# Enantioselective hydrogenation of a methoxypyrone with cinchona-modified palladium

W.-R. Huck, T. Mallat, and A. Baiker *

*Laboratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH-Hönggerberg,CH-8093 Zürich, Switzerland*

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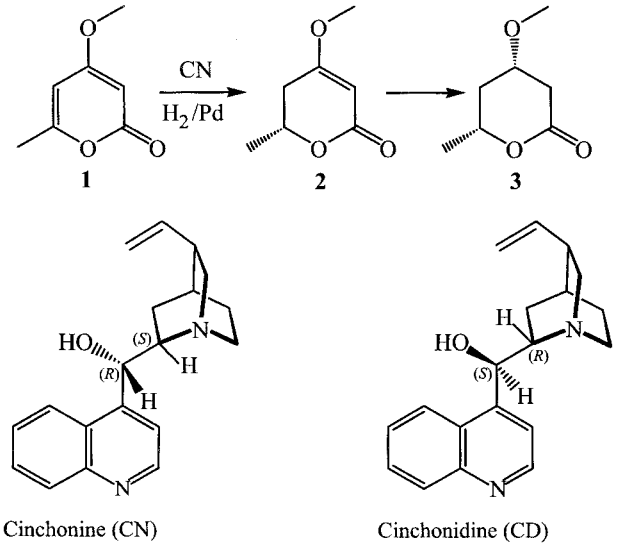
Hydrogenation of 4-methoxy-6-methyl-2-pyrone **1** has been investigated over cinchona-modified Pd/$TiO_2$. The appropriate start-up procedure including a catalyst reduction–oxidation–reduction cycle and a short pretreatment with the modifier in the absence of reactant can remarkably enhance the enantiomeric excess (ee) to the dihydropyrone **2**. Another key parameter is the alkaloid/$Pd_s$ molar ratio; the alkaloid concentration in the slurry or the alkaloid/reactant ratio is not crucial. Under the best conditions 94% ee and 95% chemoselectivity to **2** were achieved at 80% conversion of **1**, in only 30 min reaction time under ambient conditions. The ee can be further increased by kinetic resolution of **2**. In the second reaction step the diasteroselectivity to the *cis*-tetrahydropyrone **3** is about 99%.

**KEY WORDS:** enantioselective; asymmetric; hydrogenation; cinchonidine; cinchonine; palladium; 4-methoxy-6-methyl-2-pyrone.

## 1. Introduction

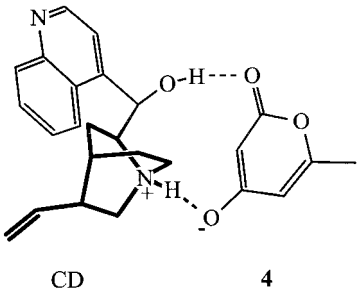
Presently, the best method for the synthesis of the biologically active di- and tetrahydropyrone derivatives [1,2] is homogeneous enantioselective catalysis. Consiglio *et al.* [3] reported excellent enantioselectivities, up to 98%, in the hydrogenation of substituted 2-pyrones with chiral Ru complexes. This catalyst was less efficient in the transformation of **1** to the corresponding 5,6-dihydropyrone **2** (scheme 1): a relatively low reactant/catalyst ratio of 50 was necessary to achieve 93% ee and the chemoselectivity was only 73% [4].




Scheme 1. Hydrogenation of 4-methoxy-6-methyl-2-pyrone **1** over cinchona-modified Pd.

* To whom correspondence should be addressed.
E-mail: baiker@tech.chem.ethz.ch

Among the chirally modified metal hydrogenation catalysts [5–10] Pd is the catalyst of choice for the enantioselective hydrogenation of C=C bonds. The best modifiers are of natural origin: cinchona alkaloids for the hydrogenation of $\alpha,\beta$-unsaturated carboxylic acids [11–14] and vinca [15,16] or ephedra alkaloids [17] for the hydrogenation of $\alpha,\beta$-unsaturated ketones.




Scheme 2. Reactant–modifier interaction responsible for enantio-differentiation in the hydrogenation of 4-hydroxy-6-methyl-2-pyrone **4** [20].

