FULL PAPERS

The Major/Minor Concept: Dependence of the Selectivity of Homogeneously Catalyzed Reactions on Reactivity Ratio and Concentration Ratio of the Intermediates

Thomas Schmidt, Zhenya Dai, Hans-Joachim Drexler, Marko Hapke, Angelika Preetz, and Detlef Heller*[a]

Dedicated to Jack Halpern

Abstract: The homogeneously catalyzed asymmetric hydrogenation of prochiral olefins with cationic Rh^I complexes is one of the best-understood selection processes. For some of the catalyst/substrate complexes, experimental proof points out the validation of the major/minor principle; the concentration-deficient minor substrate complex, which has very high reactivity, yields the excess enantiomer. As exemplified by the reaction system of [Rh(dipamp)-$(MeOH)_2]^+$/methyl (Z)-α-acetamido-cinnamate (dipamp = 1,2-bis((o-methoxyphenyl)phenylphosphino)ethane), all six of the characteristic reaction rate constants have been previously identified. Recently, it was found that the major substrate complex can also yield the major enantiomer (lock-and-key principle). The differential equa- tion system that results from the reaction sequence can be solved numerically for different hydrogen partial pressures by including the known equilibrium constants. The result displays the concentration–time dependence of all species that exist in the catalytic cycle. On the basis of the known constants as well as further experimental evidence, this work focuses on the examination of all principal possibilities resulting from the reaction sequence and leading to different results for the stereochemical outcome. From the simulation, the following conclusions can be drawn:

1) When an intermediate has extreme reactivity, its stationary concentration can become so small that it can no longer be the source of product selectivity; 2) in principle, the major/minor and lock-and-key principles can coexist depending on the applied pressure; 3) thermodynamically determined intermediate ratios can be completely converted under reaction conditions for a selection process; and 4) the increase in enantioselectivity with increasing hydrogen partial pressure, a phenomenon that is experimentally proven but theoretically far from being well-understood, can be explained by applying both the lock-and-key as well as the major/minor principle.

Keywords: asymmetric synthesis · enantioselectivity · homogeneous catalysis · hydrogenation · reaction mechanisms

Introduction

Catalytic asymmetric hydrogenation with cationic Rh^I complexes is one of the best-understood selection processes. Ac-

[a] Dr. T. Schmidt, Dr. Z. Dai, Dr. H.-J. Drexler, Dr. M. Hapke, A. Preetz, Dr. D. Heller
Leibniz-Institut für Katalyse an der
Universität Rostock e.V.
Albert-Einstein-Str. 29a
18059 Rostock (Germany)
Fax: (+49) 381-128151183
E-mail: detlef.heller@catalysis.de

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cording to Halpern and Landis[1] as well as Brown,[2] asymmetric hydrogenation proceeds by the reaction sequence presented in Scheme 1. The diastereomeric substrate complexes are formed in pre-equilibria from the solvate complex as the active species by coordination of the prochiral olefin. In a sequence of elementary steps, namely, oxidative addition of hydrogen, insertion, and reductive elimination, the substrate complexes react to give the enantiomeric products. Recent literature with regard to the so-called "hydride route" can be found in Ref. [3], and a current review about the mechanism of enantioselective hydrogenations is given in Ref. [4].

The X-ray structure of the diastereomeric complex [Rh-((S,S)-chiraphos)(eac)]ClO_4 (chiraphos = 2,3-bis(diphenyl-

phosphino)butane, eac=ethyl (Z)-α-acetamidocinnamate) determined in 1980,[1a] already proved that oxidative addition of hydrogen should lead to the S enantiomer, according to well-accepted mechanistic assumptions, but not to the experimentally observed excess of the R product. Arising from the mechanistic findings and the exclusion of other explanations, the result could only be explained by the exceedingly low reactivity of the major complex relative to the minor diastereomer.[5] Further support for selectivity dictation by the minor reaction channel was provided isochronically by Brown and Chaloner.[2a] They not only detected a hydridoalkyl complex with the chiral ligand dipamp (1,2-bis((o-methoxyphenyl)phenylphosphino)ethane) at low temperatures with NMR spectroscopy, they also demonstrated that the hydridoalkyl complex was obtained from the minor reaction channel, therefore designated as the selectivity-determining pathway.

In their fundamental work, Landis and Halpern showed that in the case of the asymmetric hydrogenation of methyl (Z)-α-acetamidocinnamate (mac) with [Rh((R,R)-dipamp)-(MeOH)$_2$]BF$_4$ at 25 °C, the thermodynamically less stable minor substrate complex is about 600 times as reactive as the major diastereomer, which is present in solution in a tenfold excess.[1d] Hence, the predominant source of selectivity is the ratio of the rate constants of the oxidative addition of hydrogen (k_{2min}/k_{2maj}).

The discovery that the less stable and therefore less concentrated intermediate in solution determines the stereochemical course of the reaction and, thus, the overall selectivity predominantly through its high reactivity came as a big surprise at the time. It entered the literature as the so-called major/minor concept, also known as the anti-lock-and-key principle.[6] So far, it has been proven experimentally in the literature for five systems.[1a,d,2a,7,8] The major/minor concept can be expressed by the following three inequations, which have to be valid simultaneously [Eq. (1)]:

Abstract in German: Die homogen katalysierte asymmetrische Hydrierung prochiraler Olefine mit kationischen Rh^I-Komplexen ist einer der am besten verstandenen Selektionsprozesse. In vorgelagerten Gleichgewichten entstehen aus dem Solvenskomplex und dem prochiralen Olefin diastereomere Substratkomplexe. Die geschwindigkeitsbestimmende oxidative Addition von Wasserstoff führt zu den enantiomeren Produkten. Experimentell konnte für einige Katalysator/Substrat-Systeme das sogenannten Major/Minor-Prinzip belegt werden; der im Unterschuss vorliegende Minor-Substratkomplex führt durch seine hohe Reaktivität zum Überschussenantiomer. Im Falle des [Rh-(dipamp)(MeOH)$_2$]$^+$ (dipamp=1,2-bis((o-methoxyphenyl)-phenylphosphino)ethan) sowie (Z)-(N)-Acetylaminozimt-säuremethylester konnten Halpern et al. alle sechs die Reaktionssequenz charakterisierenden Geschwindigkeitskonstanten ermitteln. In jüngerer Zeit wurde gefunden, dass auch der Major-Substratkomplex ebenfalls zum Hauptenantiomer führen kann (Schlüssel/Schloss-Konzept). Das aus der Reaktionssequenz resultierende Differentialgleichungssystem lässt sich mit den bekannten Geschwindigkeitskonstanten numerisch für verschiedene Wasserstoffpartialdrucke lösen. Im Ergebnis erhält man die Konzentrations-Zeit-Abhängigkeiten aller Spezies des Katalysezyklus. Auf der Basis der bekannten Konstanten sowie weiterer experimenteller Befunde war es Ziel der Arbeit, alle prinzipiellen Möglichkeiten der Reaktionssequenz zu untersuchen. Aus den Simulationen lassen sich folgende Schlussfolgerungen ziehen: 1) Die extreme Reaktivität eines Intermediates kann dazu führen, dass die stationäre Konzentration desselben so klein wird, dass es nicht mehr die Quelle der Produktselektivität ist. 2) Das Major/Minor- und das Schlüssel/Schloss-Prinzip können prinzipiell in Abhängigkeit vom Wasserstoffdruck nebeneinander vorliegen. 3) Thermodynamisch determinierte Intermediatverhältnisse können für einen Selektionsprozess unter Reaktionsbedingungen komplett invertieren. 4) Die experimentell belegte, aber bisher nicht schlüssig verstandene Steigerung der Enantioselektivität mit steigendem Wasserstoffpartialdruck lässt sich sowohl mit dem Schlüssel/Schloss- als auch mit dem Major/Minor-Konzept erklären.

