Solvent dependent asymmetric hydrogenation with self-assembled catalysts: a combined catalytic, NMR- and IR-study†

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For the first time the hydrogen bond based structure of self-aggregated Rh–phosphine complexes in fluorinated alcohols was directly determined, which gives a rationale for the high enantioselectivity observed in the asymmetric hydrogenation.

The effect of monodentate *versus* bidentate phosphorus ligands in metal-catalyzed asymmetric hydrogenation is a matter of controversial discussions in the literature.[1] In general chelating ligands are reputed to display higher stereodiscriminating properties. However, catalysts bearing bulky monodentate ligands have also been shown as highly stereoselective.[2] Unfortunately, the comparison of ligands differing strongly in steric and/or electronic properties does not really contribute to the final clarification of this issue. Some more clarity can be expected from the comparison of similar ligands under similar reaction conditions. In this connection we are interested in the solvent dependent structure of self-assembling catalysts.[3,4] Due to their particular construction originally monodentate phosphorus ligands are able to aggregate through hydrogen bonds in the coordination sphere of a metal and thus "pseudo"-chelating ligands are formed.[5] Clearly, the formation of the desired self-assembling architecture is dependent on the solvent.[5d,f] Polar solvents with strong hydrogen bonding accepting properties should interrupt the formation of the weak intramolecular interactions, whereas nonpolar solvents have a stabilizing effect.

In a recent study on the enantioselective hydrogenation with cationic Rh-complexes based on chiral 2-pyridone-phosphino ligands we noted high enantioselectivity in CH_2Cl_2 as solvent.[5d] In contrast, in methanol the catalysts induced poor ee-values. In general slow conversion took place. Superior effects on activity and stereoselectivity were found in 2,2,2-trifluoroethanol (TFE), 2-fluoroethanol and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[6a] illustrating the unique features of fluorinated alcohols, in particular high polarity, but low hydrogen bond acceptor properties.[6] ^{31}P-NMR spectroscopic investigations showed two resonances in the nonpolar solvent and in fluorinated alcohols, indicating the presence of two different phosphorus nuclei. This feature gave us a hint for the hydrogen bond based chelating structure of the ligands, where one phosphorus atom is connected to a 2-pyridinol unit and the other is part of a 2-pyridone backbone. In order to support this indirect evidence, herein we will report on a combined catalytic and spectroscopic study, including IR-investigations, which will give unambiguous proof for the chelating nature of ligands in these catalysts.[7]

We have chosen phospholane **1** and phosphepine **2**, previously described,[5d] as ligands for the Rh-catalyzed asymmetric hydrogenation capable of self-assembly. Precatalysts were prepared by reaction of $[Rh(COD)_2]BF_4$ (COD = 1,5-cyclooctadiene) with two equivalents of ligand. The hydrogenations were conducted in methanol, CH_2Cl_2 or trifluoroethanol or mixtures thereof under isobaric (1 bar) conditions. Results of the catalytic transformation using the benchmark substrates methyl *Z*-α-*N*-acetamidocinnamate (**3a**) and dimethyl itaconate (**3b**) are detailed in Table 1. In general ee-values obtained with the bulky phosphepine ligand **2** are higher than those induced with phospholane **1**. Highest enantioselectivity of 99% was observed with dimethyl itaconate as substrate in CH_2Cl_2 (run 21). As clearly shown irrespective of the ligand used in methanol low ee-values were yielded (runs 1, 7, 13 and 16). Moreover, long reaction times were required to achieve complete conversion. In contrast, in CH_2Cl_2 high activities and ee-values are noted (runs 3, 9 and 21). Similarly superior ee-values and very fast reactions were measured in pure CF_3CH_2OH (runs 2, 8, 14, 17). Interestingly also in mixtures of fluorinated alcohol and methanol the catalysts displayed high activity and enantioselectivity. Even a ratio of CH_3OH–CF_3CH_2OH 1 : 1 was sufficient to maintain the beneficial effect of the fluorinated alcohol (ee up to 94%, runs 11, 19). Further dilution with methanol led to a lowering of the enantioselectivity (runs 4, 10, 15, 18). It is worthy of note that the addition of CF_3CH_2OH to CH_2Cl_2 accelerated the reaction, but did not affect the high enantioselectivity (run 22).