Recently, we have reported an important extension of the application range of cinchona-modified Pd. Hydrogenation of the pseudo-aromatic compound 4-hydroxy-6-methyl-2-pyrone **4** to the corresponding dihydropyrone provided 85% ee [18,19]. The mechanistic model based on catalytic and spectroscopic studies, and theoretical calculations, are depicted in scheme 2 [20]. In this bidentate modifier–reactant complex the interaction of the basic quinuclidine N of CD ($pK_a = 10.0$ [21]) with the acidic OH function of **4** ($pK_a = 4.73$ [3]) plays a crucial role. Unexpectedly, further investigation of the application range of the catalyst revealed that some 2-pyrone derivatives can effectively be hydrogenated even in the absence of an acidic functional group [22]. For example, under appropriate conditions replacement of the hydroxy

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group of **4** by a methoxy function in **1** (scheme 1) is not detrimental to the enantioselectivity. Obviously, the mechanism depicted in scheme 2 is not valid for the hydrogenation of **1**.

Here we report a detailed analysis of the hydrogenation of 4-methoxy-6-methyl-2-pyrone **1** over cinchona-modified $Pd/TiO_2$. The mechanism of enantiodifferentiation will be the focus of a forthcoming study.

## 2. Experimental

4-Methoxy-6-methyl-2-pyrone **1** was synthesized as described earlier [23] and purified by sublimation in vacuum (410 K, 0.1 mbar), followed by double re-crystallization from hexane. Cinchonidine (CD) and cinchonine (CN) (both from Fluka, 99% alkaloid by titration) were used as received. DMF was distilled under reduced pressure before use; all other solvents were used as received.

Preparation of a 5 wt% $Pd/TiO_2$ (metal dispersion: 0.18, determined by $H_2$ chemisorption) has been described elsewhere [20]. For the standard procedure, small portions of $Pd/TiO_2$ were reduced in a $H_2$ flow without solvent at room temperature for 30 min and stored in air until use.

The reactions were carried out in a magnetically stirred 100 or 200 ml glass reactor, depending on the amount of solvent. In the standard procedure 20 mg $Pd/TiO_2$ (prereduced as described above and stored in air) was pretreated in 10 ml 2-propanol in flowing $H_2$ for 5 min, at 1 bar and room temperature ($\sim$298 K). Then 3.4 $\mu$mol modifier was added and after 5 min stirring the reaction was started by addition of 50 mg **1**. When a primary alcohol was the solvent, the dry $Pd/TiO_2$ was prereduced in $H_2$ for 30 min and then 10 ml alcohol and the appropriate amount of modifier were added with the exclusion of oxygen. After 5 min stirring the reaction was started by addition of 50 mg **1**. For slow reactions (longer than 3 h), an additional amount of modifier was dosed stepwise (0.24 $\mu$mol/h) to the reaction mixture to compensate the hydrogenation of the quinoline rings of the modifier [18].

Conversion, chemoselectivity (amount of **2**, related to the total amount of **2** and **3**), diastereoisomeric excess ($de = cis(\%) - trans(\%)$) and enantiomeric excess ($ee = |R(\%) - S(\%)|$) were determined by direct gas chromatographic analysis with a Chirasil-DEX CB column (Chrompack). The (*S*)-enantiomer eluded first. The chemoselectivity to **2** (scheme 1) was higher than 90% if not otherwise mentioned. The products after isolation by flash chromatography (silica gel, hexane/ethyl acetate 5:1) were identified by NMR and GC-MS analysis, and by optical rotation; for details see [18]. CN as chiral modifier afforded (*R*)-**2** in excess in all solvents, and CD produced (*S*)-2 as the major product. The initial turnover frequency (TOF) was calculated from the initial reaction rate and the number of surface Pd atoms ($Pd_s$).

## 3. Results

### 3.1. Catalyst prereduction

Preliminary screening of the effect of reaction conditions revealed that the starting procedure has a strong influence on the rate and enantioselectivity in the hydrogenation of **1**. Starting the reaction with unreduced catalyst containing hydrated palladium oxide resulted in the lowest ee and the highest conversion in 1 h (table 1). Prehydrogenation of the catalyst in the solvent for 5 min (method A) or prereduction of the dry catalyst in hydrogen at room temperature for 30 min and the subsequent addition of the reaction mixture under exclusion of oxygen (method B) improved the ee and diminished the reaction rate. No further enhancement was achieved by catalyst prereduction at higher temperature (up to 470 K) or by reoxidizing the metal surface by exposing the catalyst to ambient air (method C). Only a hydrogenation–oxidation–hydrogenation cycle afforded slightly better enantioselectivity (method D).