$$k_{2min} > k_{2maj}, \; [ES_{maj}] > [ES_{min}], \; (k_{2min}/k_{2maj}) > [ES_{maj}]/[ES_{min}] \quad (1)$$

The initial idea of an extreme reactivity of one intermediate is a basic principle in homogeneous catalysis and is reflected, for instance, in the concept of ligand-accelerated catalysis (LAC).[9]

Besides the major/minor concept, it was recently recognized that the major substrate complex can also lead to the major enantiomer as the main hydrogenation product.[10] That behavior is already known from enzyme catalysis under the term lock-and-key principle, developed by Fischer.[11]
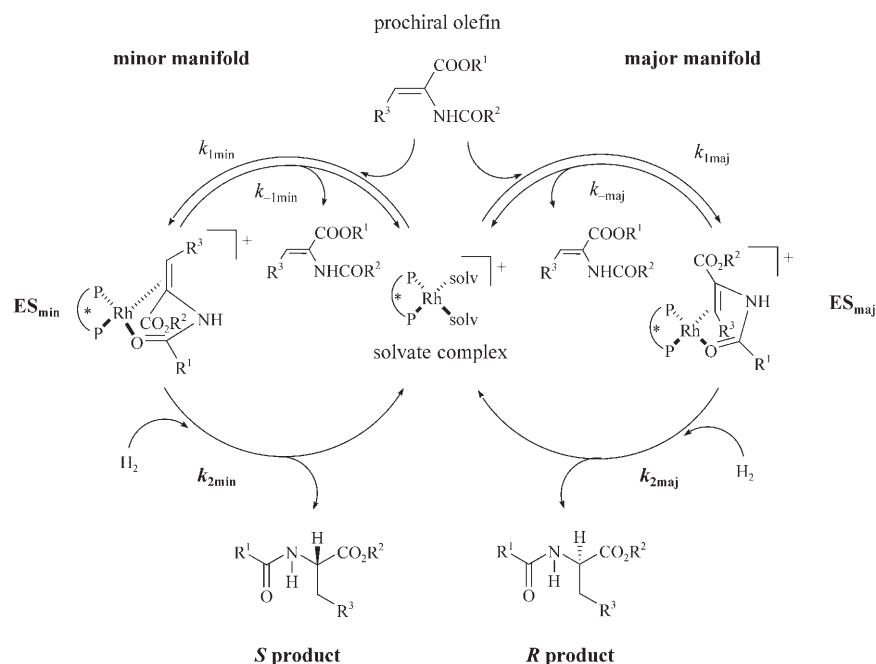
The ratio of the reaction rates for product formation in Scheme 1 leads to Equation (2), with the assumption that the solution does not contain any product at the beginning of the reaction:[1d,12]

$$\frac{[S]}{[R]} = \frac{[ES_{min}]}{[ES_{maj}]} \cdot \frac{k_{2min}}{k_{2maj}} = \left(\frac{\frac{k_{1min}}{k_{-1min}+(k_{2min}\cdot[H_2])}}{\frac{k_{1maj}}{k_{-1maj}+(k_{2maj}\cdot[H_2])}} \right) \cdot \frac{k_{2min}}{k_{2maj}} \quad (2)$$

The selectivity, defined as the ratio of the enantiomeric products is, in principle, the result of two factors, namely the intermediate ratio ([ES$_{min}$]/[ES$_{maj}$]) as the first, and the ratio of the intermediate reactivities (k_{2min}/k_{2maj}) as the second selection level.

The overall selectivity is not only the result of the intrinsic potential of the catalyst, determined by the ligand, but also the result of external parameters, such as hydrogen pressure[13] and temperature. The general influence of pressure and temperature on enantioselectivity was systematically studied and interpreted by the Halpern group.[1b–d]

Scheme 1. Selection model of the Rh[I]-catalyzed asymmetric hydrogenation of prochiral olefins to *S* amino acid derivatives as the excess enantiomer, according to Halpern, Landis, and Brown. ES_{maj} and ES_{min} are the major and the minor substrate complexes, respectively.

In their examination of the hydrogenation of geraniol with [RuCl$_2$((*S*)-tolyl-binap)]$_2\cdot$NEt$_3$ (binap $=$ 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), Blackmond and co-workers impressively demonstrated the influence of external parameters. At 5 kPa and 50 °C, (*S*)-citronellol was obtained with a selectivity of 93 % *ee*, whereas conditions of 800 kPa and 20 °C led to (*R*)-citronellol with 93 % *ee*.[14]

Notably, despite enormous success and the increasing performance of theoretical methods such as the calculation of energetic barriers for single reaction steps as well as transition states,[10d,15] the possible influence of the abovementioned external parameters on enantioselectivity cannot yet be predicted adequately.

Although, in the case of mac hydrogenation with [Rh-(dipamp)(MeOH)$_2$]BF$_4$, the ratio of the diastereomeric substrate complexes is not crucial for the overall selectivity, the intermediate ratio is, as a matter of principle, important for the experimentally observed selectivity. This can be illustrated by the following features:

- The known pressure dependence of enantioselectivity in asymmetric hydrogenation[1d,16] can be explained plausibly by a change in the stationary intermediate ratio.[17]
- The nonlinear dependence of logarithmic product ratios as a function of the reciprocal temperature (isoinversion principle)[18] can be reduced to the corresponding nonlinear change in the intermediate ratio (Scheme 1).[19]

The classical example for a disturbance of pre-equilibria is the pressure dependence of the enantioselection in asymmetric hydrogenation. By increasing the isobaric hydrogen pressure, the pseudo rate constant $k'_{2i} = k_{2i}\cdot[H_2]$ for oxidative addition of hydrogen is raised in such a way that this originally rate-determining step becomes approximately as fast as the reverse reaction of the diastereomers converting into the starting materials. Disturbance of the adjustment of one or both pre-equilibria influences the intermediate ratio owing to coupling of the ratio of the diastereomeric intermediates through the solvate complex. This change in the intermediate ratio leads to a change in the observed overall selectivity, according to Equation (2). Further increase in pressure results in a threshold at which the product ratio is only a function of the intermediate formation and is therefore independent of the applied pressure.

