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Kinetic influences on enantioselectivity in asymmetric catalytic hydrogenation

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Abstract

The influence of reaction conditions on enantioselectivity in the Ru^{II}-(binap)-catalyzed asymmetric hydrogenation of allylic alcohols is discussed. This work highlights the importance of considering kinetic influences in addition to the stereochemical aspects of the chiral catalytic environment in interpreting catalytic behavior in asymmetric hydrogenation reactions. © 1997 Elsevier Science S.A.

Keywords: Enantioselectivity; Asymmetric hydrogenation; Chiral

1. Introduction

The asymmetric hydrogenation of C = C, C = O, and C = N bonds in organic substrates using organometallic complexes has been achieved with considerable success owing to significant synthetic advances in the development of chiral ligands over the past twenty years, primarily using optically active phosphines but including other types of ligands as well [1–3]. Explanation of observed enantioselectivities has in most cases focused on understanding the nature of the chiral environment of the catalyst. As Noyori has recently pointed out [4], however, asymmetric catalysis is in fact *four*-dimensional chemistry, and the three-dimensional stereochemical aspects of chiral catalysts must be combined with an understanding of the role that the fourth dimension, that of reaction kinetics, plays in determining enantioselectivity. This paper presents examples from the Ru(binap)-catalyzed hydrogenation of unsaturated alcohols in which the role of reaction conditions was found to be of paramount importance in rationalizing the ultimate enantioselectivity achieved in the reaction.

2. Experimental

Details of the experiments described in this paper are given elsewhere [5,6]. Geraniol (Alfa, 99%) and nerol (Aldrich, 97%) were used as substrates without further purification. γ-Geraniol was prepared as described in Ref. [7]. Hydrogenation of these substrates in methanol (Aldrich, 99.9%) was carried out using $[RuCl_2(S\text{-}tolyl\text{-}binap)]_2 \cdot NEt_3$ (Strem) [8]. Temperatures and pressures ranged from 243–328 and 15–800 kPa using substrate/Ru ratios of 700–1400.

Hydrogenation reactions were carried out in a reaction calorimeter (Mettler RC1). Reaction rates were measured by monitoring the calibrated heat flow of the reaction as described previously [9]. Automated data acquisition at 6 s intervals with an accuracy of better than 0.1 W [3] afforded an extremely accurate measure-

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[3] For a typical olefinic substrate having a heat of hydrogenation of 20 kcal/mole substrate, a heat flow of 0.1 W corresponds to a reaction rate of approximately 1 μmol/s.

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ment of reaction rate throughout the reaction. Briefly, Eq. (1) shows that for an isothermal, batch reacting system, the heat flow is proportional to the reaction rate:

$$q_r = V_r \sum_i \Delta H_{rxn,i} \left(\frac{dC_i}{dt} \right), \quad (1)$$

where q_r is the heat released or consumed by the reaction, V_r is the volume of the reactor contents, (dC_i/dt) is the reaction rate and $\Delta H_{rxn,i}$ the heat of reaction of the ith reaction. Integration of the heat flow curve provides the overall heat of reaction.

Product selectivity, reported as absolute enantiomeric excess or enantioselectivity, was measured for both systems by GC on a Chiraldex B-TA chiral column:

$$ee(\%) = \frac{|[R] - [S]|}{[R] + [S]} * 100. \quad (2)$$

Enantiomeric excess defined in this way is an integral property of the batch reaction, and may also be called cumulative ee% to distinguish it from the second measure of enantioselectivity, incremental ee%, which is defined as the %ee for the product formed in the interval between two consecutive analytical data points at times t_{i-1} and t_i.

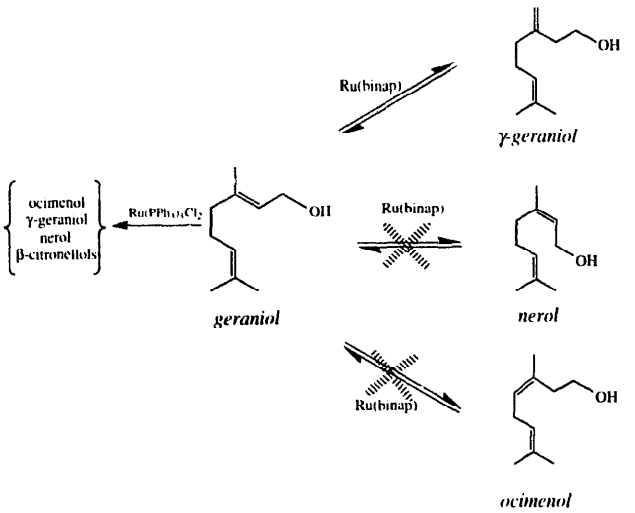
NMR studies (^{1}H (300 Mhz, ^{13}C (75 Mhz), and ^{2}H (46 MHz)), were carried out as previously described [10] using a QE-300 NMR spectrometer operated with MacNMR v. 5.1 software.