Interestingly, the ee could be improved by a short catalyst premodification step. Addition of the modifier to the prereduced catalyst slurry 5 min before starting the reaction by introducing the reactant **1** increased the ee by 5–12% (table 1). In the following experiments method D and 5 min preadsorption of the modifier were applied as the standard starting procedure. In primary alcohols this method afforded very slow reactions and some non-reproducibility in ee. This difficulty was overcome by applying the prereduction method B and 5 min premodification with the alkaloid before reactions in primary alcohols.

It has been shown earlier that the catalyst pretreatment procedure plays an important role in the Pd-catalyzed enantioselective hydrogenation of functionalized olefins,

Table 1
Influence of catalyst prereduction with $H_2$ and the subsequent premodification with cinchonidine (CD) [a]

| Prereduction method (time in min) | Preadsorption of CD | | | |
|---|---|---|---|---|
| | 0 min | | 5 min | |
| | conv., % | ee, % | conv., % | ee, % |
| None | 27 | 50 | 25 | 60 |
| A: in solvent (5) | 26 | 60 | 25 | 65 |
| B: without solvent (30) | 19 | 57 | 14 | 69 |
| C: B, then stored in air (>1500) | 17 | 58 | – | – |
| D: C, then A | 17 | 63 | 15 | 73 |

[a] Standard reaction conditions except the starting procedure; 2.5 mg CD, hydrogenation reaction time 1 h.

though no satisfactory explanation has been provided yet [20,24–27]. The adsorption of **1** and the cinchona-alkaloid on Pd is presently being studied in our laboratory to understand the effect of premodification steps.

### 3.2. Kinetic resolution of the dihydropyrone intermediate 2

Hydrogenation of **1** (scheme 1) over CN-modified Pd/$TiO_2$ afforded the (*R*)-enantiomer of the dihydropyrone **2**. Both the chemo- and the enantioselectivity varied with conversion, as illustrated in figure 1 by a typical run in 2-propanol. For example, 90% ee and 90% chemoselectivity were achieved at 90% conversion. Without modifier the chemoselectivity was very high and the reaction could be stopped at full conversion of **1** before any significant over-hydrogenation of **2** to **3** occurred. The presence of cinchona alkaloid diminished the chemoselectivity in all solvents. Apparently, the modifier accelerated the reaction of **2** to **3**, compared with the reaction of **1** to **2**. Independent of the solvent, formation of the tetrahydro derivative **3** was highly diastereoselective and the *cis*-diastereoisomer was obtained with about 99% de. For comparison, in the hydrogenation of the hydroxy-pyrone **4** over-hydrogenation of the intermediate 5,6-dihydro-4-hydroxy-6-methyl-pyrone was less important due to the tautomeric stabilization by the OH group [18].

During reaction the enantioselectivity increased slightly by a few percent (figure 1). This effect was more pronounced when CD was used as modifier in the same solvent. For example, under standard conditions the ee to (*S*)-**2** increased from 79% at 11% conversion to 86% ee at 93% conversion, and continued to increase even when the reactant **1** was consumed.

The influence of kinetic resolution on the product distribution is best illustrated by the hydrogenation of racemic **2** (figure 2). CD accelerated the hydrogenation

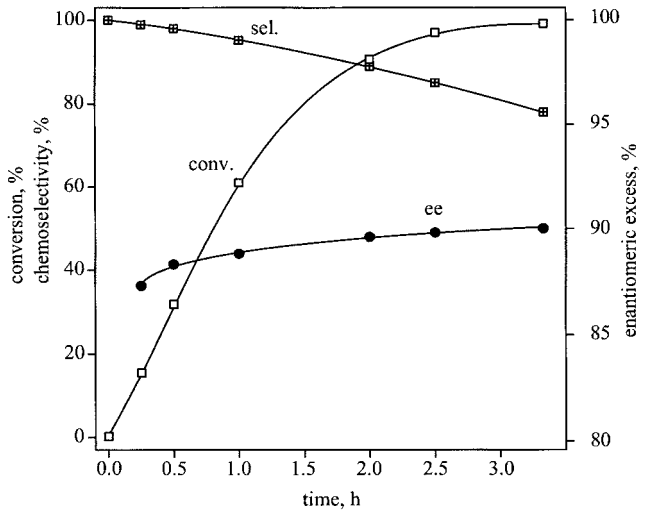


Figure 1. Influence of conversion on the enantioselectivity and chemoselectivity in the hydrogenation of **1** to **2**. Standard condition, 50 ml 2-propanol.

