DEVELOPMENT OF ENVIRONMENTALLY BENIGN CATALYTIC SYSTEMS FOR THE ASYMMETRIC TRANSFER HYDROGENATION OF PROCHIRAL KETONES

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PhD Thesis

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1. INTRODUCTION AND AIMS

Nowadays, almost 95% of the available pharmaceuticals contain chiral compounds. The enantiomers of the optically active molecules may have different physiological effects, thus their enantioselective synthesis is one of the essential goals of synthetic chemistry. Chiral resolutions and the application of optically active starting compounds are outdated processes compared to the modern, high-efficiency catalytic methods, using only a small amount of chirality source. Among the optically active molecules, chiral alcohols have a major role as intermediates in the pharmaceutical industry. An excellent example is the (*R*)-3',5'-bis(trifluoromethyl)-phenyl-ethanol, which is an important building block of aprepitant, an antiemetic, used in chemotherapy or post-operational periods. Similar ketones with various properties can be obtained in metal-catalysed asymmetric transfer hydrogenations. To stereoselectively promote these reactions, several synthetic ligands were developed in the past decades, although environmental protection and sustainability demand the reconsideration and adjustment of these methods. The application of natural, biodegradable chiral ligands, green solvents and easily available reagents, which do not generate hazardous by-products has opened new paths towards environmentally benign approaches. In addition, alternative energy transmissions are getting more and more popular for promoting organic synthetic processes. These methods allow significant shortening of the reaction time and numerous reactions can be carried out neat as well.

Based on the thorough study of the literature, the main goal of our work was to develop an environmentally benign catalytic system, using a natural and biocompatible chiral ligand, in aqueous media. The easily available chitosan with advantageous characteristics, obtained by the deacetylation of chitin, was chosen as the chiral ligand of the applied Ru-catalyst. Besides investigating the structure of the complex and the reaction mechanism, we aimed to optimise the reaction conditions to develop a universally applicable catalytic method for obtaining optically pure alcohols. To achieve an environmentally friendly system, not only aqueous media was applied, but we planned to carry out the reactions using alternative energy transitions, thereby reducing the necessary amount of solvent and the reaction time.

2. EXPERIMENTAL

In our research we used compounds from commercial sources, other ketones and alcohols used as starting molecules and the chitosan polymers were prepared based on procedures found in the literature. The magnetically stirred asymmetric transfer hydrogenations (deuterations) and oxidative kinetic resolutions were carried out in glass reactors, while for the mechanochemical reactions a Retsch MM 400 mixer mill was used. After the appropriate reaction time, the products were separated from the mixtures by dissolving them in ethyl acetate. The raw products were analysed by GC-MSD and GC-FID, the conversions and enantiomeric excesses were determined based on the chromatograms with ± 1% reproducibility. The alcohols were separated by column chromatography or recrystallization. The purified products were analysed by ^{1}H, ^{2}H and ^{13}C NMR spectroscopy. The pre-prepared complex was studied by SEM, SEM-EDX and IR spectroscopy the pre-catalyst formed in a solution was analysed ^{1}H NMR spectroscopy.

The deacetylation of chitin was carried out in 20 cm^3 glass reactors, immersed in a heated oil bath. The degrees of deacetylation of the product chitosans were determined by ^{1}H NMR, IR and UV-Vis spectroscopy. The average molecular weights of the polymers were calculated based on viscosity measurements, the degree of crystallinity and the apparent crystallite size were determined by X-ray diffractometry.

