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Journal of Catalysis 230 (2005) 499–506
JOURNAL OF CATALYSIS
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Enantioselective hydrogenation of aromatic ketones over cinchona-modified rhodium: a new opportunity?

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Received 12 November 2004; revised 23 December 2004; accepted 10 January 2005

Abstract

Alumina-supported rhodium modified with cinchonidine has been investigated with regard to its applicability in the enantioselective hydrogenation of various aromatic ketones possessing an α-hydroxy or α-methoxy group. The study revealed that depending on the substrate, rhodium can outperform the catalytic behavior of platinum. With one of the substrates, 2-hydroxy-1-(4-methoxy-phenyl)-ethanone (**4**), an enantiomeric excess (*ee*) of 80% at 89% conversion was reached, which is the highest *ee* reported so far for chirally modified rhodium. However, completely different conditions are required to achieve optimal catalytic performance with rhodium, compared with platinum. Rhodium requires a much higher modifier concentration, and high hydrogen pressure is favorable. The higher modifier concentration required is traced to the much higher activity of rhodium for the hydrogenation of the quinoline ring, which is assumed to be the anchoring moiety of the cinchona modifiers on the platinum group metals. Changing the modifier from cinchonidine to *O*-phenoxy-cinchonidine resulted in a switch of the major enantiomer of the product, as exemplified for 2-hydroxyacetophenone (**1**), which showed a switch from 73% *ee* in favor of the (*R*)-product to 68% *ee* for the (*S*)-product when the modifier was changed from cinchonidine to *O*-phenoxy-cinchonidine.

1. Introduction

Among the various methods for preparing enantiopure compounds, catalysis is probably the most elegant and promising [1,2]. Though asymmetrical homogeneous catalysis has become an important tool in asymmetrical synthesis, relatively few catalytic enantioselective processes are currently used on a commercial scale [3]. Major problems in the scale-up are linked with cost effectiveness, process robustness, and separation and stability of the catalyst. In principle, heterogeneous catalysis could offer some interesting advantages, such as easier handling and separation of the catalyst and continuous process operation [4], which could be favorable for large-scale production. However, today only a few heterogeneous enantioselective catalysts are known that are sufficiently efficient for potential practical application; among them some heterogenized homogeneous catalysts [5] and chirally modified metals [6,7] seem most promising. Chirally modified nickel [8,9], platinum [10–12], and palladium [13,14] have emerged as effective heterogeneous asymmetrical catalysts for the enantioselective hydrogenation of specific substrates. Nevertheless, the scope of reactants that can be hydrogenated with high optical yield is still rather narrow, and it remains a major challenge to extend the application range of these catalysts. For this purpose it seems promising to examine the behavior of other platinum-group metals and that of new chiral modifiers. With this in mind we have explored the behavior of alumina-supported rhodium modified by cinchonidine and *O*-phenoxy-cinchonidine in the enantioselective hydrogenation of a series of aromatic ketones. Although chirally modified rhodium has been applied in earlier studies [15–20], the enantioselectivities reached were low or at best moderate. Here, for the first time, an example is shown where an enantiomeric excess of 80% at 89% conversion could

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0021-9517/$ – see front matter
doi:10.1016/j.jcat.2005.01.008

be achieved. The main features of the chirally modified rhodium are compared with that of the corresponding platinum system.

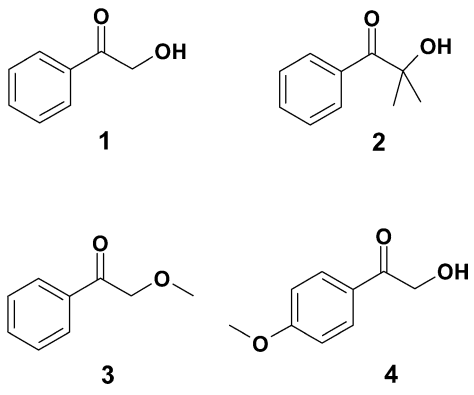
2. Experimental

All reactants (Scheme 1) and solvents were used as received: 2-hydroxyacetophenone (**1**) (Aldrich, 98%), 1-hydroxy-2-methylpropiophenone (**2**) (Aldrich, 97%), 2-methoxy-acetophenone (**3**) (Aldrich, 95%), 2-hydroxy-1-(4-methoxy-phenyl)-ethanone (**4**) (Bionet Research Ltd.), cinchonidine (CD) (Fluka), *O*-phenoxy-cinchonidine (PhOCD) (Ubichem, > 95%), *tert*-butylmethylether (*t*-BM-ether) (Fluka, > 99.5%), dioxane (Fluka, > 99.5%; over molecular sieve ($H_2O < 0.01\%$)), ethyl acetate (Merck, > 99.5%), THF (Riedel-de Haën, Spectranal, > 99.9%), and toluene (Fluka, > 99.7%).