3. Results and discussion

3.1. Competing isomerization / hydrogenation pathways

Enantioselective hydrogenation of allylic alcohols has been extensively studied by Noyori [11] using homogeneous Ru(binap) catalysts. As in many asymmetric catalytic hydrogenations, enantioselectivity was found to be strongly pressure dependent. For the hydrogenation of geraniol using a Ru-(*S*)-binap catalyst, it was found that the enantioselectivity to (*R*)-citronellol increased from 70 to 98% as the reaction pressure was increased from 4 to 100 atm.

In recent studies of the hydrogenation of geraniol using $[RuCl_2(S\text{-})\text{-tolyl-binap}]_2 \cdot NEt_3$ [5], we observed a previously unreported competing isomerization pathway that has important implications for enantioselectivity in this reaction. As illustrated in Scheme 1, geraniol isomerizes to the terminal olefin γ-geraniol in methanol under Ar in a highly regioselective reaction catalyzed by the Ru(binap) catalyst. Nerol, the Z-isomer of geraniol, was not observed, nor was the homoallylic alcohol ocimenol, although both products formed easily in unselective isomerization reactions carried out using



Scheme 1. Products of the interaction of 1 M geraniol with Ru(binap) and $Ru(PPh_3)_3Cl_2$ in methanol under Ar in the temperature range 293–318 K.

$Ru(PPh_3)_3Cl_2$. Small amounts of citronellal were observed when the isomerization was allowed to proceed over very long times [12].

Studies of the isomerization kinetics shown in Fig. 1 reveal that approximately 18% γ-geraniol could be formed at 293 K. Simple dissolution of the catalyst in a methanol solution of geraniol under Ar thus allowed isomerization to occur prior to the start of the hydrogenation reaction. The isomerization rate is slow enough, however, that significant production of γ-geraniol prior to the introduction of hydrogen may be avoided by minimizing substrate–catalyst contact.

The viability of the isomerization pathway in the presence of hydrogen is an important question. NMR investigations support the suggestion that the isomerization of geraniol does indeed proceed under hydrogenation conditions. ^{13}C, ^{1}H, and ^{2}H NMR studies of reac-

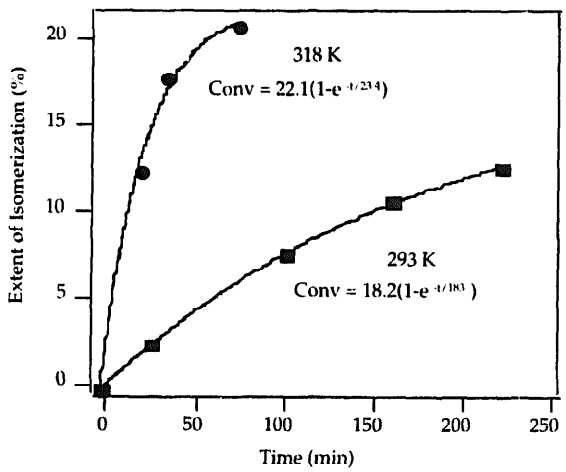


Fig. 1. Isomerization of geraniol to γ-geraniol in methanol with $[RuCl_2(S)\text{-tolyl-binap}]_2 \cdot N(C_2H_5)_3$ as a function of time at 293 K and 318 K.

tion products formed under D_2 show that deuterium appears in the terminal methyl group (indicating hydrogenation of the terminal olefin γ-geraniol) even when the isomerization reaction was not allowed to proceed prior to the introduction of deuterium to begin the reaction. The level of competition between the isomerization and reduction reactions of geraniol is pressure dependent.

Since these two substrates give the same two enantiomeric hydrogenation products, any implication of this competing isomerization pathway for enantioselectivity depend on whether the substrates react to give similar enantioselectivities under a particular set of hydrogenation conditions. Fig. 2 shows that the intrinsic activity and selectivity of the two substrates are significantly different. Over the course of the hydrogenation of the equilibrium substrate mixture, two distinct rate regimes were observed, with a significantly faster rate process being followed by a much slower one. These two processes correspond to two distinct regimes of almost opposite enantioselectivity. Thus geraniol and γ-geraniol exhibit significantly different rates of hydrogenation with respectively high enantioselectivities to β-citronellol products of *opposite* absolute stereoconfiguration. Fig. 3 shows that the (*S*)-citronellol product was produced rapidly in the beginning of the reaction from the γ-geraniol substrate, followed by production of increasing amounts of the (*R*)-citronellol product which formed more slowly from geraniol.

