Catalysis Science & Technology

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/catalysis

Catalysis Science & Technology

RSCPublishing

PAPER

Three consecutive steps over chirally modified Pt surface: asymmetric catalytic cascade reaction of 2-nitrophenylpyruvates

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

György Szőllősi,*[a] Lenke Kovács[b] and Zsolt Makra[c]

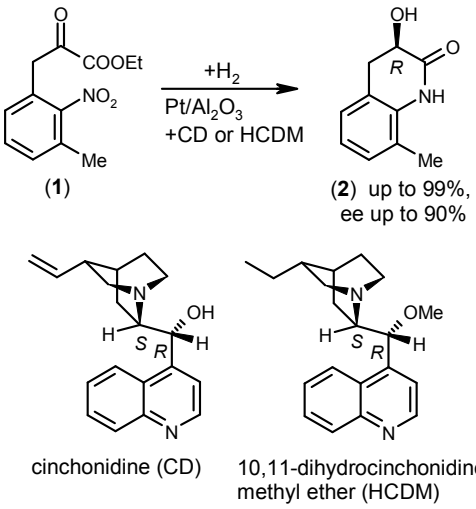
The influence of the reaction conditions on the asymmetric heterogeneous cascade reaction of 2-nitrophenylpyruvates over Pt catalysts modified by cinchonidine leading to (*R*)-3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one derivatives has been studied. Results of studies on the acetic acid or catalyst amount, nature of the Pt support, kinetic examinations, effect of the H_2 pressure, modifier and substrate concentrations showed that all three steps of this catalytic cascade takes place over the Pt surface, with the nitro group reduction following immediately the enantioselective hydrogenation of the keto group, whereas the final intramolecular amidation was preceded by desorption after complete reduction of the substrate and re-adsorption of the corresponding intermediate.

1. Introduction

Optically pure partially saturated quinoline derivatives are intermediates in the preparation of natural products and pharmaceuticals.[1,2] For the asymmetric synthesis of these valuable chiral building blocks several catalytic methods were designed.[3] Besides enantioselective catalytic hydrogenations of quinoline derivatives using chiral metal complexes,[4] recently, asymmetric organocatalytic or metal catalysed cascade reactions were applied for the construction of the hydroquinoline moiety from readily available multifunctional compounds.[5-7] Due to recent requirements of using sustainable, atom-economic and environmentally benign processes in the preparation of fine chemicals special attention is paid to the application of heterogeneous asymmetric catalysts, as easily separable and recyclable materials.[8] Modifications of supported metal catalysts by optically pure compounds are among the simplest procedures of obtaining chiral heterogeneous catalysts.[9] However, chirally modified catalysts were efficient mostly in enantioselective hydrogenations of certain prochiral compounds and were found of limited applicability.[10-13] Moreover, asymmetric catalytic cascade reactions over heterogeneous chiral catalysts were scarcely reported,[14,15] and only few reactions are known in which the stereoselective step occurs on the solid catalyst surface.[16,17]

Recently, we developed a novel asymmetric heterogeneous catalytic cascade reaction for the enantioselective preparation of 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one derivatives from 2-nitrophenylpyruvates over Pt catalyst modified by cinchona alkaloids.[18] Although, previously was reported the formation of hydroquinolone derivatives over PtO_2 catalyst,[19] the presence of the cinchona alkaloid besides inducing enantiodifferentiation also increased the yield of this product. The latter was suggested to be due to acceleration of the enantioselective hydrogenation by the modifier, phenomenon called ligand acceleration,[20,21] and also due to deceleration of the nitro group reduction. Close to exclusive formation of quinolones were observed from derivatives substituted next to the nitro group, due to decreased reduction rate of the nitro group by substituents (Scheme 1).

During our study it was found that tuning of the reaction conditions has major influence on the product composition, as the enantioselective hydrogenation of the keto group and the reduction of the nitro group are competitive, both catalysed by the Pt surface. It was also suggested that the final cyclization may also take place on the metal surface.[18] In the present study our aim was to examine the effect of several reaction parameters on the product distribution, to obtain information on the sequence leading to the desired product, and ultimately for developing other asymmetric heterogeneous catalytic cascade processes.



Scheme 1 Asymmetric catalytic cascade reaction over Pt catalyst modified by cinchona alkaloids (ee: enantiomeric excess).