The catalysts applied were 5 wt% Rh/Al_2O_3 (Engelhard 8001 ESCAT 34) and 5wt% Pt/Al_2O_3 (Engelhard 4759). Before use the catalysts were pre-reduced in flowing hydrogen for 90 min at 400 °C. The platinum dispersion was 0.27, as determined by TEM measurements. Textural and structural properties of the Rh/Al_2O_3 catalyst and the effect of the pretreatment have been reported in detail elsewhere [20].

The hydrogenation reactions up to 30 bar were carried out in a multiple reactor (Argonaut Technologies) equipped with eight 10-ml glass liners, which were mechanically stirred ($n = 500$ min^{-1}). Reactions above 30 bar were performed in a 100-ml stainless-steel autoclave equipped with a 50-ml glass liner and PTFE cover. The reactor was magnetically stirred ($n = 500$ min^{-1}). The pressure was held at a constant value with computerized constant volume–constant pressure equipment (Büchi BPC 9901). The standard reaction conditions were 21 ± 1 mg pre-reduced catalyst, 0.92 mmol reactant (0.46 mmol for reactant **1**), 6.8 μmol modifier, 5 ml solvent, a pressure of 20 bar, room temperature, and a reaction time of 6 h.

The conversions given in the tables and figures represent the total consumption of the ketons corresponding to all products (alcohol + by-products). Presentation of the total conversion was chosen because the amounts of by-products were generally low. The yields of the alcohols listed in Table 3 were calculated as yield = chemoselectivity to alcohol × conversion. The enantiomeric excess [*ee* (%) = $100 \times (|R - S|)/(R + S)$] was determined with the use of a Merck LaChrom HPLC System and a chiral column (Chiralcel OB or Chiralcel OD). The chromatographic separation was carried out at 15 °C and detection at 210 nm. We calibrated the detector by injecting mixtures of the reactant and the product of known compositions. The absolute configuration of the major enantiomer of phenylethane-1,2-diol (product of **1**) in the reaction with CD as a modifier was determined to be a (*R*)-enantiomer by comparison with the corresponding commercially available (*R*)-enantiomer (Fluka). The amounts of by-products were determined with a Thermo Finnigan Trace gas chromatograph (GC) with an Optima-5 (30 m × 0.25 mm; Macherey–Nagel) column. The ^{1}H NMR spectra were recorded on a Bruker Avance spectrometer operating at 500 MHz. Hydrogenation of CD was followed by UV–vis spectroscopy with a Cary 400 spectrometer and a 1-cm-path-length quartz cuvette. The conditions were as follows: 4 mg CD in 20 ml dioxane; 84 mg catalyst (Rh/Al_2O_3, Pt/Al_2O_3); hydrogen pressure, 5 and 90 bar, respectively. The samples were diluted with dioxane by a factor of 5 for UV–vis measurements.



Scheme 1. Overview of reactants.

Density functional theory (DFT) closed-shell calculations were performed with the use of Gaussian03 [21]. Complete optimization of all internal coordinates of the molecule was performed at the B3PW91 [22] level of theory with the use of the 6-31G(d,p) basis set [23]. The vibrational frequencies were calculated for several minimized structures. We simulated absorption and vibrational circular dichroism (VCD) spectra from calculated normal modes, dipole strengths, and rotational strengths, assuming Lorentzian band shape with a linewidth of four wavenumbers (half width at half-maximum).

VCD was used to determine the absolute configuration of the major enantiomer of the hydrogenation product of **4**. IR and VCD spectra were recorded on a Bruker PMA 50 accessory coupled to a Tensor 27 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at 1/4 retardation was used to modulate the handedness of the circular polarized light. Demodulation was performed with a lock-in amplifier (SR830 DSP). An optical low-pass filter (< 1800 cm^{-1}) put before the photoelastic modulator was used to enhance the signal/noise ratio. A transmission cell equipped with KBr windows and a 0.2-mm Teflon spacer was used. All solutions of product of **4** were prepared at a concentration of 10 mg in 500 μl CD_2Cl_2. A VCD spectrum of racemic product of **4** was subtracted from an enantioenriched sample of product of **4** (*ee* 80%) as obtained from the enantioselective hydrogenation over CD-modified Rh. We measured both the racemic and the enantioenriched samples at 4 cm^{-1} resolution by accumulating interferograms over 5 h in time slices of 1 h (total scans 21,500 for each racemic and enantioenriched sample). The spectra are pre-

sented without smoothing or further data processing. More information about the experimental procedure can be found elsewhere [24,25].

