Asymmetric Catalysis

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Enantioselective Hydrogenation with Racemic and Enantiopure Binap in the Presence of a Chiral Ionic Liquid**

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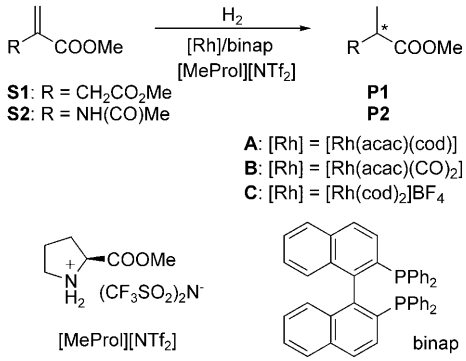
There is growing interest in the use of chiral ionic liquids (cILs)[1,2] in asymmetric catalysis as the reaction media or as an additive. Whereas chiral solvents have shown limited success in enantioselective synthesis,[3,4] the use of cILs have recently resulted in generating significant enantioselectivity in organocatalysis,[5,6] heterogeneous catalysis,[7] and transition-metal-catalyzed reactions.[8,9] As part of our interest in this area, we investigated the Rh-catalyzed homogeneous hydrogenation in amino-acid-derived cILs. Product enantioselectivities up to 69% *ee* were obtained by using rhodium catalysts derived from tropoisomeric phosphine ligands in combination with cILs as the only source of fixed chirality.[9]

Herein we report for the first time that cILs can be used to induce high levels of enantioselectivity when combined with racemic catalysts; the product enantioselectivites obtained are as high as those obtained with the corresponding enantiomerically pure ligand. We provide experimental evidence that the key role of the cIL is to effectively block the catalytic cycle for one of the two enantiomers of the catalyst (chiral poisoning[10]). In addition, the cIL can amplify and even reverse the enantioselectivity of a given enantiopure ligand in comparison to the reaction in organic solvents.

Binap (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) was selected as a prototypical ligand as it has a broad range of possible applications. The rhodium-catalyzed hydrogenation of dimethyl itaconate (**S1**) and methyl *N*-acetamido acrylate (**S2**) were chosen as benchmark reactions (Scheme 1). Under conventional conditions, enantiomerically pure (*S*)-binap leads to only moderate enantioselectivities (**P1**: 67% *ee*, (*S*);[11] **P2**: 21–25% *ee*, (*R*)[12]) in these transformations, thus providing a sensitive diagnostic tool for the effectiveness of the cIL. The methyl ester of (*S*)-proline was used as the source of chirality in the cIL ([MeProl][NTf_2]), which has already proved successful in case of the tropoiosmeric ligands.[9]



Scheme 1. Homogeneous rhodium-catalyzed hydrogenation of benchmark substrates with binap-derived catalysts in the presence of a cIL ([MeProl][NTf_2]).

The hydrogenation of **S1** was carried out under a set of standard reaction conditions employing a 5:1 mixture of CH_2Cl_2 and [MeProl][NTf_2] as the reaction medium. By using a rhodium catalyst, formed in situ from [Rh(acac)(cod)] (**A**; acac = acetylacetonate, cod = 1,5-cyclooctadiene) and racemic binap, (*S*)-2-methyl-succinic acid dimethyl ester ((*S*)-**P1**) was obtained quantitatively with an enantioselectivity of 67% *ee* (Table 1, entry 1). Almost the same enantioselectivity was achieved with complex **B** as the rhodium source (Table 1, entry 2). These results demonstrate that an identical level of enantiodifferentiation can be achieved with the combination of racemic binap and [MeProl][NTf_2], compared to that obtained with a single enantiomer of the chiral ligand.

