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Asymmetric cascade reaction of 2-nitrophenylpyruvates over chirally modified platinum catalyst

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1. INTRODUCTION AND AIMS

Nowadays, the demand for the production of optically pure enantiomers is continuously growing. Optically pure partially saturated quinoline derivatives are intermediates in the preparation of natural products and pharmaceuticals. The asymmetric catalytic methods developed for preparing chiral hydroquinolines are based on enantioselective catalytic hydrogenations of quinoline derivatives or assembly of the chiral heterocyclic ring using enantioselective catalytic cyclization.

Sustainable and environmentally benign technologies required nowadays in the production of chiral fine chemicals tend to apply heterogeneous catalytic systems, due to the inherent practical advantages connected with separation, reuse, and stability of the catalyst and the opportunity of continuous process operation. Detailed examination of these systems is in the forefront of chemical research. Possibilities to obtain heterogeneous chiral catalysts are the immobilization of homogeneous catalysts and the chirality transfer to the surface of known and active heterogeneous metal particles. Although Pt catalysts modified by cinchona alkaloids were found to be remarkably efficient in the enantioselective hydrogenation of activated ketones, these catalysts are not appropriate for the enantioselective hydrogenation of N-heterocyclic compounds.

A cascade reaction, also known as domino reaction or tandem reaction, is a chemical process in which at least two consecutive steps occur, therefore incorporate multiple bond-forming events carried out in one-pot manner. Furthermore, in cascade reactions, isolation of intermediates is not required, as each reaction composing the sequence occurs spontaneously. In spite of their numerous advantages, asymmetric catalytic cascade reactions over heterogeneous chiral catalysts were scarcely reported and only few reactions are known in which the stereoselective step occurs on the solid catalyst surface.

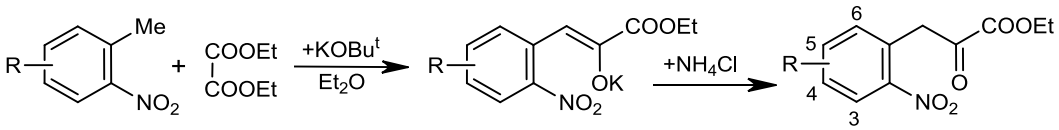
Combination of hydrogenation and continuous-flow technology could be widely used in the pharmaceutical industry for the synthesis of bioactive molecules. Huge advantage of flow systems is the opportunity of the reagent mixture recycling. Due to the fixed catalyst bed, the reaction mixture is separated from the catalyst instantaneously, unlike during batch production. Due to its advantageous characteristics flow chemistry became preferred for industrial application even in fine chemical synthesis. A current trend in the synthetic organic chemistry is the use of continuous-flow processes, which can be performed most advantageously by using modern immobilized reagents or catalysts.

More than a decade ago it was reported the formation of 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones as side products of the Reissert indole synthesis, if the reduction step was carried out with gaseous H_2 over PtO_2 catalyst. It was highlighted in the above report that during the reaction under reducing conditions, the hydrogenation of the keto group and the reduction of the nitro group are competing reactions and both are catalysed on the Pt surface, therefore the rate of these two steps determine the ratio of the two main products, i.e. the hydroquinoline and the indole derivatives. Thus, the reaction over Pt catalysts could be used for the enantioselective preparation of valuable hydroquinolines using a heterogeneous catalytic system if the step in which the chiral centre is formed could be carried out enantioselectively.

Inspired by these previous findings obtained over PtO_2 catalyst, we have developed the transformation of 2-nitrophenylpyruvates to 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one derivatives by an asymmetric cascade reaction over supported Pt catalyst modified by cinchona alkaloids in the presence of H_2. We thought that it is worth studying the effect of the reaction conditions on the rates of the two key competitive steps. As heterogeneous catalysts are suitable for use in continuous processes, we also examined the reaction in continuous-flow system using a fixed-bed reactor, in order to test whether these compounds may be efficiently and enantioselectively hydrogenated in a continuously operated experimental set-up. Thus, our aim was to develop a novel asymmetric heterogeneous catalytic cascade reaction, which may be used for the efficient, environmentally benign and sustainable preparation of valuable N-heterocyclic chiral building blocks, with possible application for the preparation of pharmaceuticals.