3. Results

To gain some information about the most suitable solvent, at first hydrogenation of reactants **1**–**4** (Scheme 1) was carried out in various solvents on the cinchonidine-modified Rh/Al_2O_3 (CD-Rh) catalyst. For comparison, with reactant **4** the corresponding CD-modified Pt/Al_2O_3 (CD–Pt) catalyst was applied as well (Table 1). Dioxane proved to be the most suitable solvent concerning *ee*. *tert*-Butylmethylether (*t*-BM-ether) and ethyl acetate showed somewhat lower *ee*, but higher conversion. A striking exception to the solvent behavior was observed with THF, which showed very low conversion for all hydrogenations performed on rhodium. The results are listed according to increasing E_T^N values (empirical parameter of solvent polarity) [26], a parameter that has been used previously for correlation with catalytic performance [27]. However, no significant tendency is discernible, indicating that in the present enantioselective hydrogenations the catalytic performance cannot be correlated with this parameter.

Based on the solvent screening results listed in Table 1, all further investigations were performed in dioxane, if not specified explicitly. The hydrogenations of substrates **1**–**4** all showed good chemoselectivity for the corresponding alcohols. By-products originated from hydrogenolysis of the C–O bond and/or saturation of the aromatic ring, as previously observed by Hess et al. [20]. At standard conditions the amount of by-products was minor (1.1–6.8%). However, at low CD concentrations a pronounced increase in by-products was observed. For instance, with reactant **1**, 13.4 and 36.0% by-products were detected at **1**/CD ratios of 1350 and 13,500, respectively. Thus the presence of modifier suppressed by-product formation strongly.

Table 2 shows the performance of CD–Rh under standard conditions. For reactants **1** and **3**, CD–Rh showed lower performance than the CD–Pt catalyst. Interestingly, with reactant **2**, *ee* and conversion were the same on both catalysts. For reactant **4** the *ee* was the same, whereas the conversion was higher on the CD–Rh system.

Next we investigated the influence of the modifier/substrate ratio on the catalytic performance. In these experiments the substrate concentration was kept constant, whereas the modifier (cinchonidine; for reactant **1** also *O*-phenoxy-cinchonidine) was varied. Fig. 1 shows the dependence of *ee* on the modifier/substrate ratio. With the CD–Rh catalyst the *ee* decreased steadily with a higher substrate/CD ratio. The strength of the decrease depended on the substrate. For the hydrogenation of **1** over the same catalyst, but modified by PhOCD (PhOCD–Rh), a similar tendency was observed. In contrast, hydrogenation of **4** over CD–Pt showed no decrease in *ee* up to a **4**/CD ratio of about 540, but also decreased strongly at higher substrate/modifier ratios.

The effect of the hydrogen pressure on *ee* and conversion in the hydrogenation of **1** over cinchonidine- and *O*-phenoxy-cinchonidine-modified rhodium is shown in Fig. 2. Enantiomeric excess and conversion increased up to 60 bar

Table 1
Influence of solvents on enantioselectivity and conversion for the hydrogenation of **1**–**4** over CD–Rh and **4** over CD–Pt

Reactant	Solvent	E_T^N [a] [26]	*ee* (%)	Conversion (%)
1	Toluene	0.10	16	40
	t-BM-Ether	0.15	39	40
	Dioxane	0.16	51	36
	THF	0.21	18	9
	Ethyl acetate	0.23	37	62
	Dichloromethane	0.31	3	48
	2-Propanol	0.55	23	99
	Acetic acid	0.65	3	100
2	Toluene	0.10	32	100
	t-BM-Ether	0.15	28	100
	Dioxane	0.16	44	21
	THF	0.21	–	0
	Ethyl acetate	0.23	31	100
	Dichloromethane	0.31	7	58
	2-Propanol	0.55	28	100
	Acetic acid	0.65	1	87
3	Toluene	0.10	21	13
	t-BM-Ether	0.15	29	33
	Dioxane	0.16	37	25
	THF	0.21	24	8
	Ethyl acetate	0.23	25	24
	2-Propanol	0.55	16	67
	Acetic acid	0.65	2	100
4	Dioxane	0.16	75	31
	THF	0.21	–	0
	Ethyl acetate	0.23	64	61
	Acetic acid	0.65	1	47
4 (Pt)	Dioxane	0.16	75	10
	THF	0.21	59	10
	Ethyl acetate	0.23	64	31
	Acetic acid	0.65	3	24

Standard conditions: 21 mg catalyst, 0.92 mmol reactant (0.46 mmol for reactant **1**), 6.8 μmol CD, 5 ml solvent, 20 bar, room temperature (21 °C), and 6 h reaction time.
[a] Empirical parameter of solvent polarity.

Table 2
Performance of CD–Rh in the enantioselective hydrogenation of **1**–**4** under standard reaction conditions with dioxane as solvent. For comparison the performance of the corresponding CD–Pt catalyst is also given

Reactant	CD–Rh		CD–Pt	
	Conversion (%)	*ee* (%)	Conversion (%)	*ee* (%)
1	35.5	50.5	41.3	70.2
2	21.2	44.0	21.3	44.3
3	20.0	36.9	20.4	68.8
4	30.5	75.0	10.2	75.2

Standard conditions are specified in Table 1. The data characterizing the performance of CD–Pt in the hydrogenation of reactants **1**–**3** are taken from [35].

