of adsorption-desorption processes of the surface-modifier-substrate intermediate complexes. The main objective of this study was to expand the field of utilization of the Orito reaction, also focusing on a better understandig of the reaction mechanism. In our opinion suitable NLP measurements carried out in continuous-flow fixed-bed reactor system (CFBR) under the Orito reaction condition may provide better knowledge of the processes occuring on the metal surface.

## 2. Experimental

We studied the nonlinear behaviour in the enantioselective heterogeneous catalytic hydrogenation of ethyl pyruvate (ETPY), ketopantolactone (KPL), methyl benzoilformate (MBF), pyruvaldehyde-1,1-dimethyl-acetal (PA) and 2,2,2-trifluoroacetophenone (TFAP) under the Orito reaction conditions over Pt catalyst modified with parent cinchona alkaloids. The hydrogenations were carried out in H-CUBE high-pressure continuous flow system purchased from Thales Nanothechnology Inc. The catalyst was rinsed with the corresponding solvent followed by 0.5 h pretreatment with $H_2$ in the same solvent. After the racemic hydrogenation, the substrate and the first modifier were dissolved in the solvent and this solution was delivered to the hydrogenation system via conventional HPLC pump, mixed with $H_2$ under the desired pressure and passed through catalyst bad obtaining an ascedant flow of the reaction components. The modifier was changed by replacing the solution delivered by the pump. Samples were taken at regular time intervals from the product flow and analysed. The products were identified by mass spectrometric analysis. Conversion and enantiomer excess (ee = $100\times|[R]-[S]|/([R]+[S])$, where [R] and [S] are the concetrations of the *(R)*- and *(S)*- enantiomers of the products were determined by gas cromatography.

## 3. Novel scientific results

*The enantoselective hydrogenation of different α-keto esters under the conditions of the Orito reaction in CFBR [1, 2, 3].*

**I.** we studied for the first the NLP in the hydroganetion of both ETPY and KPL in contiuous-flow system on Pt catalyst modified by cinchonidine (CN), cinchonine (CN), quinine (QN), and quinidine (QD). With this data we could determine, the adsoption strengths of the corresponding modifiers during the hydrogenation processes. In case of ETPY the course of the conversion (c) was $c_{CD} > c_{CN} < c_{QN,}$ and according to the enantioselectivity mesurements the adsorption strenghts (AS) followed the order: $AS_{CD} > AS_{QN} > AS_{CN}$, whereas in case of KPL $c_{CD} > c_{CN} > c_{QN,}$ and $AS_{CD} > AS_{CN} > AS_{QN}$.

| | **ee %** | | |
|---|---|---|---|
| | **CD** | **CN** | **QN** |
| **ETPY** | **92** *R* | **56** *S* | **70** *R* |
| **KPL** | **62** *R* | **55** *S* | **27** *R* |

**1. table.** With the corresponding cinchona alkaloids the mesured enantioselctivity for ETPY and KPL substrates. In the case of ETPY substrate and CD modifier: 80 mg E4759 catalyst, concentration of modifier 0,044 mM, concentration of substrate 45 mM, hydrogen pressure 80 bar, flow rate1 ml/perc, temperature of the mesurement 283 K, solvent is T:AcOH 9:1.

In the case of ETPY substrate and CN, QN modifiers: 20 mg E4759 catalyst, concentration of modifier 0,044 mM, concentration of substrate 45 mM, hydrogen pressure 40 bar, flow rate 1 ml/perc, temperature of mesurement 283 K-en, solvent is T:AcOH 9:1.

In the case of KPL substrate and CD modifier: 20 mg E4759 catalyst, concentration of modifier 0,044 mM, concentration of substrate 45 mM, hydrogen pressure 40 bar, flow rate 1 ml/perc, temperature of mesurement 283 K, solvent is T:AcOH 9:1.