So far, on the basis of the major/minor concept, it was considered that an increase in pressure always leads to a drop in selectivity. Plausible reasons for the increase in the experimentally known selectivity with rising pressure are not yet known.[20,16c]

In this work, on the basis of published rate constants for asymmetric hydrogenation,[1d] all imaginable reaction possibilities for the reaction mechanism given in Scheme 1, which is characterized by six rate constants, will be pointed out and discussed. We will focus on conditions under which the stereochemical result is determined either by the major/minor concept or the lock-and-key concept as well as the influence of hydrogen pressure on enantioselectivity.

Results and Discussion

With the known rate constants for the asymmetric hydrogenation of mac with [Rh((*R,R*)-dipamp)(MeOH)$_2$]BF$_4$ at 25 °C (Table 1, Ref. [1d]), the differential equation system derived from Scheme 1 (see Supporting Information) can be solved numerically for various pressures.[21] Thus, all relevant concentration–time curves can be calculated.[22]

Major/Minor Principle: Results from the Literature

Figure 1 shows the results for the original data, taken from Ref. [1d], for 1 and 100 bar pressures. For each pressure, the time dependence of the concentration of the prochiral olefin and the enantiomeric products are shown in Figures 1a and b, whereas the concentrations of the catalytic species, that is,

Table 1. Rate constants for the asymmetric hydrogenation of mac with $[Rh((R,R)\text{-dipamp})(MeOH)_2]BF_4$.

	k_{1min} [$L\,mol^{-1}\,s^{-1}$]	k_{1maj} [$L\,mol^{-1}\,s^{-1}$]	k_{-1min} [$L\,s^{-1}$]	k_{-1maj} [$L\,s^{-1}$]	k'_{2min}[a] [$L\,s^{-1}$]	k'_{2maj}[a] [$L\,s^{-1}$]	$[ES_{maj}]/[ES_{min}]$ ($P_{H2}=0$)	k_{2min}/k_{2maj}
Ref. [1d]	10600	5300	3.2	0.15	2.3	0.004	91.5:8.5	575
Example 1[b]	**5300**	**10600**	3.2	0.15	2.3	0.004	**97.7:2.3**	575
Example 2[b]	10600	5300	3.2	0.15	**0.004**	**2.3**	91.5:8.5	**1:575**
Example 3[b]	10600	5300	**2.3**	**0.004**	**3.2**	**0.15**	**99.6:0.4**	**21.3**

[a] The values of k'_{2i} already contain the solubility of hydrogen in methanol at an overall pressure of 1.0 bar.[23]
[b] Examples 1–3 represent simulated cases in which the rate constants are exchanged.

the solvate complex or the diastereomeric substrate complexes, respectively, are plotted in Figures 1 c and d. As shown experimentally by Landis and Halpern, the concentration of the minor substrate complex decreases with increasing pressure as the concentration of the major diastereomer increases. The reason for this behavior is the disturbance of the pre-equilibria followed by a change in the intermediate ratio, resulting in a decreasing enantioselectivity with increasing hydrogen pressure. In Figure 2, the ratio of the intermediates, $[ES_{maj}]/[ES_{min}]$ (highlighted in magenta), as well as the ratio of the enantiomers, $[S]/[R]$ (highlighted in gray), are plotted as a function of pressure. According to the major/minor concept, the *S*-configured main product (red) originates not from the dominant intermediate (blue),

which is true for the whole given pressure range. However, the area in which the selectivity is only a function of the intermediate formation is not reached in the simulation. For that, an enantiomeric ratio of 2 ($k_{1min}/k_{1maj}=10\,600:5300$; green) would have resulted. At pressures high enough to result in such low enantiomeric ratios, the enantioselectivity becomes independent of the hydrogen pressure over a wide pressure range.

Example 1: Influence of the Rate Constants on Intermediate Formation

We showed by stopped-flow measurements that the rate constant for the formation of different diolefin complexes from the solvate complex and the corresponding diolefin (COD=1,5-cyclooctadiene, NBD=norbornadiene) depends on the bisphosphane ligand (Table 2).[25] The formation of the NBD complex proceeded quicker with the ligand Ph-β-glup-OH (Phenyl-2,3-bis-(*O*-diphenylphosphino)-β-D-glyco-
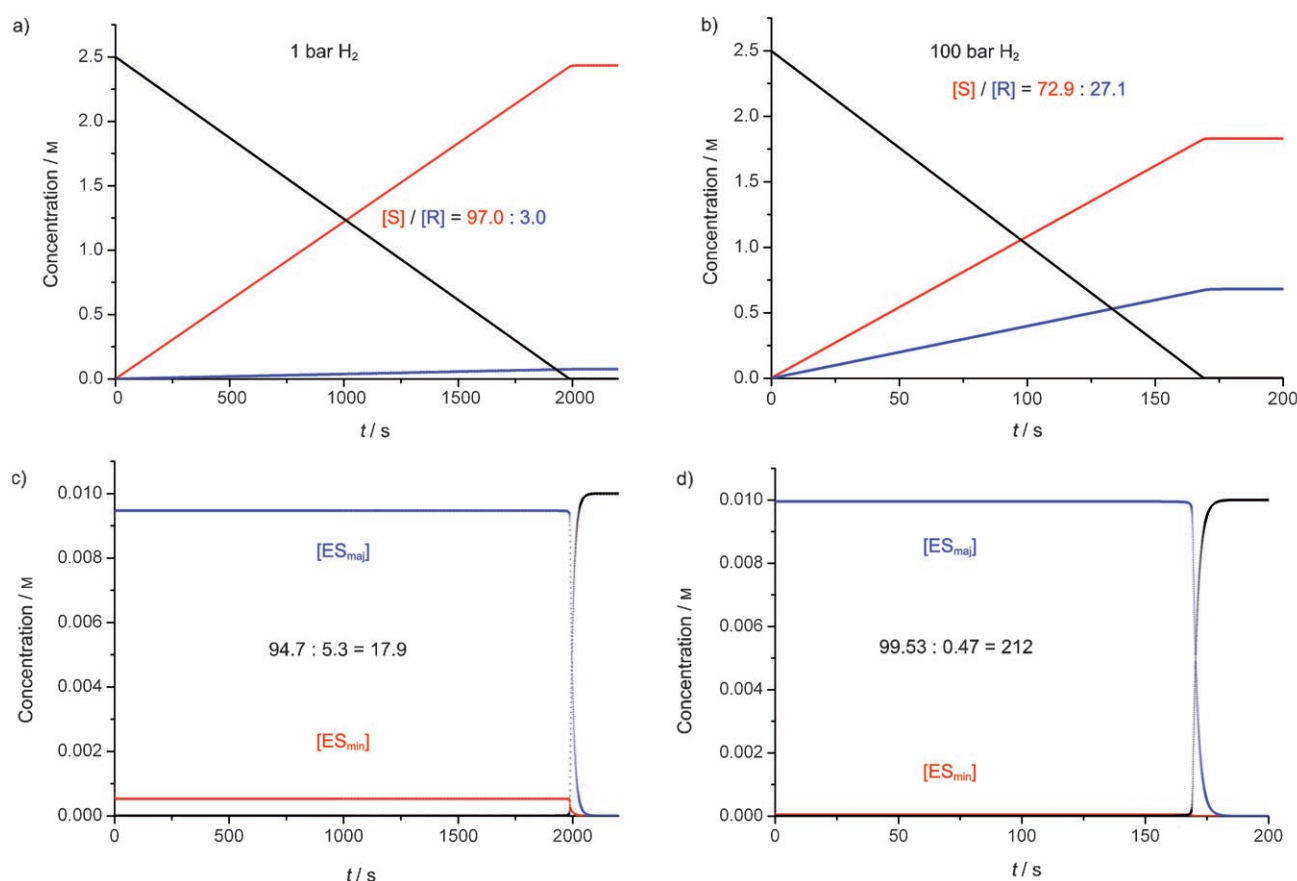