These kinetic results show how the presence of this competing isomerization pathway contributes to observed hydrogen pressure effects on enantioselectivity [13]. If it is assumed that the rate of the hydrogenation reaction is more sensitive to hydrogen pressure than is the isomerization pathway, then high hydrogen pressure increases the geraniol hydrogenation rate relative to its isomerization rate. This results in higher production of

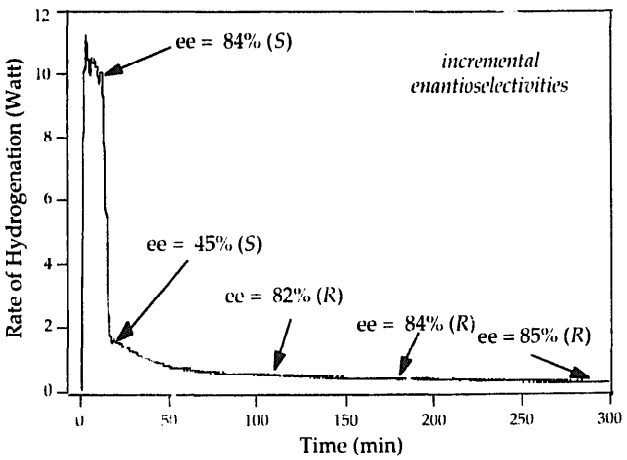


Fig. 2. Rate and instantaneous enantioselectivity of hydrogenation of geraniol with $[RuCl_2(S)\text{-tolyl-binap}]_2 \cdot N(C_2H_5)_3$ in methanol at 293 K and 500 kPa carried out at an agitation speed of 400 rpm.

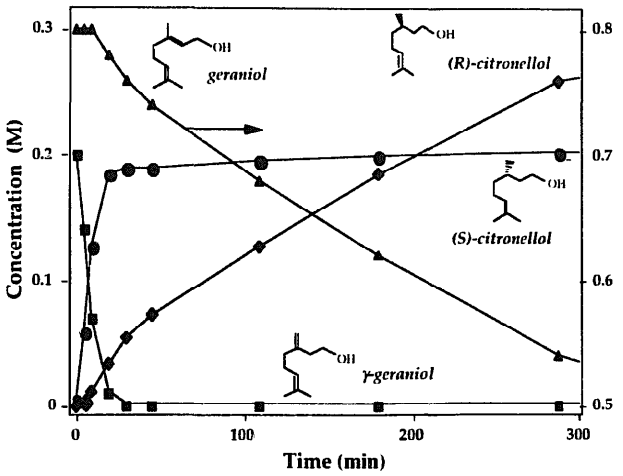


Fig. 3. Concentration of reactant and product species as a function of reaction time in the hydrogenation of geraniol and its isomer γ-geraniol in methanol to form (*R*)- and (*S*)-citronellol with $[RuCl_2(S\text{-tolyl-binap}]_2 \cdot N(C_2H_5)_3$ at 293 K and 500 kPa.

the (*R*)-citronellol, and hence high enantioselectivity, for reactions carried out at higher pressure. At low pressure, the hydrogenation of geraniol may proceed slowly enough to allow significant competition from the isomerization pathway, resulting in a greater contribution from the isomerization of geraniol to γ-geraniol and its subsequent hydrogenation to (*S*)-citronellol. This is in agreement with the suggestion that a larger fraction of the deuteration product originated from the terminal olefin under low pressure reaction than under high pressure reaction.

The observation that the competition between the isomerization and hydrogenation pathways is a function of hydrogen pressure prompted us to explore the extent to which reaction conditions might alter the dominant reaction pathway chosen by geraniol and thus alter the ultimate enantioselectivity achieved in this system. Fig. 4 demonstrates that the range of enantioselectivities achievable in the hydrogenation of geraniol is significant. Using Ru(*S*)-binap, an enantioselectivity of *either* 93% (*R*)-citronellol *or* 93% (*S*)-citronellol could be achieved simply by changing temperature and pressure over a relatively narrow (700 kPa and 35 K) range. The reaction scheme shown in Fig. 4 shows that temperature and pressure may be used to direct the substrate through the isomerization pathway to γ-geraniol, followed by hydrogenation with high enantioselectivity to the (*S*)-product, or to force the direct hydrogenation of geraniol with its concomitant high enantioselectivity to the (*R*)-product. The most striking aspect of these observations is the fact that these opposite enantioselectivities were obtained without changing the chirality of the Ru(*S*)-binap catalyst.

