Non-Linear Effects in Ruthenium-Catalysed Asymmetric Hydrogenation with Atropisomeric Diphosphanes

Christian Girard,[a] Jean-Pierre Genêt,*[a] and Michel Bulliard[b]

Keywords: Nonlinear effects / Asymmetric catalysis / Ruthenium complexes / Atropisomeric phosphanes / Hydrogenation

A strong positive nonlinear effect (*asymmetric amplification*) was found to take place during asymmetric hydrogenations using chiral atropisomeric diphosphane–ruthenium catalysts. As an example, at atmospheric pressure the use of 50% *ee* BINAP to prepare [(binap)Ru(Br)$_2$] give rise to a hydrogenated product with 91% *ee*. The influence of temperature and hydrogen pressure on this effect are presented. These nonlinear effects can be explained on the basis of a hydrogenation mechanism in which diastereomeric dimers as pre-catalytic species are present.

Introduction

Non-linear effects (*NLEs*) in asymmetric synthesis have become a tool of choice to understand molecular behavior in solution.[1] The study of results obtained by varying the enantiomeric excess (*ee*) of the ligand used to prepare a catalyst can give insights into the nature of the catalytic species involved.[2] In many cases, auto-association of catalyst molecules in solution led to diastereomeric perturbations in the system and, instead of the expected linear relationships between the enantiomeric excesses of the catalyst and the reaction product, nonlinear relationships were observed between them. Nowadays, these types of studies have been successfully extended to diastereomeric mixtures,[3] chiral poisoning,[4] and autocatalysis.[5] In the case of chiral poisoning and autocatalysis, the aggregation phenomenon is the key process by which the selectivities of those reactions can be modulated.

Despite the interest in rhodium- and ruthenium-based catalysts, there are only a few examples of studies of this type.[6] Hydrogenation catalysts prepared from ruthenium and chiral phosphanes are believed to exist as oligomers.[7] Furthermore, some results obtained by our group and by others suggested that they were at least dimeric or trimeric under the reaction conditions used (*at least prior to introduction of hydrogen over the mixture*).[7][8]

In our continuing efforts to develop ruthenium-catalyzed asymmetric hydrogenations[9] and to understand the behavior of our catalyst in this process, we chose to study hydrogenation with ruthenium catalysts prepared from enantiomerically-impure diphosphanes. We report the observed nonlinear effects in this reaction.

Results

In a first series of experiments, ethyl acetoacetate (**1**) was hydrogenated at atmospheric pressure[10] using [(binap)-Ru(Br)$_2$] prepared in situ from (*S*)-BINAP of various enantiomeric excesses giving rise to ethyl (*S*)-3-hydroxybutyrate (**2**) as depicted in Figure 1.

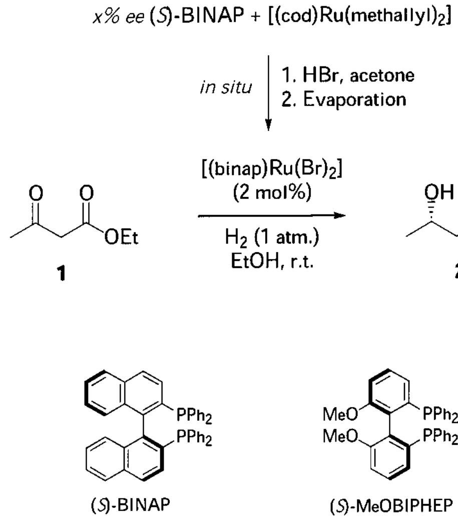

Figure 1. Enantioselective hydrogenation of ethyl acetoacetate (**1**) with (*S*)-binapRuBr$_2$ [{(*S*)-binap}Ru(Br)$_2$] catalyst at atmospheric pressure of hydrogen

Hydrogenation at this pressure allowed us to follow the process over time by taking aliquots of the mixtures. When the *ee* of ethyl (*S*)-3-hydroxybutyrate (**2**) produced was plotted against the *ee* of BINAP used to prepare the catalyst, a strong positive nonlinear effect {(+)-*NLE*} was observed as can be seen in Figure 2A. There is only a small depletion of this effect over time, but the curves remained similar in shape. After 46 h of reaction time, this (+)-*NLE* is still quite impressive. The use of 50% *ee* BINAP gave rise to ethyl (*S*)-3-hydroxybutyrate (**2**) with an *ee* of 91%.

