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Rhodium-catalyzed asymmetric hydrogenation with self-assembling catalysts in propylene carbonate

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Abstract

Propylene carbonate (PC) may serve as a perfect solvent in the asymmetric rhodium-catalyzed hydrogenations of functionalized olefins like methyl *N*-acetamido acrylate and methyl α-(Z)-*N*-acetamido cinnamate using chiral self-assembling catalysts. In several examples superior reaction rates and enantioselectivities were found in comparison to the use of dichloromethane, commonly used as a solvent. The performance of the catalyst is influenced by the bulk of the phosphorus ligands. A ^{31}P NMR spectrum registered in PC showed the same self-assembling architecture as found in other nonprotic solvents.

During the last 35 years an enormous number of trivalent phosphorus ligands has been developed for different types of homogeneous asymmetric catalysis using 'soft' metals like rhodium, ruthenium, iridium and palladium.[1] For a long time bidentate ligands dominated the field. Only in recent years catalysts based on monodentate ligands have also shown outstanding enantioselectivities.[2] Due to their easier way of synthesizing, ligands with only one ligating atom became a promising alternative. The gap between bidentate ligands and monodentate ligands was closed with the concept of self-assembling catalysts. Thereby two monodentate ligands are linked together in a metal complex by hydrogen bonds[3] or a second metal.[4] Breit's group developed self-assembling catalysts based on hydrogen-bond interactions in relation to the naturally occurring DNA.[5] For example, ligands related to an A-T base-pair are suitable and can be even used in combinatorial approaches.[6] The usefulness of this concept was shown, for example, in the Ru-catalyzed anti-Markovnikov hydration of terminal alkynes.[7]

Recently, we gave evidence that self-assembling Rh-catalysts can be employed in the asymmetric hydrogenation.[8] High enantioselectivities were found in nonpolar solvents like CH_2Cl_2. In this solvent hydrogen bonds stabilize the formation of the 'pseudo-chelate' **IIA** (Fig. 1). In contrast, the use of polar solvents like MeOH decreased the ees. Unfortunately, the high stereoselectivities in the nonpolar solvent were accompanied by low reaction rates, whereas in alcohol as solvent a fast reaction took place. Obviously both the effects are a consequence of the disturbance of the hydrogen bonds in the polar solvent (Fig. 1, **IIB**). In a subsequent work we found that both the beneficial effects can be combined by running the reaction in fluorinated alcohols, which do not affect the hydrogen bonds.[9] Alternatively,

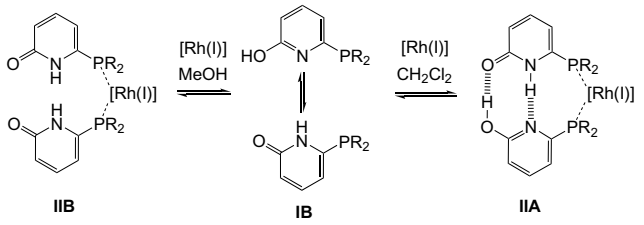

Fig. 1. Self-assembly of 6-phosphino-2-pyridone ligands in the presence of Rh(I) in dependence on the solvent.

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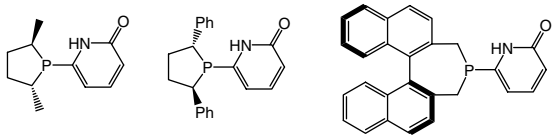
Breit and co-workers designed unique ligands for the Rh-catalyzed hydroformylations, which can act as 'pseudo-chelate ligands' even in protic solvents.[10]

In our ongoing search for cheaper and environmental friendly alternatives we were interested to investigate also the potential of propylene carbonate (PC) for the hydrogenation reaction.

In general, organic carbonates such as PC own perfect properties as solvents like a high boiling point and low toxicity.[11] PC is biodegradable and odorless. Only a very few applications of organic carbonates in homogenous catalysis were described. Thus Behr et al. used PC in the Pt-catalyzed hydrosilylation reactions of unsaturated fatty acid esters.[12] Reetz and Lohmer found that stabilization of Pd clusters takes place in PC and therefore used them advantageously for the Heck reaction with styrenes.[13] Recently, we showed for the first time the potential of PC in asymmetric Rh- and Ir-catalyzed hydrogenations of functionalized and nonfunctionalized olefins using bidentate P,P- and P,N-ligands.[14] An efficient catalyst recycling was possible by extraction of the product with *n*-hexane.

Herein, we will demonstrate that PC is also a highly suitable solvent for the asymmetric hydrogenation with self-assembling catalysts. For our studies we used three different pyridone based phosphines as ligands, which have been described recently.[8] Ligands **1** and **2** are based on a phospholane, whereas ligand **3** is derived from a phosphepine. All three ligands are capable of self-assembling via hydrogen-bond interactions in CH_2Cl_2 or fluorinated alcohols.[8,9]



As substrates the benchmark olefins **4**–**6** have been used (Fig. 2).