2. Experimental

2.1 Materials

Commercial 5 % Pt/Al_2O_3 catalyst (Engelhard, 4759, Pt dispersion 0.2-0.3 by TEM, support: γ-Al_2O_3 with acidity close to pure flame-made Al_2O_3)[22-24] was used following reduction in a fixed-bed flow reactor at 673 K in 30 mL/min H_2 flow, as described earlier.[21] Other catalysts used were either commercial products (5% Pt/C, 80982; 10% Pt/C, 80980; PtO_2 with ≥60 m^2/g, 206032 all supplied by Sigma-Aldrich) or were prepared using known methods and commercial supports (montmorillonite K 10 having 250 m^2/g and pH 3-4,[25] Nafion® SAC-13 fluorosulfonic acid Nafion® polymer on amorphous silica, 10-20%, >200 m^2/g, >10 nm pore diameter,[26] both from Sigma-Aldrich; Cab-O-Sil® M-5 SiO_2 from Cabot Corp. with 256 m^2/g and 151 μmol/g total acidity[27]). The characteristics of some of these catalysts were previously published, i.e. 0.14 metal dispersion of the 3% Pt/SiO_2, and the Pt particles deposited over montmorillonite K 10 (5% Pt/K 10) has 3.8 nm mean diameter.[28,29] Cinchonidine (CD, Alfa-Aesar, 99%) was used as received. Solvents of analytical grade and H_2 gas (99.999%, Linde AG) were used as received. Ethyl (3-methyl-2-nitrophenyl)pyruvate (**1**), ethyl (5-methyl-2-nitrophenyl)pyruvate (**6**) and ethyl (6-methyl-2-nitrophenyl)pyruvate (**7**) were prepared by condensation of 2,6-dimethylnitrobenzene, 2,4-dimethylnitrobenzene and 2,3-dimethylnitrobenzene (Sigma-Aldrich), respectively and diethyl oxalate (Sigma-Aldrich) using potassium *tert*-butoxide as earlier reported.[18] Ethyl 2-nitrophenylpyruvate (**8**) was prepared from 2-nitrophenylpyruvic acid (Sigma-Aldrich) as described in our previous report.[18]

2.2 Asymmetric catalytic cascade reaction: typical procedure

Reactions were carried out in a 45 cm^3 glass tube introduced in a stainless steel autoclave. The given amount of catalyst, solvent, modifier and substrate were introduced into the tube and placed in the autoclave which was flushed with H_2, filled to the desired H_2 pressure and the slurry was stirred magnetically with 1000 rpm at room temperature (25°C). Following the given reaction time the H_2 was released, the catalyst was filtered, washed with solvent and the organic phase was analyzed.

Identification of the products was carried out by GC-MSD (Agilent Techn. 6890N GC – 5973*inert* MSD) using a HP-1MS 60 m column. Products identified in reactions of **1** are shown in Scheme 2. Quantitative analyses was performed using GC-FID (Agilent Techn. 6890N GC – FID) equipped with chiral capillary column (Cyclodex-B, 30 m) and tetradecane as internal standard. These results were used to calculate the conversion (X), product selectivities ($S(P_i)$) and the enantioselectivities, expressed as the enantiomeric excesses (ee) according to the following formulae:

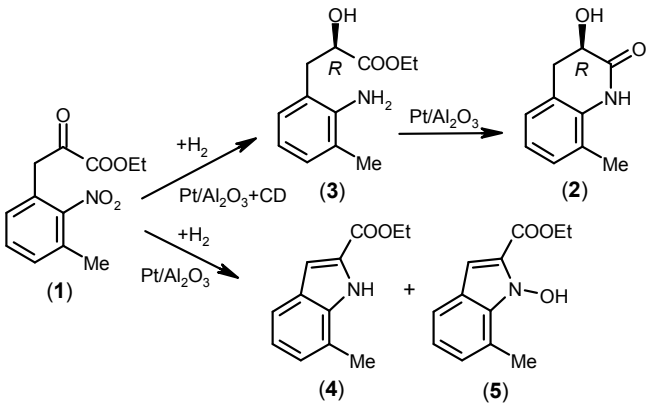
$$X\ (\%) = 100 \times (1 - c_t(\mathbf{1})/c_0(\mathbf{1}));$$

$$S(P_i)\ (\%) = 100 \times c(P_i)/(c_0(\mathbf{1}) - c_t(\mathbf{1}));$$

$$ee\ (\%) = 100 \times |c(R\text{-}\mathbf{2}) - c(S\text{-}\mathbf{2})|/(c(R\text{-}\mathbf{2}) + c(S\text{-}\mathbf{2}));$$

where $c_0(\mathbf{1})$ and $c_t(\mathbf{1})$ are the initial concentration and the concentration at time t of **1**; $c(P_i)$ is the concentration of producti; $c(R\text{-}\mathbf{2})$ and $c(S\text{-}\mathbf{2})$ are the concentrations of the *R* and *S* enantiomers of product **2**. Unless otherwise given the reactions led to complete transformation of the 2-nitrophenylpyruvates. In reactions using CD as modifier the *R* enantiomer forms in excess, as shown in our previous report.[18]

The reproducibility of the results was within ± 2% as demonstrated by reactions repeated at least three times. The



main product, i.e. the 3-hydroxy-8-methyl-3,4-dihydroquinolin-2(1*H*)-one, was isolated by flash chromatography using petroleum ether/ethyl acetate 4/1 eluent and was characterized by ^1H and ^{13}C NMR spectroscopy.[18]

Scheme 2 Products formed in the asymmetric catalytic cascade reaction of **1** over Pt/Al_2O_3 catalyst modified by CD.

3. Results and discussion

In the present study the transformation of 3-methyl substituted ethyl 2-nitrophenylpyruvate (**1**) was investigated, which provided higher hydroquinolone yield than the compound lacking methyl substituent on the aromatic moiety (see Scheme 1).[18] The product mixture resulted in the reaction of **1** over Pt/Al_2O_3 modified by CD contained the four compounds shown in Scheme 2, *i.e.* the corresponding indole (**4**) and oxindole (**5**) derivatives formed by complete or partial reduction of the nitro group and condensation with the keto group, as occurs in the Reissert indole synthesis. These compounds are formed due to easy reduction of aromatic nitro compounds to hydroxylamines and anilines over metal catalysts such as Pd, Pt or Ni.[30,31] However, the main products in our reactions were the corresponding hydrogenated amino-alcohol derivative (**3**) and the hydroquinolone (**2**). Our initial studies showed that the choice of the solvent has major influence on the product distribution, the highest **2** selectivities were obtained in toluene with addition of small amounts of acetic acid (AcOH).[18] Similarly, these two solvents (toluene and AcOH) and mixtures thereof are the best performing and most often used in the enantioselective hydrogenation of α-keto esters over Pt catalysts modified by cinchona alkaloids.[9,21,23,32] Thus, we decided to investigated the AcOH amount necessary to obtain the best results in this asymmetric cascade reaction.

