# Enantioselective hydrogenation of a cyclic imidoketone over chirally modified Pt/$Al_2O_3$

**Niklaus Künzle, Andras Szabo, Markus Schürch, Guozhi Wang, Tamas Mallat and Alfons Baiker*†**

*Laboratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich, Switzerland*

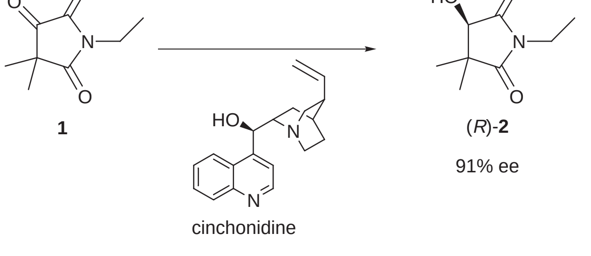
**1-Ethyl-4,4-dimethylpyrrolidine-2,3,5-trione 1 has been synthesized, and hydrogenated with 91% ee to (*R*)-1-ethyl-3-hydroxy-4,4-dimethylpyrrolidine-2,5-dione (2) using a 5 mass% Pt/$Al_2O_3$ catalyst modified by cinchonidine**

In the past decade the enantioselective hydrogenation of carbonyl compounds has been one of the most intensively studied areas in asymmetric catalysis.[1] An efficient strategy for achieving reasonable enantioselectivity over solid catalysts is the modification of an active metal by adsorbed auxiliaries from the chiral pool.[2] Since the first application of cinchona-modified Pt,[3] considerable effort has been made to broaden the application range of this catalyst system. Good to high ee values were obtained in the hydrogenation of $\alpha$-ketoesters[4] and acids,[5] and ketopantolactone.[6] The hydrogenation of other types of activated carbonyl compounds, such as $\alpha$-diketones,[7] trifluoracetophenone[8] and pyruvamides,[9] was less successful affording only 60% ee or less. It seems that the Pt-cinchona system possesses unusually high substrate specificity.

In a systematic study, intended to reveal the nature of enantioselective hydrogenation of ketoimides over chirally modified Pt metals, a remarkable ee was obtained in the reduction of 1-ethyl-4,4-dimethylpyrrolidine-2,3,5-trione **1**. The starting material **1** was synthesized from racemic pantolactone [(*R,S*)-2-hydroxy-3,3-dimethyl-$\gamma$-butyrolactone] in two steps. The lactone ring was cleaved by ethylamine and oxidation of the resulting amide with pyridinium dichromate gave **1**.‡

The hydrogenation of the cyclic imidoketone **1** (Scheme 1) was carried out in a magnetically stirred (frequency: 1000 $\text{min}^{-1}$) 100 ml stainless steel Baskerville autoclave equipped with a glass liner and PTFE cover. 60 mg of a 5 mass% Pt/$Al_2O_3$ (Engelhard 4759) catalyst was pretreated for 90 min in a hydrogen stream at 400 °C, as described earlier.[6] Under standard conditions the reaction was carried out using 3.2 mmol **1** and 10 μmol cinchonidine in 5 ml toluene, at 15 °C and 70 bar hydrogen pressure. The reaction was stopped when hydrogen consumption ceased. No other product besides **2** could be detected by gas chromatography.

For the determination of the absolute configuration of the product, the pure (*R*)-enantiomer of **2** has been synthesized starting from (*R*)-pantolactone. The hydroxyl function of (*R*)-pantolactone was protected by a tetrahydropyranyl group. After treatment with ethylamine, the resulting hydroxyamide was oxidized by pyridinium dichromate in DMF. Deprotection in the presence of TsOH gave (*R*)-**2** in optically pure form. Gas chromatographic analysis using a chiral column (WCOT Cyclodextrin-β-2,3,6-M-19, Chrompack) proved that (*R*)-**2** was identical with the major enantiomer obtained in the hydrogenation.



**Scheme 1** Hydrogenation of **1**. *Conditions:* 5 mass% Pt/$Al_2O_3$, 9 μmol $l^{-1}$ cinchonidine, 70 bar $H_2$, toluene, 15 °C.

