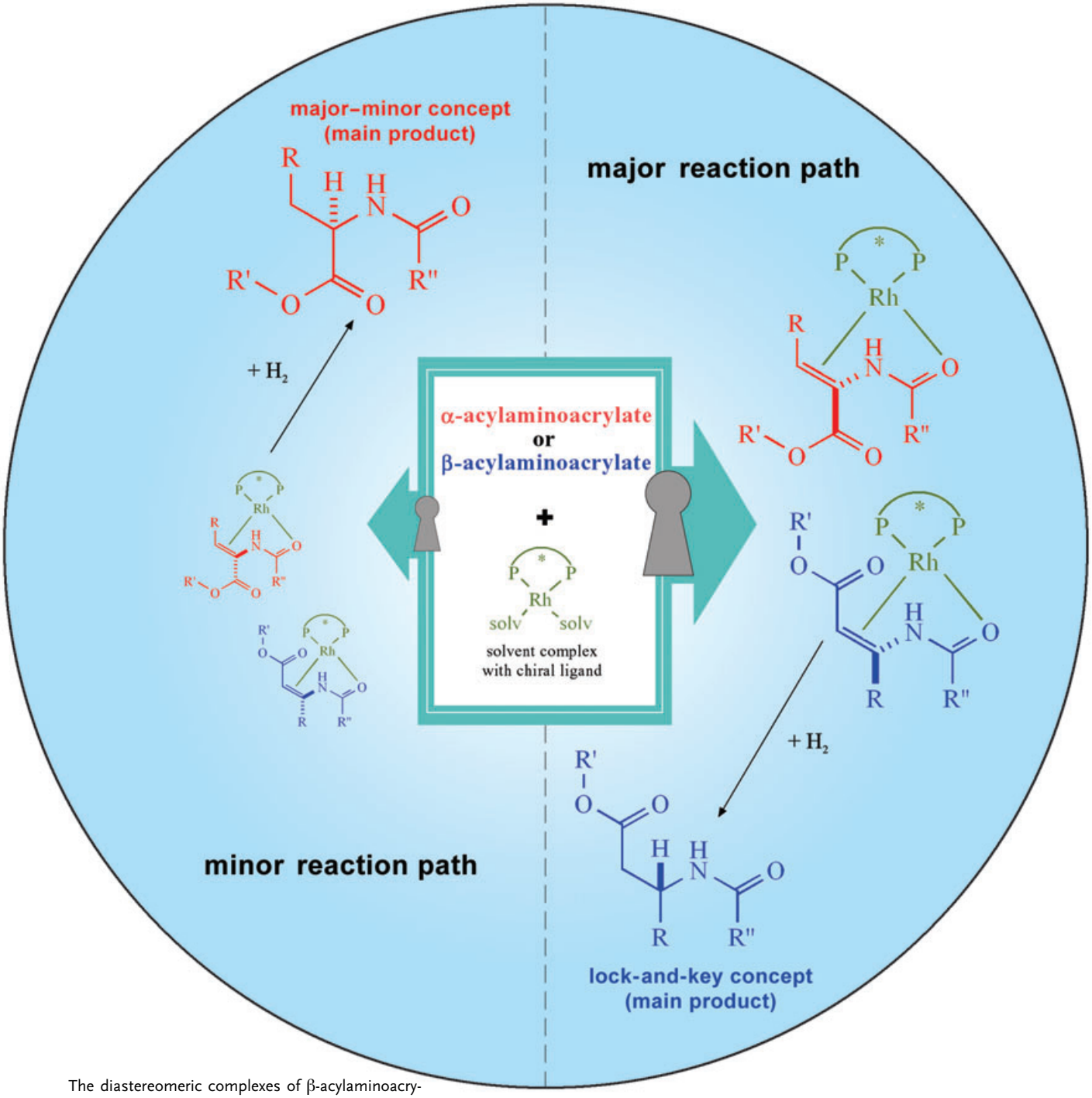
Communications



The diastereomeric complexes of β-acylaminoacrylates shown do not differ much in reactivity, in contrast to intermediates in the asymmetric hydrogenation of α-dehydroamino acids. As a result, the major intermediate determines the selectivity of the reaction in terms of the lock-and-key principle rather than the major–minor concept. D. Heller et al. describe the reaction mechanism in more detail on the following pages.