All hydrogenations were carried out in a 1 atm hydrogenation vessel with an automatically registrating hydrogen device under isothermal (25 °C) and isobaric conditions. The precatalysts of the type $[Rh(cod)(L_2)]BF_4$ (L = chiral ligand) were prepared in situ prior to the hydrogenation under an argon atmosphere. In some cases, a prehydrogenated catalyst was prepared by treatment of the precatalyst under hydrogen in PC. No significant differences were obtained in reactivity or selectivity between these two methods of preparation. The results of the hydrogenations are summarized in Table 1.

In general, the enantioselectivity is strongly dependent on the size of the phosphine unit. With all three prochiral substrates highest ee-values were achieved with the Rh-complex derived from phosphepine ligand (*S*)-**3** (84–99% ee). This catalyst also gave superior rates. In detail, in the asymmetric hydrogenation of methyl α-(*Z*)-*N*-acetamido cinnamate (**4**) with ligand (*R*,*R*)-**1** a significant higher reactivity was observed in PC than in dichloromethane, while similar ees yielded (entries 1 and 2). The reactivity in PC dropped when the bulkier ligand **2** was used, but hydrogenation was still faster in PC than in CH_2Cl_2 (entries 4 and 5). The ee decreased slightly from 70% to 63%. When phosphepine **3** was used the reaction proceeded a bit faster in dichloromethane than in PC and gave higher ees (entries 6 and 7) (Fig. 2).

Remarkably, no increase of reactivity but similar ees were observed when ligand **1** was used in the hydrogenation of dimethyl itaconate (**5**) (entries 10 and 11). With ligand **2** the reactivity increased significantly in PC but in comparison to CH_2Cl_2 the ee dropped from 47% to 28% (entries 12 and 13). In case of ligand **3** a similar reaction time with a slightly decreased enantioselectivity was noted in PC (entries 14 and 15).

Lastly, PC was used as solvent in the hydrogenation of methyl *N*-acetamido acrylate (**6**). In each case faster reactions with higher enantioselectivities were obtained in PC in comparison to CH_2Cl_2. For example, the catalyst with phospholane **1** as ligand converted the substrate in PC ca. 8x faster into the chiral product than in CH_2Cl_2 (entries 16 and 17). The reaction with catalyst based on ligand **2** took profit from the reaction in PC in terms of reactivity as well as of enantioselectivity (entries 18 and 19). The catalyst with ligand **3** displayed a higher enantioselectivity in PC (entries 20 and 21), whereas the high reaction rate observed in methylene chloride remained constant.

Since PC is chiral we were interested to investigate also the effect of this solvent in enantiopure form. Thus, the use of (−)-(*S*)-PC decreased the reactivity of the catalysts of (*R*,*R*)-**1** and (*S*)-**3** but did not affect the enantioselectivity (entry 3) or even afforded a slight increase (entry 9). Using (+)-(*R*)-PC ligand (*S*)-**3** gave the hydrogenation product of **4** with an ee similar to that observed in racemic PC (entry 8). Interestingly the reactivity of the catalyst was again lowered in comparison to the use of racemic or (*S*)-PC (compare entries 7–9).

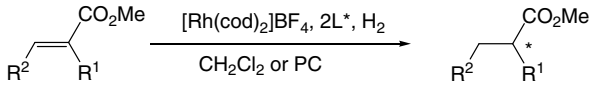
To confirm the self-assembling architecture of the catalyst in PC a Rh-complex of ligand **1** was exemplarily investigated by ^{31}P NMR spectroscopy (Fig. 3). The complex was formed by reaction of $[Rh(cod)_2]BF_4$ and 2 equiv of **1** in PC. The ^{31}P NMR spectrum showed the two characteristic doublets of doublets at δ 54.3 ppm ($J(Rh,P) = 146.8$ Hz, $J(P,P) = 36.7$ Hz) and 49.9 ppm ($J(Rh,P) = 140.2$ Hz, $J(P,P) = 36.5$ Hz). This clearly gives proof for the two nonequivalent P-nuclei quite similar to the arrangement found in deuterated dichloromethane.[8]

In summary, we have shown that PC can be the solvent of choice in the Rh-catalyzed asymmetric hydrogenation with self-assembling catalysts. In several instances enhanced reactivity and in some cases superior ees were found. The observed higher rates in PC in comparison to CH_2Cl_2 is remarkable, because they do not reflect the higher hydrogen solubilities (at 1.013 bar H_2 and 25 °C) in CH_2Cl_2 (9.3×10^{-3}) compared to PC (1.4×10^{-3}) expressed as mole H_2 in 1 L of solvent. Thus, in spite of the fact that about eight times less H_2 is placed at the

Table 1
Hydrogenation of prochiral olefins in dichloromethane and propylene carbonate (PC)[a]

