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Influence of a remote hydroxy group in the ligand on the reactivity of a chiral hydrogenation catalyst

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Abstract: A kinetic study concerning the asymmetric hydrogenation of prochiral olefins by chiral diphosphine rhodium cyclooctadiene complexes based on HO-DIOPs is presented. The investigations have been carried out in order to show the influence of a remote hydroxy group on the rate of the reaction. Since in methanol under standard conditions the reactivities of all catalysts elaborated were too high, the hydrogenation experiments have been performed under reduced hydrogen pressure affording the desired reduction in rate. To avoid the induction period caused by the hydrogenation of the cyclooctadiene all precatalysts were prehydrogenated before the prochiral substrates were added. For comparison analogous Rh–DIOP complexes with the same structural framework, but without the hydroxy group in the backbone have been proven. For all hydroxy catalysts investigated a lower reactivity has been observed compared to the parent complexes, although a direct interaction between HO-group and reaction center can be presumably excluded. This assumption is supported by the X-ray structural analysis of one of the complexes which shows the remote position of the HO-group related to the metal center.

Introduction

One of the most fascinating features in homogenous metal catalyzed asymmetric synthesis is relations between structure, enantioselectivity and reactivity of chiral catalysts. It is obvious that the high thermodynamic stability of single stereoisomeric intermediates in the catalytic cycle does not always lead to high selectivity. One of the most prominent examples was discovered by Halpern in the mechanism of the asymmetric hydrogenation of *N*-acyl dehydroamino acids by a selected diphosphine rhodium complex.[1] In this reaction, the configuration of the chiral product derives from the thermodynamically less stable diastereomeric substrate–catalyst complex (*minor* complex) and is exclusively governed by its superior reactivity with hydrogen. Recently, in another approach, Sharpless and co-workers disclosed the concept of ligand accelerated catalysis (LAC).[2] They showed that among rapidly occurring ligand exchange processes a single chiral ligand may successfully compete for the catalytically active metal. This selection process can be supported by the chelate effect. However, it should be noted that also in this case LAC will be only observed when the 'kinetic activity' of the catalyst giving the highest *ee* is superior to those of the other complexes. Unfortunately, up to now this desired result could not be predicted[3] and therefore prevented a rational ligand design.

To our knowledge, little is known about the influence of attractive secondary interactions (e.g. hydrogen bonds) between ligand and metal or substrate, respectively, on the rate and enantioselectivity

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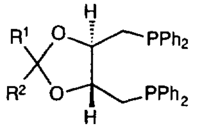
of catalytic reactions, although the high efficiency of enzymes is attributed to these type of interactions.[4] In recent contributions we and others showed that the introduction of a hydroxy group into a conventional chiral hydrogenation catalyst gives rise to a change in the enantiodifferentiating ability of the catalyst.[5] Thus, in some cases the selectivity of the parent catalyst could be improved. A similar result was achieved by the substitution of a methoxy by the hydroxy group.[6] In several examples investigated the change in selectivity was accompanied by a lowering of the reaction rate. It seems that both effects depend on the spatial position of the hydroxy group.[7] Most pronounced effects were observed with flexible ligands giving the hydroxy group the opportunity to establish a strong interaction with the metal or the substrate, respectively, during the catalytic cycle.[8] However, it is remarkable that also those complexes wherein the rigid construction of the ligands prevents the direct interaction of the hydroxy group with the catalytic center exhibited a different behaviour compared to the parent catalysts.[5a] Obviously, the effect is caused by intramolecular interactions, since applying catalysts without HO-groups in alcohols as solvents for the hydrogenation it could not be observed.[9]

Diphosphines carrying the hydroxy group in a rigid backbone are (*R*,*R*)-HO-DIOPs **1a**, **2a**, **3a**.[10] These ligands are related to (*R*,*R*)-DIOP (**1b**) synthesized for the first time by Kagan and co-worker.[11] Recently, we compared the Rh-complexes based on these hydroxy-ligands with the corresponding parent complexes **1b**, **2b**, **3b** in the hydrogenation of different substrates.[10b]



