Journal of Catalysis **193,** 1–4 (2000)
doi:10.1006/jcat.2000.2890, available online at http://www.idealibrary.com on IDEAL®

PRIORITY COMMUNICATION

Potential and Limitations of Palladium–Cinchona Catalyst for the Enantioselective Hydrogenation of a Hydroxymethylpyrone

W.-R. Huck, T. Mallat, and A. Baiker[1]

Laboratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich, Switzerland
E-mail: baiker@tech.chem.ethz.ch

Received March 17, 2000; revised April 3, 2000; accepted April 3, 2000

The palladium-catalyzed enantioselective hydrogenation of 4-hydroxy-6-methyl-2-pyrone afforded up to 85% excess to the (*S*)-enantiomer of the corresponding 5,6-dihydropyrone, under very mild conditions (1 bar, room temperature). This is the highest enantioselectivity achieved so far with chirally modified Pd, demonstrating the potential of this catalyst in the enantioselective hydrogenation of unsaturated compounds. A complicating feature of the reaction is the limited stability of cinchonidine under reaction conditions, which results in a decline of the initial enantiomeric excess (ee) with reaction time. Continuous feeding of a minute amount of cinchonidine during reaction allows maintenance of the high initial ee with an overall substrate/modifier molar ratio of ca. 20.

Key Words: **enantioselective; regioselective; asymmetric; hydrogenation; cinchonidine; palladium; platinum; nickel; 2-pyrone derivative; 4-hydroxy-6-methyl-2-pyrone.**

1. INTRODUCTION

The structure of 2-pyrone and its hydrogenation products is present in many natural compounds. The partial hydrogenation products can be used as chiral intermediates, for example, in the synthesis of tetrahydrolipstatin, a potent antiobesity drug, and that of an HIV protease inhibitor (1–3). For this reason the enantioselective hydrogenation of substituted 2-pyrones with homogeneous transition metal complexes has recently become a subject of great interest. A chiral Ru catalyst afforded excellent ee (up to 98%) and good chemoselectivities to 5,6-dihydropyrones, but only a mixture of *trans* and *cis* tetrahydropyrones formed when the substrate was not alkylated in *C*-3 position (4, 5).

There is only one report that mentions (without details) the heterogeneous enantioselective hydrogenation of a substituted 2-pyrone (3). Hydrogenation of **1** (Scheme 1) with the Raney Ni–tartaric acid–NaBr system yielded the tetrahydro-derivative **3** with only 17% ee. Among the heterogeneous metal hydrogenation catalysts only Pd affords the semihydrogenation of **1** to the dihydro-derivative **2** (6). Ni forms predominantly the *cis* **3**, while the saturated lactone **4** is the major product on Pt due to its high activity in hydrogenolysis of the C–O(H) bond.

Intrigued by the pharmaceutical importance of chiral 2-pyrone derivatives and the shortcomings of homogeneous catalysts in the enantioselective hydrogenation of **1** to **2**, we have studied this reaction over Pd, Pt, and Ni in the presence of cinchonidine (CD) as chiral modifier.

2. EXPERIMENTAL

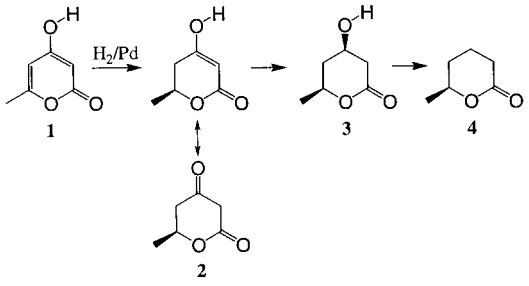
The 5-wt% Pd/alumina (Engelhard 40692, metal dispersion 0.21, determined by TEM), 5-wt% Pt/alumina (Engelhard 4759, metal dispersion 0.27, determined by TEM), and Raney-Ni (Fluka, 83440) catalysts were used as received. A 5-wt% Pd/titania (metal dispersion 0.18, determined by H_2 chemisorption) was prepared by neutralizing an aqueous H_2PdCl_4 solution with $NaCO_3$ at room temperature, in the presence of TiO_2 (P25, Degussa, 55 m^2/g). The 4-hydroxy-6-methyl-2-pyrone (**1**, Fluka 98%) was purified before use by column chromatography (silica gel, dry hexane/ethyl acetate 1 : 1) and recrystallization. All solvents were distilled before use. CD (Fluka) was used as received.