In the case of KPL substrate and CN, QN modifiers: 50 mg E4759 catalyst, concentration of modifier 0,044 mM, concentration of substrate 45 mM, hydrogen pressure 80 bar, flow rate 1 ml/perc, temperature of mesurement 283 K, solvent is T:AcOH-9:1.

According to these measurements the adsoption strengths of the parent cinchona alkaloids are dependent on the substrate structure. The change in time of the conversion and the enantiomer excess was found to be affected by numerous various type of factors during the hydrogenations.

**II.** We carried out a study on the NLP in the hydrogenation of other substrates continuous flow process. We carried out the enantioselective hydrogenation of MBF and PA registering the change in time of the conversion and the enantiomer excess. We determined the next conversion course for MBF: $c_{CD} > c_{CN} > c_{QN}$ and the order of adsorption srtengths was $AS_{CD} > AS_{CN} > AS_{QN.}$ In case of PA, the same course of conversions was obtained: $c_{CD} > c_{CN} > c_{QN} > c_{QD,}$ and of adsorption srength values were $AS_{CD} > AS_{CN} > AS_{QN} > AS_{QD.}$

| | **ee %** | | |
|---|---|---|---|
| | **CD** | **CN** | **QN** |
| **MBF** | **90** *R* | **65** *S* | **56** *R* |

**2. table.** With the corresponding cinchona alkaloids the mesured enantioselctivity for MBF substrate. 50 mg E4759catalyst, concentration of modifier 0,44 mM, concentration of substrate 45 mM, hydrogen pressure 80 bar, flow rate 1 ml/perc, temperature of mesurement 283 K, solvent is T:AcOH 9:1.

| | **ee %** | | | |
|---|---|---|---|---|
| | **CD** | **CN** | **QN** | **QD** |
| **PA** | **78** *R* | **72** *S* | **70** *R* | ***20*** *S* |

**3. table.** With the corresponding cinchona alkaloids the mesured enantioselctivity for PA substrate. 100 mg E4759catalyst, concentration of modifier 2mM, concentration of substrate 45 mM, hydrogen pressure 80 bar, flow rate 1 ml/perc, temperature of mesurement 293 K, solvent isT:AcOH 9:1.

In our opinion, the reaction rate enhancement is an intrinsic character of the system, which is determined on the structure and stability of the surface surface-modifier-substrate intermediate complex.

*The enantioselective hydrogenation of 2,2,2-trifluoroacetophenone under conditions of the Orito reaction in CFBR [4, 5, 6]*

**III.** The enantioselective hydrogenation of TFAP over $Pt/Al_2O_3$ catalyst modified by cinchona alkaloids was investigated using CFBR system. Studies on the nonlinear behaviour in the hydrogenation of this substrates were carried out after optimalization of the reaction conditions. According to these experiments the following course of the conversions was determined: $c_{CD} > c_{CN} > c_{QN} > c_{QD}$, whereas that of the adsortion strengths was $AS_{CD} > AS_{CN} > AS_{QN} > AS_{QD.}$

In toluol (T):acetic acid (AcOH) 9:1 solvent mixture, the enantioselective hydrogenations yielded the *(R)*-product in excess on Pt-CD, Pt-CN, Pt-QN and Pt-QD catalyst. Consequently, unexpected inversion took place on the Pt-CN and Pt-QD catalyst.

| | **ee %** | | | |
|---|---|---|---|---|
| | **CD** | **CN** | **QN** | **QD** |
| **TFAP** | **35** *R* | **18** *R* | **10** *R* | **5** *R* |

**4. table.** With the corresponding cinchona alkaloids the mesured enantioselctivity for TFAP substrate.

100 mg E4759 catalyst, concentration of modifier 1mM, concentration of substrate 45 mM, hydrogen pressure 10 bar, flow rate 1 ml/perc, temperature of mesurement 283 K, solvent is T:AcOH 9:1.