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Catalytic Hydrogenation

Are β-Acylaminoacrylates Hydrogenated in the Same Way as α-Acylaminoacrylates?**

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Dedicated to Jack Halpern and John M. Brown

The synthesis of amino acids is still of current interest.[1] In contrast to known and even industrially used homogeneously catalyzed hydrogenations of α-dehydroamino acid derivatives, the asymmetric hydrogenation of protected β-aminoacrylates has only lately moved into the focus of research.[2] Meanwhile, catalytic systems have been described reaching high activities and substrate/catalyst ratios, which lead to practically enantiomerically pure β-amino acid derivatives; rhodium as a transition metal seems to be most suitable.[3]

The asymmetric hydrogenation of α-dehydroamino acids was investigated intensively in the last decades, but there are still only a few indications of the reaction mechanism of β-dehydroamino acids. For the α-dehydroamino acids it is proposed that diastereomeric substrate complexes are formed from the solvent complex and the prochiral olefin in a preequilibrium. The diastereomeric substrate complexes react in a sequence of elementary steps—oxidative addition of hydrogen, insertion, and reductive elimination—to give the enantiomeric products. The research groups led by Halpern, Landis, and Brown were able to show that the major substrate complex present in distinct excess does not lead to the main enantiomer. The source of the enantioselectivity was identified as the extreme reactivity of the minor substrate complex.[4] These results were generalized in the literature as the major/minor concept, and one can certainly call it a basic principle of homogeneous catalysis. The fundamental idea of the extreme reactivity of one intermediate is reflected, for example, in the concept of "ligand-accelerated catalysis".[5] In addition to comprehensive kinetic and NMR spectroscopic studies, three X-ray structures of major substrate complexes support the mechanism, also referred to as the "anti lock-and-key motif".[4a,6]

Recently an alternative was found in studies on P,S ligands: a catalyst–substrate complex of an α-dehydroamino acid derivative, which was characterized by X-ray analysis, leads to the observed major enantiomeric form of the product.[7] Since, on the one hand, a C_1-symmetric ligand can in theory form four stereoisomeric substrate complexes coupled by inter- and possibly intramolecular equilibria, and, on the other hand, two sets of two substrate complexes lead to the two enantiomers, it is not certain that the one substrate complex detected by NMR spectroscopy and the isolated complex are identical.

First mechanistic investigations on the asymmetric hydrogenation of β-dehydroamino acid derivatives go back to Gridnev and Imamoto. They detected hydridoalkyl complexes at −100 °C after the addition of methyl (*E*)-3-*N*-acetylamino-3-methylacrylate to the dihydrido solvent complex $[RhH_2(L)(MeOH)_2]BF_4$ (L = chiral bidentate phosphine ligand).[8] Still, it is questionable whether such species are also stable under stationary hydrogenation conditions at room temperature. Nevertheless, kinetic and NMR investigations indicated that the reaction sequence of the asymmetric hydrogenation is in principle analogous to the hydrogenation of α-dehydroamino acid derivatives.[9a]

The aim of this work is the in-depth mechanistic understanding of the rhodium-catalyzed asymmetric hydrogenation of β-acylaminoacrylates. The direct comparison to the known reaction mechanism of the hydrogenation of α-acylaminoacrylates is of special interest.