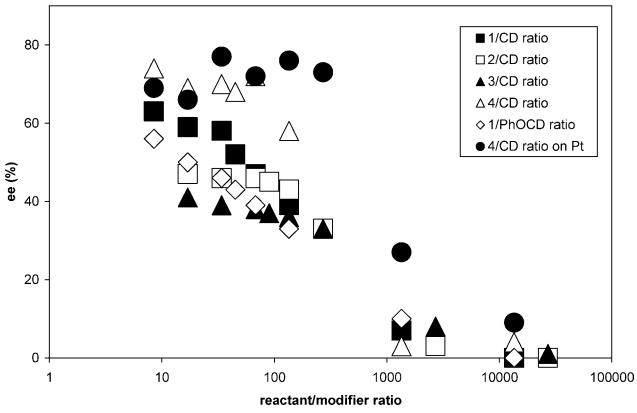


Fig. 1. Enantiomeric excess of **1**, **2**, **3**, and **4** over CD or PhOCD modified Rh/Al_2O_3 and **4** over CD modified Pt/Al_2O_3 as a function of reactant/modifer ratio. Reaction conditions: 21 mg catalyst, 0.92 mmol reactant (0.46 mmol for reactant **1**), 5 ml solvent, 20 bar, room temperature, and 6 h reaction time.

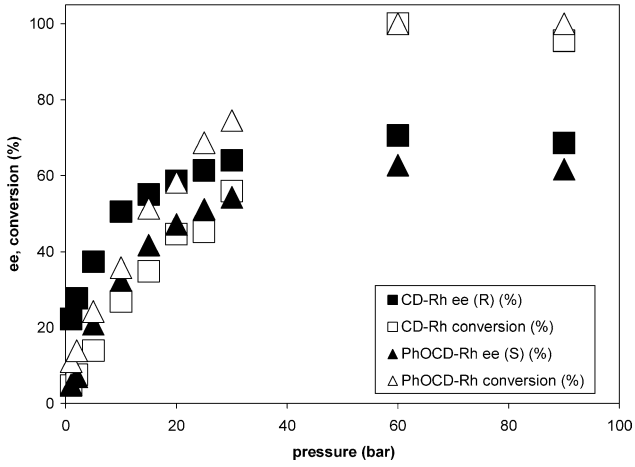


Fig. 2. Dependence of enantiomeric excess and conversion of **1** over CD or PhOCD modified Rh/Al_2O_3 on hydrogen pressure. Reaction conditions: 54.4 µmol modifier, other conditions as in Fig. 1.

with both modifiers, CD and PhOCD. However, a striking difference is that PhOCD–Rh favored the opposite enantiomer ((*S*)- instead of (*R*)-product) over CD–Rh. The *ee* in the hydrogenation of reactants **2** and **3** indicated only little dependence on pressure, whereas conversion steadily increased, reaching a plateau at around 30 bar. The pressure dependence of the hydrogenation of **4** has been investigated on both CD–Rh and CD–Pt (Fig. 3). The difference in behavior is striking. With CD–Rh the *ee* increased up to 10 bar and remained virtually constant at this level up to 90 bar. The corresponding conversion increased monotonically over the whole pressure range of 2–90 bar. This contrasts with the behavior of CD–Pt, for which the *ee* decreased with increasing pressure, whereas the conversion reached a plateau at pressures greater than 5 bar.

Table 3 compares the catalytic performance of the CD–Rh and CD–Pt systems under conditions that led to the best results. Note that an extensive optimization was not carried out, leaving the possibility for further improvement. In general higher *ee*'s were achieved with CD–Pt. Interestingly, for reactant **4** the same *ee* (80%) was achieved on both CD–Rh and CD–Pt. However, the corresponding difference in conversion is striking: 89% over the CD–Rh compared with 4% over CD–Pt. Note the remarkable differences in the conditions (modifier concentration, hydrogen pressure) required to reach best performance for the rhodium and platinum system.