The reactions at 1 bar were carried out in a magnetically stirred 100-ml glass reactor. According to a standard procedure, 40 mg catalyst in 20 ml solvent was pretreated with H_2 for 5 min, at 25–30°C. Then the appropriate amount of modifier and 300 mg **1** were added, and the stirring was started. A 100-ml stainless steel autoclave equipped with a 50-ml glass liner and a PTFE cap and stirrer was used for high-pressure experiments.

Conversion, yield, and selectivity were determined by an HP 6890 gas chromatograph (HP-5 column). The enantiomers of **2** were separated after methylation with a cyclosil B column (J&W). Derivatization was carried out in

[1] To whom correspondence should be addressed.

0021-9517/00 $35.00



SCHEME 1

3 ml methanol with 100 mg trimethylorthoformate in the presence of acidic ion exchange resin (Diaion RCP1 60H) and ca. 0.1 mmol hydrogenation product (50°C, 15 h). The products **2**, **3**, and **4** (Scheme 1), after isolation by flash chromatography (silica gel, hexane/ethyl acetate 1 : 1) were identified by NMR and GC-MS analysis and by optical rotation.

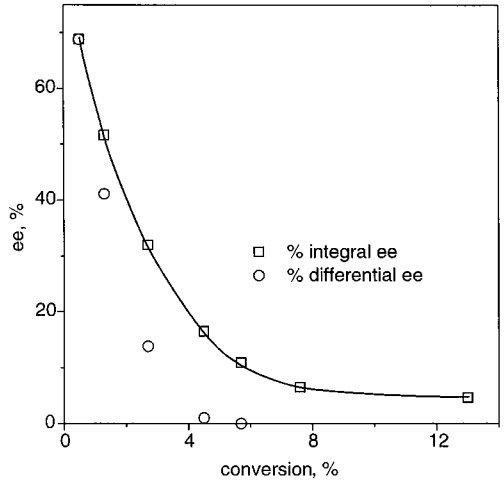


FIG. 1. Conversion dependence of enantiomeric excess (ee) in the hydrogenation of **1** in acetonitrile (standard conditions, 5 wt% Pd/titania, 3 mg CD, reaction time 1–24 h).

3. RESULTS

Hydrogenation of **1** with Pd/alumina, Raney Ni, and Pt/alumina was complete within 1 h under ambient conditions, leading predominantly to **2**, **3**, and **4**, respectively (Scheme 1). The activity and selectivity of Raney Ni was barely influenced by the presence of CD, but Pt was completely poisoned by the addition of only 3 mg alkaloid (Table 1).

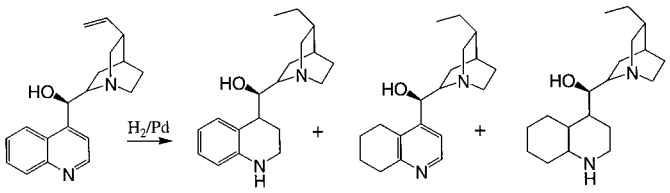
Pd preserved its good chemo- and regioselectivity to the dihydro-derivative **2** in the presence of CD, though the reaction rate decreased remarkably. For example, addition of 3 mg CD to 40 mg Pd/alumina increased the reaction time by a factor of 25. Over 95% selectivity to **2** was achieved at around 80% conversion of **1** in various solvents, except acetonitrile (Table 1). The chemoselectivity successively decreased by 10–25% at higher conversion and especially under pressure (5–50 bar). The major by-product was the tetrahydroderivative **3**, except in acetic acid, which solvent promoted the hydrogenolysis of the C–O(H) bond (7). The influence of catalyst support (titania or alumina) on the rate and chemoselectivity was small. In the following part, the study of the enantioselective transformation of **1** to **2** was carried out with supported Pd catalysts.

