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Fluorinated Alcohols as Solvents for Enantioselective Hydrogenation with Chiral Self-Assembling Rhodium Catalysts

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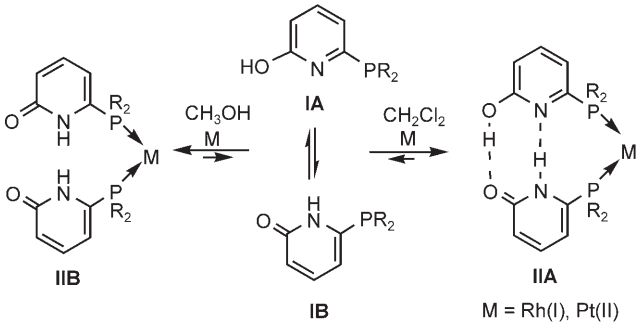
Abstract: We herein describe the beneficial effect of fluorinated alcohols on asymmetric hydrogenation using chiral self-assembling rhodium complexes. Previously, the application of these catalysts has been hampered by low reaction rates in non-polar solvents, which are essential for establishing the self-assembling architecture *via* hydrogen bonding. Excellent reaction rates are usually observed in alcohols as solvents, but the characteristic hydrogen bonds are cleaved in those media, resulting in poor *ee* values. We now show for the first time that the disadvantageous properties of both solvent classes on the catalytic reaction can be overcome by using fluorinated alcohols. Due to this key finding, homogeneous catalysis with self-assembling catalysts is much closer to practical application.

Keywords: asymmetric catalysis; hydrogenation; phosphane ligands; rhodium; self-assembly; solvent effects

The application of self-assembling catalysts has been established in recent years as a valued alternative to the employment of metal complexes based on conventional monodentate or bidentate ligands within the field of metal-catalyzed homogeneous catalysis.[1,2] Amongst other aspects, such conformationally flexible chelates can better adapt to steric requirements of a substrate ("induced fit").[3] Additionally, a reduction in the synthetic work necessary to build libraries for screening is expected.

Impressive results have been documented by Breit et al. using the 6-phosphanyl-2-pyridone system **IB**, which self-assembles through hydrogen bonding with its tautomer **IA** in the presence of a late transition metal salt (Scheme 1).[4]

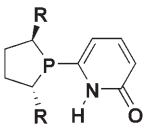


Scheme 1. Self-assembly of 6-phosphanyl-2-pyridone in the presence of a transition metal salt in dependence on the solvent.

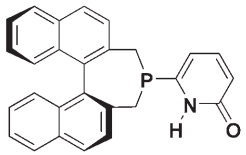
Rhodium(I) complexes of **IIA** derived from this system turned out to be highly efficient in the regioselective hydroformylation.[4a–c] Moreover, P ligands equipped with complementary H-bonding motifs, on the basis of an A–T base pair analogy, have been prepared and advantageously employed in a combinatorial approach.[5] The concept was extended to the Ru-catalyzed hydration of nitriles[4d] and *anti*-Markovnikov hydration of terminal alkynes.[4e] Furthermore, in an HTS approach, a library of self-assembling chiral phosphorus donor ligands has been studied in the course of Rh-catalyzed enantioselective hydrogenations.[6] Hydrogen bonding has been also identified as a critical issue of chiral Rh catalysts bearing monodentate phosphoramidites by Ding and co-workers.[7]

In a recent systematic study on the catalyzed enantioselective hydrogenation of dimethyl itaconate and methyl α-(*Z*)-*N*-acetamidocinnamate with cationic Rh complexes, we reported evidence that the efficiency of the reaction is strongly dependent on the bulk of the chiral phosphine moiety as well as on the solvent used.[8] Superior enantioselectivities (99% *ee*) were observed with phosphepine **2** as ligand in comparison to phospholanes **1a**, **b** in the non-polar solvent CH_2Cl_2. Unfortunately, slow conversion was noted in

most cases under these conditions. This was particularly pronounced for complexes bearing phospholane ligands **1a**, **b**. In contrast, in most cases enantioselective hydrogenations proceeded faster in polar solvents like MeOH, but in this case low *ee* values in the range of 0 to 47% were observed. Detailed NMR spectroscopic investigation showed that self-assembly and therefore chelate formation only took place in non-polar solvents, whereas in CD_3OD the hydrogen bonds were broken and metal complexes bearing monodentate ligands formed (Scheme 1, **IIB**).



1a R = Me
1b R = Ph



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Obviously unique polar solvents are required which do not disturb the self-assembling architecture of the hydrogenation catalyst in order to maintain the beneficial effect of hydrogen bonding on the enantioselectivity. At the same time the low reaction rates must be overcome. As shown in Figure 1, fluorinated alcohols with low hydrogen bond acceptor properties should be suitable solvents in terms of polarity and hydrogen bonding tolerance.