2. APPLIED MATERIALS AND METHODS

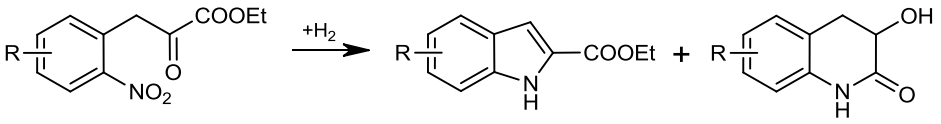
Ten 2-nitrophenylpyruvic acid esters (**1a**-**1j**) were prepared according to literature procedures (Scheme 1) from commercially available materials. Products were isolated by flash chromatography, the compounds were identified by ^1H and ^{13}C NMR spectroscopy.



(**1a**): R = H (**1b**): R = 3-Me; (**1c**): R = 5-Me; (**1d**): R = 6-Me; (**1e**): R = 3-OMe; (**1f**): R = 5-OMe; (**1g**): R = 3-OiPr; (**1h**): R = 4-F; (**1i**): R = 5-F; (**1j**): R = 6-F;

Scheme 1.

The 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one derivatives were prepared according to the Reissert indole synthesis (Scheme 2), based on recently published results.



Scheme 2.

The 5% Pt/Al_2O_3 catalyst was pre-treated in hydrogen before hydrogenations. The most often used chiral modifiers were cinchonidine (**CD**) and dihydrocinchonidine methyl ether (**dHCDM**) according to Figure 1.

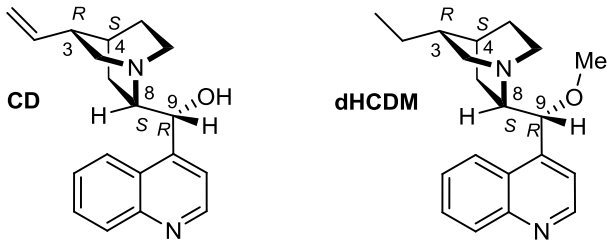


Figure 1.

The cascade reactions were carried out using a stainless steel high-pressure autoclave equipped with a glass tube. The reaction slurry was stirred magnetically under 1 or 4 MPa H_2 pressure, the time of hydrogenation was 2 or 3 hours. The flow experiments were carried out using an H-Cube® continuous-flow hydrogenation system. Experiments were conducted using 0.1-0.6 cm^{-1}/min flow rate and under 4 to 6 MPa H_2 pressure. Samples were collected at regular time intervals

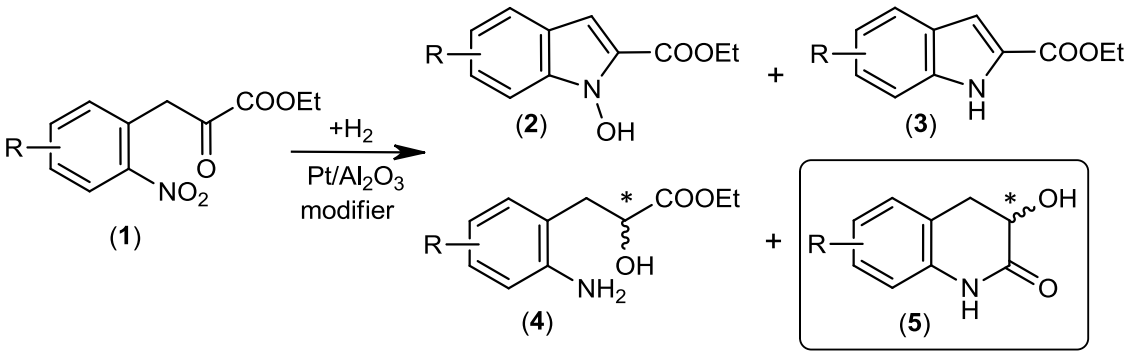
The products were analysed by GC-MSD for product identification and by GC-FID using a chiral capillary column. Based on the stereochemistry of the hydrogenations of α-keto esters investigated up to now over Pt modified by **CD**, we assumed that the use of alkaloids from this series results in excess formation of the product enantiomer having *R* absolute configuration. Enantiomeric excesses (*ee*) were calculated with the formula: *ee*(%) = 100×|[*S*]–[*R*]|/([*S*]+[*R*]), where [S] and [R] were the hydrogenated products concentration of *S* and *R* absolute configuration enantiomers. Following product analysis, the hydroquinolone derivatives were isolated by flash chromatography and characterized by NMR spectroscopy.