Hydrogenations performed with **1** and PhOCD as a chiral modifier afforded the (*S*)-product as the major enantiomer, independently of the metal catalyst used. This

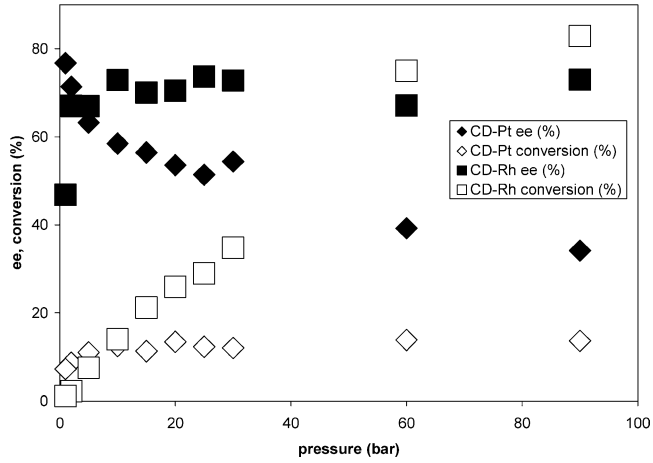


Fig. 3. Dependence of enantiomeric excess and conversion of **4** over CD modified Pt/Al_2O_3 or Rh/Al_2O_3 as a function of hydrogen pressure. Reaction conditions: 3.4 µmol CD (Pt/Al_2O_3), 54.4 µmol CD (Rh/Al_2O_3), other conditions as in Fig. 1.

Table 3
Comparison of catalytic performance of rhodium and platinum modified with CD or PhOCD in the hydrogenation of **1**–**4** under optimised reaction conditions

Reactant	Modifier (µmol)	Pressure (bar)	Conversion (%)	Yield alcohol (%)	*ee* (*R*, %)
			CD–Rh		
1	54.4	60	82.0	78.8	73.1
2	54.4	30	32.1	31.5	51.2
3	54.4	90	68.2	64.5	63.6
4	54.4	90	88.4	86.9	80.4
			CD–Pt		
1	3.4	5	52.6	49.1	82.3
2	6.8	5	61.6	60.5	56.6
3	6.8	5	69.3	64.3	81.1
4[a]	3.4	5	4.0	3.9	78.9
			PhOCD–Rh		
1	54.4	60	99.2	92.3	68.4 (*S*)
			PhOCD–Pt		
1[b]	6.8	5	57.4	54.6	34.5 (*S*)

Rhodium-catalysed hydrogenations were performed in dioxane at 15 °C and 6 h reaction time. Platinum-catalysed hydrogenations were carried out in *t*-BM-ether at 0 °C and 6 h reaction time.
[a] Reaction performed in dioxane at 15 °C.
[b] Reaction performed in *t*-BM-ether at 21 °C.

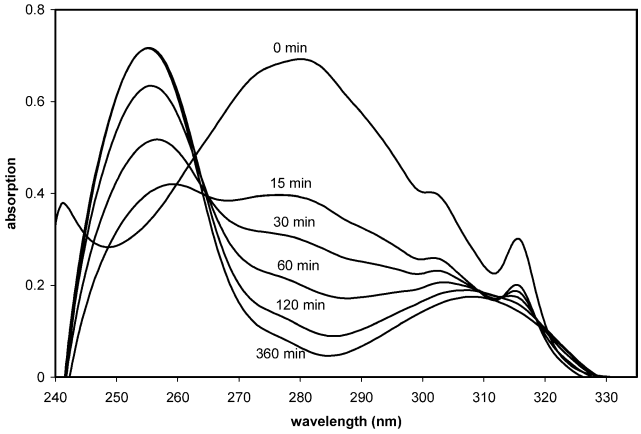


Fig. 4. Hydrogenation of the quinoline ring of CD over Rh/Al_2O_3 at 90 bar followed by UV–vis. Reaction conditions: 3.4 µmol CD, other conditions as in Fig. 1.

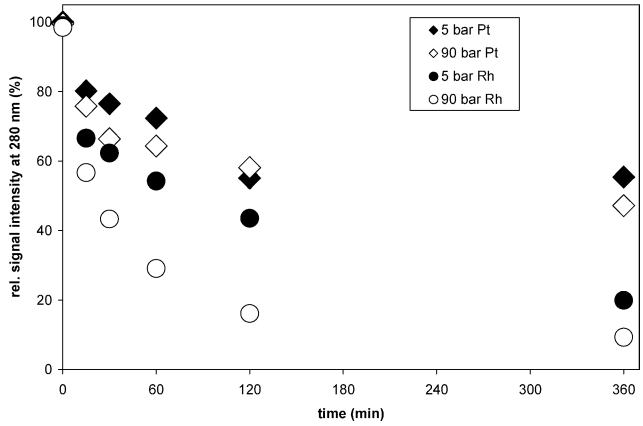


Fig. 5. Time dependence of decrease of CD concentration in solution during hydrogenation over Rh and Pt. Absorption at 280 nm was taken as a measure of CD concentration. Reaction conditions: 3.4 µmol CD, 21 mg catalyst, 5 ml dioxane, 5 or 90 bar H_2.

change in enantioselectivity when cinchonidine is replaced by *O*-phenyl-cinchonidine had been observed earlier in the platinum-catalyzed hydrogenation of ketopantolactone [28]. Particularly striking is the behavior of the rhodium-catalyzed reaction, where almost similar *ee*'s (73, 68%) were achieved for the (*R*)- and (*S*)-enantiomer of the product with CD and PhOCD, respectively.