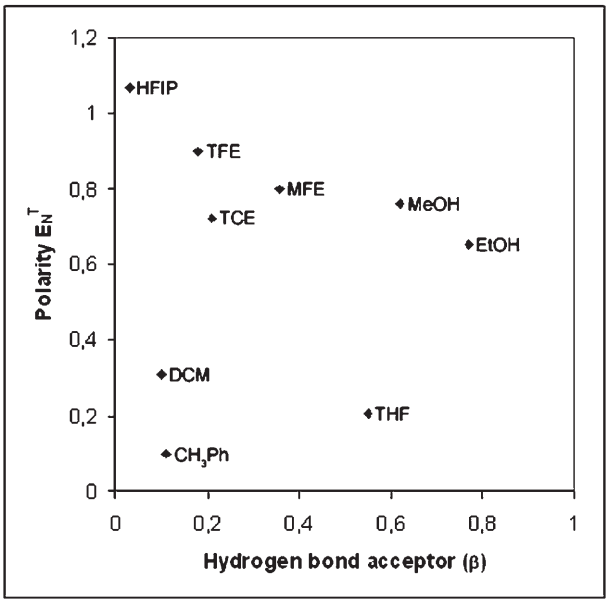


Figure 1. Correlation of the polarity (E_N^T) with hydrogen bond acceptor properties (β). HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol [$CF_3CH(OH)CF_3$], TFE = 2,2,2-trifluoroethanol [CF_3CH_2OH], MFE = 2-fluoroethanol [CH_2FCH_2OH], TCE = 2,2,2-trichloroethanol [CCl_3CH_2OH], DCM = dichloromethane [CH_2Cl_2], THF = tetrahydrofuran [C_4H_8O], MeOH = methanol [CH_3OH].[9]

Indeed, NMR investigations of a cationic Rh-complex of **1a** in CF_3CD_2OD (Figure 2) showed a similar signal pattern as found in $CDCl_3$.[8] Two doublets of doublets δ = 52.0 [dd, $J(^{31}P,^{103}Rh) = 147$ Hz, $J(^{31}P,^{31}P) = 36$ Hz] and δ = 50.4 [$J(^{31}P,^{103}Rh) = 140$ Hz, $J(^{31}P,^{31}P) = 36$ Hz] are characteristic.[10] Due to the investigations and conclusions of the preceding paper these signals can be attributed to two different P groups: one attached to a pyridone and the other to a pyridinol scaffold. This is clear evidence that the self-assembly is completely maintained in the fluorinated alcohol. Moreover, signals at lower field usually observed in $CDCl_3$ and probably characterizing polymeric species[11] or P,N complexes[12] are not visible.

Results of the asymmetric hydrogenation of the benchmark substrates methyl *Z*-α-*N*-acetamidocinnamate and dimethyl itaconate are detailed in Table 1. For comparison, results measured in CH_2Cl_2 and MeOH are also listed.[8]

Remarkably, the application of CF_3CH_2OH as solvent yielded similarly high *ee* values as those obtained in CH_2Cl_2.[13] Moreover, with the exception of run 15, reactions proceeded much faster and the rates observed even exceed those achievable in the "favourite" solvent CH_3OH. Interestingly, other fluorinated solvents are also highly useful for this catalytic reaction. Thus, the use of CH_2FCH_2OH yielded similar superior results (runs 10 and 23). With $CF_3CH(OH)CF_3$, the reaction rate was lowered. However, in general, high enantioselectivities were obtained (runs 11 and 22). Remarkably, employment of CCl_3CH_2OH gave poor results (runs 12 and 24), which clearly shows the unique properties of the fluorinated alcohols.

In order to provide additional proof for the beneficial effect of self-assembling, the "ordinary" non-assembling monodentate ligands **3a**, **b** and **4** were tested

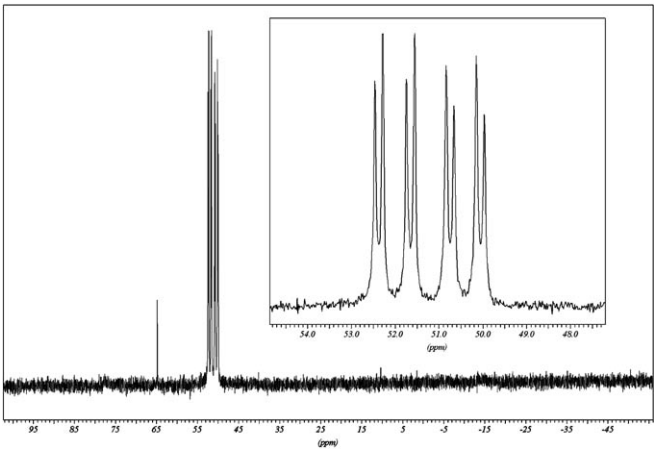
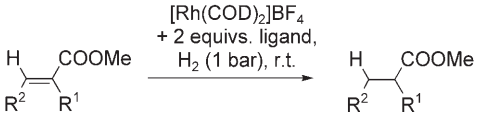


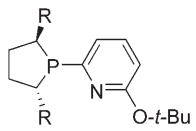
Figure 2. ^{31}P NMR spectrum of [Rh(COD)(**1a**)$_2$]BF_4 in CF_3CD_2OD at 0 °C.