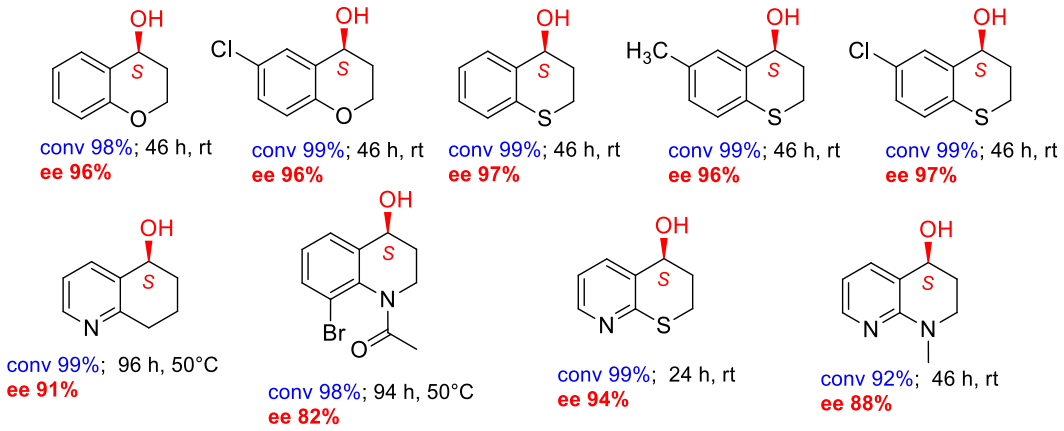
3. NOVEL SCIENTIFIC RESULTS

T1. We have developed an environmentally benign catalytic system for the transfer hydrogenation of acetophenone derivatives and carbocyclic ketones, using chitosan as a chirality source.

Chitosan had been applied in several catalytic systems, however in many cases, the polymer only had the role of heterogeneous support, or just the modified derivatives of the polysaccharide were effective. Our research is the first study of the asymmetric transfer hydrogenation of various acetophenone derivatives in aqueous media, using HCOONa as hydrogen donor and chitosan as the chiral ligand of the ruthenium catalyst, without further structural modification of the biopolymer. We also examined the applicability of this natural ligand in the reaction of carbocyclic ketones, which provided increased enantioselectivity due to more directed coordination of the compounds with rigid structures [1].

T2. We have succeeded in carrying out the synthesis of heterocyclic chiral alcohols by Ru(II)-chitosan catalysed asymmetric transfer hydrogenations.

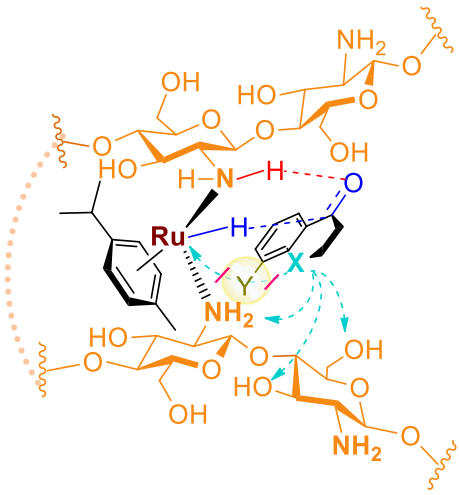
The scope of the catalytic system was extended to heterocyclic ketones. 4-Chromanone and 4-thiochromanone derivatives gave full conversions and up to 97% enantiomeric excesses, by applying the natural chirality source (**Scheme 1.**) [1]. Great results were obtained in the asymmetric transfer hydrogenation of quinolinone derivatives too, using the developed catalytic system. Our work also included the preparation of bicyclic ketones bearing a heteroatom in each ring. These compounds provided outstanding results in the Ru(II)-chitosan catalysed system as well (**Scheme 1.**). It is important that optically pure amino alcohols with similar structures were previously obtained using only enzyme catalysis [2].



Scheme 1. *Outstanding results obtained in the Ru(II)-chitosan catalysed transfer hydrogenations of heterocyclic ketones*

T3. We have investigated the formation and working mechanism of the Ru(II)-chitosan complex.