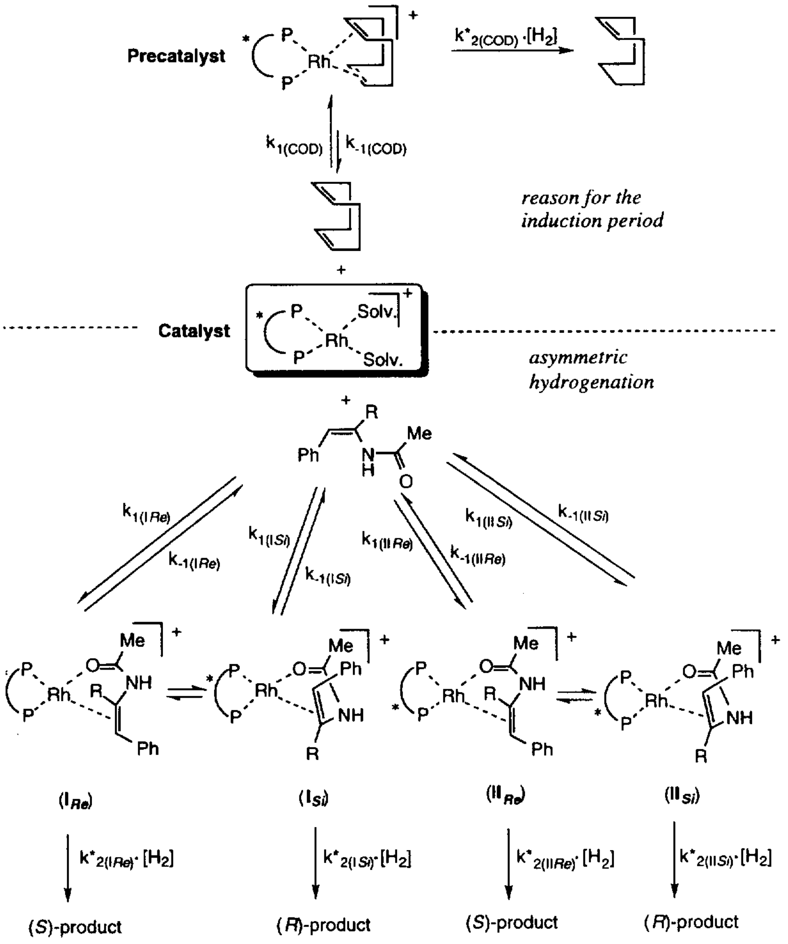
	R^1	R^2	
1a	CH_3	CH_2OH	
1b	CH_3	CH_3	**(DIOP)**
2a	C_6H_5	CH_2OH	
2b	C_6H_5	CH_3	
3a	H	C_6H_4-2-OH	
3b	H	C_6H_5	

In methanol as solvent the effects described above expressed by increased but also diminished selectivities were less pronounced, whereas differences by up to 16% *ee* have been observed in CH_2Cl_2 or toluene. However due to the different solubilities of the precatalysts or the substrates in these nonpolar solvents a reliable comparison of the reactivity between HO-catalyst and parent complex could not be performed. Unfortunately, in methanol applying standard conditions (catalyst/substrate ratio of 1/100, 0.01 mmol catalyst, 1 atm total pressure) the rates were too high for our standard hydrogenation plant and the reactions influenced by diffusion.

Another problem was faced by the concomitant hydrogenation of cyclooctadiene, because precatalysts of the type $[Rh(P\text{–}P)(COD)]BF_4$ were used. Thus, due to the high stability constants of the precatalysts a considerable, time dependent amount of the catalytically active species $[Rh(P\text{–}P)(MeOH)_2]BF_4$ was not available for the asymmetric hydrogenation of the prochiral substrate.[12] In Scheme 1 the main reaction pathways of the asymmetric hydrogenation of a prochiral olefin with a C_1 symmetric Rh–COD complex[13] are shown. Particular attention is devoted to the prehydrogenation of the cyclooctadiene.

Our recent investigations on a range of several Rh–COD-precatalysts revealed that only the beginning of the hydrogenation is influenced by this effect which is indicated by a short induction period.[12] In contrast to these findings preliminary studies with the rhodium COD complexes based on ligands of the type **1**–**3** showed that even in cases of slowly reacting substrates (e.g. dimethyl itaconate) a considerable amount of the precatalyst remained unchanged after complete conversion of the educt. In Figure 1 a typical example of a hydrogenation curve registered is depicted. For comparison the amounts of unconverted COD are indicated, which were determined by sampling and subsequent GC-analysis.