3.1 Influence of the AcOH and catalyst amount

Results obtained using different amounts of AcOH were plotted in Fig. 1. Under conditions of these experiments complete conversion of **1** was always obtained. It was observed on one hand that the relatively high amount of **3** obtained in toluene decreased by addition of small amount of AcOH concomitantly with increase in the **2** selectivity. On the other hand the indole (**4**) selectivity increased by raising the amount of AcOH, which ultimately in pure AcOH reached 38% (not shown in Fig. 1). Small increase in the ee was obtained by raising the amount of AcOH up to 5 vol %,

however, the ee values didn't changed significantly by further increase of the AcOH content of the solvent.

Accordingly, the presence of the acid on one hand promotes the cyclization, shown by the obtained amount of 3 and on the other hand also has accelerating effect on the reduction of the nitro group, as indicated by the selectivity of 4. Based on these results 2 vol % AcOH were sufficient to obtain the best 2 selectivity.

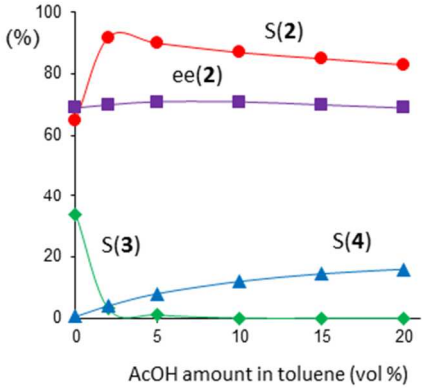


Fig. 1 Effect of the AcOH amount on the product selectivities and enantioselectivity of **2**. Reaction conditions: 100 mg Pt/Al_2O_3, 5 mL solvent, *c*(CD) 4 mM, c_0(**1**) 80 mM, pH_2 4 MPa, 25°C, 3 h, full conversions of **1**.

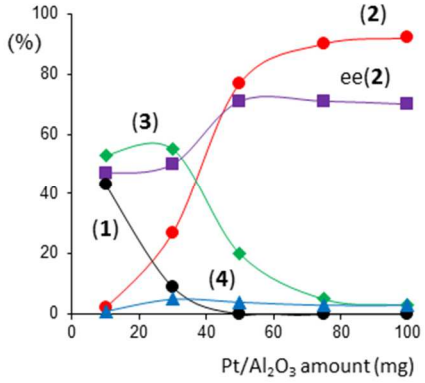


Fig. 2 Effect of the Pt/Al_2O_3 catalyst amount on the reaction mixture composition and enantioselectivity of **2**. Reaction conditions: 5 mL toluene with 2 vol % AcOH, CD amount 2×10^{-4} mmol/g catalyst, c_0(**1**) 80 mM, pH_2 4 MPa, 25°C, 3 h.

Thus, in our next study designed to investigate the role of the catalyst in the individual steps of the cascade reaction we have used the above solvent mixture. Initially, we have focused on examining the effect of the catalyst amount, while keeping the CD/Pt ratio constantly at 2.89 mmol CD/mmol surface Pt (0.27 Pt dispersion[22]) (Fig. 2).

The main products over low amounts of catalyst (10 or 30 mg) were also **3** and **2** with both reducible groups (C=O and NO_2) completely hydrogenated, even when the conversion of **1** wasn't complete. The indole **4** selectivity remained low on the whole catalyst amount range. The ee of the two chiral compounds **2** and **3** were within the limit of the determination error (not shown). Significant drop in the ee was detected by decreasing the catalyst amount under 50 mg Pt/Al_2O_3, i.e. when **1** wasn't completely transformed. This drop was probably due to decreased CD concentration, which may diminish the ee even when the CD/surface Pt ratio is kept constant due to dilution effect, thus, a higher ratio of surface sites is available for the racemic hydrogenation of the strongly adsorbing **1**.[33,34] Although, the effect of the diffusion on the two reduction steps is difficult to examine, due to fast and possible competitive occurrence of these steps, the constant ee over higher amount of catalyst (50 – 100 mg) is indicative of a hydrogen diffusion limitation free enantioselective hydrogenation, as otherwise decrease in the ee is expected to obtain.[35] We also mention that once formed, the chiral centre isn't further affected in the successive transformations, thus the obtained ee-s can't provide

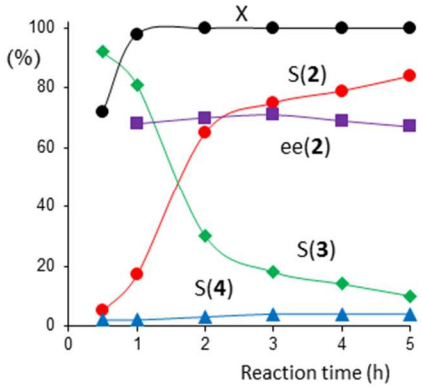


Fig. 3 Effect of the reaction time on the transformation of **1** over Pt/Al_2O_3. Reaction conditions: 50 mg catalyst, 5 mL toluene with 2 vol % AcOH, *c*(CD) 2 mM, c_0(**1**) 80 mM, pH_2 4 MPa, 25°C.

further information on the kinetics of the following steps. However, increase in the amount of **2** at the expense of **3** over higher catalyst amount showed that the intramolecular amidation took place on the catalyst surface, although was also accelerated in some extent by using small amount of AcOH (see Fig. 1).