**VI.** In T:AcOH 9:1 solvent mixture in presence 0,1 vol.% trifluoroacetic acid (TFA), the hydrogenation followed the general rule of the Orito reaction, according to which products formed in excess are *(R)*-alcohols on Pt-CD and Pt-QN and *(S)*-alcohols Pt-CN and Pt-QD, respectively. Based on these observations we proposed that in the hydrogenation of TFAP the reaction route involves the equilibrium of electrophilic and nucleophilic intermediate complexes, which was found to be dependent on the acid srength and concentration. We suggested structures of the intermadiate complexes which can explain these phenomena.

| | ee % | | | |
|---|---|---|---|---|
| | **CD** | **CN** | **QN** | **QD** |
| **TFAP** | **65** *R* | **20** *S* | **18** *R* | **12** *S* |

**5. table.** With the corresponding cinchona alkaloids the mesured enantioselctivity for TFAP substrate.

100 mg E4759catalyst, concentration of modifier 1 mM, concentration of substrate 45 mM, hidrogen pressure 40 bar, flow rate 1 ml/perc, temperature of mesurement 293 K, solvent is T:AcOH 9:1+0,1 V/V% TFA.

## 4. Publications related to the subject of the dissertation

[1.] K. Balazsik, **Sz. Cserenyi**, Gy. Szőllősi, F. Fülöp, M. Bartok: New data on the Orito Reaction: Effect of substrate structure on nonlinear phenomenon. *Catal. Lett.* **125** (2008) 401.

**IF.: 1,867**

[2.] Gy. Szőllősi, **Sz. Cserenyi**, F. Fülöp, M. Bartok: New data to the origin of rate enhancement on the Pt-cinchona catalyzed enantioselective hydrogenation of activated ketones using continuous-flow fixed-bed reactor system. *J. Catal.* **260** (2008) 245.

**IF.: 5,167**

[3] Gy. Szőllősi, **Sz. Cserenyi**, K. Balazsik, F. Fülöp, M. Bartok: New data in the enantioselective hydrogenation of ethyl pyruvate on Pt-cinchona chiral catalyst using continuous-flow fixed-bed reactor system: The origin of rate enhancement *J. Mol. Catal. A:chem* **305** (2009) 155.

**IF.: 3,135**

[4] Gy. Szőllősi, **Sz. Cserenyi,** M.Bartok: Novel evidence on the role of the nucleophilic intermediate complex in the Orito-Reaction: Unexpected inversion in the enantioselective hydrogenation of 2,2,2-Trifluoroacetophenone on Pt-Cinchona chiral catalyst using. *Catal. Lett.* **134** (2010) 264.

**IF.: 2,021**

[5] Gy. Szőllősi, **Sz. Cserenyi,** I. Bucsi, T. Bartok, F. Fülöp, M. Bartok: Origin of the rate enhancement and enantiodifferentiation in the heterogeneous enantioselective hydrogenation of 2,2,2-trifluoroacetophenone over Pt/alumina studied in continuous-flow fixed-bed reactor system *Appl. Catal. A: Gen.* **382** (2010) 263.

**IF.: 3,564**

[6] **Sz. Cserenyi**, Gy. Szőllősi, K. Szöri, F. Fülöp, M. Bartok: Reversal of the ee in enantioselectiviti hydrogenation of actived ketones in continuous-flow fixed bed reactor system. *Catal. Commun.* **12** (2010) 14.

**IF.: 3,000**

## 5. Lectures related to the dissertation

**Cserényi Szabolcs**: Enantioszelektív hidrogénezések királisan módosított heterogén katalizátoron folyamatos rendszerben. *XXXI. Kémiai Előadói Napok* 2008.

## 6. Publications not related to the dissertation

[1'] Gy. Szőllősi, I. Bucsi, **Sz. Cserenyi,** M. Bartok: Study of fragmentation pattern and adsorption of 9-O-(triphenylsilyl)-10,11-dihydrocinchonidine on platinum by hydrogen/deuterium exchange using electrospray ionization ion-trap tandem mass spectrometry *Rapid Commun. Mass. Spect.* **19** (2005) 3743.

