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Preparation of Optically Enriched 3-Hydroxy-3,4-dihydroquinolin-2(1*H*)-ones by Heterogeneous Catalytic Cascade Reaction over Supported Platinum Catalyst

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Abstract: The development of a novel heterogeneous catalytic asymmetric cascade reaction for the synthesis of tetrahydroquinolines from 2-nitrophenylpyruvates is reported. Optically enriched 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones are prepared by enantioselective hydrogenation of the activated keto group over a *Cinchona* alkaloid-modified Pt catalyst, reduction of the nitro group and spontaneous cyclization cascade. Acceleration of the enantioselective hydrogenation of the activated keto group over the catalyst modified by *Cinchona* alkaloids ensured high tetrahydroquinolinone selectivities. The scope of the reaction was checked using twelve substrates. Both yields and enantioselectivities were significantly influenced by the nature and position of the substituents on the phenyl ring. Substituents adjacent to the nitro group considerably increased the product yield, due to their effect on the nitro group's reduction rate; however, had only a limited effect on enantioselectivities.

Keywords: asymmetric synthesis; cascade reactions; *Cinchona* alkaloids; enantioselective hydrogenation; heterogeneous catalysis; hydroquinolones

Introduction

Optically pure N-heterocyclic compounds are versatile chiral building blocks in the synthesis of natural products and bioactive fine chemicals.[1] Partially saturated quinoline derivatives have attracted much attention due to their prominent pharmaceutical activities.[2] Tetrahydroquinolone derivatives are used as a heterocyclic scaffold in the preparation of drug candidates[3] or as intermediates in the synthesis of optically pure chiral tetrahydroquinoline derivatives (see Figure 1).[4] The asymmetric catalytic methods developed for preparing chiral hydroquinolines[5] are based on enantioselective catalytic hydrogenations of quinoline derivatives[6] or assembly of the chiral heterocyclic ring using enantioselective catalytic cyclization.[7] Recently developed sustainable and environmentally benign technologies use heterogeneous catalytic systems for the production of chiral fine chemicals.[8] However, in the asymmetric synthesis of hydroquinoline derivatives heterogeneous catalysts have been applied scarcely.[9] Promising heterogeneous catalytic methods are hydrogenations over chiral metal surfaces obtained by adsorption of optically pure compounds, so-called chiral modifiers.[8,10] Although Pt and Pd modified by *Cinchona* alkaloids were found to be remarkably efficient in the enantioselective hydrogenation of activated ketones and α,β-unsaturated carboxylic acids, respectively, these catalysts are not appropriate for the enantioselective hydrogenation of N-heterocyclic compounds.[11]

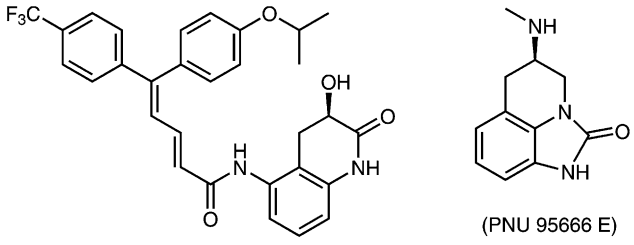


Figure 1. Examples of potential pharmaceuticals prepared from chiral 1,2,3,4-tetrahydro-2-quinolones.[3b,4b]

More than a decade ago Murakami and co-workers 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 H_2 over PtO_2.[12] Although, nitro group reduction and spontaneous cyclization cascades over heterogeneous catalyst were used in the preparation of N-heterocyclic compounds,[13] until now only one enantioselective reaction has been published.[9b] The present study reports the development of a novel asymmetric catalytic method for the preparation of optically enriched 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones using one-pot heterogeneous enantioselective hydrogenation, catalytic nitro group reduction and intramolecular amidation cascade of 2-nitrophenylpyruvates over Pt catalyst modified by *Cinchona* alkaloids.

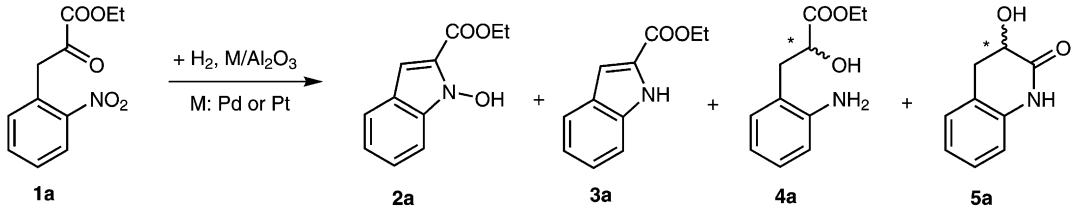
Results and Discussion

It is known that the hydrogenation of α-keto esters is accelerated over Pt due to surface modification with *Cinchona* alkaloids.[14] Accordingly, we started our study hoping that the presence of the modifier will have a double effect on the hydrogenation of 2-nitrophenylpyruvates, that is, inducing enantioselectivity and increasing the selectivity of the hydroquinolones by accelerating the ketone hydrogenation concomitantly with decreasing the reduction rate of the nitro group. Preliminary results with ethyl 2-nitrophenylpyruvate (**1a**) over supported Pd and Pt catalysts and cinchonidine (**CD**) as modifier are summarized in Table 1.