3.2 Kinetics of the cascade reaction

Results of kinetic investigations of the cascade reaction over 50 mg catalyst are illustrated in Fig. 3. We mention that similar trends were obtained over 100 mg catalyst, too (not shown). Complete conversion of **1** was obtained (except after 0.5 h) and the main products in all these experiments were **3** and **2**. The former was in excess following shorter reactions and was transformed to hydroquinolone **2** as the reaction time was extended. Obviously, under such conditions, the rates of the first two competitive steps could not be examined, and only information on the final step was gathered. The product compositions showed clearly, that the amino-alcohol **3** desorbs from the surface following the reduction steps. The formation of **2** by cyclization of **3** was also indicated by the identical ee values of **2** and **3** (not shown in Fig. 3). Desorption probably was assisted by the presence of **1** in the slurry, the latter having higher adsorption strength as compared to **3**, as shown by the adsorption strengths of nitro compounds in comparison with amines and the adsorption mode of ketones and alcohols.[36,37] Thus, **3** is a stable intermediate through which **2** is formed and which is transformed following the complete consumption of **1**.

3.3 Effect of the catalyst support

According to the above results the final step of the cascade reaction, *i.e.* the amidation, occurs on the catalyst surface following the consumption of the nitrophenylpyruvate **1**. This step may be catalyzed by acids. Thus we examined the possible involvement of the catalyst support in the final reaction step,

which may also have acidic character, similarly with the Pd catalysts supported over γ-Al_2O_3.[38] In order to investigate the role of the support the reaction was carried out using Pt deposited over various supports, including a Lewis and Broensted acidic clay (motmorillonite K 10) or Broensted acidic Nafion® SAC-13. Results obtained are summarized in Table 1.

Large variations in enantioselectivities were obtained over these catalysts, the best values were attained over the Pt/Al_2O_3, whereas the worst over Pt supported over solid acids. Although the enantioselectivity is strongly influenced by the particle size and morphology of the Pt,[9,10] the decrease in the ee observed by addition of Nafion® SAC-13 to the slurry using Pt/Al_2O_3 indicated that the acidic material probably bonded significant part of the modifier on its surface, impeding the adsorption over the metal. Thus, similar ee value was obtained as in the presence of lower amount of modifier.[18] Surprisingly, over catalysts using acidic supports the selectivity of the quinolone **2** was very low, whereas good selectivities were obtained over carbon or silica supported catalysts or even over *in situ* reduced PtO_2. Accordingly, the support was not necessary to obtain the cyclic compound **2**. The high **3** selectivities observed by addition of acidic material to the Pt/Al_2O_3 containing slurry indicates an unfavorable effect of such materials on the cyclization. Thus one may exclude the cyclization of **3** to **2** over the acidic support and consequently over the Al_2O_3 and it could be assumed that this final step also proceeds over the metal surface. The intramolecular amidation of esters as a subsequent step of reduction over metal catalyst is a known lactam preparation procedure even in neutral solvents.[19,30,39] The significant effect of the support character may be attributed to the electronic charge transfer occurred between the metal and support, as was suggested to be the reason of the selectivities obtained in the competitive hydrogenation of different functional groups.[40]

Table 1 Influence of catalyst support on the reaction of **1**.[a]

Catalyst;[b] (mg)	S(**3**) (%)	S(**2**) (%)	ee(**2**) (%)
5% Pt/Al_2O_3; 50	20	77	71
5% Pt/Al_2O_3; 100	6	90	76
5% Pt/C; 100	<1	71	36
10% Pt/C; 50	<1	77	36
3% Pt/SiO_2; 100	29	68	36
PtO_2; 50	<1	88	24
5% Pt/K 10; 100	65	3	10
5% Pt/SAC-13; 50	95	3	23
5% Pt/Al_2O_3; 50 + SAC-13; 50	57	42	59

[a] Reaction conditions: given amount of catalyst, 5 mL toluene with 2 vol % AcOH, CD amount 2 × 10^{-4} mmol/g catalyst, c_0(**1**) 80 mM, pH_2 4 MPa, 25 °C, 3 h, complete conversions of **1**. [b] For the origin and properties of the catalysts see subsection 2.1.

3.4 Influence of the H_2 pressure

Confirmation of the suggestion that all three steps of the cascade reaction proceed over the Pt particles covered by chemisorbed hydrogen was obtained from studies on the effect of the H_2 pressure on the product composition shown in Fig 4.

