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Journal of Catalysis 219 (2003) 52–58

JOURNAL OF CATALYSIS

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Palladium-catalyzed asymmetric hydrogenation of furan carboxylic acids

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Received 11 February 2003; revised 2 April 2003; accepted 4 April 2003

Abstract

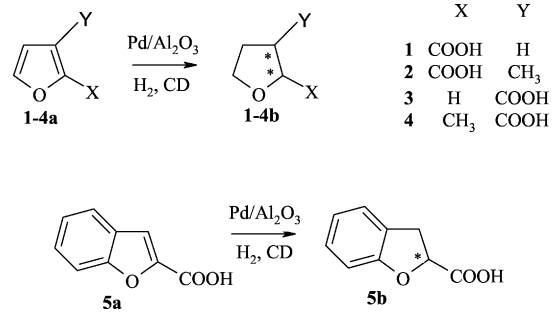
Enantioselective hydrogenation of aromatic and heteroaromatic compounds is the field where chirally modified metal hydrogenation catalysts have the biggest potential compared to homogeneous chiral transition metal complexes. Here we report the hydrogenation of furan and benzofuran carboxylic acids over a cinchonidine-modified 5 wt% Pd/Al_2O_3 catalyst. (*S*)-Tetrahydrofuran-2-carboxylic acid was synthesized in 4 h at rt and 30 bar with 95% yield and 32% *ee*. The *ee* was lower in the hydrogenation of methylfuran carboxylic acids but up to 100% *de* was achieved. In the slow hydrogenation of benzofuran-2-carboxylic acid, the *ee* went up to 50% at 29% yield. The potential application of the method is limited by the competing hydrogenation of the quinoline rings of cinchonidine in the latter reaction, necessitating the feeding of small amounts of cinchonidine during reaction. Still, this simple method using an easily available chiral modifier and catalyst affords the highest rate and *ee* reported so far in the catalytic asymmetric hydrogenation of furan and benzofuran carboxylic acids, and it may be an attractive route in combination with optical resolution. We assume that the reaction mechanism is analogous to that described for α,β-unsaturated carboxylic acids over the same catalyst, involving a 1:2-type interaction between the cinchonidine and the acid dimer.

Keywords: Asymmetric hydrogenation; Pd/Al_2O_3; Cinchonidine; Furan carboxylic acids; Benzofuran carboxylic acid

1. Introduction

Hydrogenation of aromatic and heteroaromatic compounds is a challenging topic in enantioselective catalysis as most of the reactions are characterized by very poor *ee*s [1–5]. Recently, the hydrogenation of furan-2-carboxylic acid was attempted with homogeneous Rh diphosphine catalysts [6]. Up to 24% *ee* was obtained at a substrate/catalyst molar ratio of 20 but the reaction was very slow requiring 20 h at 100 bar to achieve 3% yield. In the absence of a useful catalytic method, the optically active tetrahydrofuran-carboxylic acids are prepared by conventional methods such as optical resolution [7].

Intrigued by the importance of chiral tetrahydrofuran-carboxylic acids as useful intermediates [8], we studied the enantioselective hydrogenation of some furan carboxylic acids over heterogeneous catalysts (Scheme 1). In an early paper, Mitsui et al. [9] reported the chemoselective saturation of the aromatic ring of **1** to form tetrahydrofuran-2-carboxylic acid without hydrogenolysis-type side reactions over Pd/C and Raney Ni catalysts. It is also known that supported and unsupported Pd modified by naturally occurring chiral compounds, such as cinchona and vinca alkaloids, are effective in the enantioselective hydrogenation of C=C bonds in endo- and exocyclic alkenones (up to 55% *ee*) [10–14], α,β-unsaturated carboxylic acids (up to 72% *ee*) [15–21], and 2-pyrone derivatives (up to 94% *ee*) [22–24]. In the hy-



Scheme 1. Hydrogenation of furan and benzofuran carboxylic acids over 5 wt% Pd/Al_2O_3 modified by cinchonidine (CD).

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0021-9517/$ – see front matter
doi:10.1016/S0021-9517(03)00184-2

drogenation of other functionalized olefins chirally modified Pd is far less efficient [25–27].