The existence of competing reaction pathways in the hydrogenation of allylic alcohols using Ru(binap) cata-

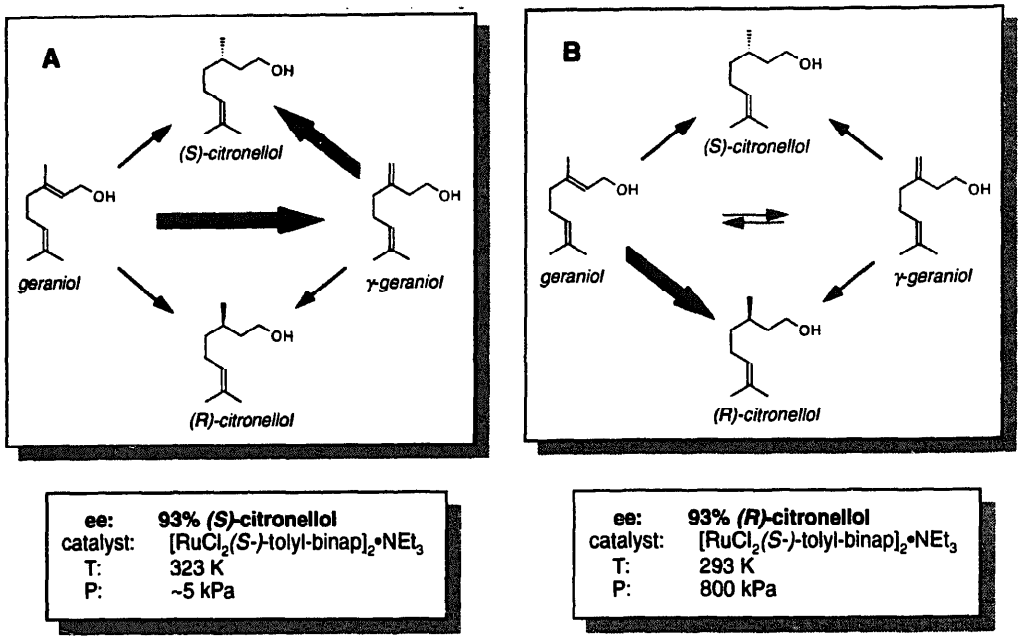


Fig. 4. Reaction scheme describing the competitive hydrogenation–isomerization network in the hydrogenation of geraniol with $[RuCl_2(S)\text{-tolyl-binap}]_2 \cdot N(C_2H_5)_3$.

lysts thus contributes to the observed effects on enantioselectivity attributed to the influence of hydrogen pressure. In such a case where two competing pathways ultimately give the same two enantiomers, albeit in dramatically different relative amounts, the monitoring of reaction progress proved to be a key to understanding the reactive behavior of the catalyst system.

3.2. Intrinsic pressure and temperature dependence of enantioselectivity

A further point to be taken from the results shown in Fig. 4 is that the two substrates yielding hydrogenation products of opposite absolute stereochemistry also have opposite requirements for optimal temperature and pressure conditions: higher pressure and lower temperature gave high enantioselectivity in the case of geraniol, while γ-geraniol required lower pressure and higher temperature for high enantioselectivity. Previous observations of such opposite dependences of pressure and temperature on enantioselectivity include the Rh^+(dipamp)-catalyzed hydrogenation of enamides [14], where low pressures and high temperatures afforded high enantioselectivity, and the Ru(binap) catalyzed hydrogenation of unsaturated alcohols and carboxylic adds [15], where high pressures and low temperatures were required in order to achieve high enantioselectivity. Seldom is an a priori rationalization given for the trends observed for any particular catalyst/substrate combination. In addition, in contrast with our observation, most often it is observed that substrates of a particular type all follow the same pressure and temperature trends with a particular catalyst. Thus it seemed interesting to explore in more detail the intrinsic effects of these reaction variables for the three prochiral isomeric alcohols, geraniol, γ-geraniol, and nerol. Hydrogenation reactions were carried out using the same Ru(*S*)-binap catalyst as above, over a range of temperatures and pressures under conditions where isomerization pathway discussed above was minimized [4].

Fig. 5 plots enantioselectivity as a function of hydrogen pressure for the three substrates, illustrating the intriguing result that enantioselectivity was affected by hydrogen concentration in a different way for each of the three isomers: For geraniol, an *increase* in pressure brought about an increase in enantioselectivity to the (*R*)-citronellol product. For γ-geraniol, increasing pressure *decreased* the high enantioselectivity observed towards (*S*)-citronellol. Changing pressure had *no* effect on enantioselectivity for nerol.