The best results were obtained under 1 MPa H_2 pressure. The increase in the pressure over this value resulted in increase in the selectivity of the unreacted **3** and decrease of the quinolone **2** selectivity. Similarly, under pressures over 1 MPa the ee also slightly decreased by raising the pressure, as observed in enantioselective hydrogenations of activated ketones.[10,41] The most plausible explanation of the ee decrease is the consumption of the modifier by hydrogenation of the anchoring quinoline moiety, resulting in formation of partially hydrogenated cinchonidine derivatives with lower enantiodifferentiating ability.[41] Considering that the selectivity of **2** followed the same trend as the ee as a function of the H_2 pressure, one may speculate that the cyclization is also unfavorably affected by the hydrogenation of CD. Possible interaction of **3** with partially hydrogenated CD on the Pt surface may decrease the cyclization rate and may lead to higher amino-alcohol product in the mixture following identical reaction time. Although this assumption should be verified in future experiments, if confirmed these results support the assumption of the third step taking place on the Pt surface.

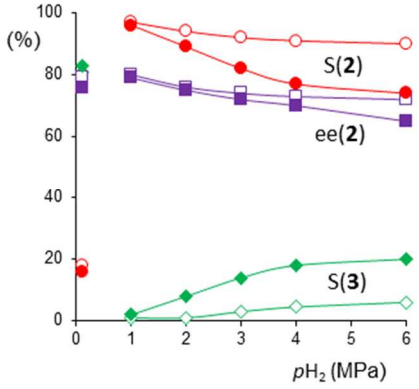


Fig. 4 Effect of the H_2 pressure on the reaction of **1**. Reaction conditions: 50 mg (open symbols) or 100 mg (closed symbols) of Pt/Al_2O_3, 5 mL toluene with 2 vol % AcOH, CD amount 2 × 10^{-4} mmol/g catalyst, c_0(**1**) 80 mM, 25°C, 3 h (over 50 mg catalyst) or 2 h (over 100 mg catalyst) reactions, complete conversions of **1**.

Observations also worth discussing are the selectivities obtained under low, *i.e.* 0.1 MPa, H_2 pressure. The high amount of **3** remained in the reaction mixture should be due to low rates of the first two steps, thus following the given reaction time the third cyclization step of the cascade was not complete. This possible explanation could also rationalize the low **2** selectivities obtained over the home made Pt/K 10 and Pt/SAC-13, which probably were less active in the reduction steps then the commercial catalysts, accordingly the third step over these materials was not complete after identical reaction times as was used in experiments over commercial catalysts.

3.5 Effect of the modifier and substrate concentration

The present study was also extended on investigating the effect of the CD and substrate concentration, carried out under 1 MPa H_2 pressure (based on the above). Although, the influence of the modifier concentration has already been discussed,[18] data obtained over lower catalyst amount presented in Fig 5 showed better the obtained tendencies, due to amplification of the CD concentration effect by increasing the modifier/catalyst ratio, as compared to our previously published experiments. Increase in the modifier coverage by increasing the CD concentration up to 2 mM had as effect a shift of the reaction pathway from the partial formation of **4** to exclusive formation of **2**, whereas further increase in the *c*(CD) resulted in gradual drop in the **2** selectivity and formation of increasing amounts of **3**. The ee value also increased up to 2 mM *c*(CD) followed by constant values upon further raising the *c*(CD). It should be mentioned that in these experiments the ee of **3** (not shown in Figs) was

always identical or very close to the ee(**2**). Based on these observations one may reach to the conclusion that the presence of CD hindered the fast reduction of the nitro group and the formation of **4**. However, over a certain CD concentration, *i.e.* coverage, the adsorbed modifier hindered the cyclization step, too. Although, one may speculate that this may occur due to alterations in the adsorption mode of the cinchona alkaloids as a function of the coverage,[42-44] the most plausible explanation is that the surface of the metal should be covered only partially by the modifier to be able to adsorb the intermediate product **3** in order to obtain **2**. This confirmed that the cyclization occurs on the metal surface.

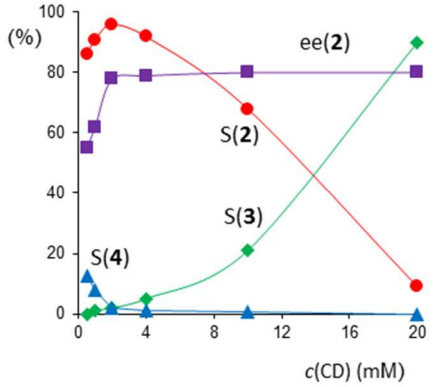


Fig. 5 Effect of cinchonidine concentration on the product selectivities and enantioselectivity of **2**. Reaction conditions: 50 mg Pt/Al_2O_3, 5 mL toluene with 2 vol % AcOH, c_0(**1**) 80 mM, pH_2 1 MPa, 25°C, 3 h, complete conversions of **1**.