Over Pd/Al_2O_3 ethyl indole-2-carboxylate (**3a**) was obtained almost exclusively. Pt/Al_2O_3 provided a product mixture containing *N*-hydroxyindole (**2a**) as the most abundant component, which is formed by cyclization of the partially reduced hydroxylamine intermediate.[15] The presence of **CD** increased the amount of the 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**5a**) up to 36%. Both chiral products, **5a** and the amino alcohol **4a**, were obtained in identically low enantiomeric excesses (*ee*). The results indicate that the activated keto group is hydrogenated before or at least simultaneously with the reduction of the nitro group when the chiral amino alcohol and subsequently the tetrahydroquinolone is formed, as was suggested by Murakami and co-workers.[12] The initial either partial or complete reduction of the nitro group leads to concomitant intramolecular cyclization by condensation with the keto group and formation of **2a** or **3a**. Thus, the formation of the hydroquinolone derivative is possible only if the keto group is not available, that is, is already transformed, by the time when the nitro group reduction occurs.

The *ee* values obtained in this preliminary study exceeded the reported *ee* obtained in the hydrogenation of activated benzyl ketones over Pt modified by **CD**.[16] Thus, we thought it worthwhile to examine the effect of the reaction conditions. We note that in spite of extensive studies of the hydrogenation of activated ketones over Pt catalyst modified by *Cinchona* alkaloids, the enantioselective hydrogenation of phenylpyruvates has not yet been reported.[8,10,14] Murakami and co-workers obtained higher 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one yields in reactions of 2-nitrophenylpyruvates substituted on the phenyl ring adjacent to the nitro group.[12] This was explained by a decrease in the reduction rate of the nitro group. Thus, we continued our studies using **1a** and ethyl 2-nitro-3-methylphenylpyruvate (**1b**). Results obtained in various solvents are summarized in Table 2. The best *ee* values were obtained in toluene (T) with 2 or 10 vol% acetic acid (AcOH), however **1a** and **1b**

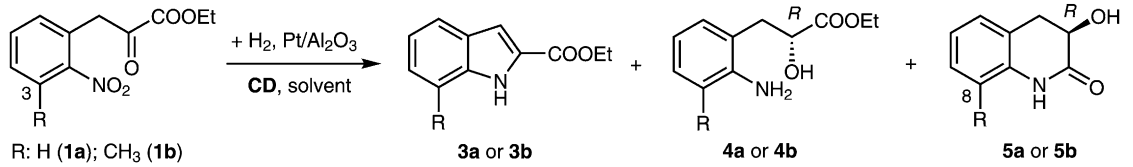
Table 1. Products formed in the hydrogenation of ethyl 2-nitrophenylpyruvate (**1a**) over supported metal catalysts.[a]



Entry	Catalyst[b]	*conc* **CD** [mM]	Sel. **2a** [%][c]	Sel. **3a** [%][c]	Sel. (*ee*) **4a** [%][c]	Sel. (*ee*) **5a** [%][c]
1	Pd/Al_2O_3	–	–	98	–	<1
2	Pd/Al_2O_3	2	–	98	–	<1
3	Pt/Al_2O_3	–	60	28	–	10 (*rac*)
4	Pt/Al_2O_3	2	36	18	8 (44)	36 (44)

[a] *Reaction conditions*: 50 mg catalyst, 5 cm^3 methanol, *conc* **1a** 80 mM, 4 MPa H_2, room temperature, 3 h, complete conversion of **1a**.
[b] Pd/Al_2O_3 5% Engelhard 40692, Pt/Al_2O_3 5% Engelhard 4759.
[c] Selectivities determined by GC, enantiomeric excesses (*ee*) in brackets.

Table 2. Solvent effect on the selectivities and *ee*s obtained in the reaction of **1a/1b** over Pt/Al_2O_3 modified by **CD**.[a]



R: H (**1a**); CH_3 (**1b**) **3a** or **3b** **4a** or **4b** **5a** or **5b**

Entry	Solvent	Sel. **3a**/**3b** [%]	Sel. **4a**/**4b** [%]	*ee* (**4a**/**4b**) [%]	Sel. **5a**/**5b** [%]	*ee* (**5a**/**5b**) [%]
1	MeOH	36/2	8/40	44/35	36/49	44/35
2	*i*-PrOH	6/2	3/52	51/59	58/43	52/59
3	EtOAc	3/<1	14/92	55/73	58/5	57/71
4	THF	3/<1	13/92	67/71	55/3	68/70
5	DCM	10/1	1/51	nd/48	73/47	63/47
6	toluene (T)	–[b]/<1	–[b]/70	–/72	–[b]/29	–/72
7	T+AcOH (9/1)	10/2	9/20	74/70	53/77	75/71
8	T+AcOH (9/1)[c]	17/10	5/<1	76/nd	54/89	75/72
9	T+AcOH (49/1)[c]	22/3	3/3	60/72	32/92	56/72