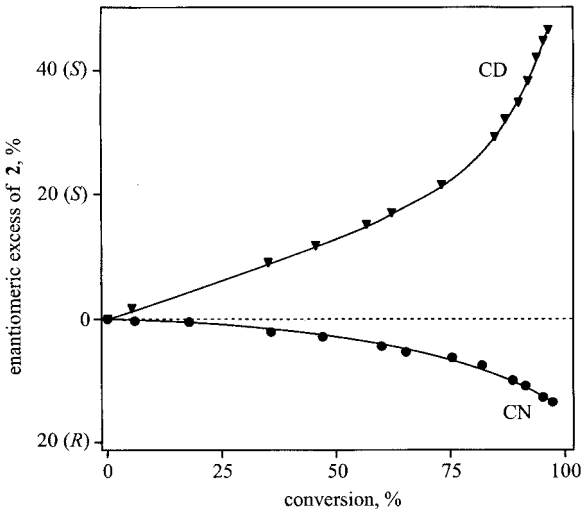


Figure 2. Kinetic resolution of racemic **2**. Conditions: 50 mg **2**, 20 mg 5 wt% $Pd/TiO_2$, 3.4 $\mu$mol (starting amount) + 0.24 $\mu$mol/h modifier, 10 ml 2-propanol, 298 K, 1 bar $H_2$, 12 h reaction time.

of (*R*)-**2** resulting in an increasing excess to the (*S*)-enantiomer, whereas CN induced a smaller effect. It is obvious that the ee achieved in the hydrogenation of **1** at full conversion can be further increased by hydrogenation of **2** to **3**. Note that a practical application of kinetic resolution for improving the ee in the hydrogenation of **1** is limited by the very slow hydrogenation of **2** and the competing hydrogenation of the modifier.

In the presence of CN the kinetic resolution was minor up to 20% conversion of **2** (figure 2). Hence, in the hydrogenation of **1** with CN as modifier the kinetic resolution of **2** is not important until the chemoselectivity exceeds 80%. For this reason CN was used in the following experiments for studying the role of other parameters.

### 3.3 Modifier concentration

The striking effect of modifier concentration on the ee and reaction rate is illustrated in figure 3. Under standard conditions in 2-propanol, a maximum in ee was measured at 0.2 mmol/l CN concentration, corresponding to a CN to surface Pd atoms ($Pd_s$) molar ratio of 1.2. Above the optimum the effect of modifier concentration was minor. The position of the optimum did not change when the amount of reactant was doubled or halved, or the amount of solvent was increased by a factor of up to 15. Apparently, in this reaction the modifer/$Pd_s$ ratio is the crucial parameter in determining the ee, not the reactant/modifier ratio or the modifier concentration in solution.

The initial reaction rate under standard conditions but without modifier was 170 mmol/h g(cat). Using the optimum amount of CN the rate dropped by a factor of 10 and decreased further by increasing the modifier concentration (figure 3). An important conclusion from

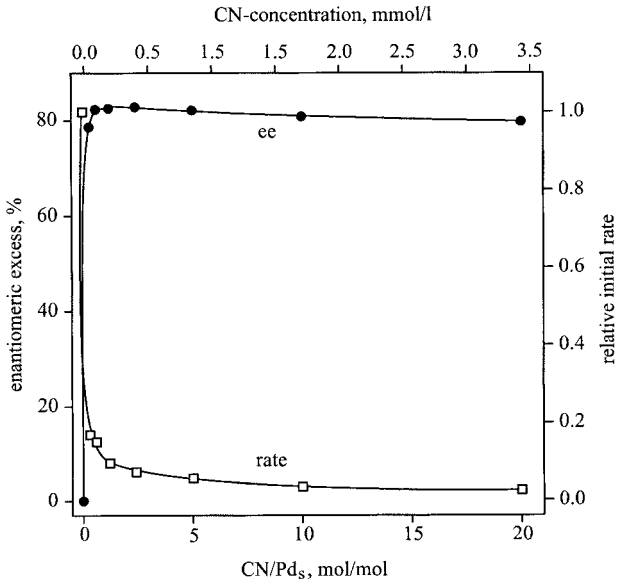


Figure 3. Effect of CN concentration on the enantioselectivity and on the initial reaction rate related to the initial rate of the unmodified reaction. Standard condition; ee and initial rate determined at 25% conversion; chemoselectivity was at least 91%.

this rate deceleration is that no significant mass transport limitation is expected when the CN/Pd$_s$ molar ratio exceeds 1.