Pd/alumina or Pd/titania with CD as chiral modifier afforded 20–50% ee to (*S*)-**2** in various solvents, such as acetic acid, 2-propanol, 3-pentanone, dimethylformamide, and water. Replacing CD with the diastereomer cinchonine yielded the opposite enantiomer (*R*) in excess, as expected. In most solvents the ee decreased slowly with conversion when only 1–3 mg CD was applied, corresponding to a modifier/Pd_s molar ratio of ca. 1–3. In acetonitrile the initial ee was higher, but the loss of enantioselectivity with increasing conversion was strikingly fast (Fig. 1). The differential curve shows that the actual (incremental) ee dropped to zero above 5% conversion of **1** (4 h reaction time). When the reaction was repeated under similar conditions but Pd/titania was prehydrogenated for 4 h in the presence of CD, no ee was observed. NMR experiments

TABLE 1

Influence of Solvent and Pressure on the Chemioselectivity of Pd, Pt, and Ni Catalysts (40 mg Catalyst, 20 ml Solvent, and 300 mg 1, rt)

						Selectivity to		
Catalyst	Solvent	CD (mg)	Pressure (bar)	Time (h)	Conv. (%)	**2** (%)	**3** (%)	**4** (%)
Raney Ni	isopropanol	10	1	1	90	0	100	0
Pt/Al_2O_3	isopropanol	0	1	1	100	2	0	98
Pt/Al_2O_3	isopropanol	3	1	10	0	—	—	—
Pd/Al_2O_3	acetic acid	10	1	24	78	96	2	2
Pd/Al_2O_3	acetic acid	10	30	7	80	83	8	7
Pd/TiO_2	isopropanol	3	1	24	75	97	3	0
Pd/TiO_2	acetonitrile	3	1	24	77	75	25	0



SCHEME 2

indicated that Pd catalysed saturation of the vinyl group and the hetereoaromatic ring of CD, while hydrogenation of the unfunctionalized aromatic ring of CD at room temperature and atmospheric pressure was minor even after 72 h (Scheme 2).

When higher amounts (10–20 mg) of modifier were used, the loss of ee with increasing conversion ceased or slowed down considerably in all solvents investigated, but hydrogenation of **1** was also sluggish. For example, in an experiment, 20 mg CD and 40 mg Pd/titania were used under standard conditions in acetonitrile containing 0.25 vol% water (substrate/modifier molar ratio 35). After 6 h the conversion was only 4%, though the ee to the (*S*)-product reached 77%. The highest enantioselectivity, of 85%, was achieved under similar conditions, but the reaction was carried out at 32°C with 22 mg CD-hydrochloride as chiral modifier. In this case 4 h was necessary to get 2% conversion.

To overcome these difficulties, the reaction was started with small amounts of modifier and some CD was added during reaction (Fig. 2). This strategy has been applied successfully for optimizing the concentration of CD on the Pt surface and thus the stereochemical outcome of ethyl pyruvate hydrogenation (8). As illustrated in Fig. 2, dosing of at least 0.5 mg/h alkaloid in 1 ml solvent stabilised the initial high ee in acetonitrile. On the other hand, no enhancement in ee could be achieved when the experiments were repeated with the same initial amount of CD (2.5–10 mg) but an increased amount of dosed CD above 0.5 mg/h.