3. NOVEL SCIENTIFIC RESULTS

3.1. Hydrogenation of 2-nitrophenylpyruvates in batch reactor

In the product mixture resulted in the reaction of **1** over Pt/Al_2O_3 modified by **CD** four compounds were identified, as shown in Scheme 3.

I. This method is based on influencing the rates of the two competitive steps, the enantioselective hydrogenation of the activated keto group and the aromatic nitro group reduction. N-hydroxyindole (**2**) is formed by cyclization of the partially reduced hydroxylamine intermediate. According to the Reissert indole synthesis, the corresponding indole (**3**) derivatives formed by complete reduction of the nitro group to amino compound. The presence of **CD** increased the amount of our target product, i.e. the 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one derivate (**5**) by reduction of the keto group. In the reaction mixture we also identified the amino-alcohol derivate (**4**), which remained due to incomplete cyclization to **5**.



Scheme 3.

II. We found that tuning the reaction conditions has a major influence on the product composition. The best results were obtained under 10 atm H_2 pressure in toluene (T)/ acetic acid (AcOH) solvent mixture, using **dHMCD** (dihydrocinchonidine methyl ether) as modifier. The best results obtained in the experiments of each compound are summarized in Table 1. In the reaction of methyl substituted and alkoxy compounds (**1b-1g**) better selectivities (Sel.) and very similar *ee* values were obtained, compared with the non-substituted compound **1a**. Lower yields were obtained generally with the fluorine substituted derivatives (**1h-1j**), which may be explained by their anchoring effect.

		Sel.(%)	***ee* (%)**	
	Reaction conditions	**5a-j**	**5a-j**	R
1a	50 mg Pt/Al_2O_3, 0,01 mmol dHCDM, T/AcOH 9/1, 10 atm H_2, 3 h	69	**90**	–
1b	100 mg Pt/Al_2O_3, 0,02 mmol dHCDM, T/AcOH 49/1, 10 atm H_2, 2 h	99	**90**	**3**-Me
1c	50 mg Pt/Al_2O_3, 0,01 mmol dHCDM,T/AcOH 9/1, 10 atm H_2, 3 h	89	**86**	**5**-Me
1d	50 mg Pt/Al_2O_3, 0,01 mmol dHCDM, T/AcOH 9/1, 10 atm H_2, 3 h	57	**88**	**6**-Me
1e	100 mg Pt/Al_2O_3, 0,02 mmol dHCDM, T/AcOH 49/1, 10 atm H_2, 2 h	98	**88**	**3**-OMe
1f	50 mg Pt/Al_2O_3, 0,01 mmol dHCDM, T/AcOH 9/1, 10 atm H_2, 3 h	76	**68**	**5**-OMe
1g	100 mg Pt/Al_2O_3, 0,02 mmol dHCDM, T/AcOH 9/1, 10 atm H_2, 3 h	99	**84**	**3**-O^{i}Pr
1h	50 mg Pt/Al_2O_3, 0,02 mmol dHCDM, T/AcOH 49/1, 10 atm H_2, 3 h	50	**80**	**4**-F
1i	50 mg Pt/Al_2O_3, 0,01 mmol dHCDM, T/AcOH 9/1, 10 atm H_2, 3 h	58	**62**	**5**-F
1j	100 mg Pt/Al_2O_3, 0,02 mmol CD, T/AcOH 49/1, 10 atm H_2, 2 h	33	**90**	**6**-F

Table 1.

III. Substituents on the aromatic ring have important influence on the hydroquinolone yields, according to Table 1. The effect of the substituent was explained by the steric effect of these substituents, namely their influence on the reduction rate of the nitro group. Accordingly, the data showed that the substituents in 3- position (**1b** and **1e**) decelerated the reduction of the -NO_2 group, whereas the substituent in position 5 and 6 has no influence when compared with the non-substituted compound **1a**. This was explained by steric reasons, namely, the adjacent substituent decreases the reduction rate of the nitro group. With this compounds up to 90% *ee* values were obtained.