[a] *Reaction conditions*: 50 mg catalyst, 5 cm^3 solvent, *conc* **CD** 2 mM, *conc* **1a** or **1b** 80 mM, 4 MPa H_2, room temperature, 3 h, complete transformation of **1a** or **1b**.
[b] Reproduction problems due to low solubility of the products
[c] Reactions over 100 mg catalyst using **CD** *conc* 4 mM, 2 h.

showed different behaviours. The former in 9/1 T/AcOH mixture over 50 mg catalyst provided better results (75% *ee*), whereas for the latter compound the 49/1 mixture was found to be more advantageous (up to 92% **5b** in 72% *ee*). Optimization of the AcOH or catalyst amount did not lead to further improvement (not shown), however decreasing the H_2 pressure to 1 MPa increased both the selectivities and *ee*s (62% **5a** in 81% *ee*, and 97% **5b** in 80% *ee*). Decreasing the substrate (**1b**) concentration had no effect, whereas, increasing it over 80 mM resulted in a drop of the **5b** selectivity and accumulation of **4b** in the reaction mixture.

A study on the modifier concentration effect (see Figure 2) showed the highest **5b** selectivity at 4 mM **CD** *conc*. However, the side products resulted at low and high **CD** *conc*s differed, that is, **2b** and **4b**, respectively. This 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** *conc*s the intramolecular amidation proceeds with low rate 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 the desorption and re-adsorption of the chiral amino alcohol. To a similar conclusion pointed the increase of the quinolone selectivity obtained by increasing the catalyst amount (not shown). Spontaneous cyclization was reported to occur during the enantioselective hydrogenation of 2-oxoglutaric acid over Pt, however, esters of this acid needed an additional step catalyzed by acids to result the cyclic product.[17]

The desorption–re-adsorption of the amino alcohol was confirmed by examining the composition of the mixture *versus* reaction time. These experiments showed that the chiral amino alcohol **4b** present in the liquid phase is transformed only in the presence of the catalyst, and is kept unaltered following filtration of the Pt/Al_2O_3. Furthermore, when solid acids (Nafion® SAC-13, Amberlyst XN-1010, montmorillonite K 10) were used either as support of Pt or as additive, the resins with strong Brønsted acidity increased only slightly the selectivity of **5a** as compared with Pt/Al_2O_3 or PtO_2, whereas the Lewis acidic clay had

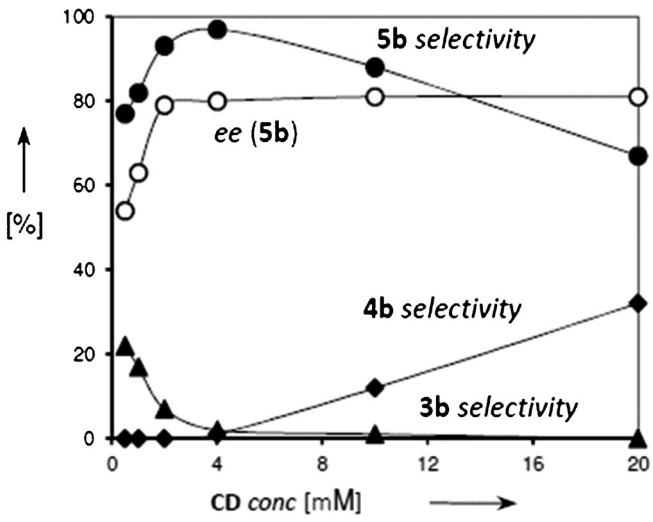


Figure 2. Effect of **CD** *conc* on the reaction of **1b**. *Reaction conditions:* 100 mg Pt/Al_2O_3, 5 cm^3 T/AcOH 49/1, *conc* **1b** 80 mM, 1 MPa H_2, room temperature, 2 h.