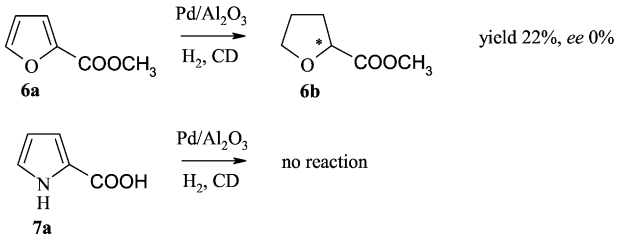
Here we report that a cinchona-modified Pd/Al_2O_3 is the best catalyst among the Pt-group metal hydrogenation catalysts for the synthesis of chiral tetrahydrofuran-carboxylic acids, and a comparison to the only known homogeneous Rh catalyst [6] is also in favor of Pd.

2. Experimental

Furan-2-carboxylic acid (**1a**, Fluka, 98%), 3-methylfuran-2-carboxylic acid (**2a**, Lancaster, 98%), furan-3-carboxylic acid (**3a**, Aldrich, 99%), 2-methylfuran-3-carboxylic acid (**4a**, Lancaster, 97%), benzofuran-2-carboxylic acid (**5a**, Fluka, 98%), and pyrrole-2-carboxylic acid (**7a**, Fluka, 98%) were purified by sublimation followed by recrystallization from hexane **(1a**, **2a**, **3a**, **4a**) or toluene (**5a)**. Methyl-2-furoate (**6a**, Fluka, 97%) (Scheme 2) was used after distillation in vacuum. Cinchonidine (CD, Fluka, 98% alkaloid) and all other chemicals were used as received.

A 100-mL autoclave equipped with a 50-mL glass liner, a PTFE cover, and a magnetic stirrer (500 rpm) was used for hydrogenations. Total pressure and H_2 uptake were controlled by a computerized constant volume constant pressure equipment (Büchi BPC 9901). Under standard conditions the catalyst pretreatment and the hydrogenation reactions were carried out at room temperature and 30 bar. At first, 40 mg 5 wt% Pd/Al_2O_3 catalyst (Engelhard 40692, Pd dispersion: 0.21 as determined by TEM) was prereduced with hydrogen for 5 min in 10 mL solvent. Then 0.45 mmol substrate and 68 μmol CD modifier were added (S/M = 6.5) and the reaction was started. No external mass transport limitation (no effect of stirring rate) was observed in the rather slow hydrogenation of the furan ring. Intraparticle diffusion effects cannot be ruled out completely, but are unlikely due to the relatively low rate compared to the corresponding racemic (unmodified) hydrogenation.

Conversion and enantioselectivity were determined after derivatization using an HP 6890 gas chromatograph and a Chirasil-DEX CB (Chrompack 7502, 25 m × 0.25 mm × 250 nm) capillary column for the hydrogenation products **1b**, **2b**, **4b**, **5b, 6b** and a CYCLOSILB (J&W 7419117, 30.0 m × 0.25 mm × 0.25 μm) column for **3b**. Conditions:



Scheme 2. Hydrogenation of methyl-2-furoate **6a** and pyrrole-2-carboxylic acid **7a**. Standard conditions, 10 mL 2-propanol, S/M = 52 and S/M = 6.5, respectively.

split injection (250 °C, 20:1), He carrier gas (42 $cm^3\,s^{-1}$), FID detector (275 °C), 80–180 °C column temperature. Derivatization was carried out by heating ca. 5 mg carboxylic acid and 0.1 mL of a 1 M solution of trimethylchlorosilane in MeOH for 2 h. After evaporation of the solvent the residue was dissolved in 1 mL toluene or ethyl acetate. Hydrogenation of **7a** was followed by NMR analysis.