Based on the transfer hydrogenation of various ketones, we drew conclusions about the interactions in the probable transition state. Our results demonstrated that the rigid structure of the carbocyclic ketones has a positive effect on the enantioselection. The outstanding conversion and enantiomeric excess values obtained in the reaction of heterocyclic ketones led to the conclusion that the heteroatom may form secondary bonds with the functional groups of the chitosan, thus directing the coordination, hence the hydrogen transfer. Although the nitrogen-containing compounds can deactivate the catalyst, a protecting group or a substituent near the N atom can hinder the strong Ru-N interaction (**Scheme 2.**). Our conclusions on the bond formations in the intermediate state and the reaction mechanism were supported by the results achieved in oxidative kinetic resolutions. Besides these, we also carried out a detailed study of the Ru(II)-chitosan complex by various spectroscopic methods to learn more about the interactions between the metal centre and the biopolymer ligand [1,2,3].



Scheme 2. *A possible structure of the Ru(II)-chitosan complex, the interactions formed in the six-membered pericyclic intermediate and the secondary bonds between the heteroatom and the biopolymer ligand*

T4. We have prepared and characterised a unique chitosan series, then we studied the effect of the polimers' properties on the asymmetric transfer hydrogenations.

In our study we synthesized 23 chitosan polymers with different degree of deacetylation – molecular weight – degree of crystallinity – apparent crystallite size values by applying various hydrolysis conditions. Compared to the studies published so far, these series of chitosan polymers are unique and provided a great opportunity to investigate the effect of the

structural characteristics of the biopolymer on the reactions. The degree of deacetylation of the chitosan can affect its complex-forming ability. The molecular weight, hence the chain length of the polysaccharide may have a major role in the formation of a chiral environment around the active centre. To study these phenomena, we carried out the transfer hydrogenation of 4-chormanone and 3'-trifluoromethyl acetophenone using the biopolymers synthesized by us. These chiral ligands provided outstanding enantioselectivity in every reaction, however, based on changes in the achieved conversions it was observed that these properties of the polymer have a major effect on the formation of the active complex. We came to the conclusion that although the presence of the amino groups is essential, the best results were obtained with chitosans having a degree of deacetylation between 80-95% and an average molecular weight fitting in the 210-230 kDa range. The degree of crystallinity and the apparent crystallite size of the chitosans did not affect the reactions [3].

T5. By using the prepared chitosan series, we have carried out the first chitosan-complex catalysed oxidative kinetic resolutions.

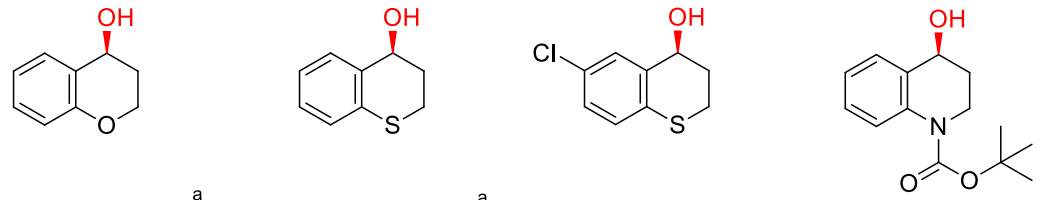
In this reaction, we also observed enantiodifferentiation using the Ru(II)-chitosan complex. In the aspect of the degree of deacetylation, we observed similar changes to the transfer hydrogenations, however, we concluded that the molecular weight had a major role in the enantioselection. Probably not just the directly coordinating monomers are responsible for the high stereoselectivity, but the chiral environment formed by the polymer chain also contributes to the appropriate coordination of the ketone to the active centre [3].

T6. We have carried out the first asymmetric catalytic transfer hydrogenations in a ball mill.

Our study is the first, which investigates the asymmetric transfer hydrogenations carried out in a ball mill. The application of the Noyori-Ikariya-type complex in aqueous media is well known, however among the environmentally friendly implementations, our process induced via mechanochemical energy transmission proved to fill a gap, thus besides the Ru(II)-chitosan complex, we also applied this catalyst during our mechanochemical studies. After the optimisation of the reaction conditions, we extended the scope of the reaction to various acetophenone derivatives, carbo- and heterocyclic ketones. It is important to highlight that the results of the mechanochemical reactions in some cases exceeded those achieved in magnetically stirred transfer hydrogenations, besides reaction time was also reduced significantly [4,5].