Our hypothesis was that in CH_2Cl_2 and in the fluorinated alcohol, hydrogen bonds within the catalyst generate a "pseudo"-chelating structure, whereas in methanol this architecture is destroyed. Due to the similar catalytic results the hydrogen bonding assembly should be maintained also in mixtures of CF_3CH_2OH–CH_3OH. In order to confirm this assumption, a sample of the precatalyst $[Rh(COD)(\mathbf{1})_2]BF_4$ dissolved in mixtures of CF_3CD_2OD and CD_3OD was investigated by $^{31}P\{^1H\}$-NMR spectroscopy.

Indeed, the spectra in CF_3CD_2OD–CD_3OD mixtures showed a similar signal pattern characterized by a doublet of doublets as found in $CDCl_3$[5d] and pure CF_3CD_2OD[6a] [δ 52.0 (dd, $J(^{31}P–^{103}Rh)$ = 147 Hz, $J(^{31}P–^{31}P)$ = 36 Hz) and δ 50.4

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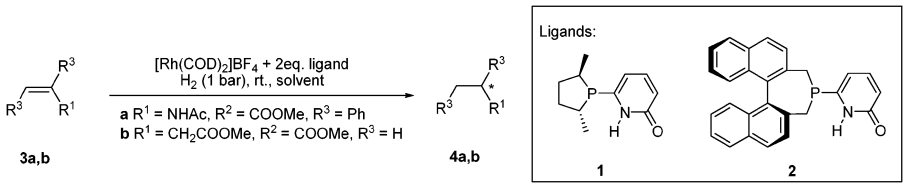
Table 1 Results of the enantioselective hydrogenation in different solvents



Run	Ligand	Substrate	Solvent	Conversion (%)	t/min^{-1}	ee (%)
1	**1**[a]	**3a**	CH_3OH	20	1300[e]	13 (*R*)[c,e]
2	**1**[a]	**3a**	CF_3CH_2OH	100	1200[e]	68 (*R*)[c,e]
3	**1**[a]	**3a**	CH_2Cl_2	100	1200[e]	69 (*R*)[c,e]
4	**1**[a]	**3a**	CH_3OH–CF_3CH_2OH (3 : 1)	100	1300	49 (*R*)[c]
5	**1**[a]	**3a**	CH_3OH–CF_3CH_2OH (1 : 1)	100	1300	57 (*R*)[c]
6	**1**[a]	**3a**	CH_3OH–CF_3CH_2OH (1 : 3)	100	1300	63 (*R*)[c]
7	**2**[b]	**3a**	CH_3OH	100	60[e]	64 (*R*)[c,e]
8	**2**[b]	**3a**	CF_3CH_2OH	100	10[e]	95 (*R*)[c,e]
9	**2**[b]	**3a**	CH_2Cl_2	100	10[e]	94 (*R*)[c,e]
10	**2**[b]	**3a**	CH_3OH–CF_3CH_2OH (3 : 1)	100	10	87 (*R*)[c]
11	**2**[b]	**3a**	CH_3OH–CF_3CH_2OH (1 : 1)	100	10	94 (*R*)[c]
12	**2**[b]	**3a**	CH_3OH–CF_3CH_2OH (1 : 3)	100	10	95 (*R*)[c]
13	**1**[a]	**3b**	CH_3OH	100	1300[e]	rac[d,e]
14	**1**[a]	**3b**	CF_3CH_2OH	100	1300[e]	68 (*S*)[d,e]
15	**1**[a]	**3b**	CH_3OH–CF_3CH_2OH (3 : 1)	100	1300	31 (*S*)[d]
16	**2**[b]	**3b**	CH_3OH	100	60[e]	64 (*S*)[d,e]
17	**2**[b]	**3b**	CF_3CH_2OH	100	10[e]	97 (*S*)[d,e]
18	**2**[b]	**3b**	CH_3OH–CF_3CH_2OH (3 : 1)	100	60	78 (*S*)[d]
19	**2**[b]	**3b**	CH_3OH–CF_3CH_2OH (1 : 1)	100	15	94 (*S*)[d]
20	**2**[b]	**3b**	CH_3OH–CF_3CH_2OH (1 : 3)	100	10	96 (*S*)[d]
21	**2**[b]	**3b**	CH_2Cl_2	100	20[e]	99 (*S*)[d,e]
22	**2**[b]	**3b**	CH_2Cl_2–CF_3CH_2OH (1 : 1)	100	12	98 (*S*)[d]

[a] Substrate–catalyst = 50 : 1, 7.5 ml solvent. [b] Substrate–catalyst = 100 : 1, 7.5 ml solvent. [c] Determined by GC, 25 m γ-cyclodextrin, Lipodex E (Machery and Nagel), fused silica, 130 °C. [d] Determined by GC, 25 m γ-cyclodextrin, Lipodex E (Machery and Nagel), fused silica, 70 °C. [e] Values derived from ref. 5*d*.