Figure 1. Concentration–time plots for all concentrations with the experimentally derived rate constants according to Table 1, Ref. [1d] for 0.01 mmol catalyst and 2.5 mmol prochiral olefin (equilibrated mixture of substrate complexes at time $t=0$[24]). Black line: a) and b) substrate concentration, c) and d) concentration of solvate complex; blue line: [R] or concentration of major diastereomer; red line: [S] or concentration of minor diastereomer.
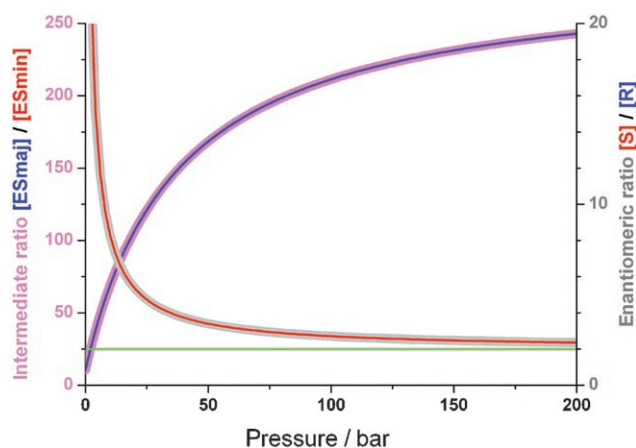
Figure 2. Dependence of intermediate ratio (highlighted in magenta, predominantly determined by major diastereomer, blue line) and enantiomeric ratio (highlighted in gray, predominantly determined by S product, red line) on the hydrogen pressure according to Table 1, Ref. [1d].
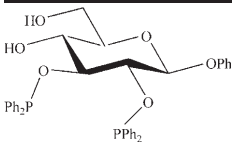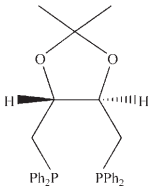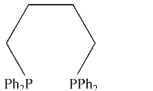
Table 2. Rate constants for the formation of the corresponding diolefin complexes from [Rh(bisphosphane)(MeOH)$_2$]BF$_4$ and the diolefins COD and NBD.[a]

Ligand		k_{1COD} [L mol^{-1} s^{-1}]	k_{1NBD} [L mol^{-1} s^{-1}]
	Ph-β-glup-OH	25	85
	(R,R)-diop	145	59
	dppb	232	136

pyranoside), whereas in case of the diop ligand (2,3-isopropylphosphino-2,3-dihydroxy-1,4-bis-(diphenylphosphino)-butane) as well as dppb (1,4-bis-(diphenylphosphino)-butane), the reaction with COD was faster. To investigate the consequences of such behavior, the rate constants determined by Landis and Halpern for the formation of the substrate complexes were interchanged (Table 1, example 1). As a result, only the ratio of the stability constants is changed slightly (Table 1). The results of the numerical solution of the differential equation system are again presented for 1 and 100 bar pressures (Figure 3). The intermediate ratio [ES$_{maj}$]/[ES$_{min}$] and the enantiomeric ratio, each as a function of hydrogen pressure, are displayed in Figure 4. Although at low pressure the expected results were obtained, interesting changes were observed at 100 bar.

The intermediate ratio [ES$_{maj}$]/[ES$_{min}$] at 100 bar (Figure 3d) yielded a value of 832. This is significantly higher than the ratio of the rate constants for oxidative hydrogen addition ($k_{2min}/k_{2maj} = 575$), which is considered to be the key source of overall selection. Surprisingly, the selectivity of the overall process is now predominantly determined by the intermediate ratio or, more exactly, the major intermediate. The result is inversion of the product selectivity.

At about 35 bar, the influence of the intermediate ratio and the ratio of reactivity are balanced, thus leading to a racemic product mixture ([S]/[R] = 1; Figure 4). A decrease in enantioselectivity with increasing hydrogen pressure, which finally leads to inversion of selectivity, is already known in the asymmetric hydrogenation of prochiral olefins[16a,b,26] and could be caused by the behavior described above.[27]

Our results clearly demonstrate that the extremely high reactivity of one species does not necessarily lead to the major selection product. The influence of extremely high reactivity, which is expressed in basic concepts such as the major/minor principle or ligand-accelerated catalysis, is limited by the nature of the systems. In other words, the extra-

ordinary reactivity of an intermediate does not lead to the major product in cases whereby the concentration of the intermediate is too low. The rate of product formation is the result of the intermediate concentration and the coupled, pressure-dependent (pseudo) rate constant.

In this context, some important remarks should be made. The small stationary concentration of the minor diastereomer, especially at high pressure,[28] is not caused by a disturbance of the pre-equilibrium ($k_{1min} = 5300$ L (mol s)$^{-1}$, $k'_{2min} = 230$ s^{-1} at 100 bar). Instead, after a catalytic cycle is finished, the solvate complex is mainly transferred to the less reactive major pathway where it accumulates because of the relatively low reactivity of the major intermediate. Consequently, the stationary concentration of the minor substrate complex becomes extremely low during the hydrogenation process arising from the solvate complex coupled system.