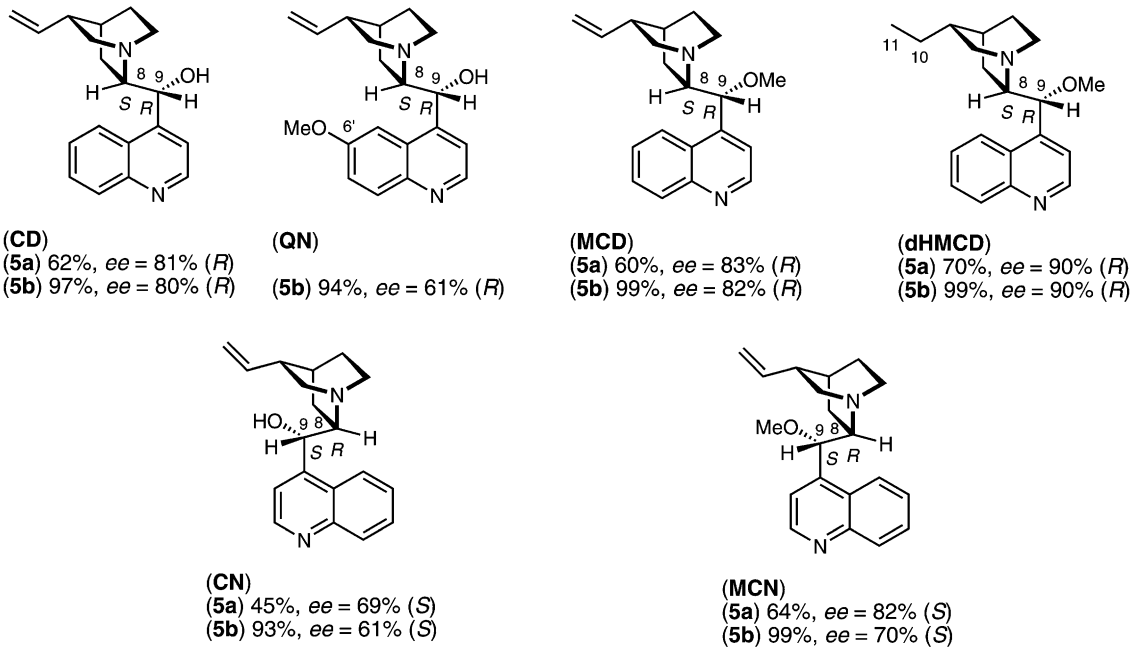


Figure 3. Selectivities and *ee*s of 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones obtained in reactions of **1a** and **1b** using various *Cinchona* alkaloids as modifiers. *Reaction conditions: conc* substrate 80 mM, 1 MPa, room temperature; (**1a**) 50 mg Pt/Al_2O_3, 5 cm^3 T/AcOH 9/1, *conc* modifier 2 mM, 3 h; (**1b**) 100 mg Pt/Al_2O_3, 5 cm^3 T/AcOH 49/1, *conc* modifier 4 mM, 2 h.

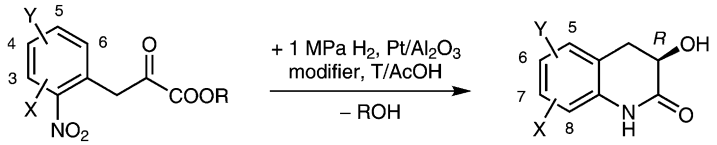
a detrimental effect, indicating that the metal particles are catalyzing the final step of the cascade reaction. It is difficult to demonstrate the relation between the rates of the first two steps of the cascade, as the transformation of the reactive functional groups is followed immediately by reaction steps in which these are consumed or both are transformed simultaneously, thus, the intermediates cannot be isolated. However, under reaction conditions far from the optimal needed for the preparation of the target hydroquinolone (over 5% Pt/MgO or Pt/montmorillonite K 10 in T/AcOH 9/1) we were able to detect in the liquid phase small amounts (up to 15%) of 2-hydroxy-3-(2-nitrophenyl)propionic acid ethyl ester by GC-MSD (over Pt/MgO *ee* 40% identical with the *ee* of **5a**). This observation supports the assumption that the hydrogenation of the keto group is the initial step in the cascade reaction which leads to formation of hydroquinolones.

Further increase of the selectivity and optical purity of **5** was obtained by altering the structure of the modifier (Figure 3). The *Cinchona* alkaloid methyl ethers provided better results in both *Cinchona* series (C-8*S*,C-9*R* and C-8*R*,C-9*S*); the best result was obtained using **dHMCD** as modifier. Based on the stereochemistry of the hydrogenations of α-keto esters investigated up to now over Pt modified by **CD**,[10,14] we assumed that the use of alkaloids from this series results in excess formation of the *R* enantiomer. The configuration of the product was checked by reducing **5a** with $LiAlH_4$ to 3-hydroxy-1,2,3,4-tetrahydroquinoline with known specific rotation.[18] The *S* product enantiomers were obtained by using cinchonine (**CN**) and its derivatives, however, in lower selectivities and optical purities as compared with the alkaloids from the **CD** series.

The scope of the enantioselective heterogeneous cascade reaction was investigated using a series of 2-nitrophenylpyruvate derivatives (Table 3). The 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-one derivatives were prepared in good optical purities with the exception of compounds substituted on the phenyl ring in the position 6 (**5h** and **5k**). The best optical purities were obtained in reactions of 2-nitrophenylpyruvates with the phenyl ring substituted in positions 3 and 6 (88–90% *ee*), however substituents in position 6 decreased the hydroquinolone yield (**1e** and **1l**). The effect of the substituent position on the hydroquinolone yield was in accordance with their probable influence on the reduction rate of the nitro group.