In this contribution we report that prehydrogenation of the COD and investigations under reduced H_2-partial pressure allow the exact measurement of the hydrogenation rate of prochiral substrates such as (Z)-2-*N*-acetamido cinnamic acid (AH) or its corresponding methyl ester (AMe). These experiments afforded reliable information concerning the influence of the hydroxy group on the rate of the hydrogenation.



R = $COOCH_3$, $k_{2i} = k_{2i}^* \cdot [H_2]$ under isobaric conditions

Scheme 1. Asymmetric hydrogenation of methyl (*Z*)-2-*N*-acetamido cinnamate (AMe) with a chiral cationic Rh-catalyst based on a C_1 symmetric ligand under particular consideration of the concomitant COD hydrogenation.213.

Results and discussion

*X-Ray structural analysis of [Rh(**1a**)(COD)]BF$_4$*

To get a better idea about the spatial position of the hydroxy group in the precatalysts considered the inspection of the X-ray structure seems to be advantageous. Suitable crystals of [Rh(**1a**)(COD)]BF_4 could be obtained by slow crystallization from a mixture of MeOH/diethyl ether. In Figure 2 the molecular structure along with selected bond lengths and angles is shown.[14] The picture illustrates clearly the remote position of the hydroxy group. The coordination mode observed is in accordance with similar rhodium complexes that form seven-membered rings and contain COD as an ancillary ligand.[15] Neither intermolecular nor intramolecular interactions between rhodium and hydroxy group were observed. This result is in agreement with recent IR investigations on HO-DIOP–rhodium complexes.[10b] Obviously, due to this arrangement interactions of the hydroxy group with the metal also in solution could be excluded by means of NMR.[10b]

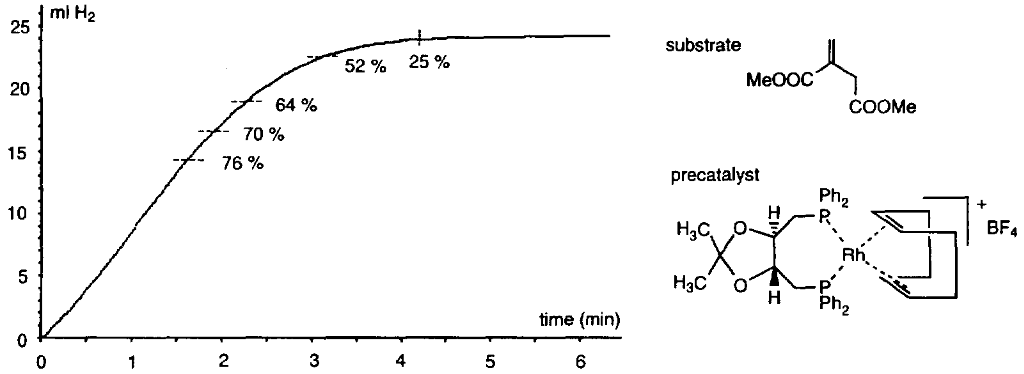


Figure 1. Hydrogenation of dimethyl itaconate with $[Rh((R,R)\text{-DIOP})(COD)]BF_4$ under standard conditions (catalyst/substrate ratio of 1/100, 0.01 mmol catalyst, 1 atm total pressure). Values attached to the curve indicate the percentage of the unconverted COD.

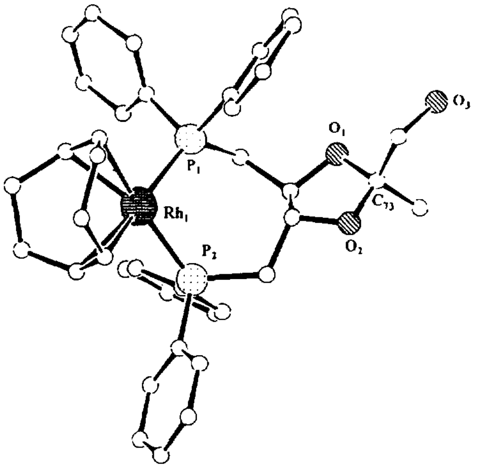


Figure 2. Molecular structure of the cation of $[Rh(\mathbf{1a})(COD)]BF_4$ in the crystal as determined by X-ray crystal structure analysis. Selected bond lengths [Å] and angles [°]: P(1)–Rh(1) 2.338(3), P(2)–Rh(1) 2.318(3); P(2)–Rh(1)–P(1) 93.23(1), O(1)–C(73)–O(2) 106.2(9), O(3)–C(74)–C(73) 106.4(16).