Figure 3 also points out another feature. Whereas at a pressure of 1 bar the main product is formed from the minor diastereomer according to the major/minor principle, at a pressure of 100 bar the main product comes from the major intermediate. In other words, the major/minor principle and the lock-and-key principle can coexist in the same system, depending on the hydrogen pressure.

In the simulated example (Figure 4), at pressures below 35 bar, the major/minor principle is valid, and the ratio of the intermediates is smaller than the reactivity ratio of 575. On the other hand, at pressures above 35 bar, the reaction proceeds according to the lock-and-key principle, and the ratio of the intermediates is larger than 575.

Example 2: Inversion of the Thermodynamically Determined Intermediate Ratio under Reaction Conditions

For the hydrogenation of COD/NBD mixtures with cationic rhodium complexes as a model reaction, we were the first to prove qualitatively, by using UV/Vis and NMR spectroscopy
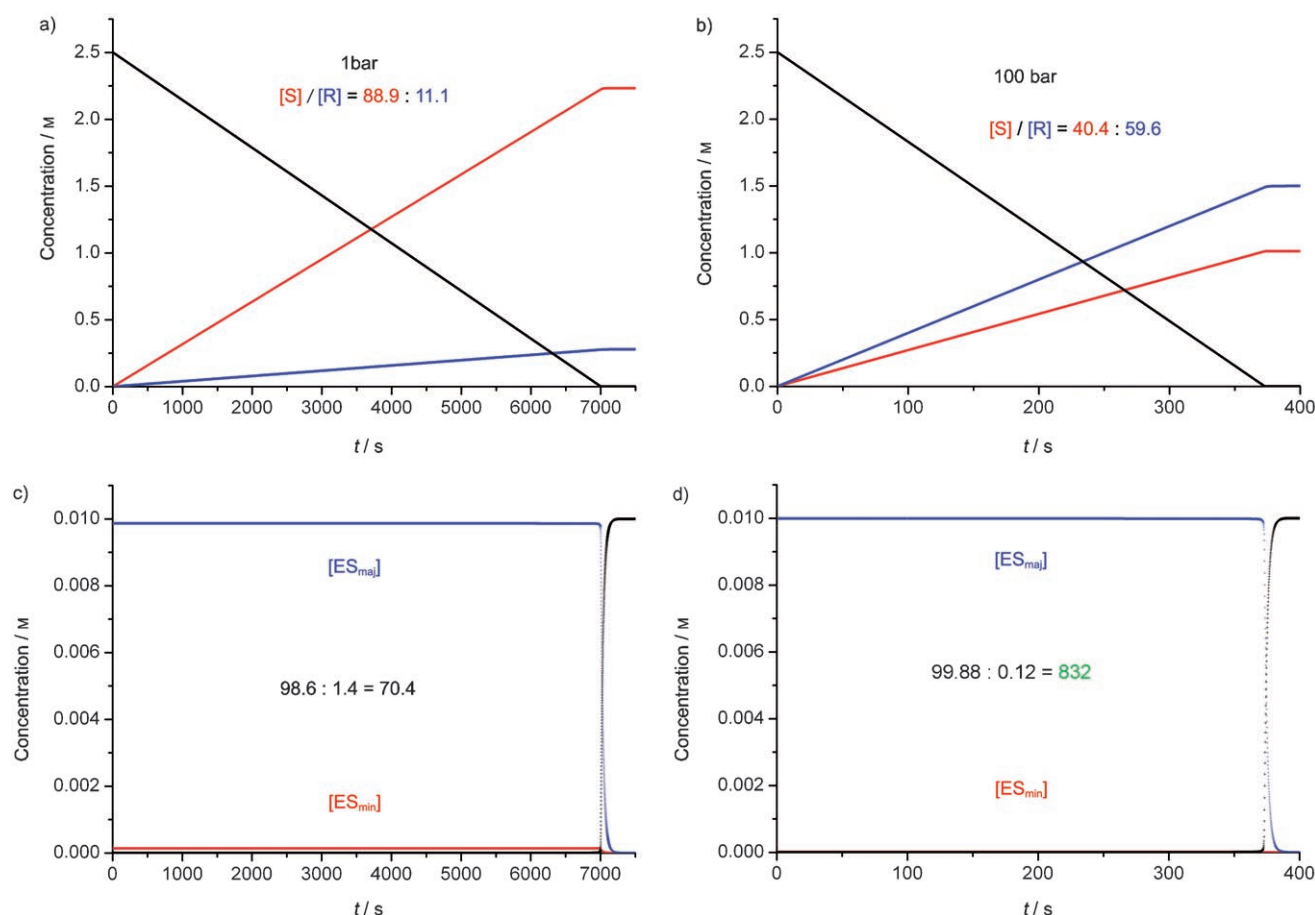
Figure 3. Simulated time dependence for all concentrations for Table 1, example 1: 0.01 mmol precatalyst and 2.5 mmol prochiral olefin (equilibrated mixture of diastereomeric substrate complexes at time $t=0$[24]). Black line: a) and b) substrate concentration, c) and d) concentration of solvate complex; blue line: [R] or concentration of major diastereomer; red line: [S] or concentration of minor diastereomer.

for rather slow hydrogenations,[29] that the thermodynamically determined ratio of intermediates can be interchanged
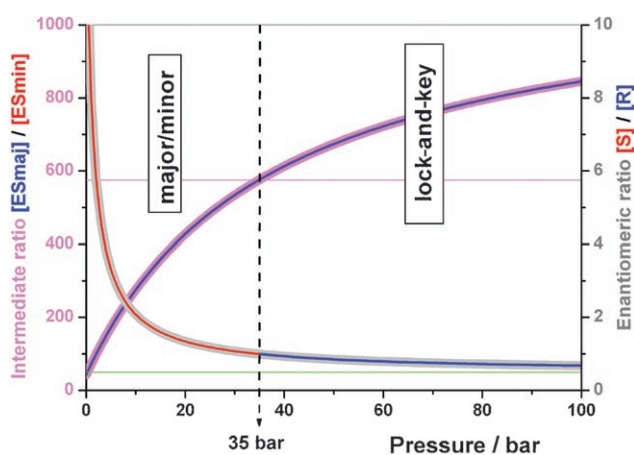

Figure 4. Dependence of intermediate ratio (highlighted in magenta, predominantly determined by major diastereomer, blue) and enantiomeric ratio (highlighted in gray, predominantly determined by S product until 35 bar, red line, then determined by R product, blue line) on the hydrogen pressure for Table 1, example 1.

under reaction conditions. Whereas under argon the NBD complexes were clearly more stable, under hydrogenation conditions, the COD complexes were the dominant species. In other words, the thermodynamic and kinetic major intermediates are different. Such an interchange of intermediate ratios by switching from inert to reaction conditions was not taken into account for the possible reaction sequences in the selection processes in any of the published discussions so far.