IV. A study on the modifier concentration effect in the reaction of **1b** showed the highest **5b** selectivity at 4 mM **CD** concentration (Figure 2). However, the side products resulted at low and high **CD** concentrations differed, namely, **2b** and **4b**, respectively. This phenomenon showed that the presence of adsorbed **CD** decelerates the reduction of the nitro group. At low modifier amount this is less accentuated, allowing the formation of **2b**. At high **CD** amount, the intramolecular amidation proceeds with lower rate, due to the smaller number of available active sites and the selectivity of **4b** increases. The latter observation shows that the final step of the cascade reaction occurs on the catalyst surface either immediately after the enantioselective hydrogenation-reduction sequence or following a desorption and re-adsorption sequence of the chiral amino-alcohol.

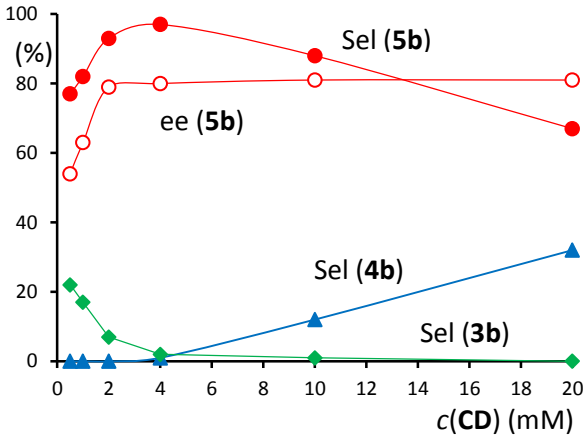
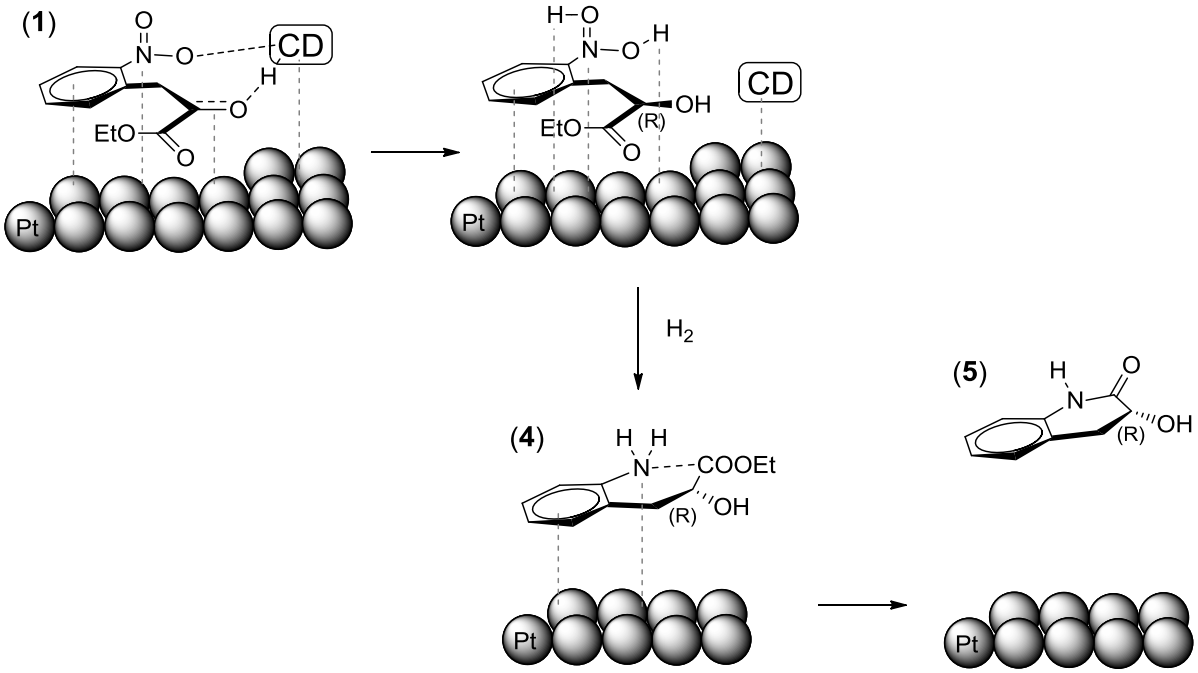


Figure 2.

V. Accordingly, the presence of the modifier had double effect on the hydrogenation of 2-nitrophenylpyruvates, that is, induced enantioselectivity and increased the selectivity of the hydroquinolone by accelerating the ketone hydrogenation concomitantly with decreasing the reduction rate of the nitro group.