Kinetic studies

The hydrogenations were carried out at 25°C with an argon/hydrogen mixture containing 9.71% H_2. As expected, also under these conditions the hydrogenation of the prochiral olefin is accompanied by the hydrogenation of the COD. Thus, for the precatalyst based on **1a** and AH as substrate after complete formation of *N*-acetyl-phenylalanine approximately 37% of COD could be still detected. To avoid this induction period the precatalyst was pretreated for 30 min with pure undiluted H_2 under normal pressure before the prochiral substrate was added. Taking the rate constant of the COD hydrogenation into account[12] the time chosen was sufficient to convert the whole amount of the COD-complex into the catalytically active species.

Our quantitative analysis of the product proportional H_2 consumption is based on the assumptions of Halpern and co-workers for the asymmetric hydrogenation and the corresponding kinetic equations.[1c] In extension of these studies we have shown recently that in case of disturbed intermolecular preequilibria or intramolecular exchange processes consisting of diastereomeric substrate complexes[16]

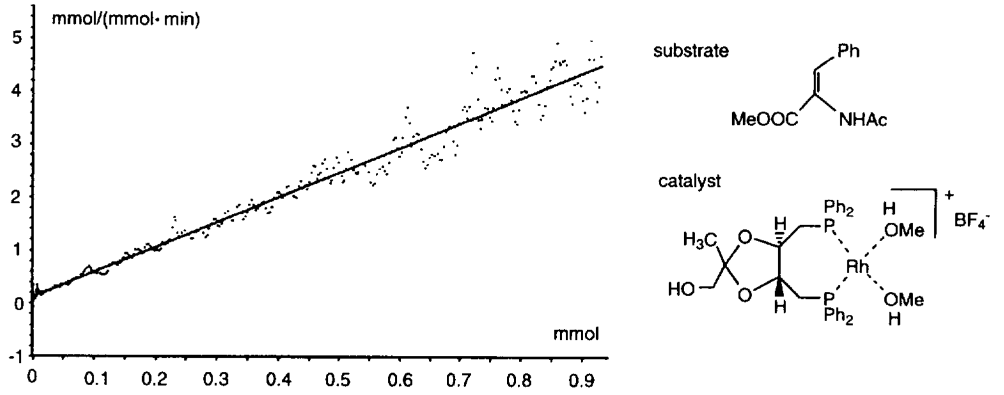


Figure 3. Hanes-plot of the asymmetric hydrogenation of methyl (*Z*)-2-*N*-acetamido cinnamate (AMe) in MeOH with $[Rh(\mathbf{1a})(MeOH)_2]BF_4$ as catalyst applying a H_2 partial pressure of 62 Torr.

as well as by application of C_1 symmetric ligands, the basic equation of the Michaelis–Menten-relation is valid.[17]

$$\frac{dH_2}{dt} = \frac{k_{obs.} \cdot E_0 \cdot S}{K_M + S} \qquad \textbf{(Equation 1)}$$

(K_M=Michaelis constant, $k_{obs.}$=brutto rate constant, E_0=initial catalyst concentration, S=concentration of the noncoordinated substrate)

Although in dependence of the specific catalytic system, the physical meanings of the macroscopic constants $k_{obs.}$ and K_M are different, a uniform interpretation is possible. The value of $1/K_M$ corresponds in all models to the ratio of the concentrations being the sum of all catalyst substrate complexes and the product E·S under stationary conditions. The $k_{obs.}$ values as activity are characterized as the quotient of the maximal accessible rate divided by the applied catalyst concentration [$k_{obs.}=(r_{max}/E_0)$]. Thus, $k_{obs.}$ represents the sum of all rate constants of the oxidative addition of hydrogen, each multiplied with the molar fraction of the catalyst–substrate complex.