In the hydrogenation of **1a**, the (*S*)-(−)-**1b** enantiomer was formed in excess over CD-modified Pd, as confirmed by using commercially available (*R*)-(+)-tetrahydrofuran-2-carboxylic acid (*ee* 98%, Lancaster). On the basis of analogous separation of the products we assume that also in the hydrogenation of **3a** and **5a** the (*S*)-enantiomer formed in excess. Two diastereomers (*cis* and *trans*) may be formed in the hydrogenation of **2a** and **4a**. All four enantiomers could be detected by GC analysis but determination of *ee* was reliable only for the two *cis*-isomers. In these reactions the major enantiomer was not identified.

The incremental *ee* was calculated as follows: $\Delta ee = (ee_1 \cdot \text{yield}_1 - ee_2 \cdot \text{yield}_2)/(\text{yield}_1 - \text{yield}_2)$.

CD consumption during reaction was followed by UV–vis spectroscopy using a Cary 400 spectrophotometer. Before analysis the samples were diluted with 2-propanol by a factor of 5. NMR measurements were carried out on a DPX 300 spectrometer.

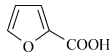
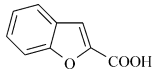
3. Results and discussion

3.1. Choice of catalyst and reaction conditions

At first, various Pt, Rh, Ru, and Pd catalysts supported on Al_2O_3, active C, TiO_2, or $CaCO_3$ were tested in the hydrogenation of furan-2-carboxylic acid (**1a**). Cinchonidine was applied as chiral modifier in toluene, at room temperature and 30 bar (standard conditions). A 5 wt% Pd/Al_2O_3 provided 83% conversion in only 3 h and 31% *ee* to (*S*)-**1b**. Substituting CD with its diastereomer cinchonine led to somewhat lower conversion (72%) and to inversion of configuration (27% (*R*)-**1b**). The chemoselectivity of cinchona-modified Pd/Al_2O_3 was also good, at least 95%, depending on the conditions (solvent, pressure, and temperature). CD-modified Rh/Al_2O_3 afforded only 4% *ee* at 5% conversion and supported Ru and Pt were inactive.

The role of catalyst pretreatment was investigated in the hydrogenation of benzofuran-2-carboxylic acid (**5a**). Prereduction of the catalyst stored in air before addition of the substrate was necessary to reduce the oxidized metal surface and thus avoid metal leaching by the acidic substrate. Already 5 min stirring in H_2 at room temperature in the solvent was sufficient to reduce the surface Pd oxides. In the hydrogenation of **5a** the best results were obtained when CD and the substrate were added together to the catalyst slurry after prereduction. When the modifier was added first to the prereduced catalyst and stirred for 2 min before addition of the substrate, the *ee* was not affected but the hydrogena-

Table 1
The role of solvent polarity in the hydrogenation of **1a** and **5a** under standard conditions (20 mL solvent)

Substrate	Solvent	E_T^N	Time (h)	Conversion (%)	*ee* (%)
 **1a**	H_2O	1.00	1	100	10
	AcOH	0.64	3	88	22
	2-Propanol	0.54	3	38	35
	3-Pentanone	0.27	3	19	39
	THF	0.21	3	12	42
	Toluene	0.10	3	83	31
 **5a**	AcOH	0.64	4	8	23
	2-Propanol	0.54	4	6	45
	3-Pentanone	0.27	4	3	34
	THF	0.21	4	3	19

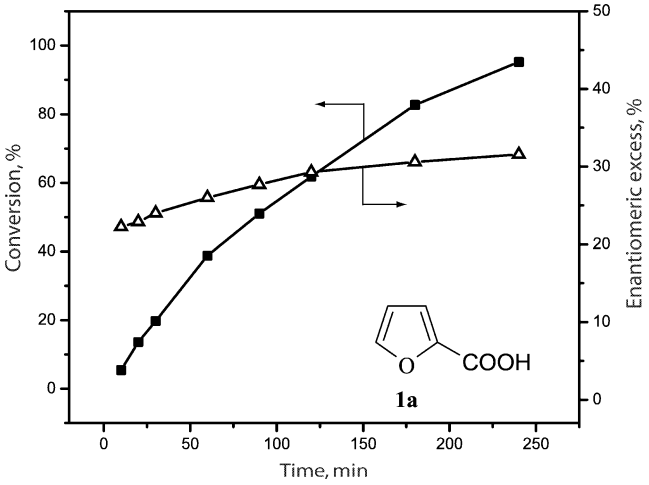


Fig. 1. Variation of *ee* with conversion in the hydrogenation of **1a**. Standard conditions, 20 mL toluene, S/M = 6.5.