Table 1. Comparison of results of the enantioselective hydrogenation in different solvents.[a]



Entry	Ligand	Substrate R^1	R^2	Solvent	t [min]	Conversion [%]	*ee* [%]
1	**1a**[b]	NHAc	Ph	CH_2Cl_2	1400	100	69 (*R*)[d,e]
2	**1a**[b]	NHAc	Ph	CH_3OH	1300	20	13 (*R*)[d,e]
3	**1a**[b]	NHAc	Ph	CF_3CH_2OH	1200	100	68 (*R*)[d]
4	**1b**[b]	NHAc	Ph	CH_2Cl_2	3900	92	83 (*R*)[d,e]
5	**1b**[b]	NHAc	Ph	CH_3OH	2760	100	27 (*R*)[d,e]
6	**1b**[b]	NHAc	Ph	CF_3CH_2OH	1800	100	84 (*R*)[d]
7	**2**[c]	NHAc	Ph	CH_2Cl_2	10	100	94 (*R*)[d,e]
8	**2**[c]	NHAc	Ph	CH_3OH	50	100	64 (*R*)[d,e]
9	**2**[c]	NHAc	Ph	CF_3CH_2OH	10	100	95 (*R*)[d]
10	**2**[b]	NHAc	Ph	CH_2FCH_2OH	6	100	96 (*R*)[d]
11	**2**[b]	NHAc	Ph	$CF_3CH(OH)CF_3$	800	100	94 (*R*)[d]
12	**2**[b]	NHAc	Ph	CCl_3CH_2OH	1380	2	n.d.
13	**1a**[b]	CH_2COOMe	H	CH_2Cl_2	1300	88	83 (*S*)[e,f]
14	**1a**[b]	CH_2COOMe	H	CH_3OH	400	100	rac[f]
15	**1a**[b]	CH_2COOMe	H	CF_3CH_2OH	1400	93	68 (*S*)[e]
16	**1b**[b]	CH_2COOMe	H	CH_2Cl_2	2880	53	51 (*S*)[e,f]
17	**1b**[b]	CH_2COOMe	H	CH_3OH	2880	100	47 (*S*)[e,f]
18	**1b**[b]	CH_2COOMe	H	CF_3CH_2OH	300	100	40 (*S*)[f]
19	**2**[c]	CH_2COOMe	H	CH_2Cl_2	20	100	99 (*S*)[e,f]
20	**2**[c]	CH_2COOMe	H	CH_3OH	60	100	64 (*S*)[e,f]
21	**2**[c]	CH_2COOMe	H	CF_3CH_2OH	10	100	97 (*S*)[f]
22	**2**[b]	CH_2COOMe	H	$CF_3CH(OH)CF_3$	30	100	96 (*S*)[f]
23	**2**[b]	CH_2COOMe	H	CH_2FCH_2OH	25	100	89 (*S*)[f]
24	**2**[b]	CH_2COOMe	H	CCl_3CH_2OH	1050	1	n.d.

[a] *Conditions:* Precatalyst generated *in situ* by reaction of $[Rh(COD)_2]BF_4$ with two equivs. of ligand.
[b] Substrate:catalyst = 50:1, 7.5 mL solvent.
[c] Substrate:catalyst 100:1, 7.5 mL solvent.
[d] Determined by GC, 25 m γ-cyclodextrin, Lipodex E (Machery and Nagel), fused silica, 130 °C.
[e] See Ref.[8]
[f] Determined by GC, 25 m γ-cyclodextrin, Lipodex E (Machery and Nagel), fused silica; 70 °C.



3a R = Me
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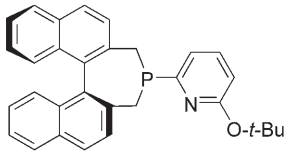

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in the enantioselective hydrogenation in CF_3CH_2OH as a solvent.

As it can be seen in Table 2 catalysts with non-assembling ligands induce much lower enantioselectivity. In accordance to results of the reaction in polar (CH_3OH) or non-polar solvents (CH_2Cl_2), where only small differences in *ee* values were noted,[8] also only small deviations in CF_3CH_2OH are visible. These results give evidence that these catalysts work rather independent of the solvent used. In contrast, the catalytic effect of complexes with self-assembling properties is strongly dependent on the solvent used.