In the case of substrate **S1**, the presence of the cIL does not affect the principle mode of enantiodifferentiation of the chiral ligand. This is demonstrated by the observation that the use of enantiomerically pure (*R*)-binap leads to enantioselectivities of 66–71% for (*R*)-**P1** in the presence of [MeProl]-[NTf_2] (Table 1, entry 3 and 4). The use of (*S*)-binap results in (*S*)-**P1** having almost identical enantioselectivities of 64–70%

Table 1: Rhodium-catalyzed hydrogenation of dimethyl itaconate (**S1**) in the presence of [MeProl][NTf_2] as the cIL.[a]

Entry	Ligand	[Rh]	*ee* [%]
1	*rac*-binap	**A**	67 (*S*)
2	*rac*-binap	**B**	65 (*S*)
3	(*R*)-binap	**A**	71 (*R*)
4	(*R*)-binap	**B**	66 (*R*)
5	(*S*)-binap	**A**	64 (*S*)
6	(*S*)-binap	**B**	70 (*S*)

[a] Reaction conditions: [Rh] = 0.01 mmol, binap/[Rh] = 1:1, substrate/[Rh] = 300:1, $p(H_2)$ = 40 bar, [MeProl][NTf_2] (0.2 mL), CH_2Cl_2 (1 mL), 16 h, RT; conversion and enantioselectivity determined by GC analysis (Lipodex E); full conversion in all entries.

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(Table 1, entry 5 and 6). In all cases, the absolute configuration of the preferred enantiomer is identical to that obtained under conventional reaction conditions.

The results summarized in Table 1 indicate that product **P1** is formed predominantly, or even exclusively, by an (*S*)-binap-containing rhodium complex even when *rac*-binap is employed. This conclusion is additionally substantiated by the significantly different rates observed for the hydrogenation of **S1** with the single enantiomers in the presence of [MeProl][NTf_2] (Figure 1). The conversion/time profiles obtained by monitoring the hydrogen uptake clearly show that the catalyst formed form (*S*)-binap leads to much faster hydrogenation than that obtained from the (*R*)-binap. The relative initial rates can be estimated at 6.7:1 in favor of the (*S*)-configured ligand, indicating that more than 90% of the product will be formed via the [{(*S*)-binap}Rh] complex under competitive conditions.

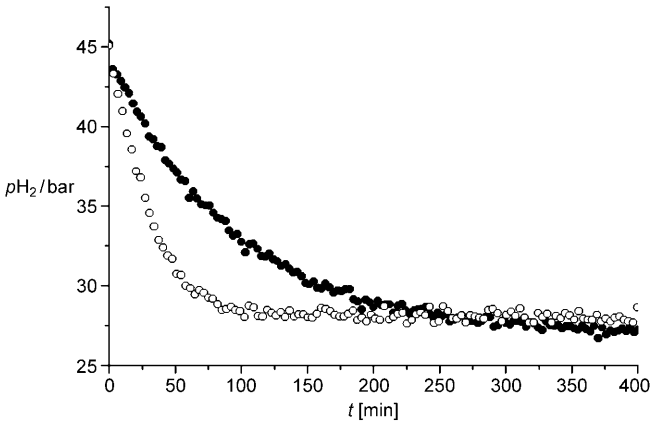

Figure 1. Hydrogen uptake for rhodium-catalyzed hydrogenation of **S1** with (*R*)-binap (●) and (*S*)-binap (○). [Rh(acac)$(CO)_2$] (0.017 mmol), **S1**/[Rh] = 500:1, binap/[Rh] = 1.1:1, CH_2Cl_2 (2 mL), [MeProl][NTf_2] (0.2 mL), RT. Off-line GC analysis confirmed full conversion in both reactions.