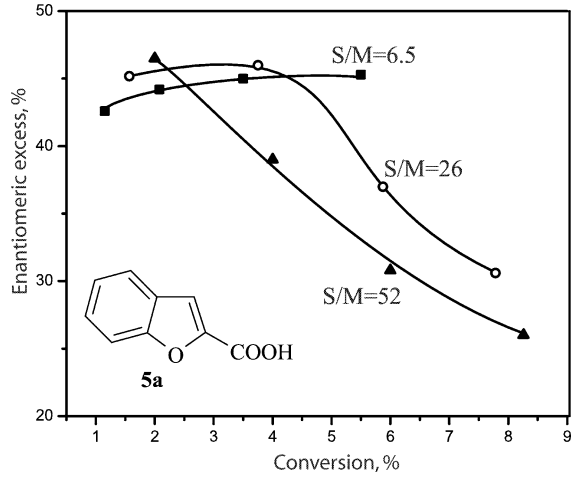


Fig. 2. Effect of substrate/modifier molar ratio (S/M) on the conversion dependence of *ee* in the hydrogenation of **5a**. Standard conditions, 10 mL 2-propanol, S/M = 6.5, 26, and 52 corresponding to 20, 5, and 2.5 mg CD, respectively.

tion rate dropped to less than one-half. In the reverse case, when adding first the substrate and stirring it with the pre-reduced catalyst for 2 min before adding the modifier, the *ee* decreased by 10–25%, compared to the reaction with simultaneous addition of the reaction components. The likely explanation for these effects is the strong, almost irreversible adsorption of CD and benzofuran-2-carboxylic acid on the Pd surface.

The reaction temperature and pressure had only a small influence on the catalyst efficiency. For example, in the hydrogenation of furan-2-carboxylic acid in toluene, the reaction rate increased with increasing temperature (10–40 °C), as expected, and the *ee* varied in a narrow range 31–36% with a maximum at 25 °C. Similarly, the hydrogenation rate increased at higher pressure in the range 5–30 bar and the *ee* barely changed. Higher pressures, however, were detrimental to the enantioselectivity: e.g., hydrogenation of benzofuran-2-carboxylic acid was attempted to accelerate by working at 85 bar but the *ee* dropped to about one-half. We assume that at this high pressure the quinoline ring of the modifier is rapidly hydrogenated, leading to a weaker adsorption of the modifier and a loss in *ee* [22,28]. This point will be discussed below. Accordingly, further experiments were carried out at room temperature and 30 bar (standard conditions).

The effect of solvent depended on the structure of the substrate as illustrated in Table 1 on two examples. In the hydrogenation of furan-2-carboxylic acid (**1a**), in most solvents except toluene, the *ee* increased with decreasing solvent polarity characterized by the empirical solvent parameter E_T^N [29], while the rate of conversion decreased. In the reduction of benzofuran-2-carboxylic acid (**5a**) the effect of solvent polarity on the reaction rate was similar but no clear correlation could be established between solvent polarity and *ee*. Note that toluene and water could not be used in the latter reaction due to the low solubility of the reactant. In the solvents tested, hydrogenation of **5a** was 5–15 times slower than that of **1a**. The difference is attributed to the stronger adsorption of **5a** on Pd, and to the larger number of Pd^0 sites covered by one molecule.