We also note that the high *ee*s obtained in this reaction are in contrast with the poor values previously reached in the hydrogenation of trifluoromethyl benzyl ketone.[16] Accordingly, one may assume that the presence of the nitro group has a beneficial effect on the enantiodifferentiation. To ascertain that the nitro group has indeed a beneficial effect we investigated the hydrogenation of phenylpyruvate ethyl ester (Scheme 1). Under identical conditions both conversions and *ee*s were much lower than in the hydrogenation of **1a**. Accordingly, the presence of the nitro group was found to be essential for the enantio-

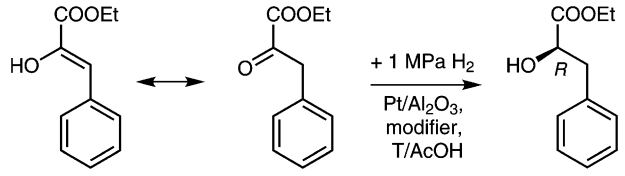
Table 3. Scope of the asymmetric heterogeneous catalytic cascade reaction.[a]



(**1a**–**1l**) (**5a**–**5l**)

Entry	Substrate	X	Y	R	Reaction conditions	Yield **5** [%][b]	*ee* **5** [%] (*R*)
1	**1a**	H	H	Et	50 mg Pt/Al_2O_3, T/AcOH 9/1	65	90
2	**1b**	3-Me	H	Et	100 mg Pt/Al_2O_3, T/AcOH 49/1	97	90
3	**1c**	3-Me	H	Me	50 mg Pt/Al_2O_3, T/AcOH 9/1	95	86
4	**1d**	5-Me	H	Et	50 mg Pt/Al_2O_3, T/AcOH 9/1	88	86
5	**1e**	6-Me	H	Et	50 mg Pt/Al_2O_3, T/AcOH 9/1	55	89
6	**1f**	4-Me	5-Me	Et	50 mg Pt/Al_2O_3, T/AcOH 9/1	80	88
7	**1g**	3-MeO	H	Et	50 mg Pt/Al_2O_3, T/AcOH 9/1	97	88
8	**1h**	5-MeO	H	Et	50 mg Pt/Al_2O_3, T/AcOH 9/1	75	69
9	**1i**	3-*i*-PrO	H	Et	100 mg Pt/Al_2O_3, T/AcOH 49/1	97	85
10	**1j**	4-F	H	Et	50 mg Pt/Al_2O_3, T/AcOH 9/1	50	82
11	**1k**	5-F	H	Et	100 mg Pt/Al_2O_3, T/AcOH 9/1[b]	55	68
12	**1l**	6-F	H	Et	100 mg Pt/Al_2O_3, T/AcOH 9/1[b]	35	90

[a] *Reaction conditions*: 5 cm^3 solvent, **dHMCD** 0.2 mmol g^{-1} Pt/Al_2O_3, *conc* substrate 80 mM, 1 MPa H_2, room temperature, 2–3 h.
[b] Isolated yields of the corresponding hydroquinolone derivatives.
[c] **CD** was the modifier.



(**CD**) 30% conversion, *ee* = 38%
(**MCD**) 65% conversion, ee = 33%

Scheme 1. Hydrogenation of phenylpyruvate ethyl ester over modified Pt/Al_2O_3. *Reaction conditions:* 50 mg catalyst, 5 cm^3 T/AcOH 9/1, *conc* modifier 2 mM, *conc* substrate 80 mM, 1 MPa H_2, room temperature, 3 h, conversions determined by GC, 2-hydroxy-3-phenylpropionic acid ethyl ester was the sole product.

selective hydrogenation of these activated ketones, possibly playing a role in the formation of the surface intermediate responsible for the enantioselective hydrogenation either by interaction with the Pt surface (co-adsorption with the nitro group) or/and with the adsorbed *Cinchona* alkaloid. Thus, the nitro group contributes to the stereoselective anchoring of the substrate in the chiral surface pocket.

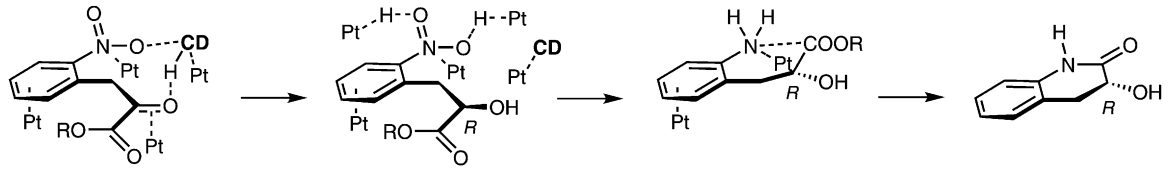
Conclusions

We developed the first heterogeneous catalytic asymmetric cascade reaction for the efficient synthesis of tetrahydroquinoline derivatives starting from 2-nitrophenylpyruvates. The method is based on influencing the rates of the enantioselective hydrogenation and of the aromatic nitro group reduction by modification of supported Pt surface with *Cinchona* alkaloids. Fortunately, the enantioselection was improved by participation of the nitro group in the interaction of the phenylpyruvates with the surface chiral site, making it possible to obtain good *ee*s. The significant influence of substituents situated on the aromatic ring on the hydroquinolone yields was explained by their effect on the reduction rate of the nitro group. It was also found that the final cyclization step of the cascade reaction occurs on the catalyst surface. Although, detailed mechanistic studies are still needed, the collected observations allow us to propose a reaction sequence with the assumed steps illustrated schematically in Scheme 2. 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.