VI. According to these interpretations the possible reaction pathway leading to the formation of the desired product is shown in Scheme 4. Eventually, it was concluded that all three steps of this unique cascade reaction, which leads to optically enriched N-heterocyclic compounds, take place on the Pt surface.



Scheme 4.

3.2. Hydrogenation of 2-nitrophenylpyruvates in continuous flow system

We have investigated the possibility of carrying out the reaction in an H-Cube® continuous-flow hydrogenation system (Figure 3) using a fixed-bed reactor filled with Pt/Al_2O_3 modified by cinchonidine.

VII. The high selectivities and enantioselectivities of the main (*R*)-3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one products obtained in previous studies in batch reactor were not achieved, due to perturbed rate balance of the first two competitive steps.

VIII. Under flow conditions very low **5b** selectivities were obtained, the main product was the amino-alcohol (**4b**). This confirmed that the final cyclization step of the cascade occurs only at higher conversions of 2-nitrophenylpyruvates (**1b**), which was interpreted by desorption and re-adsorption of **4b** based on the results obtained in batch experiments. Because no full conversion and relatively low **5b** selectivities were reached by passing once the solution of the substrate through the catalyst bed, the resulting product mixture was continuously recirculated over the catalyst. Recirculation of the product mixture besides increasing the conversion and selectivity, didn't cause a drastic change in *ee*.

IX. The presence of the modifier accelerating the ketone hydrogenation, therefore pre-modification of the Pt/Al_2O_3 catalyst with the cinchona modifier enhanced the product selectivity.

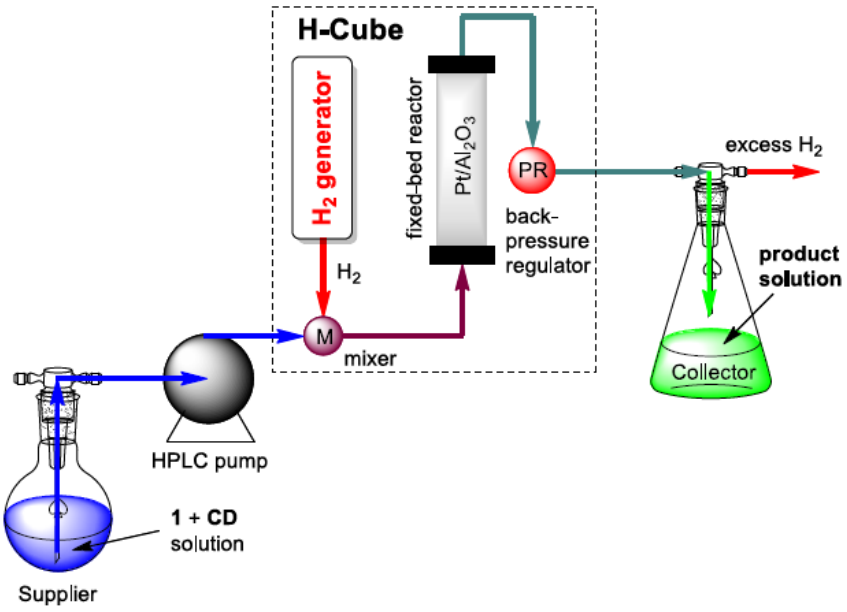


Figure 3.

4. SUMMARY

In conclusion we developed the first heterogeneous catalytic asymmetric cascade reaction for the efficient synthesis of hydroquinolone derivatives starting from 2-nitrophenylpyruvates using supported Pt catalysts modified by cinchona alkaloids, in which we obtained high yields and good enantioselectivities. It was shown that the cascade leading to these products started with the enantioselective hydrogenation of the activated keto group, followed by the reduction of the nitro group and finally the intramolecular amidation, all steps occurring on the Pt surface. We found that tuning the reaction conditions has a major influence on the product composition, as the enantioselective hydrogenation and the reduction of the nitro group are competing reactions. Substituents on the aromatic ring have important influence on the hydroquinolone yields, which was explained by their effect on the reduction rate of the nitro group. It was demonstrated, that the final cyclization step of the cascade reaction occurs on the catalyst, i.e. metal surface.

We have investigated the possibility of carrying out the reaction in continuous-flow hydrogenation system. However, the high selectivities and enantioselectivities of the main (*R*)-3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one products obtained in batch reactor were not achieved, due to perturbed rate balance of the first two competitive steps. Pre-modification of the Pt/Al_2O_3 catalyst with the cinchona modifier enhanced the product selectivity, whereas recirculation of the product mixture besides increasing the conversion and selectivity, didn't cause a drastic change in *ee*.