For the nonlinear regression of Equation 1 the rates of the H_2 uptake (r_{H2}) at the time t were determined by numerical differentiation of the temporal H_2-consumption. Based on the substrate balance (S_0=S+P) taking into account that the prochiral olefin can be present in the reaction mixture either as enantiomeric product (P) or as uncoordinated substrate (S) the concentration of the later at time t was calculated.[18] The determination of the starting parameters for the nonlinear regression was carried out by linearization. For one example Figure 3 shows the so-called Hanes-plot.[19] In this linearization of Equation 1 the quotient S/r is plotted as a function of S.

The results obtained for the activity ($k_{obs.}$) are illustrated in Figure 4. The most important feature of this correlation is the inferior activity measured for all catalysts bearing hydroxy groups (**1a**,**2a**,**3a**) compared to the parent complexes (**1b**,**2b**,**3b**). Although the hydroxy group is spatially so arranged that direct interaction with the reaction center can be excluded, it causes a decelerating effect.[20] It should be noted that these results are independent of the degree and direction contributed by the HO-group to the overall enantioselectivity of the catalyst.[21]

Up to this date, the reason for this unique behaviour is not clear. As pointed out above, the value of $k_{obs.}$ corresponds to the sum of all rate constants for the oxidative addition step each multiplied by the molar fraction of the corresponding catalyst–substrate-complex concentration. Changes of $k_{obs.}$ can therefore only be observed if the ratios of the concentrations of the substrate complexes[22] or the ratio of the rate constants k_{2i} to each other are changed. In other words, the remote HO-group has either an influence on the equilibria of the formation of the catalyst–substrate complexes or on the rate

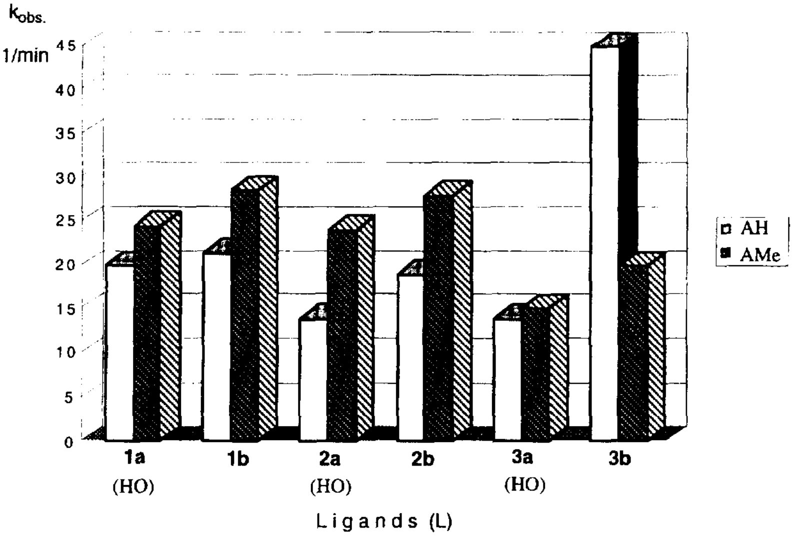


Figure 4. Activity ($k_{obs.}$ values) of catalysts of the type $[Rh(L)(MeOH)_2]BF_4$ (L=**1a**–**3b**) in the asymmetric hydrogenation of (*Z*)-2-*N*-acetamido cinnamic acid (AH) and methyl (*Z*)-2-*N*-acetamido cinnamate (AMe) in MeOH at a H_2 partial pressure of 62 Torr

determining step of the oxidative addition of hydrogen. The simultaneous influence on both processes is likewise possible.

Another interesting feature derived from Figure 4 concerns the comparison of the hydrogenation activity for the substrate-ester (AMe) and the corresponding acid (AH). Thus, with the exception of the complex derived from **3b** the ester was always reduced faster than the corresponding acid. This result is in contrast to several experiences[23] and remains to be clarified in further investigations.

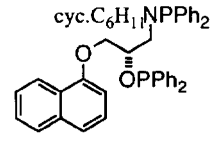
In summary, we have shown that a remote hydroxy group in chiral diphosphine rhodium complexes has a significant influence on the rate of the hydrogenation. Without exception all DIOP-complexes bearing the hydroxy group were less active than the corresponding parent complexes. This result attracts particular attention since due to its spatial position the hydroxy group cannot establish a strong interaction with the catalytic center. Tentatively, we attribute this effect to interactions mediated by solvent molecules.[24] Other investigations on related chiral hydroxy phosphines are in progress.