Experimental Section

General Remarks

The commercial 5% Pd/Al_2O_3 (Engelhard, 40692) and 5% Pt/Al_2O_3 (Engelhard, 4759), with known properties,[19] were pre-treated in an H_2 flow at 523 K and 673 K, as described earlier.[20] *Cinchona* alkaloids were purchased from Alfa



Scheme 2. Proposed steps of the studied asymmetric heterogeneous catalytic cascade reaction.

Aesar or Sigma–Aldrich or prepared by known procedures.[21] Analytical grade solvents and reagents were used as received. 2-Nitrophenylpyruvic acid and 2-nitrotoluene derivatives were purchased from Sigma–Aldrich. Products were identified by NMR spectroscopy (^{1}H and ^{13}C) recorded on an AVANCE DRX 400 NMR instrument using $(CH_3)_4Si$ as internal standard and by gas chromatography coupled with mass selective detector (GC-MSD): Agilent Techn. 6890N GC-5973 inert MSD, column: HP-1MS 60 m × 0.25 mm i.d., oven temperature: 100 °C for 10 min, 10 °C min^{-1} to 200 °C and 200 °C for 100 min, head pressure 22 psi. The products resulted in the cascade reactions were analyzed using GC equipped with flame ionization detector (FID): Agilent Techn. 6890N GC-FID equipped with Cyclodex-B 30 m × 0.25 mm i.d., chiral capillary column. Optical rotation measurements were carried out using Polamat A polarimeter in MeOH (*c* 1, *l* 0.5, λ 546 nm).

Preparation of 2-Nitrophenylpyruvic Acid Esters (1a–1l)

Ethyl 2-nitrophenylpyruvate (**1a**) was prepared by esterification of 2-nitrophenylpyruvic acid. To 0.55 g (3.2 mmol) *p*-toluenesulfonic acid dissolved in 100 cm^3 EtOH was dropped in 2 h a solution of 3 g (14.3 mmol) 2-nitrophenylpyruvic acid dissolved in 50 cm^3 EtOH. The solution was refluxed overnight, the solvent was evaporated, and the oily residue was dissolved in 100 cm^3 diethyl ether, washed twice with 10% Na_2CO_3 solution, once with brine and dried over Na_2SO_4. The ether was evaporated to give ethyl 2-nitrophenylpyruvate as a pale yellow oil which according to ^{1}H NMR, GC-MSD and GC-FID analysis was of ≥ 97% purity and was used without further purification; yield: 3.26 g (96%).

Substituted 2-nitrophenylpyruvates (**1b**–**1l**) were prepared by a literature method according to the Reissert indole synthesis.[12] In a typical reaction to a vigorously stirred suspension of 9 g (80 mmol) *t*-BuOK in 200 cm^3 diethyl ether, 11 cm^3 (80 mmol) diethyl (or dimethyl) oxalate were added and after 10 min stirring 80 mmol of the corresponding 2-nitrotoluene derivative were introduced dropwise. The suspension was stirred at room temperature for 24–48 h. The reaction was quenched by addition of 150 cm^3 saturated NH_4Cl solution, the ethereal solution was separated, the aqueous phase was washed with 2 × 100 cm^3 ethyl acetate and the combined organic phases were dried overnight over Na_2SO_4. The solvents were removed by evaporation and the 2-nitrophenylpyruvates were purified by flash chromatography using petroleum ether/ethyl acetate mixtures as eluent (8/1–6/1). Products of at least 97% purity (unless otherwise noted) were obtained in 30–60% yields (see the Supporting Information). The preparation of few derivatives was carried out on a 40-mmol scale.

Typical Procedure for the Asymmetric Cascade Reactions

The cascade reactions were carried out using a stainless steel high-pressure autoclave equipped with a glass tube of 45 cm^3 and two gas inlets. The reaction slurry was stirred magnetically at 1000 rpm. In a typical reaction the given amount of catalyst was suspended in 5 cm^3 of the corresponding solvent followed by addition of the modifier and the 2-nitrophenylpyruvate derivative. The tube was placed in the autoclave, flushed with H_2 five times and pressurized to the desired H_2 pressure. The reaction was commenced by stirring the slurry. After the given reaction time the catalyst was filtered and washed twice with 3 cm^3 solvent and the unified solutions were analyzed by GC-MSD for product identification and by GC-FID using a chiral capillary column for determination of conversions, selectivities and *ee*s; $ee[\%] = 100 \times |R\text{-}\mathbf{5} - S\text{-}\mathbf{5}|/(R\text{-}\mathbf{5} + S\text{-}\mathbf{5})$. Following product analysis the hydroquinolone derivatives **5** were isolated by flash chromatography using petroleum ether/ethyl acetate eluent (4/1–2/1) for determination of yields, characterization by NMR spectroscopy and determination of the sign of the optical rotations (see the Supporting Information).