Finally, the heterogeneous cascade reaction disclosed here is a novel application of the Orito reaction and could also be a starting point for developing attractive strategies for the synthesis of various optically pure N-heterocyclic compounds.

5. PAPERS RELATED TO THE THESIS

I. György Szőllősi, Zsolt Makra, Lenke Kovács, Ferenc Fülöp, Mihály Bartók
Preparation of optically enriched 3-hydroxy-3,4-dihydroquinolin-2(*1H*)-ones by heterogeneous catalytic cascade reaction over supported platinum catalyst
Advanced Synthesis & Catalysis **2013**, 355, 1623-1629 IF: 5.542

II. György Szőllősi, Lenke Kovács, Zsolt Makra
Three consecutive steps over the chirally modified Pt surface: asymmetric catalytic cascade reaction of 2 nitrophenylpyruvates
Catalysis Science & Technology **2015**, 5, 697-704 IF: 5.426

III. Lenke Kovács, György Szőllősi, Ferenc Fülöp
Pt-cinchonidine catalysed asymmetric catalytic cascade reaction of 2-nitrophenylpyruvates in flow system
Journal of Flow Chemistry **2015**, 5(4), 210-215 IF: 1.878

Summarized impact factors of the publications related to the thesis: 12.846

6. OTHER PAPER

IV. András Gurka, Imre Bucsi, Lenke Kovács György Szőllősi, Mihály Bartók
Reversal of the enantioselectivity in aldol addition over immobilized di- and tripeptides: studies under continuous flow conditions
RSC Advances **2014**, 4, 61611-61618 IF: 3.840

7. SCIENTIFIC LECTURES RELATED TO THE THESIS

V. Kovács Lenke, Szőllősi György
Tetrahidrokinolon származékok enantioszelektív előállítása heterogén katalitikus reakcióval
TDK kémia II. szekció
Szeged, Hungary, 26 April 2012.

VI. Kovács Lenke, Szőllősi György
Tetrahidrokinolon származékok enantioszelektív előállítása heterogén katalitikus reakcióval
A *Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 12. Tudományos Előadóülése*
Szeged, Hungary, 8 May 2012.

VII. Kovács Lenke, Szőllősi György
Tetrahidrokinolon származékok enantioszelektív előállítása heterogén katalitikus reakcióval

XXX: Országos Tudományos Diákköri Konferencia, Kémia és Vegyipari szekció
Eger, Hungary, 4-6 April 2013.

VIII. Szőllősi György, Makra Zsolt, Kovács Lenke, Bartók Mihály
Heterogén katalitikus kaszkád reakció királis hidrokinolin származékok enantioszelektív előállítására
Vegyészkonferencia
Hajdúszoboszló, Hungary, 26-28 July 2013.

IX. György Szőllősi, Zsolt Makra, Lenke. Kovács, Ferenc Fülöp, Mihály Bartók
Heterogeneous asymmetric catalytic cascade reaction for the preparation of 3-hydroxy-3,4-dihydroquinolin-2(*1H*)-ones
11th European Congress on Catalysis – EuropaCat-XI,
Lyon, France, 1-6 September 2013.

X. Kovács Lenke, Szőllősi György, Fülöp Ferenc
2-nitrofenilpiroszőlősav észterek reakciója cinkonidinnel módosított Pt katalizátoron átáramlásos rendszerben
MKE 2. Nemzeti Konferencia
Hajdúszoboszló, Hungary, 31 August - 2 September 2015.

XI. Kovács Lenke, Szőllősi György, Fülöp Ferenc
2-Nitrofenilpiroszőlősav-etilészter származékok aszimmetrikus kaszkád reakciója királisan módosított platina katalizátoron
Katalízis Munkabizottsági Ülés
Szeged, Hungary, 11 December 2015.

8. OTHER SCIENTIFIC LECTURE

XII. György Szőllősi, Lenke Kovács
Cinchona alkaloid catalysts in the asymmetric Michael-addition of fluorinated C-nucleophile to β-nitrostyrene
Chirality 2014 (26th International Symposium on Chiral Discrimination)
Prague, Checz Republic, 27-30 July 2014.