With reactant **4**, ^{1}H NMR spectra were recorded for d_8-dioxane to see if the keto or the enol form prevails in solution. The experiments were carried out with the following mixtures, mimicking reaction conditions: (i) 7.6 mg **4** in 0.5 ml dioxane; (ii) 7.6 mg **4**, 0.1 mg CD in 0.5 ml dioxane; and (iii) 7.6 mg **4**, 2 mg CD in 0.5 ml dioxane. In all reaction mixtures (i)–(iii) only the keto form could be observed.

3.1. Hydrogenation of cinchonidine over rhodium and platinum

The hydrogenation of the aromatic quinoline ring of CD, which is known to be the anchoring group on Pt [29–31], was investigated over both Rh/Al_2O_3 and Pt/Al_2O_3 under conditions similar to those used in the enantioselective hydrogenation of substrates **1**–**4** (3.4 µmol CD, 5 ml dioxane, 5 and 90 bar H_2, respectively). From observation of the intensity of the absorption at 280 nm, indicative of the aromatic quinoline ring, the hydrogenation of CD could be followed. Fig. 4 shows UV–vis spectra for CD (0 min) and spectra for CD and its hydrogenation products after different time intervals. Note that 3.4 µmol CD is hydrogenated quite quickly over Rh at 90 bar. Fig. 5 shows a decrease in the intensity of the absorption at 280 nm versus time, which is a measure for the hydrogenation rate of the quinoline ring of CD. It emerges from Fig. 5 that the hydrogenation rate was much faster on rhodium than on platinum. The hydrogenation rate increased in the following order: 5 bar Pt < 90 bar Pt < 5 bar Rh < 90 bar Rh. After hydrogenation of CD at 90 bar (H_2) for 360 min, over Rh/Al_2O_3 about 5 times less CD existed in solution compared with the corresponding experiment with Pt/Al_2O_3 as a catalyst. This behavior was less drastic for hydrogenations performed at 5 bar, where 2.8 times less CD existed in solution for the rhodium-catalyzed hydrogenation than with the platinum-catalyzed reaction after 360 min. NMR analysis from a reaction solution where 54.4 µmol CD was hydrogenated at 90 bar for 360 min over rhodium (optimum condition for reactant **4**) showed about equal amounts of CD and fully hydrogenated CD (quinoline ring fully hydrogenated). Partially hydrogenated CD (1,2,3,4-tetrahydroquinoline) was found as a minor species.

*3.2. Determination of the absolute configuration of alcohol produced from 2-hydroxy-1-(4-methoxy-phenyl)-ethanone (**4**)*

Vibrational circular dichroism (VCD) has recently emerged as a reliable technique for assigning the absolute configuration of chiral samples in solution [24,25,32–34]. This strategy relies on the comparison between theoretical and calculated spectra and has become possible since the calculation of VCD spectra of organic molecules has predictive character. As a first step the most stable conformers have to be determined. DFT calculations showed that the alcohol of **4** is relatively flexible, adopting multiple minima. The relevant degrees of freedom are the position of the methoxy group, torsions around two C–C bonds, and the position of the hydroxyl hydrogens. It turned out that the two possible positions of the methoxy group have only a minor effect on stability. The CH_2OH group prefers the position out of the aromatic plane of the molecule, and the O–H groups form a hydrogen bond, where each group can act as donor or acceptor. We have located eight stable conformers. The most stable four of them are shown in Fig. 6. The other four conformers are at least 1.4 kcal/mol less stable than the most stable conformer and are thus expected to be barely detectable at room temperature.

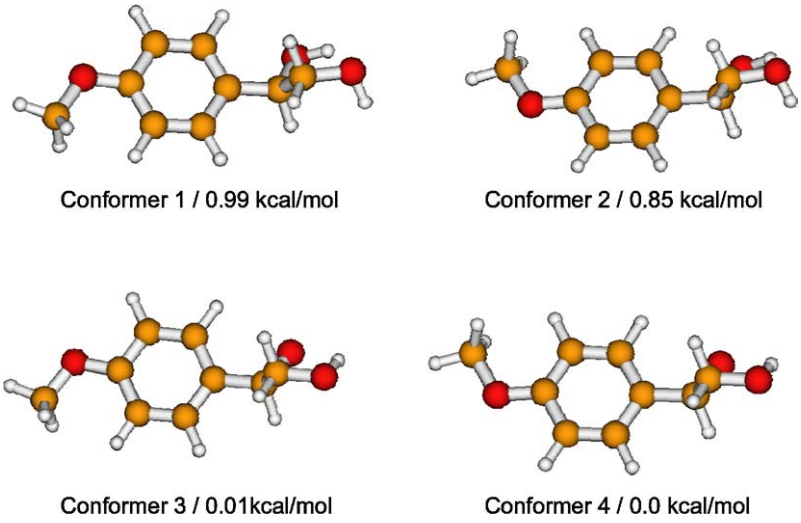


Fig. 6. Structure of the four most stable conformers of the alcohol produced by hydrogenation of **4**, calculated by DFT B3PW91 using a 6-31G(d,p) basis set. The energies are relative to the most stable conformer **4**.