Catalyst–substrate systems particularly appropriate for mechanistic investigations are those for which the rate of product formation is independent of the substrate concentration, that is, the hydrogenation follows a zero-order rate law. For this borderline case of Michaelis–Menten kinetics characterized by preequilibria, only the stable catalyst–substrate complexes are present in the reaction solution during the hydrogenation; this can be proved easily by ^{31}P NMR spectroscopy.[9] In contrast to the (*E*)-β-acylamino-β-arylacrylates, which are hydrogenated in a first-order reaction,[3b] the *Z* substrates show the desired kinetic behavior. It should be possible to isolate and characterize such stable catalyst–substrate complexes. We succeeded with a complex formed from the substrate methyl (*Z*)-3-*N*-acetylamino-3-phenylacrylate (**1**). This complex, [Rh((*R*,*R*)-Et-duphos)(**1**)]BF_4, is the first rhodium complex with a β-acylaminoacrylate (see the Supporting Information).[10]

Like the known cases with α-acylaminoacrylates,[4a,6,7] the *Z* substrate is bound as a chelate to the rhodium through the double bond and the amide oxygen atom. This is particularly surprising, because the enantioselectivities for the hydrogenation of the *Z* isomers, which are in general lower than those of the *E* isomers, were explained by the nonchelating binding of the substrate caused by an intramolecular hydrogen bond in the substrate. Indeed, for several *Z* isomers these

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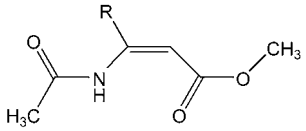
intramolecular hydrogen bonds[11] were proven by X-ray crystal structures (see refs. [2,12] and the Supporting Information). However, this interaction is apparently cancelled upon complexation of the substrate to the transition metal.

The hydrogenation of methyl (*Z*)-3-*N*-acetylamino-3-phenylacrylate (**1**) with the catalyst system Rh/(*R*,*R*)-Et-duphos (Et-duphos = 1,2-bis(2,5-diethylphospholanyl)benzene) in methanol at 25 °C and 1.0 bar overall pressure provides the *S* enantiomer in 85 % *ee* (59 % *ee* in isopropyl alcohol). In contrast, the isolated catalyst–substrate complex leads to the *R* enantiomer. Yet assigning the crystallized intermediate as either the major or minor substrate complex is not reasonable, since the ratio of the complexes at room temperature in both solvents is approximately 56:44 (^{31}P NMR spectrum).

However, several complexes formed with the catalyst system Rh/(*S*,*S*)-dipamp (dipamp = 1,2-ethanediylbis[(2-methoxyphenyl)phenylphosphane]) and β-acetylamino-β-arylacrylates show ^{31}P NMR signals for one substrate complex in great excess in methanol at room temperature (Table 1, column 2). Here, too, we were able to analyze these catalyst–substrate complexes by X-ray crystallography. The complexes

Table 1: [Rh((*S*,*S*)-dipamp)((*Z*)-β-acetylamino-β-arylacrylate)]BF_4 in methanol: ratios of the diastereomeric substrate complexes at different temperatures, enantioselectivities (25 °C, normal pressure), and reactivity ratios of the intermediates.



1 – 4

	R	[Major]/[minor] ratio (*T*)		*S* Sel. [% *ee*] (e.r.)	k_{maj}/k_{min}
1	C_6H_5	90:10 (RT)	96:4 (−87 °C)	50 (3.0)	0.33
2	*p*-ClC_6H_4	88:12 (RT)	93:7 (−87 °C)	38 (2.2)	0.30
3	*m*-$NO_2C_6H_4$	81:19 (RT)	86:14 (−84 °C)	20 (1.5)	0.35
4	*p*-MeC_6H_4	91:9 (RT)		60 (4.0)	0.39

of methyl (*Z*)-3-*N*-acetylamino-3-(*p*-chlorophenyl)acrylate (**2**) and methyl (*Z*)-3-*N*-acetylamino-3-(*m*-nitrophenyl)acrylate (**3**) are shown in Figure 1 (see the Supporting Information for details). One peculiarity of all four substrate complexes is that the OMe group of the dipamp ligand interacts with the rhodium center as a hemilabile ligand. This type of coordination is often discussed but to the best of our knowledge has never been proven by X-ray analysis.[13]

The four isolated substrate complexes each lead to the *S* enantiomer. Surprisingly, the *S* enantiomer is also the major product of the asymmetric hydrogenation in methanol (although the enantioselectivities are only 20–60 % *ee*, Table 1, column 4).