($J(^{31}P–^{103}Rh)$ = 140 Hz, $J(^{31}P–^{31}P)$ = 36 Hz], indicating that the chelating species is still present, but the amount is reduced depending on the concentration of methanol (Fig. 1).

In order to get information on the hydrogen bonds IR-investigations were performed. For comparison the tautomeric model system 2-hydroxypyridine–2-pyridone (**5a,b**) was also studied.[7] The measured IR-spectra together with the relevant calculated spectrum are shown in Fig. 2.

Ab initio calculations at the B3LYP level[8] on the model system **5a,b** reveal that only the pyridine form **5a** contributes to the CO-stretching vibration ν_{CO} whereas the tautomeric

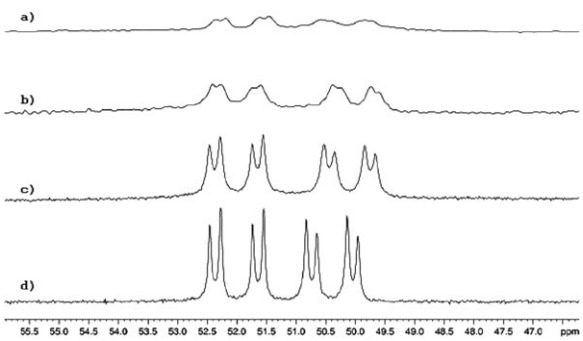


Fig. 1 $^{31}P\{^1H\}$-NMR (202.4 MHz) spectrum of $[Rh(COD)(\mathbf{1})_2]BF_4$ in mixtures of CF_3CD_2OD–CD_3OD at 0 °C. (a) CF_3CD_2OD–CD_3OD = 1 : 3; (b) CF_3CD_2OD–CD_3OD = 1 : 1; (c) CF_3CD_2OD–CD_3OD = 3 : 1, (d) CF_3CD_2OD.

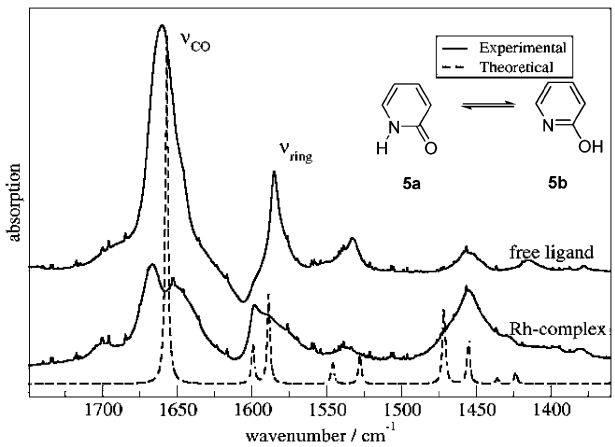
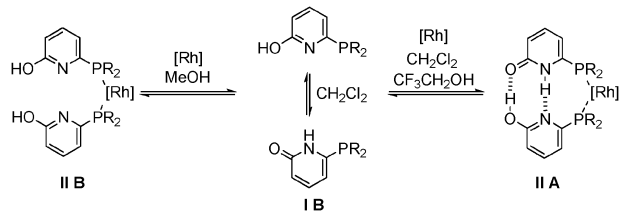


Fig. 2 IR-spectra of the free ligand **1** and $[Rh(COD)(\mathbf{1})_2]BF_4$ in CH_2Cl_2 at 25 °C. The dotted line gives the B3LYP 6-31+G* calculated IR-spectrum for the tautomeric equilibrium **5a–b** for comparison.

pyridinol (**5b**) gives large contributions at slightly different wavenumbers to ν_{ring}. By inspection of the measured IR-spectrum of the free ligand **1** in CH_2Cl_2 it can be therefore concluded that the pyridone structure of **IB** (Scheme 1) is the dominant species. When the complex $[Rh(COD)(\mathbf{1})_2]BF_4$ is formed, both tautomers of the ligand are present in solution (Scheme 1, **IIA**). This can be concluded from the reduced



Scheme 1 Self-assembly of two monodentate 6-phosphino-2-pyridone ligands with rhodium in dependence on the solvent.

intensity of the band of ν_{CO} and the broadening of the band for ν_{ring}. Also the increasing band at 1455 cm^{-1} is due to the presence of the pyridinol form.