3.2. Competing hydrogenation of cinchonidine

The above parameter study was obscured by the sometimes strong variation of *ee* with conversion. For exam-

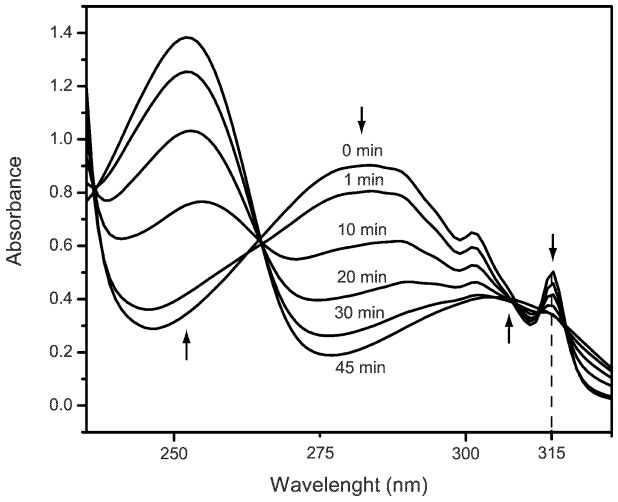


Fig. 3. Hydrogenation of CD over Pd/Al_2O_3 in the absence of substrate followed by UV–vis spectroscopy. Standard conditions, 10 mL 2-propanol.

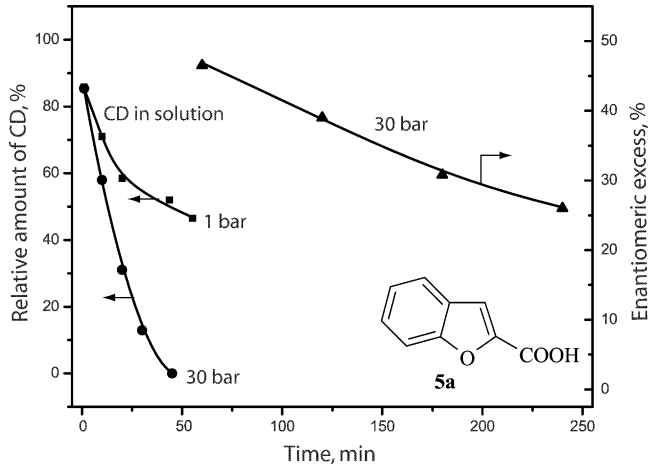
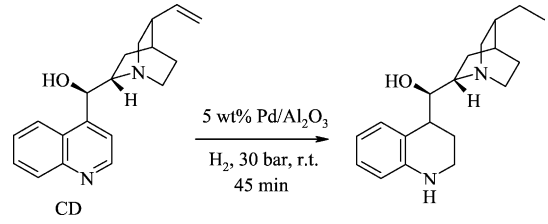


Fig. 4. Conversion of cinchonidine (CD) followed by UV–vis analysis and variation of *ee* with time in the hydrogenation of **5a**. Standard conditions, 10 mL 2-propanol, S/M = 52.



Scheme 3. Hydrogenation of cinchonidine (CD) over 5 wt% Pd/Al_2O_3 under standard conditions, in 2-propanol (S/M = 52).

ple, during hydrogenation of furan-2-carboxylic acid (**1a**) in toluene the *ee* slightly increased with conversion (Fig. 1), while it was constant in acetic acid (not shown). The conversion dependence of enantioselectivity was affected also by the substrate/modifier ratio as shown in Fig. 2 for the hydrogenation of benzofuran-2-carboxylic acid (**5a**).

Variation of *ee* with time and substrate/modifier ratio in solution is attributed to changes in the actual surface concentration of the modifier. The observation that *ee* increases with increasing modifier concentration is a common feature of all hydrogenation reactions over chirally modified metal catalysts [30]. In some cases this correlation is valid up to very high modifier concentrations [31], while in other reactions a maximum is observed [32]. A plausible explanation for the decay of *ee* at higher CD concentrations is the change of the adsorption mode of alkaloid on the metal surface which diminishes the *ee*.

Over Pd catalysts, hydrogenation of the quinoline ring system of CD is an important side reaction that weakens its adsorption on Pd and thus reduces the actual surface CD concentration with time [22,28]. As a consequence, the *ee* varies also with time (conversion). This effect is clearly indicated in Fig. 2 by the rapid loss of *ee* at the highest substrate/modifier molar ratio of 52, corresponding to the lowest modifier concentration. At higher modifier concentrations there is sufficient unreacted modifier in solution or on the support to replace the hydrogenated modifier on the metal surface, and thus the *ee* does not drop with increasing conversion, but may even increase by approaching the optimum surface concentration (S/M = 6.5). Note that hydrogenation of the vinyl group of CD is fast but this transformation has no influence on the enantioselection [33,34].