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[a] École Nationale Supérieure de Chimie de Paris,
Laboratoire de Synthèse Sélective Organique et Produits Naturels, UMR 7573 CNRS,
11 rue Pierre et Marie Curie, F-75231 Paris cedex 05, France
[b] PPG-Sipsy, La Croix Cadeau,
F-49242 Avrillé cedex, France

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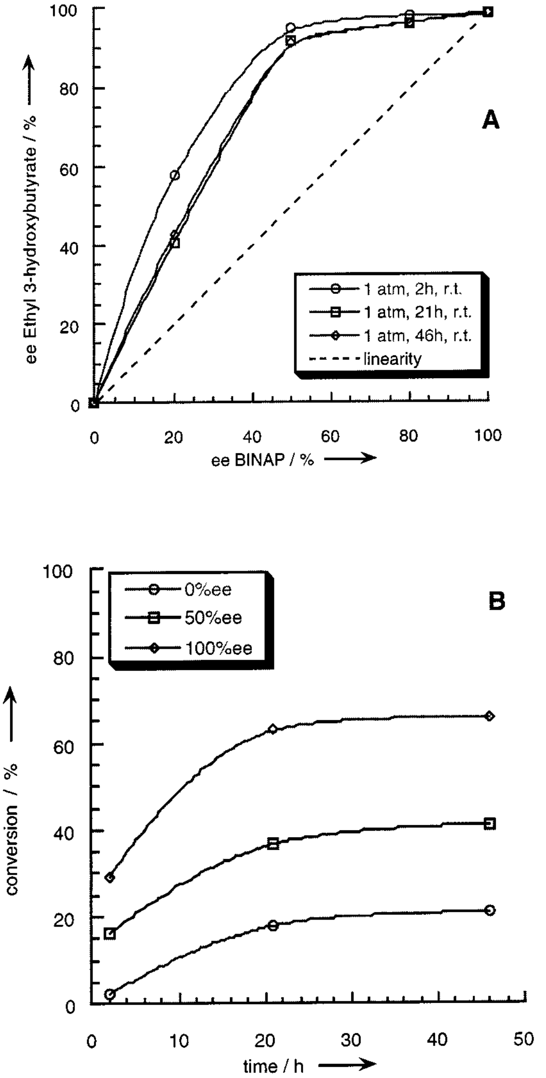

Figure 2. Asymmetric hydrogenation of ethyl acetoacetate (**1**) at room temperature under 1 atm of hydrogen: **A**: *ee* of ethyl (*S*)-3-hydroxybutyrate (**2**) as a function of *ee* of (*S*)-BINAP used to prepare the ruthenium catalyst. **B**: Conversion as a function of time for different values of *ee* of BINAP

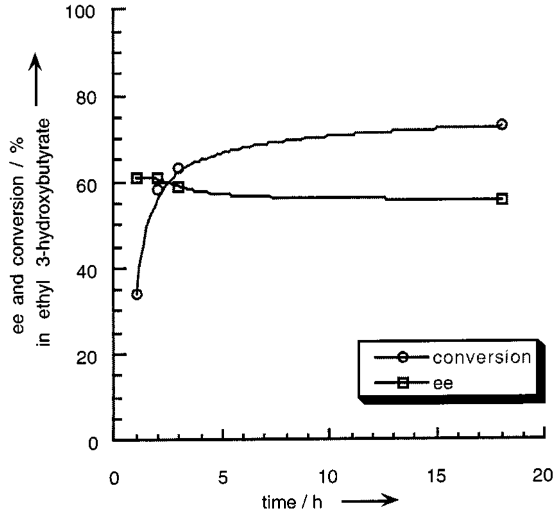

Figure 3. *Ee* and conversion in ethyl (*S*)-3-hydroxybutyrate (**2**) for the hydrogenation at room temperature and 1 atm of hydrogen using a ruthenium catalyst prepared with 50% *ee* of (*S*)-MeO−BIPHEP

The conversions were also analyzed during the hydrogenation process and the curves obtained are presented in Figure 2B. The conversions evolve with time and give similar curves, reaching a plateau after 20 h. Better conversions, however are obtained with higher *ee* of BINAP.

If the biphenyl-based ligand MeO−BIPHEP is used instead of BINAP, there is still a (+)-*NLE* present but of less importance. The use of 50% *ee* (*S*)-MeO−BIPHEP leads to a β-hydroxy ester **2** with 61% *ee* (34% conversion) after 1 hour to 56% *ee* after 18 h (72% conversion) as can be seen in Figure 3.