To investigate whether such behavior is a general possibility for asymmetric hydrogenations, the original reactivities of the intermediates according to Ref. [1d] were interchanged (Table 1, example 2).

The interchange of the reactivity ratio did not influence the principal reactivity difference between the substrate complexes. However, the major substrate complex now dominated the selectivity owing to its higher reactivity. The thermodynamic ratio of the diastereomers did not differ from the original result of Landis and Halpern (Table 1).

Figure 5 shows the results of the numerical solution of the differential equation system for 0.25 and 4 bar pressures. In Figure 6, the intermediate ratio as well as the enantiomeric ratio are plotted against hydrogen pressure.
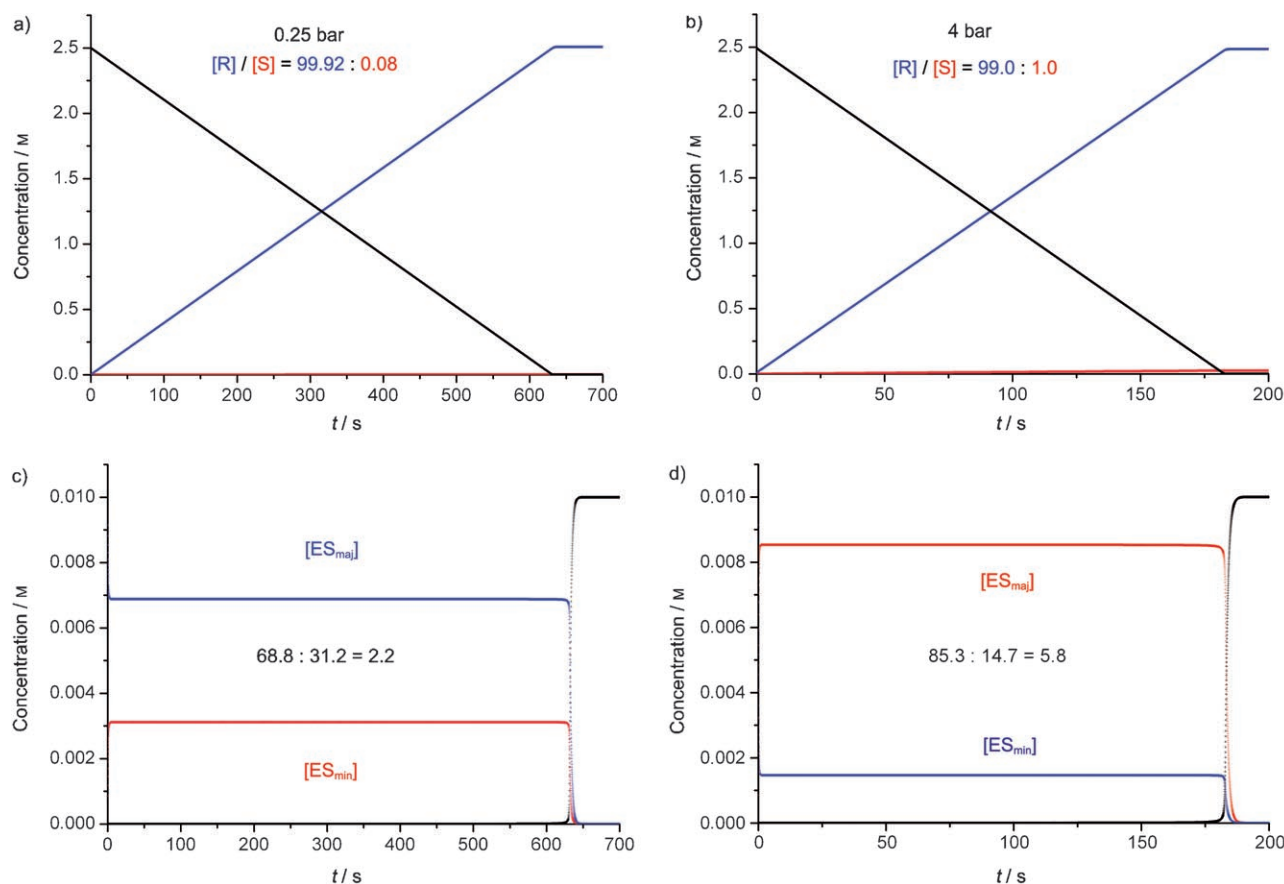
Figure 5. Simulated concentration–time graphs for all concentrations for Table 1, example 2: 0.01 mmol precatalyst and 2.5 mmol prochiral olefin (equilibrated mixture of diastereomeric substrate complexes at time $t = 0$[24]). Black line: a) and b) substrate concentration, c) and d) concentration of solvate complex; blue line: [R] or concentration of former major diastereomer; red line: [S] or concentration of former minor diastereomer.

At a pressure of 0.25 bar, the stationary concentration of the major substrate complex (68.8%) was remarkably lower and the concentration of the minor diastereomer (31.2%)
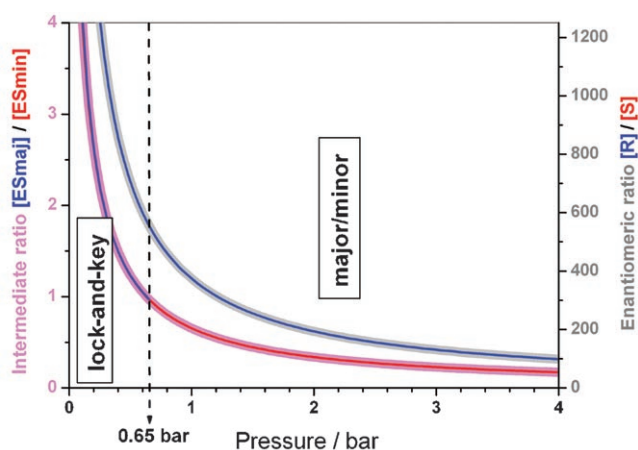

Figure 6. Dependence of intermediate ratio (highlighted in magenta, predominantly determined by major diastereomer until 0.65 bar, blue line, then determined by minor enantiomer, red line) and enantiomeric ratio (highlighted in gray, predominantly determined by R product, blue line) on the hydrogen pressure for Table 1, example 2.

tremendously higher than expected under thermodynamic conditions (91.5%:8.5%). The main reason is the small k_{-1maj}/k_{2maj} ratio, which leads to a disturbance of the pre-equilibrium that is already at a very low partial hydrogen pressure.[24] The simulation demonstrates that at 4 bar hydrogen pressure, the former minor complex is now dominant in solution. In other words, the thermodynamically more stable complex is no longer the dominating species during the hydrogenation. At a hydrogen pressure of about 0.65 bar, the intermediate ratio is 1, that is, both intermediates have equal concentrations in solution.