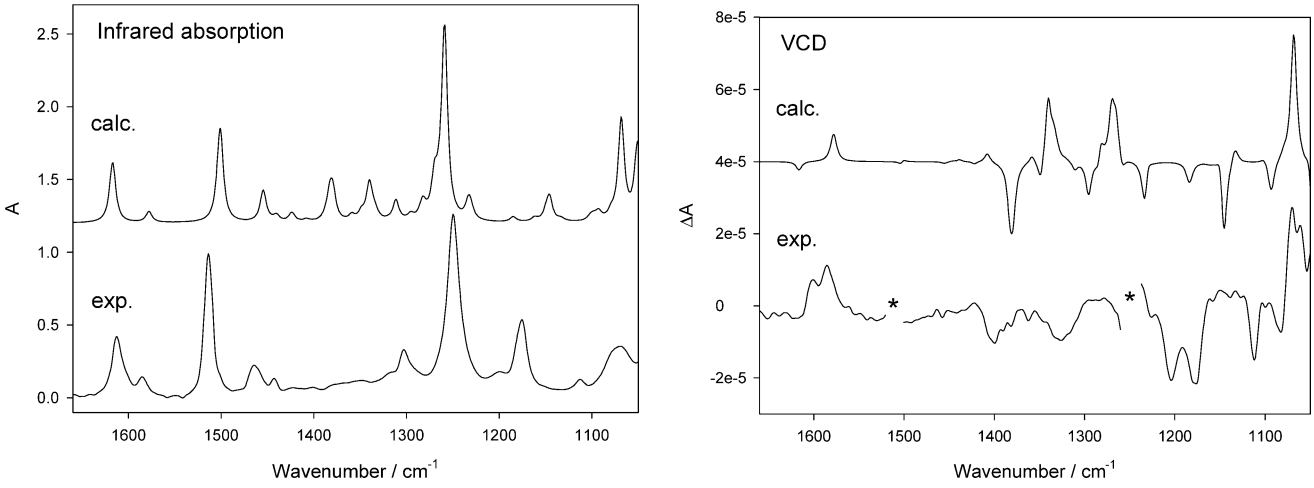


Fig. 7. Experimental and calculated infrared absorption and vibrational circular dichroism (VCD) spectra. The calculated spectra represent the Boltzmann average of the calculated spectra of the four most stable conformers (Fig. 6). The experimental spectra were recorded from solutions of 10 mg/500 µl CD_2Cl_2 with a path length of 0.2 mm. Asterisks in the experimental VCD spectra represent two regions where the infrared absorption was too high to reliably measure the VCD signal.

Fig. 7 shows a comparison of the experimental and calculated infrared absorption and VCD spectra. The calculated spectra were obtained from the calculated spectra of the individual conformers (considering only the four most stable ones); these were weighed by the appropriate Boltzmann factor at 298 K. The agreement between experimental and calculated infrared spectra is reasonable, considering the relatively large flexibility of the molecule. Some bands can be unequivocally assigned, such as the relatively weak band slightly below 1600 cm^{-1} associated with a ring deformation mode. This latter mode is actually not sensitive to conformation. This is also true for the calculated VCD spectra for the conformers shown in Fig. 6, for which the latter band is always positive. In the experiment this band is also positive. Since the calculations were performed for the (*R*)-enantiomer, the results presented above show that the hydrogenation over CD-modified Pt provides the (*R*)-enantiomer in excess. Furthermore, the region below 1250 cm^{-1} with a number of negative bands leaves no doubt about the assignment of the absolute configuration. Note that VCD spectra of enantiomers have an opposite sign but are otherwise identical. It should be noted that the VCD signals are rather small, in agreement with the relatively large flexibility of the molecule, but the spectral features can be reproduced very well.

4. Discussion

The present study of the enantioselective hydrogenation of different α-hydroxy or α-methoxy ketones indicates that cinchona-modified rhodium can in certain cases show a su-

perior catalytic behavior compared with platinum. This is exemplified by the hydrogenation of reactant **4**, in which an *ee* of 80% was achieved at 89% total conversion (Table 3). Over platinum at slightly lower *ee* the conversion was only 4%. It is very likely that **4** is hydrogenated in the keto form, even at high CD concentration, because the corresponding enol could not be observed in the ^{1}H NMR experiments. The behavior of rhodium when it is modified with PhOCD in the hydrogenation of **1** is striking (Table 3). Platinum is far less suitable for this reaction than rhodium, with respect to both *ee* and conversion. With reactant **2**, *ee* and conversion are higher on the Pt system under optimized conditions (Table 3), whereas under standard conditions the performances of the two metals were similar. Under both optimized and standard conditions in the hydrogenation of **3**, the *ee* was higher on platinum, whereas the conversion was the same with the two systems.