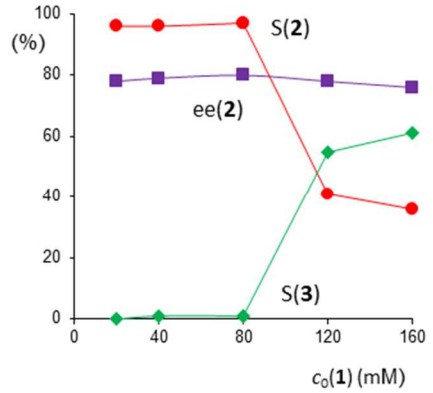


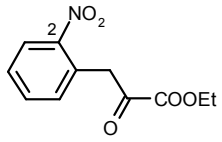
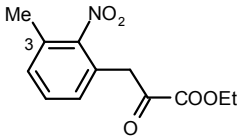
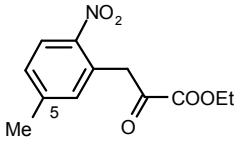
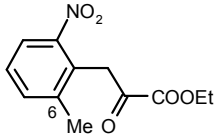
Fig. 6 Effect of substrate initial concentration on the product selectivities and enantioselectivity of **2**. Reaction conditions: 100 mg Pt/Al_2O_3, 5 mL toluene with 2 vol % AcOH, c(CD) 4 mM, pH_2 1 MPa, 25°C, full conversions in 2 h.

The effect of the nitrophenylpyruvate **1** concentration on the product selectivities and the ee of **2** is presented on Fig 6. No significant variations in the ee were observed, thus the ee was influenced by the catalyst/CD ratio (at low CD concentrations, see Fig 5) and was practically independent on the **1**/CD ratio (in the c_0(**1**) range studied, see Fig 6). Almost exclusive formation of **2** was detected up to 80 mM c_0(**1**), however, over this concentration the cyclization was not complete and intermediate **3** was detected in the product mixture. As the reduction steps were complete in these experiments, even when the highest c_0(**1**) was used, selectivities were governed by the cyclization rate of **3**. Thus, under these conditions the first two steps of the cascade, *i.e.* the enantioselective hydrogenation and the reduction of the nitro group, occurred without desorption of partially reduced intermediates even at 8 mmol substrate/g catalyst ratio. The decrease in the **2** selectivity over a certain c_0(**1**) (80 mM) showed that the cyclization rate wasn't influenced significantly by the c_0(**1**) and longer reaction times are necessary for the complete transformation of larger amounts of **3** to **2**.

3.6 Influence of the position of the methyl substituent

The 3-methyl substituted ethyl 2-nitrophenylpyruvate (**1**) was chosen as substrate for these examinations, based on results obtained over unmodified Pt[19] and our previous study.[18] The 3-methyl substituent was suggested to hinder in some extent the reduction of the nitro group, which altered the ratio of the –C=O

Table 2 Influence of the methyl substituent position on the asymmetric cascade reaction of 2-nitrophenylpyruvates.[a]

Substrate	S(**In**[b]) (%)	S(**Red**[b]) (%)	S(**Hq**[b]) (%)	ee(**Hq**) (%)
 (**8**)	20	1	55	80
 (**1**)	2	<1	97	80
 (**6**)	20	1	65	52
 (**7**)	45	8	35	79

[a] Reaction conditions: **A**: 100 mg Pt/Al_2O_3, 5 mL toluene with 2 vol % AcOH, c(CD) 4 mM, c_0(**1**) 80 mM, pH_2 1 MPa, 25°C, 2 h, full conversions. [b] Abbreviations: the corresponding indole (**In**), the reduced intermediate (**Red**) and the hydroquinolinone (**Hq**).

hydrogenation/–NO_2 reduction rates. However, the position of the substituent may alter the adsorption of the substrate and thus affect the reactivity of the functional groups, especially that of the –NO_2 group bonded to the phenyl ring. The influence of the position of the methyl substituent has been evidenced by comparison of results obtained under identical conditions in the reaction of three methyl derivatives (**1**, **6**, **7**) with those obtained using the compound lacking methyl substituent on the phenyl ring (**8**). Results obtained are summarized in Table 2. Variations in the amount of indole derivative (**In**) formed during reactions may be considered as indication of the effect of the substituent on the reduction rate of the –NO_2 group, considering that the methyl substituent has

less effect on the rate of the enantioselective hydrogenation of the –C=O group. Accordingly, the data showed that the 3-methyl substituent decelerated the reduction of the $–NO_2$ group, whereas the substituent in position 5 had no influence when compared with the unsubstituted compound **8**. On the contrary the methyl substituent in position 6 increased the selectivity of **In**. This may be explained by tilting of the adsorbed substrate on the metal due to steric repulsions between the methyl group and the surface, thus allowing easier interaction of the $–NO_2$ group with the Pt and chemisorbed hydrogen. The selectivities of the hydroquinolone derivatives (**Hq**) increased in the presence of the methyl substituent in positions 5 or 3, in case of the latter almost exclusive formation of the target product was obtained. Only in the reaction of the compound substituted in position 6 the **Hq** amount decreased. It must be noted that very similar ee values were obtained with the exception of the reaction of **6**, which may be ascribed to possible hindering of the CD–substrate interaction on the surface by the methyl group in this position. One can also observe that under these conditions only in the reaction of **7** resulted significant amount of reduced uncyclized product (**Red**). Thus, the methyl group only in this position hindered the re-adsorption of the amino-alcohol intermediate.

Conclusions

Results disclosed in this report on the effect of the reaction conditions on the recently published asymmetric cascade transformation of 2-nitrophenypyruvates over Pt catalyst modified by cinchonidine,[18] allowed to draw novel conclusions compared to our previous report, which could be edifying for future design of asymmetric cascade reactions, particularly using chiral surfaces as heterogeneous catalyst.