Acknowledgements

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References

[1] a) *Heterocycles in Natural Product Synthesis*, (Eds.: K. C. Majumdar, S. K. Chattopadhyay), Wiley-VCH, Weinheim, **2011**; b) *Chiral Drugs Chemistry and Biological Action*, (Eds.: G.-Q. Lin, Q.-D. You, J.-F. Cheng), John Wiley & Sons, Hoboken, **2011**.

[2] a) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031–15070; b) N. Toyooka, in: *Asymmetric Synthesis of Nitrogen Heterocycles*, (Ed.: J. Royer), Wiley-VCH, Weinheim, **2009**, pp 95–138.

[3] a) M. M. Claffey, A. B. Dounay, M. M. Hayward, S. Rong, P. R. Verhoest, J. B. Tuttle, X. Gan, (Pfitzer Inc.), U.S. Patent 2010/0324043A1, **2010**; b) O. Saku, H. Ishida, E. Atsumi, Y. Sugimoto, H. Kodaira, Y. Kato, S. Shirakura, Y. Nakasato, *J. Med. Chem.* **2012**, *55*, 3436–3451.

[4] a) Y. Ito, K. Ishida, S. Okada, M. Murakami, *Tetrahedron* **2004**, *60*, 9075–9080; b) A. R. Jagdale, R. S. Reddy, A. Sudalai, *Org. Lett.* **2009**, *11*, 803–806.

[5] V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157–7259.

[6] For a few recent examples, see: a) M. T. Reetz, X. Li, *Chem. Commun.* **2006**, 2159–2160; b) N. Mršić, L. Lefort, J. A. F. Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv. Synth. Catal.* **2008**, *350*, 1081–1089; c) C. Wang, C. Li, X. Wu, A. Pettman, J. Xiao, *Angew. Chem.* **2009**, *121*, 6646–6650; *Angew. Chem. Int. Ed.* **2009**, *48*, 6524–6528; d) F.-R. Gou, W. Li, X. Zhang, Y.-M. Liang, *Adv. Synth. Catal.* **2010**, *352*, 2441–2444; e) W. Tang, Y. Sun, L. Xu, T. Wang, Q. Fan, K.-H. Lam, A. S. C. Chan, *Org. Biomol. Chem.* **2010**, *8*, 3464–3471; f) Z. Yu, W. Jin, Q. Jiang, *Angew. Chem.* **2012**, *124*, 6164–6177; *Angew. Chem. Int. Ed.* **2012**, *51*, 6060–6072.

[7] For recent examples, see: a) H. Sundén, R. Rios, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 827–832; b) M. Xie, X. Chen, Y. Zhu, B. Gao, L. Lin, X. Liu, X. Feng, *Angew. Chem.* **2010**, *122*, 3887–3890; *Angew. Chem. Int. Ed.* **2010**, *49*, 3799–3802; c) X. Liu, Y. Lu, *Org. Lett.* **2010**, *12*, 5592–5595; d) K. Mori, K. Ehara, K. Kurihara, T. Akiyama, *J. Am. Chem. Soc.* **2011**, *133*, 6166–6169; e) L. Ren, T. Lei, J.-X. Ye, L.-Z. Gong, *Angew. Chem.* **2012**, *124*, 795–798; *Angew. Chem. Int. Ed.* **2012**, *51*, 771–774.

[8] a) *Chiral Catalysts Immobilization and Recycling*, (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**; b) *Handbook of Asymmetric Heterogeneous Catalysis*, (Eds.: K. Ding, Y. Uozumi), Wiley-VCH, Weinheim, **2008**; c) *Catalytic Methods in Asymmetric Synthesis. Advanced Materials, Techniques, and Applications*, (Eds.: M. Gruttadauria, F. Giacalone), John Wiley & Sons, Hoboken, **2011**.

[9] a) L. Wu, Y.-M. He, Q.-H. Fan, *Adv. Synth. Catal.* **2011**, *353*, 2915–2919; b) Gy. Szőllősi, M. Bartók, *Arkivoc* **2012**, *v*, 16–27.