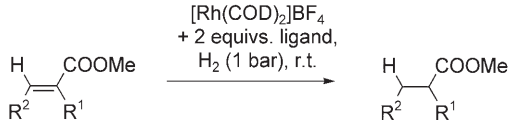
In conclusion, the beneficial effect of fluorinated alcohols on the asymmetric hydrogenation with self-assembling catalyst has been documented for the first time. Due the broad availability of fluorinated solvents our findings are also of great practical importance.[13] Moreover, our observation should also be of great importance for other catalysts bearing two monodentate ligands where intramolecular interactions *via* hydrogen bondings have been assumed.[7,13g]

Experimental Section

General Remarks

All reactions involving phosphanes were performed under an inert atmosphere of argon by using standard Schlenk

Table 2. Comparison of results of the enantioselective hydrogenation with monodentate ligands **3a**, **b** and **4**.[a]



Entry	Ligand	Substrate R^1	R^2	Solvent	*t* [min]	Conversion [%]	*ee* [%]
1	**3a**	NHAc	Ph	CF_3CH_2OH	40	100	27 (*R*)
2	**3a**	NHAc	Ph	CH_2Cl_2	30	100	23 (*R*)
3	**3a**	NHAc	Ph	CH_3OH	400	100	22 (*R*)
4	**3a**	CH_2COOMe	H	CF_3CH_2OH	10	100	18 (*S*)
5	**3a**	CH_2COOMe	H	CH_2Cl_2	1400	100	11 (*S*)
6	**3a**	CH_2COOMe	H	CH_3OH	300	100	12 (*S*)
7	**3b**	NHAc	Ph	CF_3CH_2OH	200	100	31 (*R*)
8	**3b**	NHAc	Ph	CH_2Cl_2	60	100	71 (*R*)
9	**3b**	NHAc	Ph	CH_3OH	70	100	77 (*R*)
10	**3b**	CH_2COOMe	H	CF_3CH_2OH	60	100	57 (*R*)
11	**3b**	CH_2COOMe	H	CH_2Cl_2	40	100	49 (*R*)
12	**3b**	CH_2COOMe	H	CH_3OH	45	100	76 (*R*)
13	**4**	NHAc	Ph	CF_3CH_2OH	25	100	13 (*R*)
14	**4**	NHAc	Ph	CH_2Cl_2	7	100	56 (*R*)
15	**4**	NHAc	Ph	CH_3OH	2	100	90 (*R*)
16	**4**	CH_2COOMe	H	CF_3CH_2OH	4	100	61 (*S*)
17	**4**	CH_2COOMe	H	CH_2Cl_2	8	100	87 (*S*)
18	**4**	CH_2COOMe	H	CH_3OH	2	100	58 (*S*)

[a] For reaction conditions and analysis of products, see Table 1.

techniques. Solvents were dried and freshly distilled under argon before use. The 1,1,1,3,3,3-hexafluoro-2-propanol and 2-fluoroethanol were purchased from ABCR and Alfa Aesar, respectively. Syntheses of the phospholane ligands **1**, **3** and phosphepine ligands **2**, **4** were reported recently.[8] ^1H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker Spectrometer AVANCE 500 and 300 (^1H: 500.13 MHz and 300.13 MHz; ^{13}C: 125.8 MHz and 75.5 MHz; ^{31}P: 162.0 MHz). Chemical shifts of ^1H, ^{13}C and ^{31}P NMR spectra are reported in ppm. The calibration of ^1H and ^{13}C spectra was carried out on solvent signals [δ ($CDCl_3$) = 7.25 and 77.0]. The ^{31}P chemical shifts are referenced to 85% H_3PO_4. The optical rotations were measured on a "gyromat-HP" instrument (Fa. Dr. Kernchen). Mass spectra were recorded on a MAT 95XP (Finnigan).

General Procedure for the Enantioselective Hydrogenation

All hydrogenation reactions were carried out under standard conditions: isothermal (25 °C) and isobaric (1 bar) conditions in an automatically registrating hydrogenation device. Precatalysts were prepared *in situ* by mixing [Rh(COD)$_2$]BF_4 (1 equiv.) and chiral ligands (2 equivs.) under an argon atmosphere (catalyst loading S/C 50/1 or 100/1). Then the prochiral olefin (0.5 mmol) and the solvent (7.5 mL) were added and after changing of argon by hydrogen the hydrogenation was started. The conversion of the prochiral olefins was determined by GC. For the enantiomer ratio determinations GC columns with chiral stationary phases (lipodex E column) from Macherey–Nagel GmbH were used.

Acknowledgements

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