Although, the first two steps of the reaction studied are competitive, both may occur only on the metal surface and their rates are comparable, modification of the Pt particles by cinchona alkaloids besides imparting asymmetry to the surface, also increased the rate difference between these two steps, by decelerating the $–NO_2$ group reduction and accelerating the enantioselective hydrogenation of the activated keto group. This difference is even more accentuated when a substituent adjacent to the $–NO_2$ group further decelerates the reduction of this group. Thus, in the reaction of **1** these competitive steps became subsequent reactions over chirally modified Pt catalyst, which proceeded without desorption of the partially reduced intermediates between the steps, as indicated by effect of the substrate concentration. The kinetic study shown here also indicted that the amino alcohol **3** is a stable intermediate through which **2** is formed and which is transformed mostly following the complete consumption of **1** from the reaction mixture. Results of examining the influence of the catalysts amount indicted that the third, final step of the reaction, *i.e.* the intramolecular amidation also proceeded on the catalyst, however, it was shown that the support wasn't necessary, thus, this final step may occur over the metal surface. The latter conclusion was supported by the influence of the H_2 pressure, modifier and substrate concentration on the selectivities of the products. The accumulation of the intermediate **3** in the reaction mixture showed that the cyclization takes place on the Pt surface following desorption and re-adsorption of this intermediate.

Based on these conclusions the steps of this asymmetric heterogeneous catalytic cascade reaction may be illustrated as shown in Fig. 7. Eventually, it was concluded that all three steps of this unique cascade reaction, which leads to optically enriched *N*-heterocyclic compounds takes place on the Pt surface.

Acknowledgements

Financial support by the Hungarian National Science Foundation (OTKA Grant K 109278) is highly appreciated. This research was supported in the framework of TÁMOP 4.2.4. A/2-11-1-2012-0001 „National Excellence Program – Elaborating and operating an inland student and researcher personal support system" key project. The project was subsidized by the European Union and co-financed by the European Social Fund.

Notes and references

[a] MTA-SZTE Stereochemistry Research Group, University of Szeged, Department of Organic Chemistry, H-6720, Szeged, Dóm tér 8, Hungary. Fax: +36-62-544200; E-mail: szollosi@chem.u-szeged.hu.
[b] University of Szeged, Institute of Pharmaceutical Chemistry, H-6720, Szeged, Eötvös utca 6, Hungary.
[c] University of Szeged, Department of Organic Chemistry, H-6720, Szeged, Dóm tér 8, Hungary.

1 *Heterocycles in Natural Product Synthesis*, eds. K. C. Majumdar and S. K. Chattopadhyay, Wiley-VCH, Weinheim, 2011.
2 *Chiral Drugs Chemistry and Biological Action*, eds. G.-Q. Lin, Q.-D. You and J.-F. Cheng, John Wiley & Sons, Hoboken, New Jersey, 2011.
3 V. Sridharan, P. A. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157-7259.
4 Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357-1366.
5 H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237-294.
6 H. Clavier and H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 3347-3403.
7 L.-Q. Lu, J.-R. Chen and W.-J. Xiao, *Acc. Chem. Res.*, 2012, **45**, 1278-1293.
8 *Handbook of Asymmetric Heterogeneous Catalysis*, eds. K. Ding and Y. Uozumi, Wiley-VCH, Weinheim, 2008.
9 T. Mallat, E. Orglmeister and A. Baiker, *Chem. Rev.*, 2007, **107**, 4863-4890.

Catalysis Science & Technology RSCPublishing

PAPER

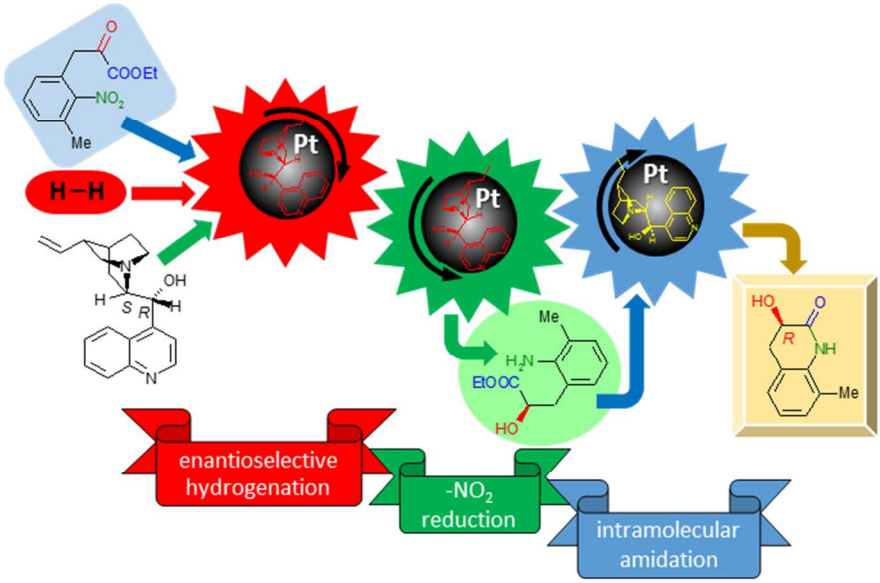


Fig. 7 Reaction pathway leading to the formation of chiral 3-hydroxy-3,4-dihydroquinolin-2(1H)-ones.