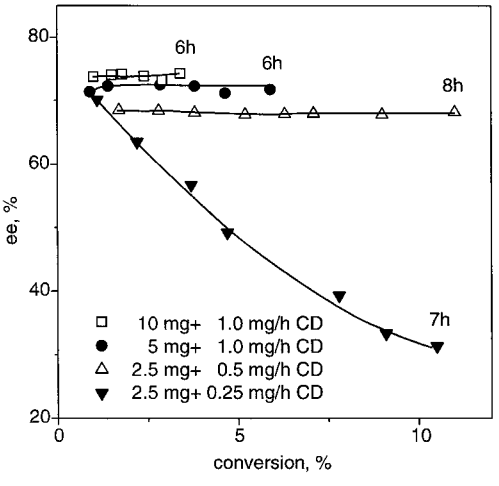


FIG. 2. Influence of feeding CD during hydrogenation of **1** in acetonitrile (standard conditions, 5 wt% Pd/titania).

4. DISCUSSION

The chemical behaviour of 2-pyrones can be described by the reactivity of an endocyclic ester possessing a conjugated double bond system, or it may be attributed to a pseudo-aromatic character. Indications to the former approach are the facile hydrogenation of 2-pyrones under ambient conditions, the ring opening by the attack of hydrides, and the missing NMR evidence for aromaticity (9). On the other hand, the indications for partial aromaticity are that hydrogenation leads to tetrahydro-pyrones except when the C=C double bond in the intermediate is stabilised by two alkyl groups at the *C*-3 and *C*-4 positions, or a hydroxy or alkoxy group at the 4 position (10, 11). Also theoretical calculations showed a small amount of aromaticity (9), and methylation of the carbonyl group to form the aromatic pyryllium derivative cannot be explained without assuming a partially aromatic character (12). Accordingly, in many publications this structure is described as pseudo-aromatic.

Independent of considering **1** as an endocyclic enol ester or a pseudo-aromatic compound, the 85% ee achieved with CD-hydrochloride is the highest enantioselectivity reported so far for chirally modified Pd. Limitations arise from the low reaction rate and moderate stability of the modifier under reaction conditions. A possible solution to maintain the initial enantioselectivity up to high conversions is the continuous feeding of minute amounts of modifier. This strategy is demonstrated in Fig. 2. Further improvement by optimization of reaction conditions aiming at increasing reaction rate and optical yield (conversion × ee) is possible. As an example, increasing the amount of catalyst from 20 to 200 mg (at constant Pd/modifier ratio) afforded a conversion of 22% in 4 h, and an ee of 82%. In the enantioselective hydrogenation of α-functionalized olefins, Pd modified by cinchona- or vinca-type alkaloids afforded 52–72% ee (13–16). Note that higher ee has never been reported even at lower conversions. Efforts aiming at the enantioselective hydrogenation of (hetero)-aromatic compounds with chirally modified Ni and Rh catalysts were barely efficient (17, 18).

The results presented in Figs. 1 and 2 demonstrate the application limit of cinchona alkaloids as chiral modifiers. Palladium is more active in the (partial) hydrogenation of the aromatic ring system of CD than other platinum metals (19). This transformation leads to a weaker adsorption and a loss of enantio-differentiating ability of the modifier. This side reaction is likely accelerated by the protonation of the quinoline N-atom by the acidic substrate. It has been reported that the pK_a of **1** (4.73) is similar to that of acetic acid (4.76) (4). When the target reaction is slow, consumption

of the modifier results in a significant drop in enantioselectivity during reaction. The feeding of additional CD to the batch reactor can compensate for the detrimental effect of modifier consumption. The smallest feed of CD, which provided constant ee, was 0.5 mg/h. Taking this value as the approximate rate of CD consumption during hydrogenation of **1** under ambient conditions, we calculated the rate of modifier consumption related to that of hydrogenation of **1**. These calculations indicated that the hydrogenation of 20 molecules of **1** is accompanied by the consumption of 1 CD molecule.

Despite the partial hydrogenation of the aromatic rings of CD during reaction, the overall substrate/modifier ratio of ca. 20 is not unusually low for chirally modified Pd. For comparison, achieving 72% ee in the hydrogenation of phenyl-cinnamic acid required a substrate/CD ratio that was lower by sixfold (16), and an equimolar amount of ephedrine was necessary to obtain the best ee in the hydrogenation of pyruric acid oxime (20). Apparently, the low modifier/substrate ratio is, so far, a general feature of Pd-catalysed enantioselective hydrogenation.