Experimental section

The basic construction of the apparatus for the investigation of gas consuming reactions under isobaric conditions and *reduced pressure* of the reactive gas was described previously.[25b] In this arrangement the gas phase over the reaction solution and the gas buret are separated by a bubble counter preventing the mixing of gases of different hydrogen content. The gas buret contained pure hydrogen, whereas the gas phase over the reaction mixure was filled with the gas mixture (hydrogen/argon) commercially available. During the hydrogenation only the hydrogen consumed was supplied from the gas buret. To avoid the formation of a concentration gradient the bubble counter was placed directly above the reaction mixture in the gas phase of the hydrogenation vessel. Additionally, vigorous stirring was required.

In order to test the precedingly described apparatus the catalytic hydrogenation of COD or NBD (norbornadiene) with rhodium complexes based on 7-membered ring chelates was utilized,[12] which shows an easy to evaluate Michaelis–Menten kinetic in the saturation domain. The slope of the measured straight-line corresponds to the maximal rate ($r_{max.}$) and is directly proportional to the product of the H_2 concentration in the solution $[H_2]$ and to the diolefin-complex concentration [cat].

Table 1. Rate constants ($k_{obs.}$) for the diolefin hydrogenation with catalysts of the type $[Rh(L)(Diolefin)]BF_4$ at different H_2 partial pressures and 25°C[27,28]

Ligand (L)	Diolefin	$k_{obs.}$ (1/min) 638 Torr H_2[a]	$k_{obs.}$ (1/min) 62 Torr H_2[b]
$Ph_2P(CH_2)_4PPh_2$	norbornadiene	1.51	0.15
 (Ref. 27)	cyclooctadiene	5.44	0.52

[a] Normal pressure under consideration of the vapour pressure of MeOH at 25 °C. (Ref. 28)

[b] Commercial Ar/H_2-mixture (AGA) was used containing 9.71 % of H_2.

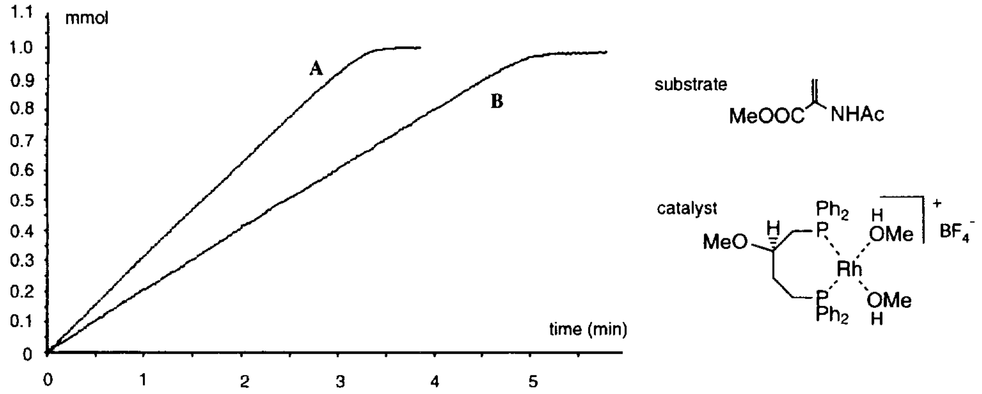


Figure 5. Asymmetric hydrogenation of methyl 2-*N*-acetamido acrylate (aMe) with [Rh((*S*)-1,4-bis(diphenylphosphino)-2-methoxybutane)$(MeOH)_2$]BF_4 (Ref. 6) under normal and reduced hydrogen pressure. (**A**: 638 Torr H_2, 0.005 mmol precatalyst, 1.0 mmol aMe, 25°C; $k_{obs.}$=65 1/min, K_M=720 l/mol. **B**: 62 Torr H_2, 0.033 mmol precatalyst, 1.0 mmol aMe, 25°C; $k_{obs.}$=6.32 1/min, K_M=695 l/mol

The latter corresponds to the initial precatalyst concentration because of its high stability constant ($r_{max.}=k_{obs.}\cdot cat_0 \cdot H_2$).[26] By validity of Henry's law the H_2-concentration in solution is directly proportional to the H_2-partial pressure over the solution. In Table 1 the results for two catalysts — more suitable than complexes based on HO-DIOPs — of the hydrogenation under normal and under reduced pressure are summarized. The comparison gives proof for the reliablity of the results obtained with the working technique described above for the investigation of the hydrogenation under reduced H_2-pressure at isobaric conditions. The catalytic systems utilized exhibit a similar behaviour as the precatalysts described above.