Temperature changes also caused different effects on enantioselectivity for each substrate, as shown in Fig. 6. High enantioselectivity is favored by low temperature

[4] Contribution from the isomerization of γ-geraniol to geraniol under hydrogen may be neglected due to the much faster hydrogenation rate of the terminal olefin compared to isomerization under all conditions of temperature and pressure we studied. Isomerization from nerol to either of the other two isomers was never observed. In the case of geraniol, however, although it is possible to minimize isomerization by minimizing pre-hydrogenation substrate/catalyst contact, it is impossible to be certain that isomerization is not a factor under some conditions, most notably at very low pressures.

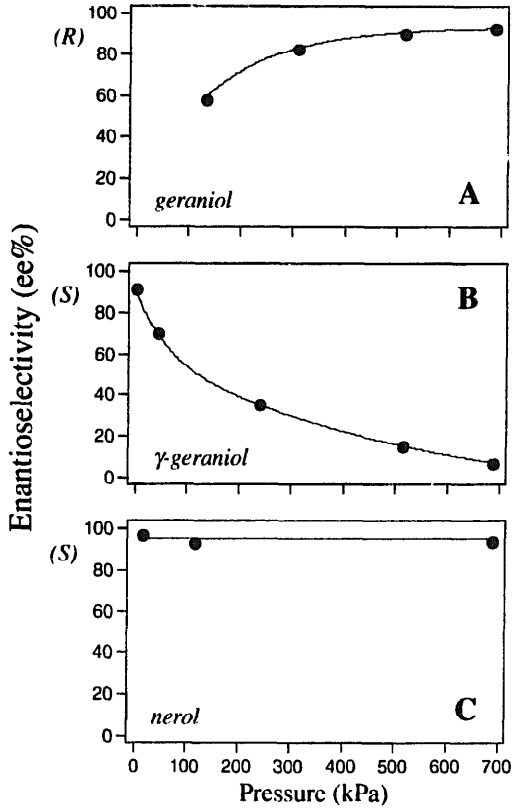


Fig. 5. Enantioselectivity as a function of hydrogen pressure for the hydrogenation of three unsaturated alcohol isomers at 293 K in methanol with $[RuCl_2(S)\text{-tolyl-binap}]_2 \cdot N(C_2H_5)_3$: A) geraniol; B) γ-geraniol; and C) nerol.

for geraniol and by high temperature for γ-geraniol. The third isomer, nerol, exhibited no effect of changing reaction temperature, with enantioselectivity to (*S*)-citronellol remaining very high over the 50 K range studied.

It is also important to note that a wide range of enantioselectivities was observed for geraniol and γ-geraniol over a relatively small range of conditions. Comparison may be made between our conditions of hydrogen pressure, which varied from subambient to less than 10 atm (5–800 kPa), and the conditions of other similar studies, where pressure is often varied from 1–100 atm (100–10000 kPa). In particular, γ-geraniol exhibited the widest range of enantioselectivities for any prochiral substrate to our knowledge in an asymmetric hydrogenation reaction. Fig. 7 shows that the racemic line could be crossed and the sense of the chiral induction inverted as a function of either temperature or pressure for this substrate.

The plots shown in Fig. 7 raise the question of the significance of the "sense" of chiral induction and of the meaning of crossing the racemic line. This line is in fact an artificial (and perhaps misleading) barrier based on the definition of enantioselectivity. As in any chemical reaction, selectivity in an asymmetric catalytic reaction is a measure of relative rates of formation of different products; a racemic mixture of enantiomers is formed whenever the rates of (*R*) and (*S*) formation are equal. The curves in Fig. 7 show simply that the (*R*)-citronellol formation increased faster than that of (*S*)-citronellol as a function of either increasing pressure or decreasing temperature in the hydrogenation of γ-geraniol.