Because of the strong solvent absorption from 1500 cm^{-1} down to lower wavenumbers it was not possible to examine the same spectral range for the alcoholic solutions. Therefore it is advantageous to focus on ν_{CO} and the ring mode ν_{ring} around 1590 cm^{-1}. The free ligand **1** exists in both tautomeric forms **IB** in methanol as well as in TFE (Fig. 3, Scheme 1). In TFE in comparison with methanol ν_{CO} is shifted to lower wavenumbers. This observation illustrates the excellent hydrogen bond donor properties of this solvent. When the Rh-complex is formed in TFE ν_{CO} is shifted to nearly the same wavenumber as in CH_2Cl_2 (Fig. 3), which is in agreement with results of the ^{31}P-NMR study and the hydrogenation and therefore a proof for a comparable structure. Because TFE molecules are poor hydrogen bond acceptors, they do not disturb the self-assembly of the catalyst.

The situation in methanol is completely different. Thus, ν_{CO} is decreased and much broader for the Rh-complex than for the free ligand while ν_{ring} to which also the pyridinol structure contributes is increased considerably. Because of the good hydrogen bond acceptor properties of methanol the pyridinol form is stabilized and donates hydrogen bonds to surrounding solvent molecules rather than to the second ligand; the hydrogen bonds in the complex are interrupted. This situation explains the increase in intensity of ν_{ring} and the shift of ν_{CO} to higher wavenumbers as well as the broadening of the singlet observed in the $^{31}P\{^1H\}$-NMR spectrum in CD_3OD.[5d] Based

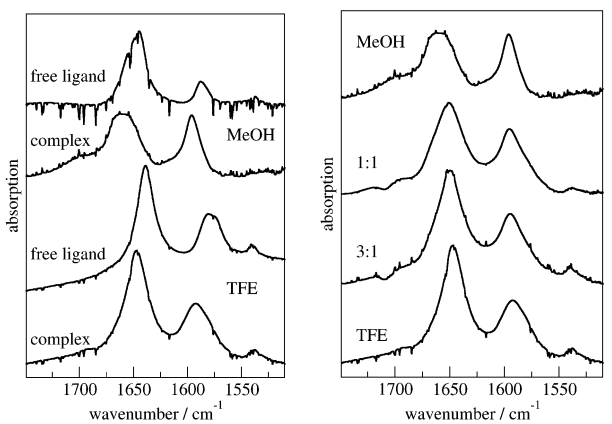


Fig. 3 IR-spectra of the free ligand and the Rh-complex in CF_3CH_2OH (TFE) and CH_3OH, respectively, to the right. IR-spectra of the Rh-complex in CF_3CH_2OH (TFE), CH_3OH and their mixtures to the left.

on this result the usually assumed bis-pyridone structure of the Rh-complex in methanol has to be revised.

The Rh-complex in mixtures of MeOH–TFE is dominated by the self-assembled structure of complex **IIA**, which is typical for the pure TFE solution. This fact gives an explanation why the high enantioselectivities observed in the asymmetric hydrogenation remains approximately constant in solvent mixtures.

In summary, the asymmetric hydrogenation of model substrates in mixtures of trifluoroethanol and methanol as solvent was investigated. The results of the catalytic reaction, of IR- and NMR-investigations as well as of chemical calculations show that a self-assembling hydrogen bond based architecture exists. This "pseudo"-chelate is apparently responsible for the superior catalytic activities in nonpolar solvents and fluorinated alcohols. Moreover, our results show that the amount of the precious fluorinated alcohol, necessary for the achievement of high rates and enantioselectivities, can easily be halved without losing the advantageous self-assembling properties of the catalyst.

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