The rate and extent of the hydrogenation of CD were followed by UV–vis measurements, which method offers a sensitive detection of the (partial) saturation of the quinoline ring system that is the chromophore moiety of the alkaloid. Details of the method have been reported earlier [35,36]. The relative amount of modifier remaining in solution after filtering off the catalyst was determined by subtracting the reference spectrum of CD (initial solution, corresponding to 0 min) from the measured spectrum (Fig. 3). Since the band of partially hydrogenated CD (280–335 nm) is much broader than the characteristic band of CD (315 nm), quantification of CD concentration is not hindered.

Fig. 4 illustrates the consumption of CD on the 5 wt% Pd/Al_2O_3 catalyst in the presence of hydrogen. The experiment corresponding to a substrate/modifier molar ratio of 52 in 2-propanol, shown in Fig. 2, was repeated at 1 and 30 bar, but in the absence of benzofuran-2-carboxylic acid (**5a**). After 1 min preadsorption, in both cases 86% of the initial amount of CD remained in solution, the rest being adsorbed on the catalyst (starting point of the two CD hydrogenation curves in Fig. 4). At 30 bar no more alkaloid molecule remained in solution after 45 min, as illustrated in Figs. 3 and 4. However, it is very likely that at this point some unhydrogenated CD was present on the surface of Pd and Al_2O_3 support. As expected, the saturation of the quinoline ring of CD was much slower at 1 bar: 52% of the initial amount of CD was still present in solution after 45 min, as determined by UV–vis analysis (Fig. 4).

To confirm the transformation of CD, the experiment at 30 bar was repeated and after 45 min the solution was analyzed by NMR. In agreement with the UV–vis analysis, conversion of the alkaloid was complete and the only detectable

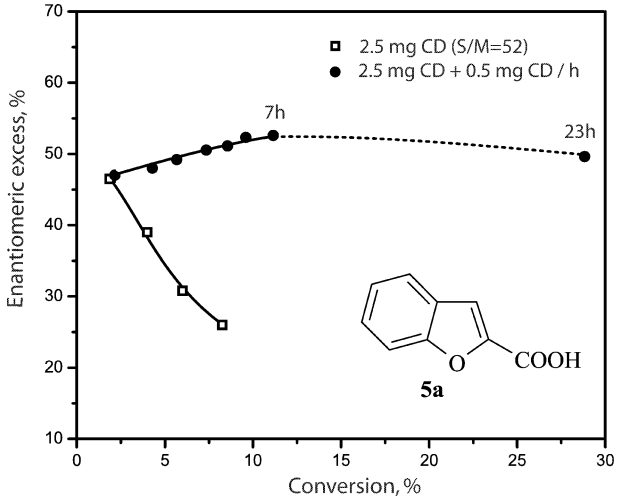


Fig. 5. Influence of feeding CD (0.5 mg/h) during hydrogenation of **5a**. Standard conditions, 10 mL 2-propanol, initial S/M = 52.

product was formed by saturation of the C=C double bond and the heteroaromatic ring (Scheme 3).

When both **5a** and CD were present in the reaction mixture, hydrogenation of CD was somewhat slower, due to competing adsorption of substrate and modifier on the Pd surface. For example, after 45 min there was still about 10% of the initial amount of CD present in solution. Note that in this series the analysis of CD consumption was less accurate as the signals overlapped and **5a** and 5**b** had to be separated from solution before analysis.

Using these data, interpretation of the decay of *ee* with time is straightforward. For convenience, the curve in Fig. 2 corresponding to a substrate/modifier molar ratio of 52 is replotted in Fig. 4. Clearly, the drop in *ee* is induced by the saturation of the quinoline ring system of CD, which is the anchoring moiety of the modifier providing fixed adsorption on the Pd surface [32,37–39]. The hydrogenated modifier is expected to adsorb weaker and thus afford lower *ee*. The calculated incremental *ee* was constant after 120 min at the level of 13–14%, confirming the assumption.