When the reaction with the BINAP-derived catalyst was performed at 60 °C under atmospheric pressure, a very similar *NLE* was observed. In this case (Figure 4A), the effect was less pronounced than at room temperature, leading to the depicted curves. At the early stage of the hydrogenation reaction, the (+)-*NLE* is more pronounced than it is after 18 hours of reaction time but the curves are still similar in shape. A product of 75% *ee* can however be obtained by using BINAP of 50% *ee*.

The conversion is better at this temperature (60 °C), but the same behavior as before is encountered here (Figure 4B). The lowest *ee* BINAP mixtures give poor yields relative to the enantiomerically-enriched ones.

The hydrogenation reaction was finally conducted at room temperature, but this time using a 5 bar hydrogen pressure in a steel autoclave. Figure 5 presents the curves obtained in this case, where the conversion is complete for all the *ee* values of BINAP.

A positive nonlinear effect is still present here, but it has been affected more by the increase in hydrogen pressure than by the temperature in the preceding example. The curve shows a resemblance to all those drawn before, but the effect is much smaller. The 50% *ee* BINAP-derived catalyst produces the β-hydroxy ester **2** with an *ee* of almost 70%.

Discussion

These first results showing a (+)-*NLE* are consistent with the usual hypothesis of the formation of dimeric (or trimeric) species of the pre-catalyst.[7,8,11] Furthermore, the formation of an heterochiral dimer, in which the minor enantiomer is trapped, explains the (+)-*NLE* observed here if it is more stable than the homochiral one.[1]

The structure of the oligomeric pre-catalytic species was, however, never clearly determined. During the preparation step of the catalyst, which is the same for all hydrogenations, a precipitate readily appears within minutes after the addition of hydrobromic acid. NMR studies[12] suggested the presence of two species with chemical shifts tentatively attributed to the trimeric $[(binap)_3Ru_3(\mu_2\text{-}Br)_3(\mu_3\text{-}Br)_2]Br$ (**3**) and dimeric $[(binap)(Br)Ru(\mu_2\text{-}Br)_3Ru(acetone)(binap)]$ (**4**, solv = acetone) complexes (Figure 6).

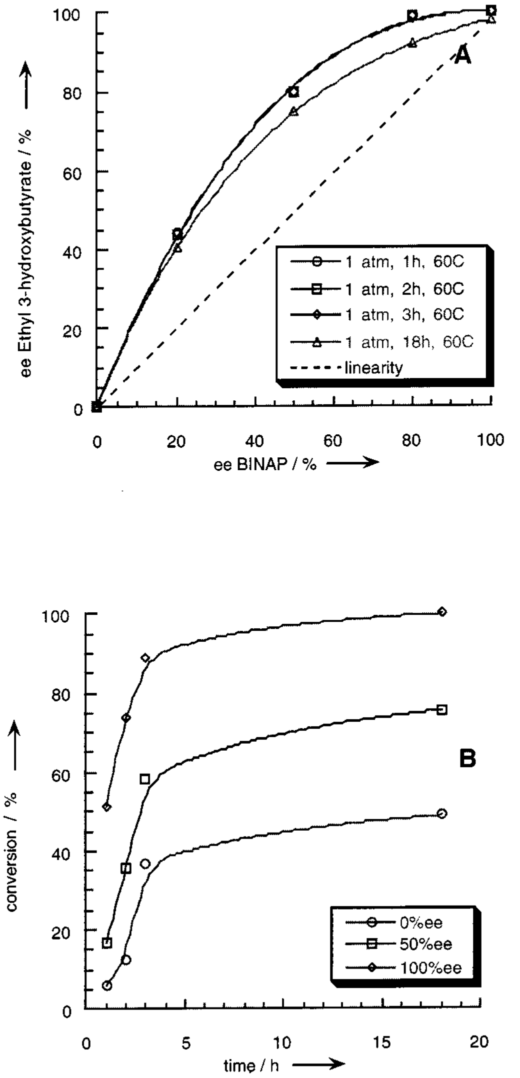

Figure 4. Enantioselective hydrogenation of ethyl acetoacetate (**1**) under 1 atm of hydrogen at 60 °C: **A**: *ee* of ethyl (*S*)-3-hydroxybutyrate (**2**) as a function of *ee* of (*S*)-BINAP used in the ruthenium catalyst. **B**: Conversion as a function of time for different values of *ee* of BINAP