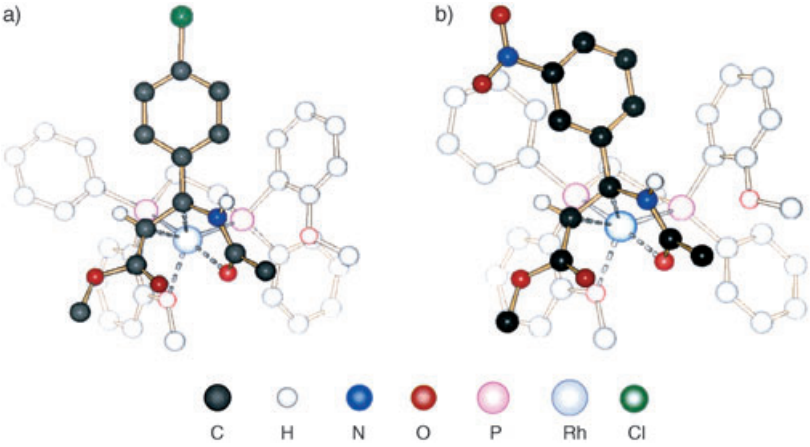


Figure 1. Structures of the cations in a) [Rh((*S*,*S*)-dipamp)(**2**)]BF_4 and b) [Rh((*S*,*S*)-dipamp)(**3**)]BF_4 determined by X-ray crystal structure analysis.

There are several ways to eliminate the possibility that only the minor substrate complexes crystallize, including complicated NOE measurements and solid-state NMR spectroscopy. However, we chose a different, simpler variant and tried to "freeze out" the interconversion between the diastereomeric catalyst–substrate complexes at low temperatures. It is crucial to this method that both of the substrate complexes are clearly detectable even at the lowest temperature employed (Table 1, column 3) and furthermore that the crystals are sufficiently soluble.

The results for the substrate methyl (*Z*)-3-*N*-acetylamino-3-(*p*-chlorophenyl)acrylate (**2**) are represented in Figure 2.[14] When we dissolved single crystals of the substrate complex in a sealed NMR tube at approximately −90 °C, only the major substrate complex was visible in the spectrum at −83 °C (Figure 2a). When we allowed the very same NMR tube to warm over several hours to room temperature, both of the substrate complexes were again evident in the known ratio of 88:12 (Figure 2b, Table 1). The spectrum recorded after recooling this NMR tube is shown in Figure 2c. The agreement between the major/minor ratio determined at room temperature and at low temperature (Figure 2, Table 1) proves that the thermodynamic equilibrium between the substrate complexes has been reached in both cases.

Analogous results were obtained for the substrates methyl (*Z*)-3-*N*-acetylamino-3-phenylacrylate (**1**) and methyl (*Z*)-3-*N*-acetylamino-3-(*m*-nitrophenyl)acrylate (**3**) (see the Supporting Information). These findings support the unequivocal conclusion that the major substrate complexes crystallized. Thus, it has been proven for the first time that the substrate complex dominant in solution controls the stereochemistry of the product. This is in keeping with the lock-and-key mechanism known from enzyme catalysis.

The enantiomeric ratio is the result of two factors: the ratio of the concentrations of the intermediates ([major substrate complex]/[minor substrate complex]) as the first level of selection in the reaction sequence and the ratio of their reactivities (k_{maj}/k_{min}) as the second level of selection.[15] In case of [Rh((*R*,*R*)-Et-duphos)(**1**)]BF_4 the selectivity must arise from the difference in reactivity of the diastereomeric