The "sense" of the chiral induction may be a less important consideration than the efficiency of a chiral catalyst in choosing the pathway to one enantiomer over another under various conditions. Fig. 8 shows that for γ-geraniol, the magnitude of the change in enantioselectivity for a given change in pressure was similar at three temperatures in the range 263–318 K, caused by an approximately 15% decrease in the relative rate of formation of the (*S*)-citronellol, although the lowest temperature case happened to show an "inversion" in the sense of the chiral induction over this pressure range. Under low temperature conditions, the Ru(binap) catalyst exhibited less efficiency in differentiating between the (*R*) and (*S*) pathways in γ-geraniol hydro-

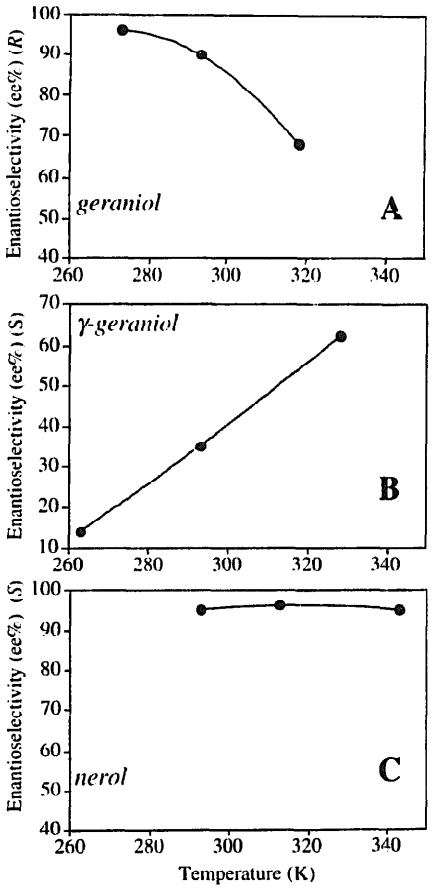


Fig. 6. Enantioselectivity as a function of reaction temperature for the hydrogenation of three unsaturated alcohol isomers at constant pressure in methanol with $[RuCl_2(S)\text{-tolyl-binap}]_2 \cdot N(C_2H_5)_3$: A) geraniol at 689 kPa; B) γ-geraniol at 241 kPa; and C) nerol at 689 kPa.

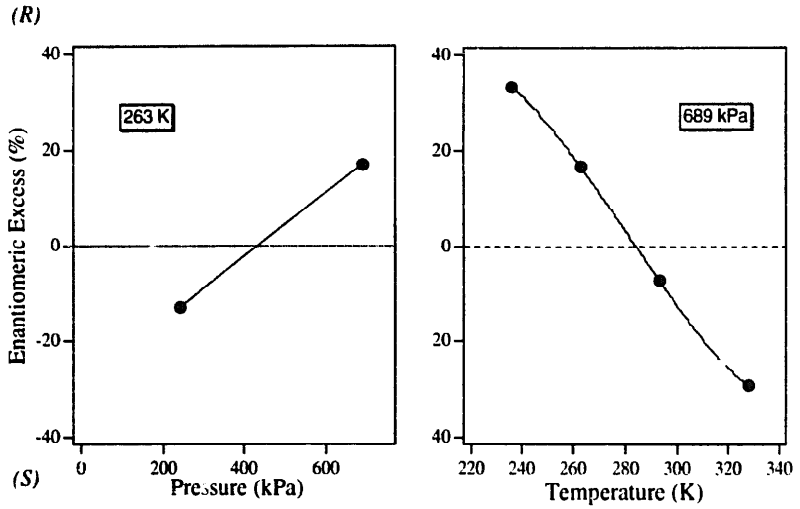


Fig. 7. Enantioselectivity as a function of A) pressure; and B) temperature; in the hydrogenation of γ-geraniol in methanol with $[RuCl_2(S)\text{-tolyl-binap}]_2 \cdot N(C_2H_5)_3$.

genation than it did at higher temperatures. The observed inversion is simply part of a continuous change in the relative rates of (*R*) and (*S*) production over a range of pressures. Thus in this case the influence of pressure on enantioselectivity may be considered to be of equal significance whether or not an inversion in the sense of the chiral induction occurred.

The opposite influence of pressure on enantioselectivity for the two substrates, geraniol and γ-geraniol, may also be examined in the context of relative reaction rates. In fact it may be seen that in the case of both substrates, the effect of increasing pressure is to increase the relative rate of formation of the (*R*)-citronellol product. This results in *increasing* ability to enantiodifferentiate in the case of geraniol hydrogenation,

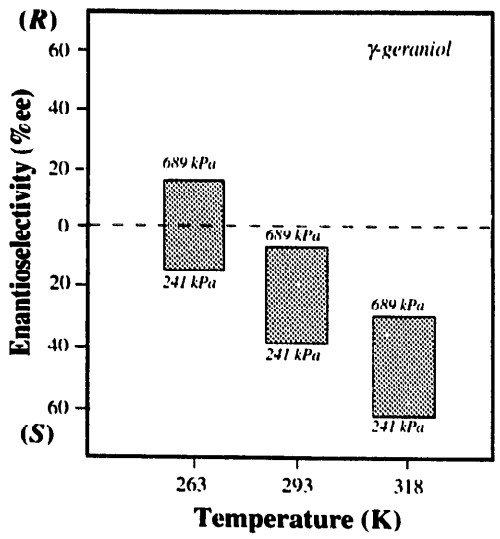


Fig. 8. Change in enantioselectivity in the hydrogenation of γ-geraniol in methanol with $[RuCl_2(S)\text{-tolyl-binap}]_2 \cdot N(C_2H_5)_3$ observed for reactions carried out betwen 241 kPa and 689 kPa at three different temperatures.