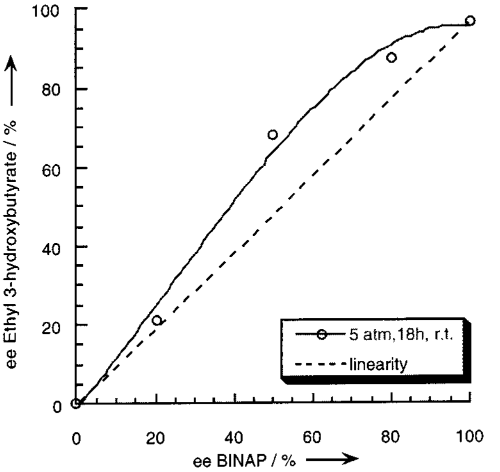

Figure 5. *ee* of ethyl (*S*)-3-hydroxybutyrate (**2**) as a function of *ee* of (*S*)-BINAP in the enantioselective hydrogenation of ethyl acetoacetate (**1**) under 5 atm of hydrogen at room temperature

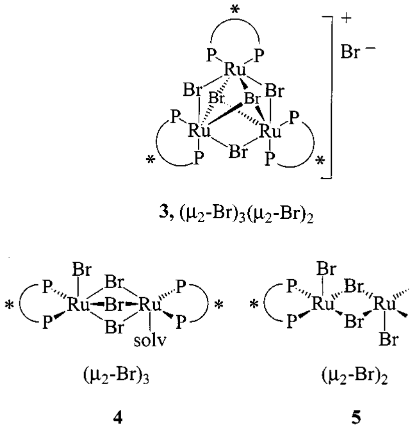

Figure 6. Oligomeric species formed during the preparation of the pre-catalyst: the cationic trimeric $[(\text{binap})_3\text{Ru}_3(\mu_2\text{-Br})_3(\mu_3\text{-Br})_2]\text{Br}$ (**3**) and the dimeric $[(\text{binap})(\text{Br})\text{Ru}(\mu_2\text{-Br})_3\text{Ru}(\text{acetone})(\text{binap})]$ (**4**, solv = acetone) and $[(\text{binap})(\text{Br})\text{Ru}(\mu_2\text{-Br})_2\text{Ru}(\text{Br})(\text{binap})]$ (**5**) neutral complexes

The solution should contain the $(\mu_2\text{-Br})_3(\mu_3\text{-Br})_2$ **3** trimeric cationic species, while the isolated precipitate was assumed to have the $(\mu_2\text{-Br})_3$ **4** dimer structure. At the end of the catalyst preparation, evaporation of the volatiles from this mixture (*to dryness*) led to only one solid pre-catalytic species as determined by ^{31}P-NMR analysis and which was assumed to be the $[(\text{binap})(\text{Br})\text{Ru}(\mu_2\text{-Br})_3\text{Ru}(\text{acetone})(\text{binap})]$ (**4**, solv = acetone) or $[(\text{binap})(\text{Br})\text{Ru}(\mu_2\text{-Br})_2\text{Ru}(\text{Br})(\text{binap})]$ (**5**) neutral dimers.[12]

In the present case, the dimeric pre-catalytic species consisted of a mixture of so-called hetero- (or *meso*-) and homodimers. Since the heterodimer is more stable, and traps most of the minor enantiomer, the homodimeric species left has an enantiomerically richer composition than the phosphane used to prepare the catalyst. Thus the more stable heterochiral complex is merely acting as a spectator, leaving the less stable homochiral one to enter the catalytic cycle.[13]

Hydrogenation of the pre-catalyst, under its dimeric or monomeric form, led to enantiomerically-enriched monomeric ruthenium hydride which then acts as the hydrogenating species, thus generating a product with a higher *ee* than the one expected from the hydrogenation cycle. The $(\mu_2\text{-Br})_2$ dimers were arbitrarily chosen to illustrate this phenomenon as can be seen in Figure 7. The major homochiral dimer, in this case the (*S*)•(*S*) one, is mainly involved, thus liberating the (*S*)-phosphaneRu(H)Br catalyst in the cycle.[8][14]

In order to confirm the hypothesis of the formation of dimeric species, as well as to get some quantitative analysis of their behavior, it is possible to use mathematical models of *NLE* developed by Kagan et al.[1a,b] In this hydrogenation reaction, good fits between experimental data and mathematical models can be obtained with the $\text{ML}_2/[\text{ML}]_2$ dimerization model. The curves presented in Figure 8 were generated using this model (*with no statistical distribution of the dimers*).