The differences in the hydrogenation rates can be corroborated with the distinct reactivity and stability of the two enantiomeric [(binap)Rh] fragments in the presence of the cIL, as revealed from NMR spectroscopic investigations. The precatalyst [{(*R*)-binap)}Rh(acac)] (^{31}P NMR: $\delta = 53.7$ ppm ($J_{PRh} = 191.7$ Hz) reacts cleanly with an excess of [MeProl][NTf_2] in CD_2Cl_2 to quantitatively form a new complex having two signals in the ^{31}P NMR spectrum at $\delta = 52.5$ ppm ($J_{PRh} = 205.5$ Hz, $J_{PP} = 65.5$ Hz) and $\delta = 46.3$ ppm ($J_{PRh} = 170.4$ Hz, $J_{PP} = 65.5$ Hz), respectively (Figure 2, lower trace). On the basis of full multinuclear NMR analysis, this species was assigned as the cationic complex [{(*R*)-binap}Rh{(*S*)-MeProl}]$^+$ with NTf_2^- as the counterion. The formation of this complex can be rationalized by protonation of the acac ligand through the prolinium cation and subsequent coordination of the free methyl ester of (*S*)-proline to the rhodium center. Carrying out the same reaction sequence with *rac*-binap results in the formation of the two diastereomeric

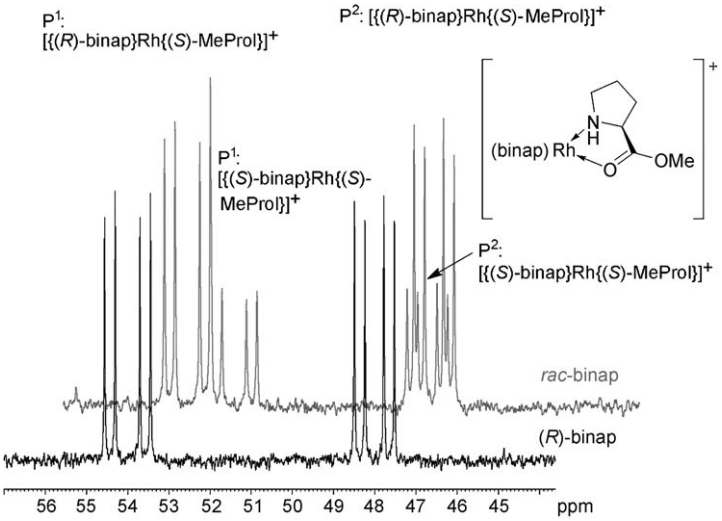

Figure 2. ^{31}P NMR spectra of CD_2Cl_2 solutions of [{(*R*)-binap}Rh(acac)] (lower trace) and [(*rac*-binap)Rh(acac)] (upper trace) in the presence of [MeProl][NTf_2] (cIL:[Rh] = 5:1).

complexes [{(*R*)-binap}Rh{(*S*)-MeProl}]$^+$ and [{(*S*)-binap}Rh{(*S*)-MeProl}]$^+$ in a ratio of 2.5:1 (Figure 2, upper trace), demonstrating the preferred arrangement of the *R* phosphine together with the *S* amino acid ester in the matched coordination environment at rhodium.

Thus the lower catalytic activity of the [{(*R*)-binap}Rh] fragment compared to the *S* congener can be traced back to the formation of a more stable and hence less reactive diastereomeric complex in presence of [MeProl][NTf_2]. This unprecedented high level of chiral poisoning[10] in hydrogenation catalysis nicely explains why the observed *ee* value is practically identical if either *rac*-binap or (*S*)-binap is used for substrate **S1**.

Whereas the cIL affects only the rate of the hydrogenation of **S1** with respect to the individual enantiomers of binap, a drastic effect on the enantioselectivity is observed with dehydro amino acid **S2** as the substrate (Scheme 1 and Figure 3). In pure CH_2Cl_2, the catalyst derived from (*R*)-binap and precursor [Rh$(cod)_2$]BF_4 yields (*S*)-**P2** preferentially with a moderate *ee* value of 25%. The addition of small amounts of [MeProl][NTf_2] leads to a significant decrease of the enantioselectivity. In a 1:1 mixture of organic solvent to cIL, the enantiodifferentiation is even reversed, leading to (*R*)-**P2** preferentially. This trend continues, and when [MeProl][NTf_2] is used as the solvent, (*R*)-**P2** is formed with 41% *ee*.