which intrinsically exhibits a preference for producing (*R*)-citronellol with the Ru(*S*)-binap catalyst. For γ-geraniol, the increase in (*R*)-citronellol production with increasing pressure results in a *deterioration* of the high enantiodifferentiation to the (*S*)-citronellol which may be obtained using Ru(*S*)-binap.

The fact that enantioselectivity in the hydrogenation of the third isomer, nerol, was insensitive to changes in pressure and temperature suggests that in this case stereochemical considerations outweigh kinetic influences. It is interesting to consider that these three isomers, which produce the same two enantiomeric hydrogenation products using the same catalyst, exhibit three different trends in enantioselectivity as a function of changing conditions. The simple kinetic model introduced by Landis and Halpern [14] in the Rh-catalyzed asymmetric hydrogenation of enamides may be proposed here to describe the behavior of all three isomers. This model couches the observed trends in terms of the relative dominance of different elementary reaction steps in the reaction network under different conditions. This reasoning has recently been extended to rationalize temperature effects on enantioselectivity [16]. Mechanistic investigations of the current work will be published separately.

This example demonstrates that even in the absence of a competing reaction which may alter enantioselectivity, reaction conditions may have a significant influence on the chiral efficiency of Ru(binap) catalysts in the asymmetric hydrogenation of prochiral alcohols. In the case of the terminal isomer γ-geraniol, the ability of the catalyst to direct the hydrogenation spans a range from nearly none (racemic product) to nearly perfect (over 99%ee to (*S*)-citronellol). In addition, preference for either the (*R*) or the (*S*) product could be observed without changing the chirality of the binap ligand.

These results provide a clear illustration of the importance of considering the role that kinetic parameters may play in determining the chiral efficiency in a given catalyst/substrate system.

4. Influence of diffusion limitations on enantioselectivity

Homogeneous catalytic hydrogenation reactions represent complicated systems of mass transfer in which the two reactants, an organic substrate and hydrogen, are initially present in two separate phases. The transport of hydrogen gas into the liquid phase appears as the first rate step in the sequence of binding and reaction steps that characterize the overall reaction mechanism. An assumption implicit in most studies is that the solution is saturated with hydrogen under reaction conditions. In this case the gas–liquid mass transfer step is analogous to a pre-equilibrium step in a reaction mechanism, and the gas-phase hydrogen pressure may be used as a kinetic parameter to describe the concentration of this reactant at the catalyst site. However, this assumption is valid only when the rate of consumption of hydrogen in the catalytic reaction is very low compared with the maximum rate of gas-liquid mass transfer. The maximum rate of hydrogen mass transfer provides an upper limit to the rate at which hydrogen may be supplied to the catalyst for reaction and is given by Eq. (3), in which the first-order rate constant for mass transfer is given by $k_L a$ and $[H_2]^{sat}$ is the hydrogen solubility in the solution at the temperature and pressure of the experiment.

$$r_{max} = k_L a * [H_2]^{sat}. \quad (3)$$

The rate constant for gas–liquid mass transfer is affected by a number of experimental parameters including the agitation speed of the reactor. It may be assumed that the reaction is not governed by this mass transfer process if the observed rate of the catalytic reaction is at least ten times lower than the maximum hydrogen gas–liqud mass transfer rate. If this condition is not met, the concentration of hydrogen available for reaction at the catalyst site will be lower than when the solution is saturated at the temperature and pressure of the reaction [6].

The implications of hydrogen diffusion limitations for asymmetric hydrogenation reactions which exhibit a pressure dependence on enantioselectivity are clear: The concentration of hydrogen in solution during reaction under such diffusion constraints will correspond to that of a solution saturated with hydrogen at an "effective" pressure lower than the actual hydrogen pressure above the solution. The measured enantioselectivity under diffusion limitations will correspond to that observed in a kinetically controlled reaction at the lower "effective" pressure.