T7. We have investigated the synthetic applicability of the Ru(II)-chitosan catalysed systems at larger scales.

As the environmentally benign implementations are gaining importance in the industrial processes, we have studied the practical applicability of both magnetically stirred and mechanochemical reactions by carrying out the transfer hydrogenations with 1-8 mmol ketones, achieving a fourfold to thirty-fourfold increase. Good conversions can be obtained even at larger scales, with similar enantiomeric excess values to the ones achieved in the 0.25 mmol reactions. The chiral alcohols were isolated from the product mixtures in good yields corresponding to the chosen purification methods. The optical purity of the solid products could be enhanced by recrystallization (**Scheme 3.**) [1,2,5].

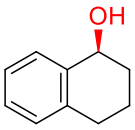


MS: H_{cr} 83% (99); ee_{cr} >99%[a]
MC: H_{cr} 75% (83); ee_{cr} 99%[b]

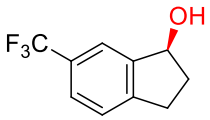
H_{cr} 75% (92); ee_{cr} 99%[a]
H_{cr} 85% (>99); ee_{cr} >99%

H_{cc} 70% (94); ee_{cc} 97%
H_{cr} 70% (97); ee_{cr} >99%

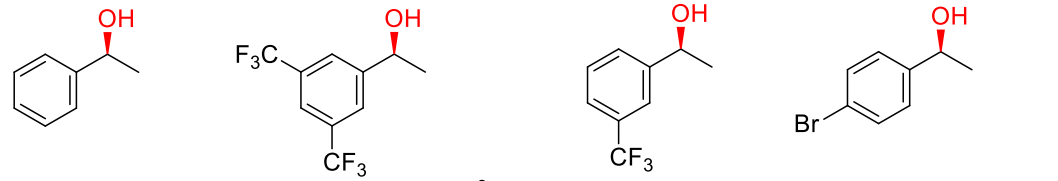
H_{cc} 82% (90); ee_{cc} 94%
H_{cr} 32% (44); ee_{cr} 91%



MS: H_{cc} 63% (80); ee_{cc} 91%
MC: H_{cc} 66% (72); ee_{cc} 87%



H_{cc} 51% (65); ee_{cc} 93%
H_{cc} 62% (79); ee_{cc} 84%



MS: H_{cc} 70% (95); ee_{cc} 79%
MC: H_{cc} 84% (86); ee_{cc} 66%

H_{cc} 76% (81); ee_{cc} 85%[c]
H_{cc} 77% (99); ee_{cc} 75%

H_{cc} 75% (98,5); ee_{cc} 83%
H_{cc} 84% (99); ee_{cc} 73%

H_{cc} 82% (98); ee_{cc} 82%
H_{cc} 88% (95); ee_{cc} 69%

Scheme 3. *Results achieved in the study of the practical applicability of the Ru(II)-chitosan catalysed systems (MS: magnetically stirred, MC: mechanochemical, Y_{cr}: yield after recrystallization, Y_{cc}: yield after column chromatography, ee_{cr}, ee_{cc}: enantiomer excesses achieved after recrystallization or column chromatography)*

4. PUBLICATIONS IN REFEREED JOURNALS RELATED TO THE TOPIC OF THE DISSERTATION

(MTMT identifier:10065012)

[1] Szőllősi, Gy.; **Kolcsár, V. J.**:
Highly enantioselective transfer hydrogenation of prochiral ketones using Ru(II)-chitosan catalyst in aqueous media
ChemCatChem **2019**, *11*, 820-830.

IF: 4.853

[2] **Kolcsár, V. J.**; Fülöp, F.; Szőllősi, Gy.:
Ruthenium(II)-chitosan, an enantioselective catalyst for transfer hydrogenation of N-heterocyclic ketones
C*hemCatChem* **2019**, *11*, 2725-2731.