Obviously, as to be seen in Figure 5 with the proposed technique also hydrogenations with rates of approx. 5 ml/min can be measured without the influence of diffusion.

Hydrogenations

The experiments have been carried out under normal pressure and isobaric conditions with an automatically registrating gas measuring device (1.0 atm overall pressure over the solution. The correction of the atmospheric pressure serving as reference was carried out by application of the software CANALYS.). The basic construction and the performance of the hydrogenation experiments have been described previously.[25a,12b] The experiments were carried out under standard conditions with 0.01 mmol precatalyst, 1.0 mmol of prochiral olefin in 15 ml solvent at 25°C. Since it was necessary to prehydrogenate the precatalysts (*vide supra*), the prochiral olefin in 1.0 ml of MeOH was fused in a glass ampulla considering strictly anaerobic conditions. To start the hydrogenation of the prochiral olefin after completion of the COD hydrogenation and thermic equilibration (vapour pressure and H_2-solubility) the ampulla was destroyed by the magnetic stirrer.

Substrates

Commercially available AH or AMe, prepared according to the literature[29] was recrystallized under Ar. *cis,cis*-Cycloocta-1,5-diene (COD) and norborna-2,5-diene (NBD) have been dried with CaH_2 and distilled under Ar.

Analysis

The conversion of COD and the prochiral olefins was determined by GC. AH was esterified with trimethylsilyl diazomethane before the GC-measurements. GC 5890 Serie II; FID, Carrier gas: Ar: 1 ml/min. AMe: fused silica; 10 m, XE-60-L-valin-tert.butylamide; ID 0.2 mm; oven temperature: 150°C.

Acknowledgements

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13. Since four stereoisomeric catalyst–substrate complexes are possible, the formation of one enantiomeric product may result from two independent pathways. For the corresponding DIOP-complex

Rh(**1b**)(COD)]BF_4 the number of the possible diastereomeric complexes is divided by two due to its C_2 symmetry.

14. X-Ray structural analysis of [Rh(**1a**)(COD)]BF_4: STOE-IPDS-Diffractometer, graphite monochromated Mo–Kα-radiation, λ=0.71069 Å, structure solution with direct methods (SHELXS-86: Sheldrick, G. M. *Acta Crystallogr. Sect. A* **1990**, *46*, 467), refinement against F^2 (SHELXL-93: Sheldrick, G. M. unpublished), structure representation: Schakal-92, red-orange prism, 0.5×0.4×0.3 mm, space group P1 triclinic, a=11.045(2), b=11.707(2), c=17.183(3) Å, V=1862.8(6) $Å^3$, Z=2, $\rho_{calc.}$=1.448 g cm^{-3}, 5583 collected, 5583 unique reflections, 4925 observed [$I=2\sigma(I)$], R=0.049, wR^2 (all data)=0.128, 837 parameters. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at Cambridge Crystallographic Data Centre. Copies of the data can be obtained from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (Telefax: Int. +44 1223/3 36 0 33; Email: teched@chemcrys.cam.ac.uk).
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21. In general, the HO-group bearing catalysts with the ligands **1a**, **2a**, **3a** were superior in the hydrogenation of AMe compared to the parent catalysts, whereas in the case of AH the *ee*-differences were not significant (Ref. 10b).
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24. Since trifunctional substrates have been hydrogenated, direct interactions with suitable situated functional groups of the substrate (e.g. carboxylic group) and the HO-group of the ligand cannot be excluded. Such interactions may occur by hydrogen bonds or other attractive interactions, respectively. However, due to the small differences in the catalytic performance of HO-catalyst and parent catalysts basic changes in the hydrogenation mechanism are unlikely (e.g. changed coordination mode of the substrate).
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