Similar correlations between the amount of modifier and the ee and initial rate have been reported for the hydrogenation of $\alpha,\beta$-unsaturated carboxylic acids and isophorone over chirally modified Pd [14,15,28]. An optimum in the CD/Pd$_s$ molar ratio of 1.8 can be calculated for the hydrogenation of 2-methyl-2-pentenoic acid over Pd/alumina [28]. The rate deceleration by a factor of 10, observed in the hydrogenation of **1** in the presence of an optimum amount of modifier, is moderate compared with earlier data in the range 2–140 [14,15,19,28].

### 3.4. Solvent effect

A broad range of solvents have been tested in the hydrogenation of **1** using either CN or CD as modifier (table 2). The most important observation is that there is no clear correlation between the enantioselectivity and the solvent polarity characterized by Reichardt's empirical solvent parameter $E_T^N$ or the relative permittivity $\varepsilon_r$ [29].

However, an unusual correlation was found when the ee was plotted as a function of conversion (figure 4). Higher than 60% ee was obtained only in those solvents which facilitated the fast hydrogenation of **1**. Not included here are the results in hexane and water, which solvents poorly dissolve **1** and/or the modifier.

### 3.5. Comparison of cinchonine and cinchonidine

A comparison of the CN–CD diastereomer pair revealed an interesting feature of the hydrogenation of

Table 2
Comparison of CD and CN as modifiers in various solvents [a]

| Solvent | $E_T^N$ | $\varepsilon_T$ | CD | | CN | |
|---|---|---|---|---|---|---|
| | | | conv., % | ee, % | conv., % | ee, % |
| Toluene | 0.099 | 2.38 | 3 | 30 (*S*) | 3 | 40 (*R*) |
| Tetrahydrofuran | 0.207 | 7.58 | 10 | 58 (*S*) | 13 | 68 (*R*) |
| Ethyl acetate | 0.228 | 6.02 | 1 | 28 (*S*) | 2 | 42 (*R*) |
| 3-Pentanone | 0.265 | 17.0 | 2 | 48 (*S*) | 2 | 50 (*R*) |
| Dimethylformamide | 0.404 | 36.7 | 10 | 58 (*S*) | 10 | 77 (*R*) |
| Acetonitrile | 0.460 | 35.9 | 1 | 41 (*S*) | 1 | 53 (*R*) |
| 2-Propanol | 0.546 | 19.9 | 16 | 72 (*S*) | 19 | 80 (*R*) |
| Acetic acid | 0.648 | 6.17 | 0.5 | 39 (*S*) | 0.5 | 45 (*R*) |
| Water | 1.00 | 78.3 | 21 | 38 (*S*) | 22 | 39 (*R*) |

[a] Conditions: 100 mg **1**, 20 mg 5 wt% Pd/$TiO_2$, 1.5 mg modifier, 10 ml solvent, 1 bar, 26 °C, 1 h; chemoselectivity >95%.

2-pyrones. In all solvents the hydrogenation of **1** is faster and the ee higher when CN is used as modifier. Note that the results in water may be distorted by the poor solubility of the alkaloids. The difference in ee can be as high as 19% in favor of CN, as illustrated by the results in the hydrogenation of **1** in table 2. Similarly, in the hydrogenation of 4-hydroxy-6-methyl-2-pyrone **4**, CN provided higher ee by up to 15% ee in all solvents except acetonitrile, which was the best solvent of this reaction. To our knowledge, these are the first cases when CN offers better enantioselectivities than CD in a platinum metal-catalyzed hydrogenation reaction.

### 3.6. Other reaction parameters

With increasing temperature the reaction rate increased as expected but a maximum in ee was observed at about 295–300 K. For example, decreasing the

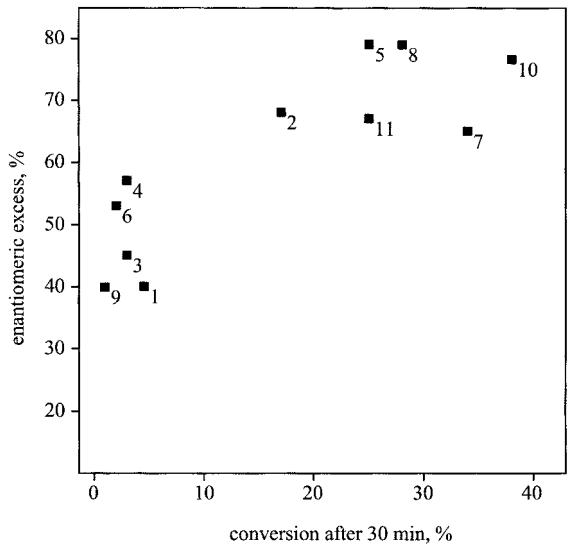


Figure 4. Correlation between the enantioselectivity and the conversion achieved in 30 min. Standard condition; solvents: 1, toluene; 2, THF; 3, ethyl acetate; 4, diethylketone; 5, DMF; 6, acetonitrile; 7, cyclohexanol; 8, 2-propanol; 9, AcOH; 10, ethanol; 11, methanol.