The use of the $[\text{ML}]_2$ model enabled us to extract the values of g and K, parameters that describe the stability by

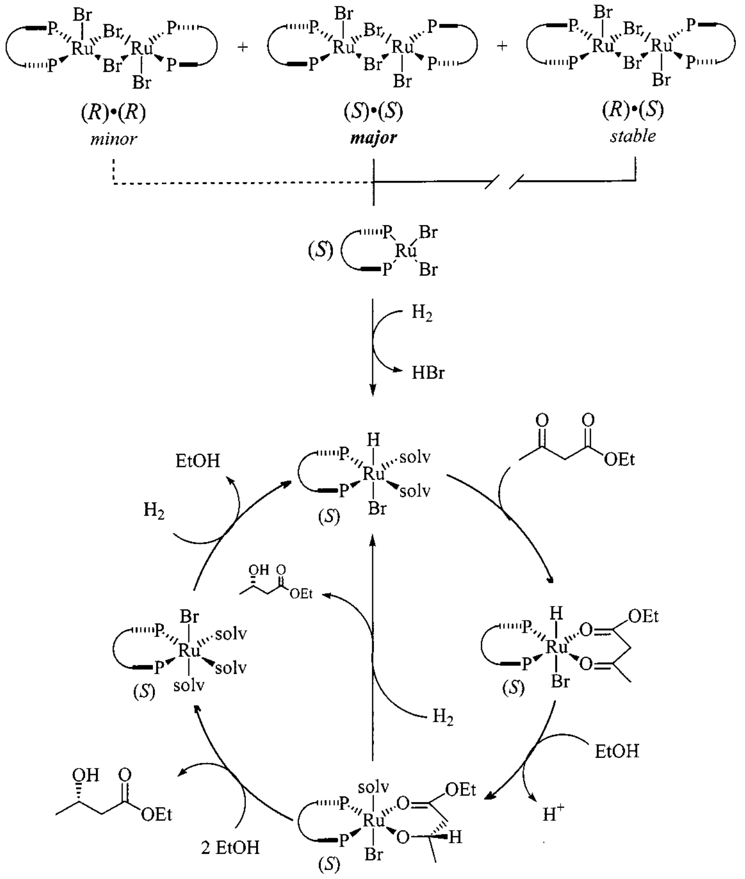

Figure 7. Catalytic cycle of enantioselective hydrogenation with the homochiral (*S*)•(*S*)-dimer as the major pre-catalyst

means of the relative reactivities of the dimers and their distribution between hetero- and homodimers.

For both reactions conducted at room temperature, the best fits were obtained by using *K* = 25 (Figure 8A and 8C). For atmospheric pressure hydrogenation, the fits between experimental data at the early stage and at the end are difficult to obtain but can be approximated using *K* values of 35 and 15, respectively. This gives a mean value of 25, which is the same as for hydrogenation at higher pressure. Since the pre-catalyst is prepared under the same conditions for those reactions, and they are conducted at the same temperature and concentration, it is obvious that the same *K* will be found, which reflects the predominant formation of the heterochiral species. The pressure increase from 1 to 5 bars of hydrogen however, modifies the relative reactivities of the dimers. The *g* value at one atmosphere of hydrogen is very low (0.01), which indicates that the homochiral complex is 100 times more reactive. When hydrogen pressure was increased to 5 bar, it seems that the discrimination between hetero- and homodimers towards hydrogenation is less pronounced with *g* = 0.5 (only twice the difference) and this led to the less pronounced positive nonlinear effect observed in this case.

For the hydrogenation at 60 °C under one atmosphere of hydrogen, the fits are presented in Figure 8B. The best correlation was found using *K* = 75 and *g* values between 0.25 and 0.3. When these values are compared to the hydrogenation at room temperature under the same pressure, it seems that the heterochiral dimer is present in larger proportions (*K* = 75 vs. 25) even if the pre-catalyst is prepared under the same conditions. This increase in the distribution between the hetero- and the homodimers, showing the presence of larger amounts of the *meso* dimer, can be attributed to the temperature effect on the monomer−dimer equilibrium, with a predominant reactivity of the homochiral pre-catalyst.