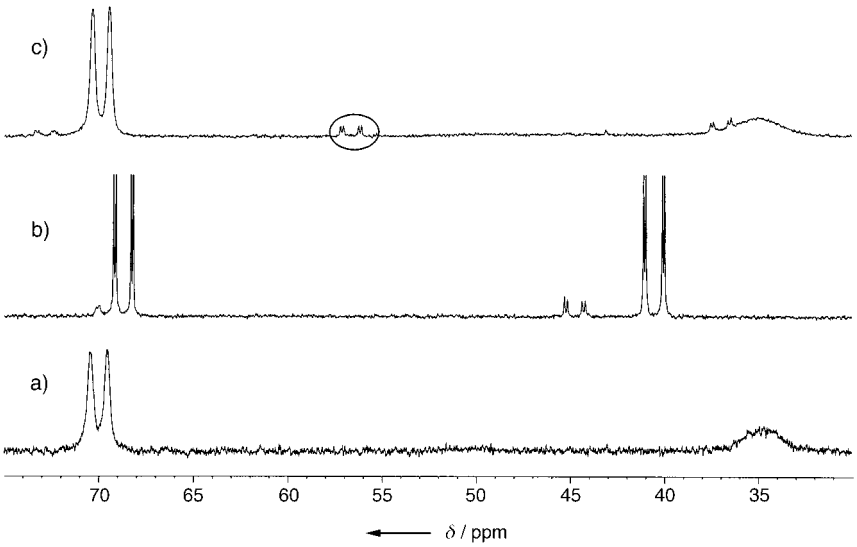


Figure 2. ^{31}P NMR spectra of a solution prepared from single crystals of [Rh((*S*,*S*)-dipamp)(**2**)]BF_4 dissolved at −90 °C in methanol a) immediately after dissolving ($T = -83$ °C), b) after warming to 25 °C and equilibration ([major]/[minor] = 88:12), and c) after recooling the sample from (b) to $T = -78$ °C ([major]/[minor] = 93:7).

substrate complexes because their concentrations are roughly equal at room temperature (ratio 56:44). The experimentally determined enantiomer ratio is 12.3 in methanol (85 % *ee*) and 3.9 in isopropyl alcohol (59 % *ee*), which indicates that the difference in the reactivities of the two intermediates cannot be very great.

The situation is similar with dipamp as the ligand. For the examples investigated the diastereomer ratios of the catalyst–substrate complexes and the enantiomer ratios of products of the asymmetric hydrogenation indicate that in each case the minor substrate complex reacts approximately only three times faster than the major substrate complex (Table 1, column 5).[16] The fact that the minor substrate complexes are only slightly more reactive than the major substrate complexes does not agree with the known ratios of reactivity of diastereomeric catalyst–substrate complexes containing α-acylaminoacrylates. Kinetic investigations of the hydrogenation of methyl (*Z*)-*N*-acetylaminocinnamate with [Rh(dipamp)$(MeOH)_2$]$^+$ resulted in a reaction rate for the minor substrate complex that was 580 times greater for the oxidative addition of hydrogen at 25 °C than for the major substrate complex.[4d] With chiraphos as the chiral ligand this difference in reactivity was estimated at more than 1000 when the analogous ethyl ester was the substrate.[4c]

In conclusion we have determined that reaction sequence for the hydrogenations of β- and α-acylaminoacrylates with cationic rhodium(I) complexes is the same. For the first time catalyst–substrate complexes for several β-dehydroamino acid derivatives were characterized by X-ray structure analysis. The chelating binding of the prochiral olefin to rhodium occurs—as in the α-substituted analogues—through the double bond and the amide oxygen.

While in case of α-acylaminoacrylates the catalyst–substrate complex dominant in solution does *not* lead to the major product of the asymmetric hydrogenation,[17] in our study three single crystals unequivocally identified as major substrate complexes by low-temperature ^{31}P NMR spectroscopy show opposite behavior. The major intermediate determines the selectivity (lock-and-key principle). The main cause for this apparently lies in the slight difference in reactivities of the diastereomeric substrate complexes. The classic major/minor concept is based on the fact that the minor substrate complex is much more reactive than the major substrate complex, but this extreme difference in reactivity is not evident in the substrate complexes with β-acylaminoacrylates in this work. Therefore for the examples studied the complexation of the substrate as the first level of selection plays an even bigger role than previously assumed.

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