IF: 4.853

[3] **Kolcsár, V. J.**; Szőllősi, Gy.:
Chitosan as a chiral ligand and organocatalyst: preparation conditions-property-catalytic performance relationships
Catal. Sci. Technol. **2021**, *11*, 7652-7666.

IF: 6.119*

[4] **Kolcsár, V. J.**; Szőllősi, Gy.:
Mechanochemical, water-assisted asymmetric transfer hydrogenation of ketones using Ruthenium catalyst
ChemCatChem ***2022****, 14,* e202101501*.*

IF: 5.686*

[5] **Kolcsár, V. J.**; Szőllősi, Gy.:
Ru-catalyzed mechanochemical asymmetric transfer hydrogenations in aqueous media using chitosan as chirality source
Mol. Catal. **2022**, *520*, 112162.

IF: 5.062*

Total IF: 26.573

*Impact factors of 2020

5. CONFERENCE PARTICIPATIONS RELATED TO THE TOPIC OF THE DISSERTATION

Oral presentations:

1. **Kolcsár, V. J.**; Szőllősi, Gy.:
   Enantioszelektív transzfer hidrogénezések ruténium-kitozán királis komplex használatával
   XL. Kémiai Előadói Napok, **2017**, Szeged.

2. **Kolcsár, V. J.**:
   Természetes biopolimerek kiralitásának használata ketonok enantioszelektív transzfer hidrogénezésében
   Országos Tudományos Diákköri Konferencia, **2017**, Miskolc.

3. **Kolcsár, V. J.**:
   Ru-kitozán katalizátor alkalmazása nitrogéntartalmú prokirális vegyületek aszimmetrikus transzfer hidrogénezésére
   Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány, a SZAB Szerves és Gyógyszerkémiai Munkabizottság és a Magyar Kémikusok Egyesülete Csongrád Megyei Csoportjának 17. tudományos előadóülése, **2018**, Szeged.

4. **Kolcsár, V. J.**:
   Ru-kitozán katalizátor alkalmazása nitrogéntartalmú prokirális vegyületek aszimmetrikus transzfer hidrogénezésében
   Országos Tudományos Diákköri Konferencia, **2019**, Budapest.

5. **Kolcsár, V. J.**; Szőllősi, Gy.:
   The mechanochemical implementation of the environmentally friendly asymmetric transfer hydrogenation of ketones
   26th International Symposium on Analytical and Environmental Problems, **2020**, Szeged.
   Proceedings of the 26th International Symposium on Analytical and Environmental Problems, 30-34.

6. **Kolcsár, V. J.**:
   Fenntartható szintézisek: mechonakémiai aszimmetrikus transzfer hidrogénezés természetes kiralitásoforrással
   Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány, a SZAB Szerves es Gyógyszerkémiai Munkabizottság és a Magyar Kémikusok Egyesülete Csongrád Megyei Csoportjának 21. tudományos előadóülése, **2021**, Szeged.

Poster presentations:

1. **Kolcsár, V. J.**; Szőllősi, Gy.:
   Chitosan, a natural ligand for highly enantioselective Ru catalyzed transfer hydrogenation of ketones
   13th European Congress on Catalysis, **2017**, Firenze, P3.64.

2. **Kolcsár, V. J.**; Szőllősi, Gy.:
   Ketonok enantioszelektív transzfer hidrogénezése Ru-kitozán királis katalizátorral
   Magyar Kémikusok Egyesülete, Vegyészkonferencia, **2017,** Hajduszoboszló, P-26.

3. **Kolcsár, V. J.**; Szőllősi, Gy.:
   Environmentally benign catalysis: Chitosan, a natural ligand for highly enantioselective Ru catalysed transfer hydrogenation of ketones
   23th International Symposium on Analytical and Environmental Problems, **2017**, Szeged, P85.