Conclusion

We presented in this paper one of the few examples of nonlinear effects in asymmetric hydrogenation. Catalysts prepared from atropisomeric diphosphanes and ruthenium salts were tested and generated a strong (+)-*NLE* at atmospheric pressure and room temperature. This effect was explained by the formation of dimeric pre-catalytic species in which the heterochiral dimer was more stable than its homochiral counterpart (*g* = 0.01, *K* = 25). The effect of temperature and hydrogen pressure on the nonlinear effect were deleterious, leading to strong (*g* = 0.3, *K* = 75) to moderate (*g* = 0.5, *K* = 25) *NLE*, respectively, due to increased participation of the heterochiral species. A deleterious effect of the formation of heterochiral dimers on the conversion rates was also observed for the atmospheric pressure reactions.[13]

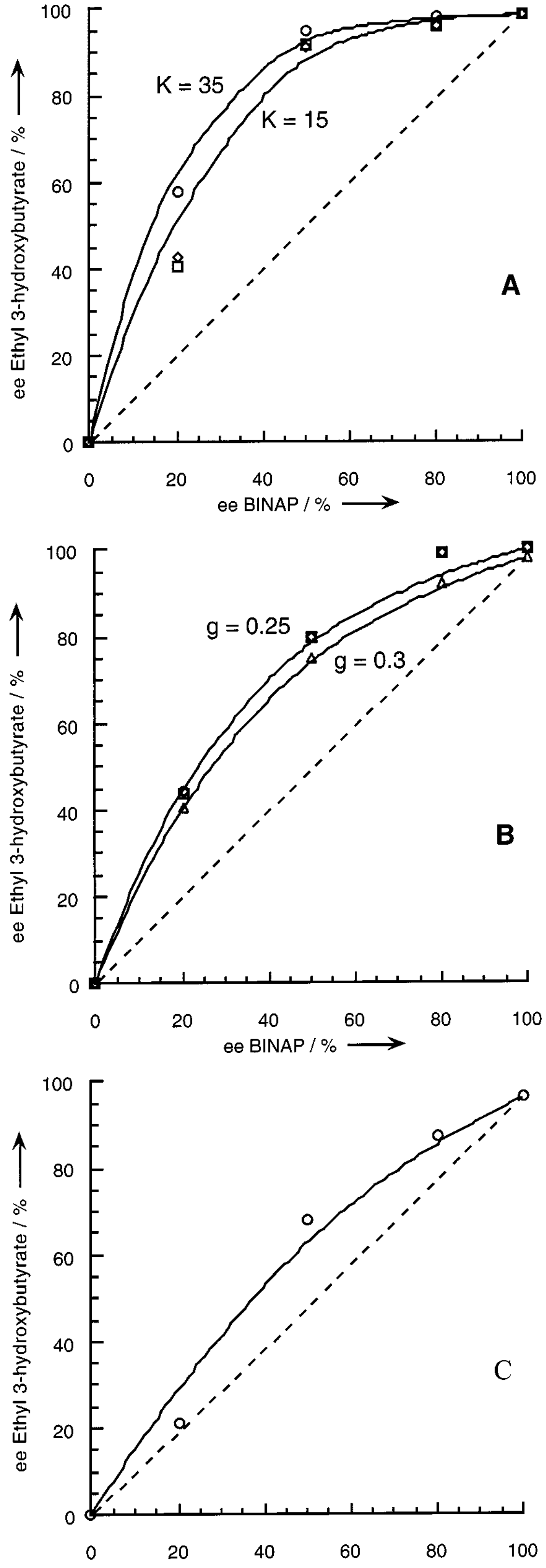

Figure 8. Curves fits of experimental data using Kagan's $[ML]_2$ model:[1] **A**: Hydrogenation at room temperature, 1 atm, $g = 0.01$, $K = 35$ and 15. **B**: Hydrogenation at 60°C, 1 atm, $g = 0.25$ and 0.3, $K = 75$. **C**: Hydrogenation at room temperature, 5 atm, $g = 0.5$, $K = 25$

The observation of this effect in solution during the hydrogenation process, together with previously-reported structures of such catalysts determined by X-ray or NMR studies, contributed to a better understanding of the behavior of the efficient ruthenium-based hydrogenation catalysts