[10] a) D. Yu. Murzin, P. Mäki-Arvela, E. Toukoniitty, T. Salmi, *Catal. Rev. Sci. Eng.* **2005**, *47*, 175–256; b) T. Osawa, T. Harada, O. Takayasu, *Curr. Org. Chem.* **2006**, *10*, 1513–1531; c) M. Bartók, *Curr. Org. Chem.* **2006**, *10*, 1533–1567; d) T. Mallat, E. Orglmeister, A. Baiker, *Chem. Rev.* **2007**, *107*, 4863–4890; e) H.-U. Blaser, M. Studer, *Acc. Chem. Res.* **2007**, *40*, 1348–1356; f) F. Zaera, *J. Phys. Chem. C* **2008**, *112*, 16196–16203.

[11] a) H.-U. Blaser, H. Hönig, M. Studer, C. Wedemeyer-Exl, *J. Mol. Catal A: Chem.* **1999**, *139*, 253–257; b) Gy. Szőllősi, I. Kun, M. Bartók, *Chirality* **2001**, *13*, 619–624; c) Gy. Szőllősi, K. Szőri, M. Bartók, *J. Catal.* **2008**, *256*, 349–352.

[12] H. Suzuki, H. Gyoutoku, H. Yokoo, M. Shinba, Y. Sato, H. Yamada, Y. Murakami, *Synlett* **2000**, 1196–1198.

[13] a) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, John Wiley & Sons, New York, **2001**, pp 315–389; b) D. A. Dudley, J. J. Edmunds, (Warner-Lambert Co), U.S. Patent 6,855,726 B1, **2005**; c) Y. Luo, F. Tao, Y. Liu, B. Li, G. Zhang, *Can. J. Chem.* **2006**, *84*, 1620–1625; d) F.-X. Felpin, J. Coste, C. Zakri, E. Fouquet, *Chem. Eur. J.* **2009**, *15*, 7238–7245.

[14] a) M. Garland, H.-U. Blaser, *J. Am. Chem. Soc.* **1990**, *112*, 7048–7050; b) G. J. Hutchings, *Chem. Commun.* **1999**, 301–306; c) A. Vargas, T. Bürgi, A. Baiker, *New J. Chem.* **2002**, *26*, 807–810; d) D. Yu. Murzin, *J. Mol. Catal. A: Chem.* **2008**, *289*, 91–94; e) Gy. Szőllősi, Sz. Cserényi, F. Fülöp, M. Bartók, *J. Catal.* **2008**, *260*, 245–253; f) E. Tálas, J. L. Margitfalvi, O. Egyed, *J. Catal.* **2009**, *266*, 191–198.

[15] K. C. Nicolaou, A. A. Estrada, G. C. Freestone, S. H. Lee, X. Alvarez-Mico, *Tetrahedron* **2007**, *63*, 6088–6114.

[16] B. Török, K. Balázsik, Gy. Szőllősi, K. Felföldi, M. Bartók, *Chirality* **1999**, *11*, 470–474.

[17] a) K. Balázsik, K. Szöri, K. Felföldi, B. Török, M. Bartók, *Chem. Commun.* **2000**, 555–556; b) K. Szöri, K. Felföldi, M. Bartók, *Appl. Catal. A: Gen.* **2003**, *251*, 457–460.

[18] D. R. Boyd, N. D. Sharma, J. G. Carroll, J. F. Malone, D. G. Mackerracher, C. C. R. Allen, *Chem. Commun.* **1998**, 683–684.

[19] For Pt/Al_2O_3 Engelhard 4759, see: a) A. Baiker, *J. Mol. Catal. A: Chem.* **1997**, *115*, 473–493; b) M. von Arx, T. Mallat, A. Baiker, *J. Catal.* **2000**, *193*, 161–164; for Pd/Al_2O_3 Engelhard 40692, see: c) K. Borszeky, T. Bürgi, Z. Zhaohui, T. Mallat, A. Baiker, *J. Catal.* **1999**, *187*, 160–166; d) M. Casagrande, S. Franceschini, M. Lenarda, O. Piccolo, A. Vaccari, *J. Mol. Catal. A: Chem.* **2006**, *246*, 263–267.

[20] a) M. Bartók, Gy. Szőllősi, K. Balázsik, T. Bartók, *J. Mol. Catal. A: Chem.* **2002**, *177*, 299–305; b) Gy. Szőllősi, Sz. Cserényi, F. Fülöp, M. Bartók, *J. Catal.* **2008**, *260*, 245–253; c) Gy. Szőllősi, B. Hermán, K. Felföldi, F. Fülöp, M. Bartók, *J. Mol. Catal. A: Chem.* **2008**, *290*, 54–59; d) Gy. Szőllősi, B. Hermán, K. Felföldi, F. Fülöp, M. Bartók, *Adv. Synth. Catal.* **2008**, *350*, 2804–2814.

[21] a) C. Exner, A. Pfaltz, M. Studer, H.-U. Blaser, *Adv. Synth. Catal.* **2003**, *345*, 1253–1260; b) Sz. Cserényi, K. Felföldi, K. Balázsik, Gy. Szőllősi, I. Bucsi, M. Bartók, *J. Mol. Catal. A: Chem.* **2006**, *247*, 108–115.