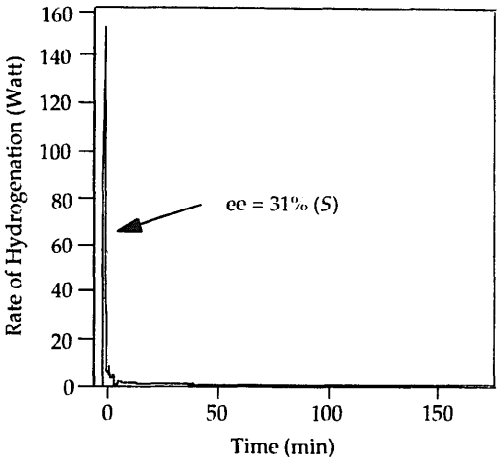


Fig. 9. Rate of hydrogenation for reaction of an equilibrium mixture of geraniol and γ-geraniol, shown in Fig. 1. All experimental parameters are identical with the exception of the agitation speed of 1600 rpm instead of 400 rpm. Enantioselectivity is given as incremental value at the reaction time marked.

A graphic illustration of a diffusion-limited reaction may be given by comparing Figs. 1 and 8. In each case, a plot of reaction rate vs. time is shown for an equilibrium mixture of geraniol and γ-geraniol substrates using Ru(*S*)-binap. It is interesting to focus on the first rate regime, which corresponds to the hydrogenation of the terminal isomer, γ-geraniol. The only experimental difference between the reactions shown in the two figures is that the agitation speed was increased four-fold for the reaction shown in Fig. 9. This increase resulted in a dramatic, 15-fold increase in the hydrogenation rate of γ-geraniol. (Compare the y-axis values in Fig. 1 and Fig. 9). The rate curve in this regime spans 0–20 min in Fig. 1 and is given by a sharp spike of less than 2 min in Fig. 8. The area under these two curves, however, is identical, since in both cases this area is proportional to the heat of reaction of ca. 0.19 M γ-geraniol, as described by Eq. (1).

This comparison clearly shows that the hydrogenation of γ-geraniol was severely hydrogen diffusion limited under the conditions shown in Fig. 1, and that the effective pressure experienced by the catalyst was significantly lower than the 500 kPa measured in the gas phase above the solution [5]. The consequences for enantioselectivity are as striking as those for reaction rate: γ-geraniol hydrogenation under the conditions in Fig. 1,

[5] The hydrogenation of geraniol would not be diffusion-limited at this agitation speed since it reacts at a much slower rate than does γ-geraniol. However, in this reaction of a mixture of substrates, geraniol hydrogenation-also proceeded at the lower effective pressure because of the rapid consumption of hydrogen by γ-geraniol.

corresponding to a lower effective pressure, gave 85 ee% to (*S*)-citronellol. When more efficient agitation caused the effective pressure to approach the actual pressure, the enantioselectivity dropped to 31 ee% to (*S*)-citronellol, see Fig. 9. This is in agreement with the results discussed in the section above showing that higher hydrogen pressure causes decreased enantioselectivity in γ-geraniol hydrogenation.

Such a large difference in enantioselectivities for the same reaction carried out at the same constant gas-phase hydrogen pressure confirms the importance of knowledge of the actual solution concentration of hydrogen. These findings also clearly illustrate that kinetic control of the reaction must be assured if a rational interpretation of rate and enantioselectivity dependences is to be made in asymmetric catalytic hydrogenation reactions which exhibit a pressure dependence on enantioselectivity.

5. Conclusions

The critical role that reaction conditions may play in determining enantioselectivity was demonstrated for a number of examples of the hydrogenation of unsaturated alcohols using a Ru(*S*)-binap catalyst. In the first example, the relative rates of hydrogenation and a competing isomerization reaction dictated the enantioselectivity that was ultimately observed in the hydrogenation of geraniol.

The second example illustrated that a wide range of enantioselectivities may be obtained due to intrinsic temperature and pressure dependences even in the absence of a competing reaction such as the isomerization pathway described above. The magnitude and sense of these effects is substrate dependent, as shown by the very different behavior exhibited by the three isomers studied. Where high enantioselectivity is favored by high pressure and low temperature for geraniol, γ-geraniol requires low pressure and high temperature, and nerol is insensitive to changes in temperature and pressure.

The third example demonstrated the critical role that gas–liquid mass transfer plays in determining solution hydrogen concentration, which is not necessarily kinetically equivalent to the measured hydrogen pressure. The wide variation in enantioselectivity observed in these examples demonstrates that a general understanding of reaction kinetics and pathways must accompany considerations of the three-dimensional stereochemical aspects of the chiral catalyst when interpreting the enantioselective efficiency of a catalyst system for asymmetric hydrogenation.

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