temperature from 298 to 273 K diminished the ee by 15%. This behavior is similar to that observed in the hydrogenation of the hydroxy-pyrone **4** [19]. The chemoselectivity was barely affected by the reaction temperature.

An initial TOF of $120\,h^{-1}$ (at 25% conversion) was calculated for 298 K. This value is much smaller than the TOF of 8900 achieved in the hydrogenation of 2-methyl-2-pentenoic acid over CD-modified Pd/alumina [11]. The main reasons for the slow reaction in the hydrogenation of **1** are the lower activity of Pd in the saturation of the pseudo-aromatic pyrone structure and the 10 times lower reactant concentration, compared with the hydrogenation of the alkenoic acid.

Higher than ambient pressure had no positive effect on the enantioselectivity in 2-propanol. For example, at 5 bar the ee decreased by 3% and the initial rate increased by 40%, compared with the reaction under ambient conditions. The negative effect of high surface hydrogen concentration may partly be due to the accelerated saturation of the quinoline rings of the alkaloid modifier.

A limited optimization of the reaction conditions involving the temperature, pressure, and the amounts of reactant, solvent and catalyst afforded 94% ee at 80% conversion of **1** and 95% chemoselectivity to **2**, in only 30 min reaction time. The conditions are similar to the standard conditions, except for the amount of **1** (1 mg) and the solvent 2-propanol (50 ml).

## 4. Discussion

Hydrogenation of the pseudo-aromatic 4-methoxy-6-methyl-2-pyrone **1** takes place in two distinct reaction steps over $Pd/TiO_2$. At first **1** is reduced to the dihydropyrone **2** (scheme 1). Further hydrogenation to **3** occurs before complete consumption of **1** only in the presence of the cinchona alkaloid modifier. Obviously, the reactant–modifier interaction does not cease after the uptake of one equivalent hydrogen. This conclusion is supported also by the observed considerable kinetic resolution of **2**.

The study revealed a major role of the start-up procedure including the appropriate redox cycle catalyst pretreatment and premodification of Pd by the alkaloid in the absence of reactant. Interpretation of these effects requires further investigations. Another parameter which can improve the reaction rate and the selectivities is the composition and preparation method of the supported Pd catalyst.

The best results achieved in this study are 94% ee and 95% chemoselectivity at 80% conversion. This is the highest enantioselectivity reported for any enantioselective hydrogenation reaction over chirally modified Pd. The ee may still be increased by kinetic resolution, though the further transformation of **2** is very slow and necessitates the feeding of modifier in minute amounts to compensate its hydrogenation and destruction [18]. The tetrahydropyrone **3** can easily be separated from **2** by recrystallization from hexane. Application of kinetic resolution seems to be more reasonable for the CD-modified reaction, which modifier affords 2-3 times bigger enhancement in ee.

Hydrogenation of **1** over cinchona-modified Pd offers a real alternative to the homogeneous catalytic hydrogenation with a chiral Ru catalyst. The chiral Ru complex provided up to 93% ee for **2** [3,4], but the chemoselectivity and the reaction rate were lower (*e.g.* 80% chemoselectivity at 91% conversion after 20 h) than in the Pd-catalyzed reactions.

A critical point in both methods is the low reactant/catalyst or reactant/modifier ratio. In the Pd-catalyzed reaction 90% ee was achieved with a 105 **1**/CN ratio, but a ratio of 2.1 was necessary to improve the ee to 94%. In the Ru-catalyzed homogeneous reaction a reactant/catalyst ratio of 500 afforded 91% ee and a ratio of only 50 increased of the ee to 93%.

## 5. Conclusions

Hydrogenation of the 4-methoxy-pyrone **1** and the 4-hydroxy-pyrone **4** represent important new applications of Pd modified by cinchona alkaloids. These studies demonstrate that the potential of chirally modified Pd is much broader than has been commonly considered and its efficiency is comparable with those of Pt-cinchona and Ni-tartrate systems.

## Acknowledgment

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