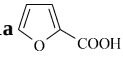
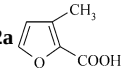
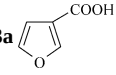
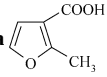
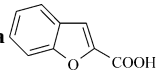
A practical solution to this difficulty is the feeding of small amounts of modifier to the reaction mixture [22,32]. For example, when starting the experiment with 2.5 mg CD, the *ee* dropped rapidly with the conversion of benzofuran-2-carboxylic acid (**5a**) (Fig. 5). Repeating the experiment with a stepwise feeding of 0.5 mg/h CD was sufficient to maintain the *ee* above the initial value even when feeding was ceased after 7 h. Under these conditions the overall substrate/modifier ratio was 22.

3.3. Effect of substrate structure

The efficiency of CD-modified Pd/Al_2O_3 in the hydrogenation of some furan and benzofuran carboxylic acids varied in a broad range (Table 2). Changing the carboxyl group from 2 to 3 position in the furan ring (**3a**) lowered the enantioselectivity but increased the reaction rate. This shift may be attributed to electronic effects as indicated by the different acidity of **3a** and **1a** ($pK_a = 3.16$ and 4.03, respectively) [40]. Assuming an acid-base type interaction between the substrate and the 1,2-aminoalcohol-type modifier (see below), this interaction is likely influenced by the pK_a value of the carboxyl group. Besides, the adsorption strength of the substrate on Pd may also depend on the acidity of the carboxyl function.

Insertion of a methyl group (**2a** and **4a**) slowed down the formation of tetrahydrofuran-carboxylic acids and lowered the *ee*. The low reactivity of trisubstituted C=C bonds on Pd and other hydrogenation catalysts is well known [41]. A further explanation for the loss in activity and selectivity is the

Table 2
Structural effects in the enantioselective hydrogenation of furan carboxylic acids[a]

Substrate	S/M molar ratio	Time (h)	Yield (%)	*ee* (%)	*de* (%)	Degree of rate deceleration[b]
1a 	6.5	2	22	36	–	4.5
	6.5[c]	4	95	32	–	–
	52	2	47	18	–	2.1
2a 	6.5	3	6	15	100	1.9
	6.5[d]	20	56	10	92	–
3a 	6.5	3	100	23	–	5.6
4a 	52	3	2	22	100	1.2
5a 	6.5	4	6	45	–	8.6
	22[e]	23	29	50	–	–
	52	1	2	47	–	3.2

[a] 0.446 mmol substrate, 10 mL 2-propanol, 40 mg 5% Pd/Al_2O_3, standard conditions.
[b] Initial rate of conversion in the absence of CD, related to the rate observed with CD.
[c] In 20 mL toluene.
[d] At 40 °C and 3 bar.
[e] CD is fed stepwise in the first 7 h.

steric hindrance by the methyl group against the interaction with the modifier. Two diastereomers (*cis* and *trans*) may be formed in the hydrogenation of **2a** and **4a** but under standard conditions only the two enantiomers of one diastereoisomer could be detected by GC analysis. In the hydrogenation of C=C double bonds the very high diastereoselectivity to the *cis* isomer over supported Pd, including cinchona-modified Pd/Al_2O_3, is not unusual [42–44]. To prove that really the thermodynamically less stable *cis* isomers were produced, the hydrogenation of **2a** was repeated under conditions that favor isomerization [45]. Increasing the temperature from 20 to 40 °C and lowering the surface hydrogen concentration by reducing the pressure from 30 to 3 bar decreased the diastereomeric excess (*de*) to 92% (Table 2).

The presence of the carboxyl function in the molecule was inevitable for achieving significant enantioselectivity, as indicated by the hydrogenation of the ester derivative **6a** (Scheme 2). Apparently, an acid-base interaction between the substrate and the basic quinuclidine N of CD is crucial in the enantio-differentiating step. A further limitation to the application range of cinchona-modified Pd is the failed hydrogenation of the analogous pyrrole derivative **7a** (Scheme 2). It is known that pyrrols are more resistant against hydrogenation than the corresponding benzene and furan derivatives [41].