The fact that a comparison of the catalytic behaviors of the two metals provides a changing picture, depending on whether standard (Table 2) or optimized conditions (Table 3) are used, indicates that the most suitable conditions are greatly different for rhodium than for platinum. Generally, the modifier concentration that is necessary for rhodium (Table 3) is much higher than that needed for platinum. This also emerges when the dependence of the *ee* on the reactant/modifer ratio is compared, as shown for reactant **4** in Fig. 1. For rhodium, the *ee* decreased steadily with increasing reactant/modifier ratio. This tendency was observed for all reactants **1**–**4**, although the loss in *ee* was different, depending on the reactant. In contrast with platinum, a broad maximum for the reactant/modifier ratio was observed and the decrease in *ee* set in at a much higher reactant/modifier ratio (Fig. 1). This behavior of the platinum system had already been observed for reactants **1**–**4** in a previous study [35].

Remarkable differences between the rhodium- and platinum-catalyzed reactions are also evident from the investigated hydrogen pressure dependences. Fig. 2, which compares the hydrogen pressure dependence of *ee* and conversion on rhodium modified with CD and PhOCD for the hydrogenation of **1**, shows that both *ee* and conversion increase steadily with higher pressure, independently of the modifier used. For reactant **4** a somewhat different behavior was observed (Fig. 3); the *ee* reached a constant value at about 10 bar, whereas conversion increased steadily with hydrogen pressure. Thus the pressure dependence of *ee* seems to vary depending on the reactant, whereas the increase in conversion with higher pressure appears to be a more common feature. The pressure dependence of the rhodium-catalyzed hydrogenations shows significant differences compared with that of corresponding platinum-catalyzed reactions. This emerges from a comparison of the present results with corresponding earlier investigations of the platinum-catalyzed reactions [35]. Fig. 3 illustrates this behavior with the example of the hydrogenation of reactant **4**. The most striking difference is that with rhodium, conversion increased steadily to the highest pressure (90 bar), whereas with platinum, above ca. 10 bar conversion was hardly affected by the hydrogen pressure. In addition, the pressure dependence of *ee* shows significantly different behavior; with rhodium the *ee* increases and reaches a constant level at a pressure lower than 10 bar, whereas with platinum the *ee* decreases steadily with increasing pressure.

The functional group in the α-position to the carbonyl plays a crucial role in the enantioselection. This has already been stated by Vargas et al. based on theoretical calculations [36], and it has been shown for reactant **1** experimentally [35]. A comparison of the *ee* of reactant **4** (79%, CD–Pt) with the *ee* of 4′-methoxyacetophenone (11%) reported in an earlier study [37] corroborates this finding.

Finally, the present work indicates that rhodium chirally modified by cinchona alkaloids can provide considerably better catalytic performance in enantioselective hydrogenation then previously reported. Further work toward a deeper understanding of this system may lead to new opportunities in heterogeneous asymmetrical hydrogenation.

5. Conclusions

Rhodium has been shown to be an interesting candidate for the extension of the range of cinchona-modified metal catalysts for enantioselective hydrogenation. This emerges from a comparison of the hydrogenations of reactants **1**–**4** on rhodium and platinum. In some cases, rhodium showed superior catalytic behavior compared with platinum, indicating that extending the range of metals suitable for heterogeneous enantioselective hydrogenation may be rewarding. A problem is that considerably different conditions have to be applied for these metals to provide optimal performance. It seems that with rhodium, the modifier concentration and hydrogen pressure needed to reach optimal catalytic behavior are higher than those required to reach optimal behavior with platinum. Specifically, for the α-hydroxy ketones studied in this work, low CD concentration and low hydrogen pressure are most suitable for the platinum-catalyzed hydrogenations, whereas with rhodium high CD concentration and high pressure are optimal. Moreover, the choice of the optimal solvent depends on the metal applied. A disturbing property of rhodium is its much higher activity in the hydrogenation of the aromatic quinoline ring in cinchona-type modifiers. Saturation of this anchoring group and the accompanying loss of adsorption strength may explain the much higher concentration of modifier required for the rhodium-catalyzed hydrogenations. The findings of this study corroborate the importance of adjusting and tuning of all parameters of the chirally modified metal system for achieving best catalytic performance. It is hoped that a better understanding of the important interactions occurring in these systems may pave the way to more efficient and versatile chirally modified metal catalysts.

Acknowledgments

Financial support by the Swiss National Science Foundation is gratefully acknowledged. The Swiss National Supercomputer Centre (CSCS) in Manno is acknowledged for computing time.

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