Experimental Section

General: All solvents and ethyl acetoacetate (**1**) were purchased as analytical grade, and used as such after being degassed. BINAP and $[(cod)Ru(methallyl)_2]$ were purchased from ACROS Organics. MeO−BIPHEP was a generous gift from Hoffmann-La Roche. HBr solution in methanol was prepared by adding concentrated HBr solution (47−49%) to degassed methanol, in order to reach 0.16−0.18 M HBr, as determined by phenolphthalein titration with 0.1 M NaOH. Hydrogenations at atmospheric pressure were conducted in Schlenk tubes with hydrogen balloons while those at 5 bars were carried out in a steel autoclave. The reactions were followed up by taking 100 μL aliquots and diluting them in 1−2 mL of pentane. The samples were injected (250°C) on a FS-Lipodex A column on a Hewlett−Packard 5890 Serie II gas chromatograph at 30°C isothermal, with helium as vector gas at 1.5 mL·min^{-1} flow and flame ionization detection (250°C). The retention times are: R_t(**1**) = 47 min, R_t(*S*-**2**) = 49 min, R_t(*R*-**2**) = 54 min.

General Procedure for Asymmetric Hydrogenation. − Catalyst Preparation: Mixtures of (*S*)- and (*R*)-BINAP (16 mg, 26 μmol) were prepared to achieve the required enantiomeric excess. The BINAP mixture and $[(cod)Ru(methallyl)_2]$ (8 mg, 26 μmol) were treated with HBr (360 μL of 0.18M solution in methanol, 65 μmol, 2.5 equiv.) in acetone (2 mL) for 2 h. The solution turned orange upon addition of HBr and a precipitate was readily observed. The volatiles were then evaporated directly under vacuum in the Schlenk tube and kept under argon.

Hydrogenation Reaction: Absolute ethanol (2.6 mL) and ethyl acetoacetate **1** (166 μL, ≈170 mg, 1.3 mmol) were added to the catalyst (2 mol-%) and the hydrogenation was conducted at the relevant temperature and under the indicated pressure of hydrogen. Conversions[15] and enantiomeric excesses were determined by chiral GC on aliquots (see General).

Acknowledgments

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[12] During the *in situ* preparation of the catalyst using 100% *ee* BINAP as diphosphane, the ^{31}P-NMR of the different phases were recorded.[11] Analysis of the global mixture after the acidic treatment showed the presence of two species identified as the $(\mu_2\text{-Br})_3(\mu_3\text{-Br})_2$ **3** trimeric complex (s, $\delta = 42$) and the $(\mu_2\text{-Br})_3$ **4** dimer (2AB, $\delta = 30$, $J = 40$ Hz and $\delta = 45$, $J = 43$ Hz). While the supernatant solution contained complex **3** (s, $\delta = 42$) the isolated precipitate consisted exclusively of **4** (2AB, $\delta = 30$, $J = 40$ Hz and $\delta = 45$, $J = 43$ Hz). Evaporation of the total mixture (solution and precipitate) led to a solid which existed only as a dimeric form (**4**, 2AB, $\delta = 30$, J 40 Hz and $\delta = 45$, $J = 43$ Hz).

[13] In this study, other qualitative observations of importance were recorded. During in situ preparation of the ruthenium catalyst, the solutions produced a precipitate after a few minutes, which was identified as the pre-catalyst itself (vide supra). Furthermore, the solutions prepared from low *ee* diphosphanes produced more solids than the enantiomerically-enriched ones. Since the formation of a larger amount of heterochiral dimer is expected at lower *ee* of phosphane, the formation of a larger amount of precipitated solid can be associated with this species, which can be more stable and may be less soluble than its homochiral counterpart. After evaporation of the volatiles from the catalytic preparation, the hydrogenation was conducted in ethyl alcohol in which, once again, the catalysts prepared from less enantiomerically pure diphosphanes are less soluble than those of higher *ee*. This indicates that the possible lower solubility, as well as the greater stability of heterodimer towards hydrogenation, can both contribute to the (+)-*NLE* observed here. The lower conversion at low *ee* of diphosphane can then be explained by the formation of larger amounts of the less reactive heterochiral dimer. The quantity of the homochiral species is then lower at low *ee*, thus resulting in a decreased conversion rate during the hydrogenation process when using nonenantiomerically-pure phosphane. As an example, hydrogenations using 100% *ee* BINAP are usually complete within 3 hours at 60 °C.[10]

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[15] Since some decomposition of ethyl acetoacetate (**1**) occurred under the GC analysis conditions, the conversions are only indicated here to demonstrate the progression of the hydrogenation.

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