Preliminary studies revealed that the enantiodifferentiation in the hydrogenation of **1** over the Pt–cinchonidine catalyst system was rather sensitive to the reaction medium. Good ee could be obtained only in weakly polar solvents, such as toluene. In polar and protic polar solvents (*e.g.* DMF, EtOH) the ee dropped to 20% or below. The only exception was acetic acid. The polarity of this solvent characterized by the empirical solvent parameter,[10] $E^{\mathrm{T}}_{\mathrm{N}}$, is about the same as that of EtOH, but the ee was remarkably higher (*ca.* 70 % instead of 20%, respectively, under standard conditions). Previously, the outstanding ee in acetic acid in the enantioselective hydrogenation of ethyl pyruvate was attributed to the protonation of the quinuclidine N atom of cinchonidine in acetic acid.[11] We assume that, similarly to the hydrogenation of ethyl pyruvate and ketopantolactone,[6] in the transition complex the quinuclidine N atom of cinchonidine interacts with the O atom of the activated carbonyl group *via* hydrogen bonding. Catalytic studies and molecular modeling are presently being carried out to confirm this assumption and uncover the role of acid in the enantiodifferentiation.

High hydrogen concentration on the Pt surface favoured the enantiodifferentiation, as illustrated in Fig. 1. This condition can be achieved by applying at least 30 bar hydrogen pressure and efficient stirring.

A reliable kinetic analysis based on the rate of hydrogen consumption could not be carried out owing to the small amount of substrate. In order to check the possible influence of mass transport limitation on the enantioselectivity, the stirring frequency was varied between 250 and 1000 $\text{min}^{-1}$. No significant change in ee was observed in this range of stirring frequency.

The influence of modifier concentration is illustrated in Fig. 2. A maximum of 91% ee was achieved at 9 μmol $l^{-1}$ cinchonidine concentration in toluene; this value corresponds to a substrate : modifier molar ratio of 70 000. It should be

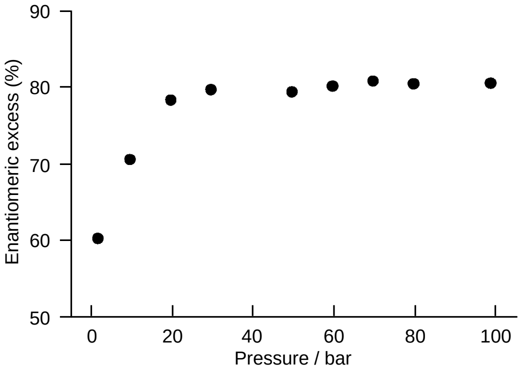


**Fig. 1** Influence of hydrogen pressure on the enantiomeric excess (standard conditions except the pressure)

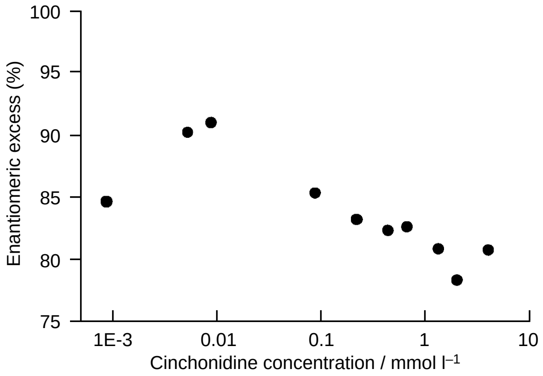


**Fig. 2** Influence of modifier concentration on the enantiomeric excess (under otherwise standard conditions)

emphasized that no special pretreatment is required for establishing the 'chiral environment' on the Pt surface; the surface cinchonidine concentration is controlled by its bulk concentration and by the competitive adsorption of hydrogen, substrate and solvent.

The ee decreased with increasing temperature but the change (only 5% under standard conditions) was minor between +15 and −20 °C.

The influence of the above discussed reaction parameters is rather similar to those reported for the enantioselective hydrogenation of α-ketoesters[4] and ketopantolactone[6] over the same catalyst system, but distinctly different from that observed in the hydrogenation of trifluoracetophenone.[8]

Finally it should be mentioned that so far, there was no other substrate besides ethyl pyruvate[3] which could be hydrogenated with an ee exceeding 90% using the Pt–cinchona system. The chiral tertiary alcohol **2** can be used as an auxiliary in enantioselective Diels–Alder reactions. Promising results have already been reported for a similar application of (*R*)-pantolactone and an (*S*)-*N*-methyl-2-hydroxysuccinimide.[12]

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## Notes and References

† E-mail: baiker@tech.chem.ethz.ch

‡ A detailed description of the synthesis of **1** and (*R*)-**2** is available from the authors on request.

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