By using *rac*-binap in [MeProl][NTf_2] as the solvent under identical conditions, the overall enantioselectivity is 15% for the (*S*)-**P2**. The absolute configuration of the product shows that its formation occurs predominantly at the [{(*S*)-binap}Rh] fragment. This result indicates that chiral poisoning is the common basic selection mechanism for both substrates, although the differentiation between the two enantiomers of the chiral ligand appears to be less efficient for **S2** than for **S1** (>90% retention of enantioselectivity for **S1** versus 40% in case of **S2**). Importantly, however, the results obtained with **S2** demonstrate that the combination of a chiral ligand with a cIL can influence the enantioselectivity of an organometallic-mediated reaction to the point at which

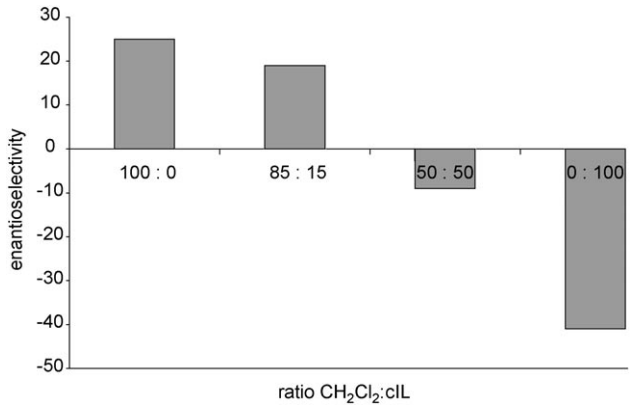

Figure 3. Change and increase of enantiodifferentiation in the rhodium-catalyzed hydrogenation of **S2** by using (*R*)-binap as the ligand and [MeProl][NTf_2] as the cIL. Used [Rh(acac)(cod)] or [$Rh(cod)_2$]BF_4 (0.01 mmol, [Rh]), **S2**/[Rh] = 300:1, binap/[Rh] = 1:1, pH_2 = 30 or 40 bar, RT, total volume of solvent = 0.8–1.6 mL.

the absolute configuration of the predominant product is inverted (at even higher enantioselectivities compared to standard conditions). This evidence strongly suggests that additional control factors beyond chiral poisoning are operating on a molecular basis for this substrate.[13]

In summary, the results reported herein demonstrate that the combination of a racemic ligand and a chiral ionic liquid as an additive or reaction medium for asymmetric hydrogenation can lead to enantioselectivities that are identical to those obtained with the enantiopure ligand in an organometallic catalytic cycle. Moreover, the use of the cIL together with an enantiomerically pure ligand can result in an enhanced enantioselectivity and an inverted absolute configuration in the product compared to those obtained when organic solvents are used. Convincing kinetic as well as spectroscopic evidences substantiate chiral poisoning as a principle mechanism for the differentiation of two enantiomeric catalytically active species at least for the rhodium-catalyzed hydrogenation studied here. The extension of this approach to other catalytic processes and additional studies on the enantiodifferentiation in such complex systems is ongoing in our laboratories.

Experimental Section

Typical procedure: The catalyst was formed by the in situ mixing of binap (6.2 mg, 0.01 mmol) and an equimolar amount of rhodium precursor [Rh(acac)(cod)], [Rh(acac)$(CO)_2$], or [$Rh(cod)_2$]BF_4 in CH_2Cl_2 for 2 h at RT. Then, all volatiles were removed under vacuum and the residue was dissolved in [MeProl][NTf_2] (0.2 mL) and CH_2Cl_2 (0.8 mL). The substrate (3 mmol) was added and the resulting solution was transferred into a stainless steel reactor (10 mL). The reactor was pressurized with hydrogen (40 bar) and the reaction mixture was stirred for 16 h at RT. After venting the reactor, a small sample of the reaction mixture was withdrawn by cannula, diluted with CH_2Cl_2, and then analyzed by GC methods (Lipodex E). Notably, although a 16 h standard reaction time was chosen, the reaction proceeds much more rapidly as constant pressure was usually observed within less than one hour (see Figure 1).

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