Hence, it is possible under the abovementioned circumstances, that an increase in pressure leads to a switch from the lock-and-key to the major/minor principle. Despite the dramatic change in the intermediate ratio, the macroscopic change in enantioselectivity would be rather small. This example illustrates that an extensive understanding of the selectivity of such catalytic reactions must not be solely derived from the macroscopic selectivity being dependent on different influences such as hydrogen pressure. Further information is necessary for a deeper understanding; the ratio of the intermediates under catalytic conditions, and not under the thermodynamic conditions (under argon) usually chosen, should at least be known.

Example 3: Disturbance of the Pre-equilibria

In the results discussed above, the pre-equilibrium of the more reactive intermediate always experienced a stronger disturbance with rising pressure than that of the less reactive diastereomer. That is, however, not an essential requirement. If the equilibrium of the less reactive intermediate is disturbed more with increasing pressure, the enantioselectivity should improve when the pressure is raised. To simulate such behavior, the values of k_{-1} and k_2 were interchanged (Table 1, example 3). This switch of the rate constants enhanced the dominance of the major intermediate even more under thermodynamic conditions, but the reactivity difference between the diastereomers was significantly lower than in the other examples. This behavior has no influence whatsoever on the actual discussion and has already been proven experimentally.[10b]

Figure 7 shows the results of the numerical solution of the differential equation system for example 3 (Table 1) for 0.3 and 10 bar pressures. In Figure 8, the enantiomeric and intermediate ratios are plotted against hydrogen pressure.

At 0.3 bar, the lock-and-key principle was valid, although the minor substrate complex was the more reactive one.

This was caused by the dominance of the intermediate ratio over the reactivity ratio. At a pressure of about 0.7 bar, both influences compensated each other. The outcome was then
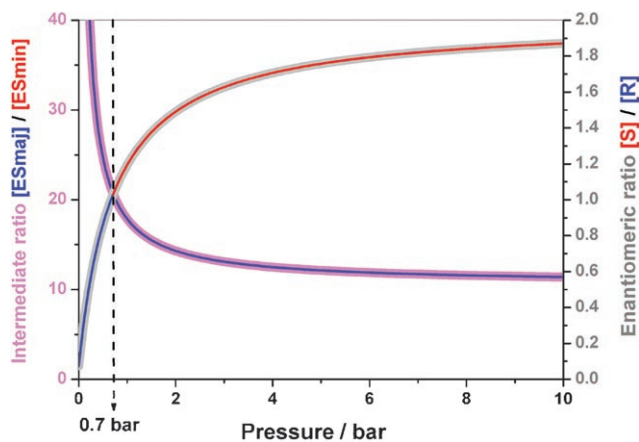
Figure 8. Dependence of intermediate ratio (highlighted in magenta, predominantly determined by major diastereomer, blue line) and enantiomer ratio (highlighted in gray, predominantly determined by R product until 0.7 bar, blue line, then determined by S product, red line) on the hydrogen pressure for Table 1, example 3.
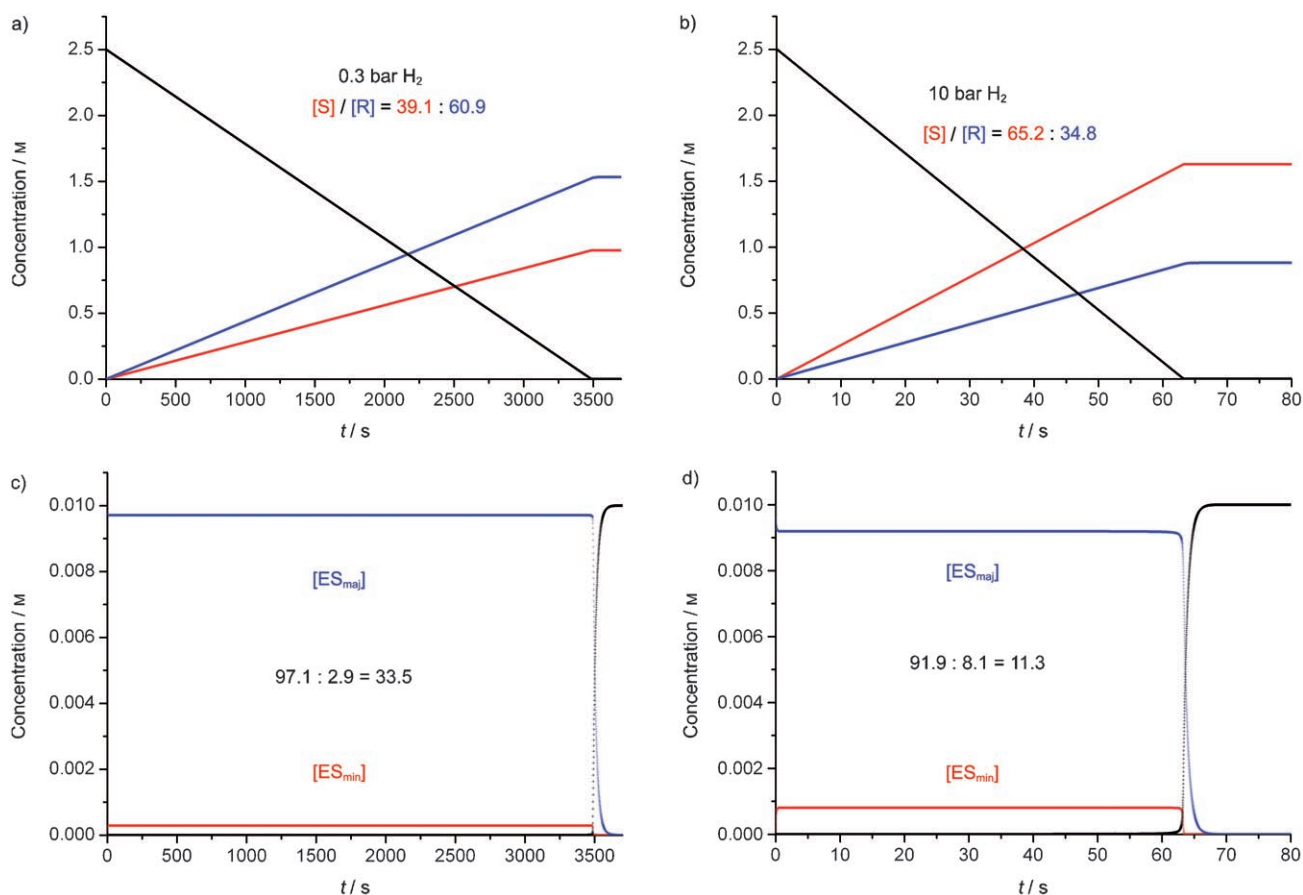
Figure 7. Simulated concentration–time graphs for all concentrations for Table 1, example 3: 0.01 mmol precatalyst and 2.5 mmol prochiral olefin (equilibrated mixture of diastereomeric substrate complexes at time $t=0$[24]). Black line: a) and b) substrate concentration, c) and d) concentration of solvate complex; blue line: [R] or concentration of major diastereomer; red line: [S] or concentration of minor diastereomer.

a racemate. Further increase in pressure led to the classical major/minor principle. If the pressure were increased from 1 bar, the observation would be a macroscopic increase in enantioselectivity with rising pressure, even though the major/minor concept would be valid. This possibility had not been taken into account either.