4. **Kolcsár, V. J.**; Szőllősi, Gy.:
   Chitosan, a natural ligand for highly enantioselective Ru catalysed transfer hydrogenation of ketones
   14th Pannonian International Symposium on Catalysis, **2018**, Starý Smokovec P-1.1, 104.

5. **Kolcsár, V. J.**; Szőllősi, Gy.:
   Chitosan, a natural ligand for sustainable and environmentally benign asymmetric transfer hydrogenation
   25th International Symposium on Analytical and Environmental problems, **2019**, Szeged, P86.
   Proceedings of the 25th International Symposium on Analytical and Environmental Problems, 338-341.

6. PUBLICATIONS IN REFEREED JOURNALS NOT RELATED TO THE DISSERTATION

1. Szőllősi, Gy.; Kovács, L.; Kozma, V.; **Kolcsár, V. J.**:
   Asymmetric Michael addition catalyzed by a cinchona alkaloid derivative non-covalently immobilized on layered inorganic supports
   Reac. Kinet. Mech. Cat. **2017***, 121,* 293-306.

   IF: 1.515

2. Sápi, A.; Halasi, Gy.; Kiss, J.; Dobó, D. G.; Juhász, K. L.; **Kolcsár, V. J.**; Ferencz, Zs.; Vari, G.;Matolín, V.; Erdőhelyi, A.; Kukovecz. Á.; Kónya, Z.:
   In Situ DRIFTS and NAP-XPS Exploration of the Complexity of CO_2 Hydrogenation over Size-Controlled Pt Nanoparticles Supported on Mesoporous NiO
   J. Phys. Chem. *C* **2018**, *122*, 5553-55565.

   IF: 4.309

3. Varga, G.; Kozma, V.; **Kolcsár, V. J**.; Kukovecz, Á.; Kónya, Z.; Sipos, P.; Pálinkó, I.; Szőllősi, Gy.:
   β-isocupreidinate-CaAl-layered double hydroxide composites-heterogenized catalysts for Michael addition
   Mol. Catal. **2020**, *487*, 110675.

   IF: 5.062

Total IF: 10.886

7. CONFERENCE PARTICIPATIONS NOT RELATED TO THE DISSERTATION

Poster presentations:

1. Szőllősi, Gy.; Mogyorós, A. Zs., Gombkötő, D.; Fancsali, B.; **Kolcsár, V. J.**; Kozma, V.; Kőhl G.:
   Heterogeneous asymmetric Michael additions catalyzed by proline-inorganic oxide hybrid materials
   14th Pannonian International Symposium on Catalysis, **2018,** Starý Smokovec, P-2.16.

2. Szőllősi, Gy.; Kovács L.; Kozma, V.; **Kolcsár, V. J**.:
   Asymmetric Michael-addition catalyzed by a cinchona alkaloid derivative non-covalently immobilized over layered materials
   13th Pannonian International Symposium on Catalysis, **2016**, Siófok, P40.

3. Szőllősi, Gy., **Kolcsár V. J**.; Kozma, V.; Fancsali, B.; Mogyorós, A. Zs.; Gombkötő, D.; Kőhl, G.:
   Heterogeneous asymmetric Michael additions using environmentally friendly catalysis: application of chiral inorganic-organic hybrid materials
   25th International Symposium on Analytical and Environmental Problems, **2019**, Szeged, P108.
   Proceedings of the 25th International Symposium on Analytical and Environmental Problems, 409-413.

4. **Kolcsár, V. J.**; Szőllősi, Gy.
   Preparation of N-heterocyclic compounds by environmentally benign cascade reactions
   27th International Symposium on Analytical and Environmental Problems, **2021.**
   Proceedings of the 27th International Symposium on Analytical and Environmental Problems, 171-176.

8. TOTAL IMPACT FACTOR AND CITATIONS

Publications directly related to the topic of the dissertation:	**26,573**
Publications not related to the topic of the dissertation:	**10,886**
All publications:	**37,459**
All citations:	**87**
Independent citations:	**59**

(MTMT, 2022. 05. 02.)