Entry	Ligand	Substrate	Ratio[b]	Solvent	Time (min)	Conv.[c] (%)	ee[c] (%)
1	(*R*,*R*)-**1**	**4**	100:2:1	CH_2Cl_2	1400	100[d]	69 (*R*)[d]
2	(*R*,*R*)-**1**	**4**	100:2:1	PC	75	100	70 (*R*)
3	(*R*,*R*)-**1**	**4**	100:2:1	(−)-(*S*)-PC	360	15	70 (*R*)
4	(*R*,*R*)-**2**	**4**	50:2:1	CH_2Cl_2	1400	59[d]	70 (*S*)[d]
5	(*R*,*R*)-**2**	**4**	50:2:1	PC	600	100	63 (*S*)
6	(*S*)-**3**	**4**	100:2:1	CH_2Cl_2	10	100[d]	94 (*R*)[d]
7	(*S*)-**3**	**4**	100:2:1	PC	15	100	89 (*R*)
8	(S)-**3**	**4**	100:2:1	(+)-(*R*)-PC	80	81	91 (*R*)
9	(*S*)-**3**	**4**	100:2:1	(−)-(*S*)-PC	80	100	94 (*R*)
10	(*R*,*R*)-**1**	**5**	50:2:1	CH_2Cl_2	1300	88[d]	83 (*S*)[d]
11	(*R*,*R*)-**1**	**5**	50:2:1	PC	1200	86	80 (*S*)
12	(*R*,*R*)-**2**	**5**	50:2:1	CH_2Cl_2	3120	48[d]	47 (*R*)[d]
13	(*R*,*R*)-**2**	**5**	50:2:1	PC	1200	100	28 (*R*)
14	(*S*)-**3**	**5**	100:2:1	CH_2Cl_2	20	100[d]	99 (*S*)[d]
15	(*S*)-**3**	**5**	100:2:1	PC	25	100	95 (*S*)
16	(*R*,*R*)-**1**	**6**	100:2:1	CH_2Cl_2	80	100[d]	51 (*R*)[d]
17	(*R*,*R*)-**1**	**6**	100:2:1	PC	11	100	55 (*R*)
18	(*R*,*R*)-**2**	**6**	50:2:1	CH_2Cl_2	1140	100[d]	12 (*S*)[d]
19	(*R*,*R*)-**2**	**6**	50:2:1	PC	180	100	22 (*S*)
20	(*S*)-**3**	**6**	100:2:1	CH_2Cl_2	10	100[d]	85 (*R*)[d]
21	(*S*)-**3**	**6**	100:2:1	PC	10	100	94 (*R*)

[a] Conditions: the catalyst was prepared by stirring $[Rh(cod)_2]BF_4$ with 2 equiv of the ligand in solvent for 20 min under argon or hydrogen, the substrate was added and hydrogenation was conducted under 1 atm H_2 pressure.
[b] Ratio: substrate/ligand/$[Rh(cod)_2]BF_4$.
[c] Determined by GC using 25 m γ-cyclodextrin, Lipodex E (Machery and Nagel), silica, 130 °C.
[d] Data from Ref. 8.



4: R^1 = NHAc, R^2 = Ph
5: R^1 = CH_2COOMe, R^2 = H
6: R^1 = NHAc, R^2 = H

Fig. 2. Rh-catalyzed hydrogenation of prochiral olefins.

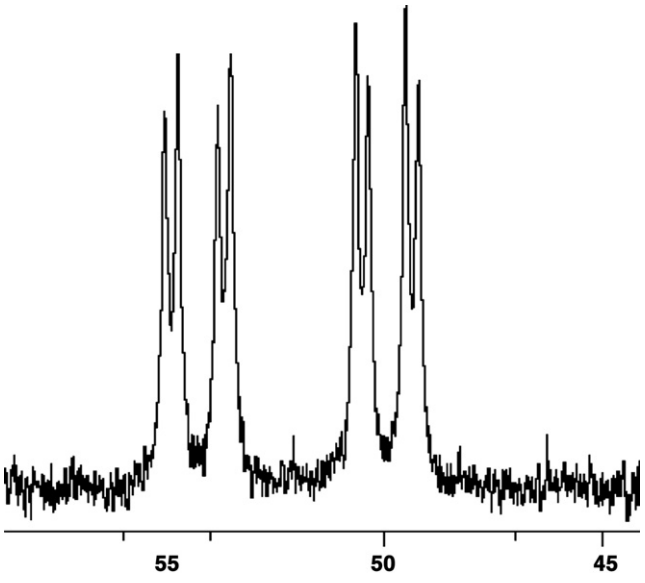


Fig. 3. ^{31}P NMR spectrum of $[Rh(cod)((R,R)\text{-}\mathbf{1})_2]BF_4$ showing Rh–P and P–P couplings (solvent: propylene carbonate/$CDCl_3$).

disposal for the hydrogenation in PC, reaction rates are substantially higher in this solvent. This issue will be addressed in a forthcoming publication.[15]

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