**IF.: 3,087**

[2'] **Sz. Cserenyi**, K. Felföldi, K. Balazsik, Gy. Szőllősi, I. Bucsi, M. Bartok: C9-O-substituted derivatives of cinchona alkaloids as chiral modifiers in the Orito-reaction: Effects of structure of modifiers on sense of enantioselectivity *J. Mol. Catal. A: Chem.* **247** (2006) 108.

**IF.: 2,511**

[3'] **Sz. Cserenyi,** I. Bucsi, K. Felföldi: Role of the C3-substituted derivatives of cinchonidine in the enantioselective hydrogenation of ethyl pyruvate on Pt-alumina catalyst in AcOH *React. Kinet. Catal. Lett.* **87** (2006) 395.

**IF.: 0,514**

[4'] I. Bucsi, **Sz. Cserenyi,** K. Felföldi, M. Bartok: New chiral catalysts: Synthesis and fragmentation pattern of C9-O-silanized cinchonidines *React. Kinet. Catal. Lett.* **87** (2006) 281.

**IF.: 0,514**

[5’] **Sz. Cserenyi,** K. Felföldi, P. Forgó, I. Palinkó: Preparation of 3-substituted and 2,3-disubstituted-4,4,4-trifluoro-2-butenoic acids - Perkin condensation of activated aromatic ketones. *J. Fluor. Chem.* **127** (2006) 850.

**IF.: 1,515**

[6’] Gy. Szőllősi, T. Varga, K. Felföldi, **Sz. Cserenyi**, M. Bartok: Enantio selective hydrogenation of fluorinated unsaturated carboxylic acids over cinchona alkaloid modified palladium catalysts. *Catal. Commun.* **9** (2008) 421.

**IF.: 2,791**

[7’] K. Balazsik, I. Bucsi, **Sz. Cserenyi,** Gy. Szőllősi, M. Bartok: Methylethers of cinchona alkaloids in Pt-catalyzed hydrogenation of ethyl pyruvate and ketopantolactone: Effect of stereochemical factors on the enantioselectivity. *J. Mol. Catal. A: Chem.* **280** (2008) 87.

**IF.: 2,814**

[8’] K. Balazsik, I. Bucsi, **Sz. Cserenyi,** Gy. Szőllősi, M. Bartok: Methylethers of cinchona alkaloids in Pt-catalyzed hydrogenation of methyl benzoylformate and pyruvaldehyde dimethyl acetal - Part 2: Effect of stereochemical factors on the enantioselectivity *J. Mol. Catal. A: Chem.* **285** (2008) 84.

**IF.: 2,814**

[9’] K. Szöri, K. Balazsik, K. Felföldi, I. Bucsi, **Sz. Cserenyi,** Gy. Szőllősi, E. Vass, M. Hollosi, M. Bartok: 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: Chem.* **294** (2008) 14.

**IF.: 2,814**

[10’] K. Szöri, K. Balazsik, **Sz, Cserenyi,** Gy. Szőllősi, M. Bartok: 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.

**IF.: 3,564**

## 7. Lectures not related to the subject of the dissertation

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

2. K. Balázsik, **Sz. Cserényi**, Gy. Szőllősi, and M. Bartók: Enantioselective Hydrogenations of Activated Ketones on Pt-Cinchona alkaloid catalyst: effect of modifiers and substrates on enantiomeric excess. *Europacat VIII*, P5-65, **2007**, Turku, (Finnland).

3. K. Balázsik, K. Szőri, **Sz. Cserényi**, Gy. Szőllősi and M. Bartók: Unexpected inversion of enantioselectivity in the Orito reaction: 2,2,2-trifluoroacetophenone hydrogenation. *EuropaCat IX Catalysis for a Sustainable World*, P2-89, **2009**, Salamanca, (Spain).

**8. Summarized impact factor**

Sum of the impact factor of the publications related to the dissertation: 18,754

Sum of the impact factor of the publications not related to the dissertation: 22,938

Sum of the impact factor of all publications: 41,692