Finally, in all reactions addition of CD resulted in a rate deceleration by a factor of 1.2 to 9; some examples are shown in Table 2. The lower reaction rate of C=C bond hydrogenation over Pd modified by cinchona or vinca alkaloids is apparently a general feature of these catalyst systems [31,46,47]. In fact, poisoning of Pd by strongly adsorbed N-heteroaromatic compounds, including quinoline, is well known [41].

3.4. Substrate–modifier interaction

As noted above, the complete loss of *ee* in the hydrogenation of **6a** indicates that the carboxyl function of furan carboxylic acids is involved in the substrate–modifier interaction. From this respect the hydrogenation of furan carboxylic acids resembles that of α,β-unsaturated carboxylic acids over cinchona-modified Pd. Two different models have been described for the latter reaction, involving 1:1 or 1:2-type interactions (Fig. 6). According to Nitta's model [48], the deprotonated carboxyl group interacts with the protonated quinuclidine N of CD. A second H-bond involving the OH function of CD stabilizes the structure of the complex on the metal surface. We proposed a 1:2-type interaction [19] that is supported by catalytic data, spectroscopic analysis, and ab initio calculations [43,49,50]. In this structure the unsaturated carboxylic acid, present as dimers in apolar medium, interacts via two H-bonds with the alkaloid modifier, as depicted in Fig. 6. Theoretical calculations revealed that the 1:1 model is less feasible due to steric hindrance against adsorption on the Pd surface. We assume that hydrogenation of furan carboxylic acids obeys an analogous mechanism that may be described by replacing the R (alkenyl) group in the substrate by a furyl group (Fig. 6). The validity of this model is currently under investigation in our laboratory.

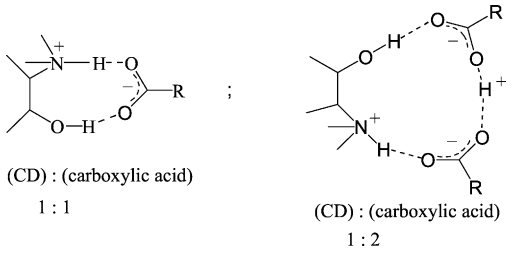


Fig. 6. Schematic representation of cinchonidine (CD)–alkenoic acid interactions involving 1:1 and 1:2 (acid dimer) structures.

4. Conclusions

Cinchona-modified Pd/Al_2O_3 is a moderately effective heterogeneous catalyst for the enantioselective hydrogenation of furan and benzofuran carboxylic acids. At room temperature and 30 bar, this catalyst system afforded 32% *ee* at full conversion of furan-2-carboxylic acid (**1a**) to its tetrahydro derivative **1b** (3 h, $S/M = 6.5$), or 50% *ee* at 29% conversion of benzofuran-2-carboxylic acid (**5a**) to its dihydro derivative **5b** (23 h, $S/M = 22$). In the latter reaction the slow hydrogenation of the quinoline rings of CD was compensated and the loss of *ee* prevented by the stepwise feeding of small amounts of CD. These *ee* values are the highest obtained so far in the asymmetric hydrogenation of furan derivatives [6]. Under standard conditions, at room temperature and 30 bar, hydrogenation of methylfuran carboxylic acids **2a** and **4a** afforded 100% *de* to the *cis* isomers. At higher temperature and lower hydrogen concentration (pressure) the diastereoselectivity decreased likely due to isomerization of a reaction intermediate.

A major limitation of cinchona-modified Pd is the competing hydrogenation of the alkaloid modifier, necessitating low substrate/modifier molar ratios (6.5–22). For comparison, in the hydrogenation of ketopantolactone only 4 ppm CD ($S/M = 237,000$) was sufficient to induce over 90% *ee* on Pt/Al_2O_3 [51].

We assume that the nature of substrate–modifier interaction on the Pd surface resembles that of alkenoic acid hydrogenation over cinchona-modified Pd. An important consequence of this analogy is that the method might be extended to the enantioselective hydrogenation of other aromatic carboxylic acids. Enantioselective hydrogenation of aromatic compounds is an unsolved, challenging problem.

Acknowledgment

Financial support by the Swiss National Science Foundation is gratefully acknowledged.

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