5. CONCLUSIONS

The Pd-catalysed hydrogenation of 4-hydroxy-6-methyl-2-pyrone afforded 77–85% excess to the (*S*)-enantiomer of 4-hydroxy-6-methyl-5,6-dihydro-2-pyrone, in the presence of CD or CD-hydrochloride as chiral modifiers. Presently this is the only catalytic enantioselective hydrogenation method available for this transformation. Limitations arise from the limited stability of the modifiers under reaction conditions. Although continuous dosing of a minute quantity of modifier can alleviate this limitation, the development of similarly functioning but more stable modifiers is desirable.

REFERENCES

1. Spino, C., Mayes, N., and Desfossés, H., *Tetrahedron Lett.* **37**, 6503 (1996).
2. Romines, K. R., Morris, J. K., Howe, W. J., Tomich, P. K., Horng, M.-M., Chong, K.-T., Hinshaw, R. R., Anderson, D. J., Strohbach, J. W., Turner, S. R., and Mizsak, S. A., *J. Med. Chem.* **39**, 4125 (1996).
3. Schmid, R., Broger, E. A., Cereghetti, M., Crameri, Y., Foricher, J., Lalonde, M., Müller, R. K., Scalone, M., Schoettel, G., and Zutter, U., *Pure Appl. Chem.* **68**, 131 (1996).
4. Fehr, M. J., Consiglio, G., Scalone, M., and Schmid, R., *New J. Chem.*, 1499 (1998).
5. Fehr, M. J., Consiglio, G., Scalone, M., and Schmid, R., *J. Org. Chem.* **64**, 5768 (1999).
6. Bacardi, R., and Moreno-Manas, M., *Tetrahedron Lett.* **21**, 551 (1980).
7. Rylander, P. N., *in* "Catalysis in Organic Synthesis" (W. H. Jones, Ed.), p. 155. Academic Press, New York, 1980.
8. LeBlond, C., Wang, J., Liu, J., Andrews, A. T., and Sun, Y.-K., *J. Am. Chem. Soc.* **121**, 4920 (1999).
9. Brogden, P. J., Gabbutt, C. D., and Hepworth, M., *in* "Comprehensive Heterocyclic Chemistry" (A. R. Katritzky, C. W. Rees, A. J. Boulton, and A. McKillop, Eds.), Vol. 3, p. 634. Pergamon, Oxford, 1984.
10. Wiley, R. H., and Hart, A. J., *J. Am. Chem. Soc.* **77**, 2340 (1955).
11. Smyrniotis, P. Z., Miles, H. T., and Stadtman, E. R., *J. Am. Chem. Soc.* **80**, 2541 (1958).
12. Sib, S., *Tetrahedron* **31**, 2229 (1975).
13. Borszeky, K., Mallat, T., and Baiker, A., *Catal. Lett.* **41**, 199 (1996).
14. Tungler, A., Nitta, Y., Fodor, K., Farkas, G., and Mathe, T., *J. Mol. Catal. A* **149**, 135 (1999).
15. Borszeky, K., Mallat, T., and Baiker, A., *Tetrahydron Asym.* **10**, 4781 (1999).
16. Nitta, Y., and Kobiro, K., *Chem. Lett.*, 897 (1996).
17. Nasar, K., Fache, F., Lemaire, M., Gallezot, P., Besson, M., and Béziat, J. C., *J. Mol. Catal.* **87**, 107 (1994).
18. Laine, R. M., Hum, G., Wood, B. J., and Dawson, M., *Stud. Surf. Sci. Catal.* **7**, 1478 (1999).
19. Bond, G., and Wells, P. B., *J. Catal.* **150**, 329 (1994).
20. Borszeky, K., Mallat, T., Aeschiman, R., Schweizer, W. B., and Baiker, A., *J. Catal.* **161**, 451 (1996).