10 D. Yu. Murzin, P. Mäki-Arvela, E. Toukoniitty and T. Salmi, *Catal. Rev. Sci. Eng.*, 2005, **47**, 175-256.
11 M. Bartók, *Curr. Org. Chem.*, 2006, **10**, 1533-1567.
12 H.-U. Blaser and M. Studer, *Acc. Chem. Res.*, 2007, **40**, 1348-1356.
13 Gy. Szőllősi, B. Hermán, K. Felföldi, F. Fülöp and M. Bartók, *Adv. Synth. Catal.*, 2008, **350**, 2804-2814.
14 J. Muzart, F. Hénin and S. J. Aboulhoda, *Tetrahedron: Asymmetry*, 1997, **8**, 381-389.
15 L. Deiana, S. Afewerki, C. Palo-Nieto, O. Verho, E. V. Johnston and A. Córdova, *Scientific Reports*, 2012, **2**, art. no. 851.
16 K. Felföldi, K. Szőri and M. Bartók, *Appl. Catal. A: Gen.*, 2003, **251**, 457-460.
17 Gy. Szőllősi and M. Bartók, *Arkivoc*, 2012, (v), 16-27.
18 Gy. Szőllősi, Zs. Makra, L. Kovács, F. Fülöp and M. Bartók, *Adv. Synth. Catal.*, 2013, **355**, 1623-1629.
19 H. Suzuki, H. Gyoutoku, H. Yokoo, M. Shinba, Y. Sato, H. Yamada and Y. Murakami, *Synlett*, 2000, 1196-1198.
20 M. Garland and H.-U. Blaser, *J. Am. Chem. Soc.*, 1990, **112**, 7048-7050.
21 Gy. Szőllősi, Sz. Cserényi, F. Fülöp and M. Bartók, *J. Catal.*, 2008, **260**, 245-253.
22 M. von Arx, T. Mallat and A. Baiker, *J. Catal.*, 2000, **193**, 161-164.
23 C. Exner, A. Pfaltz, S. Studer and H.-U. Blaser, *Adv. Synth. Catal.*, 2003, **345**, 1253-1260.
24 B. Schimmoeller, F. Hoxha, T. Mallat, F. Krumeich, S. E. Pratsinis and A. Baiker, *Appl. Catal. A: Gen.*, 2010, **374**, 48-57.
25 T. Cseri, S. Békássy, F. Figueras, E. Cseke, L.-C. de Menorval and R. Dutartre, *Appl. Catal. A: Gen.*, 1995, **132**, 141-155.
26 M. A. Harmer and Q. Sun, *Appl. Catal. A: Gen.*, 2001, **221**, 45-62.
27 J. A. Cecilia, I. Jiménez-Morales, A. Infantes-Molina, E. Rodríguez-Castellón and A. Jiménez-López, *J. Mol. Catal. A: Chem.*, 2013, **368-369**, 78-87.
28 Gy. Szőllősi, Á. Mastalir, Á. Molnár and M. Bartók, *React. Kinet. Catal. Lett.*, 1996, **57**, 29-36.
29 Gy. Szőllősi, B. Török, L. Baranyi and M. Bartók, *J. Catal.*, 1998, **179**, 619-623.
30 S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, John Wiley & Sons, Hoboken, New Jersey, 2011, chap. 9, pp. 315-389.
31 H. U. Blaser, U. Siegrist, H. Steiner and M. Studer, *Fine Chemicals through Heterogeneous Catalysis*, eds. R. A. Sheldon and H. van Bekkum, Wiley-VCH, Weinheim, 2001, pp. 389-406.
32 H. U. Blaser, H. P. Jalett and J. Wiehl, *J. Mol. Catal.*, 1991, **68**, 215-222.
33 K. Balázsik, K. Szőri, Gy. Szőllősi and M. Bartók, *Chem. Commun.*, 2011, **47**, 1551-1552.
34 K. Balázsik, K. Szőri, Gy. Szőllősi and M. Bartók, *Catal. Commun.*, 2011, **12**, 1410-1414.
35 U. K. Singh, R. N. Landau, Y. Sun, C. LeBlond, D. G. Blackmond, S. K. Tanielyan and R. L. Augustine, *J. Catal.*, 1995, **154**, 91-97.
36 Q. Chen, S. Haq, B. G. Frederick and N. V. Richardson, *Surf. Sci.*, 1996, **368**, 310-317.
37 A. Vargas, S. Reimann, S. Diezi, T. Mallat and A. Baiker, *J. Mol. Catal. A: Chem.*, 2008, **282**, 1-8.
38 M. Casagrande, S. Franceschini, M. Lenarda, O. Piccolo and A. Vaccari, *J. Mol. Catal. A: Chem.*, 2006, **246**, 263-267.
39 E. R. Blout and D. C. Silverman, *J. Am. Chem Soc.*, 1944, **66**, 1442-1443.
40 S. Santiago-Pedro, V. Tamayo-Galván and T. Viveros-García, *Catal. Today*, 2013, **213**, 101-108.
41 Gy. Szőllősi, P. Forgó and M. Bartók, *Chirality*, 2003, **15**, S82-S89.
42 D. Ferri and T. Bürgi, *J. Am. Chem. Soc.*, 2001, **123**, 12074-12084.
43 D. Ferri, T. Bürgi and A. Baiker, *J. Catal.*, 2002, **210**, 160-170.
44 M. Bartók, M. Sutyinszki, K. Balázsik and Gy. Szőllősi, *Catal. Lett.*, 2005, **100**, 161-167.