Selectivity enhancement with rising hydrogen pressure is described in the literature[16c,20,26b] and may have its origin in the behavior described above. Furthermore, the example illustrates that the major/minor principle, as a matter of principle, cannot be ruled out even in the case of increased selectivity with increasing hydrogen pressure. Instead, the comparison with Figure 4 (for pressures above 35 bar) proves the possibility for both the major/minor and lock-and-key principles in such cases.

Principal Possibilities: A Compilation

In the following section, all possible variations of the ratios of the resulting rate constants for the reaction sequence of Scheme 1 will be briefly derived and discussed. With respect to the dependence of the major/minor indexing on the catalytic system, the ligand chirality, as well as the experimental conditions (e.g., solvent and temperature), the following discussion refers only to the general model presented in Scheme 2.

As pointed out in the Introduction, the major/minor concept can be expressed unambiguously by the three inequa-
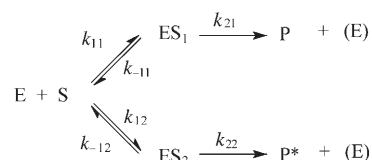
Scheme 2. General selectivity model for the asymmetric hydrogenation with a C_2-symmetrical and selectivity-inducing chelate ligand. E = solvate complex, S = prochiral olefin, ES_i = diastereomeric substrate complexes, P and P* = enantiomeric products.

tions in Equation (1). To formulate all principle possibilities, one has to consider not just the reactivity ratio and the stationary intermediate ratio, but also the ratio of these two variables [Eq. (2)].

Eight different possibilities result for the corresponding ratios, which are summarized in Scheme 3. With careful inspection, it is possible to refine four of the eight possible cases owing to inversion of ligand chirality, which will not be considered in the following discussion.

Assuming that both intermediates have different reactivities, there are two possibilities for the intermediate ratio. The more reactive intermediate has either the higher (cases 1 and 2) or the lower stationary concentration (cases 3 and 4) in solution relative to the other diastereomer. Again, for each of these cases, two possibilities exist. In the first, the reactivity ratio dominates over the intermediate ratio (cases 2 and 4). In the second, the diastereo-

Scheme 3. General possible reaction sequences for the selectivity model presented in Scheme 2.

mer ratio dominates over the reactivity ratio and thus determines the absolute configuration of the hydrogenation product (cases 1 and 3).

If there is one intermediate that is both more reactive as well as the dominant component in solution, the lock-and-key principle results, regardless of whether the reactivity ratio (case 2) or the intermediate ratio (case 1) prevails. If, in contrast, the dominant intermediate is the less reactive, there are basically two options. When the reactivity ratio is smaller than the intermediate ratio, the selectivity is again determined by the major intermediate, and thus the lock-and-key principle is valid (case 3). A different behavior occurs when the reactivity ratio is higher than the intermediate ratio. Only then does the often-discussed major/minor concept result (case 4).

To summarize the outcome of Scheme 3, the statistical probability for the validity of the major/minor principle is as low as 25% and therefore much less probable than the occurrence of the lock-and-key principle (75%).

A further important feature should be noted in the following. As demonstrated in our extensive discussion of examples 1, 2, and 3 in Table 1, it is clearly possible to switch between the different alternatives, for example, by changing the partial hydrogen pressure. For such a changeover between the reaction possibilities, there are, in principle, two optional cases: either the changeover is accompanied by an inversion of the stationary intermediate ratio or no inversion can be observed.

With example 1 in Table 1, the changeover from case 4 to case 3 in Scheme 3 is realized without a changeover between the diastereomers, that is, the dominant intermediate does not change while it is independent of the hydrogen pressure. However, the contribution of each selectivity level to the overall selectivity changes. At low pressures, the selectivity is dominated by the reactivity ratio (major/minor principle), whereas at high pressures, the selectivity is dominated by the intermediate ratio (lock-and-key principle).

For example 2 in Table 1, raising the hydrogen pressure leads from case 1 to case 4 in Scheme 3. The macroscopically attainable selectivity does not change, but the ratio of the intermediates inverts with increasing pressure. That leads to a switch from the lock-and-key to the major/minor principle.

Example 3 in Table 1 represents the changeover from case 3 to case 4 (Scheme 3). As for example 2, an increase in hydrogen pressure leads from the lock-and-key principle to the major/minor principle, but here the same intermediate is dominant in solution over the whole pressure range.

Conclusions

From our simulations based on experimentally determined rate constants as well as the experimental results of a model reaction, the following conclusions can be drawn:

1. The high reactivity of one intermediate as the origin of high product selectivity, which is reflected in the major/

minor principle by Halpern/Landis and Brown, as well as the concept of ligand-accelerated catalysis by Sharpless, is limited. With increasing reactivity, the stationary concentration of the intermediate that causes this reactivity may be lowered. The consequence is decreasing selectivity owing to the nature of the rate being the product of concentration and rate constant.

2. The major/minor and the lock-and-key principles can in principle coexist within one system.

3. Thermodynamically determined intermediate ratios may invert completely under reaction conditions. The ratio of intermediates has an essential influence on the enantioselectivity and should therefore be determined under reaction conditions to obtain reliable data. The common way of determining the intermediate ratio under argon may lead to false conclusions.

4. The known but not thoroughly understood increase in enantioselectivity with increasing hydrogen partial pressure can be explained both with the lock-and-key principle and the major/minor principle. The pressure dependence of the enantioselectivity alone cannot be used to conclude the underlying model.

Selectivity as a kinetic phenomenon is the result of differentiation between the reaction channels. Hence, selectivity should be understood as a relativizing value between the reaction channels. From this statement, it follows that one has to compare all reaction channels as a whole to explain selectivity. Thus, it is not possible to determine for certain the source of selectivity by comparing calculated activation parameters of single reaction sequences.

The reaction channels as a whole are not only determined by the chirality of a selectivity-inducing ligand as an intrinsic potential of a catalytic system, but also by external parameters. In particular, the often-neglected or underestimated intermediate ratio under catalytic conditions has central relevance because it co-determines the overall selectivity as the first selection level and is highly influenced by external parameters.

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