On the Enantioselective Hydrogenation of Isomeric Methyl 3-Acetamidobutenoates with Rh^I Complexes

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In memory of Professor Kurt Madeja

Abstract: The enantioselective hydrogenation of *E*- and *Z*-methyl 3-acetamidobutenoate, key intermediates in the synthesis of a pharmaceutically important chiral β-amino acid, with Rh^I catalysts in MeOH as solvent has been investigated in detail. As chiral ligands, Et-DuPHOS, Me_4-BASPHOS, DIPAMP, DIOP, HO-DIOP and Et-FerroTANE have been employed. The particular role of oxyfunctionalization in some diphosphine catalysts is addressed in relation to the *E*/*Z* geometry of the substrate and the dependency of the *ee* on the H_2 pressure. Kinetic investigations with [Rh(diphosphane)$(MeOH)_2$]-BF_4, taking into consideration the special nature of the precatalyst {[Rh$(cod)_2$]BF_4/ligand versus [Rh(cod)ligand)]BF_4}, NMR spectroscopic measurements and the H_2 pressure dependence of the observed enantioselectivity provide evidence that the reaction proceeds via an "unsaturated route" mechanism. This mechanism correlates to catalytic features found in the past for the hydrogenation of related unsaturated α-amino acid precursors. The influence of the temperature was similarly investigated. A nonlinear dependency of the enantiomeric ratio as a function of the reciprocal of the temperature has been found. The correlation between temperature and H_2 pressure and their effects on the enantioselectivity is discussed. In general, the highest enantioselectivities for the hydrogenation of both isomeric substrates can be achieved at room temperature and below, whereas the fastest conversion takes place at 30 – 50 °C.

Keywords: β-amino acids · asymmetric synthesis · hydrogenation · phosphanes · rhodium

Introduction

Enantiopure β-amino acids are compounds of broad biological importance.[1] They are produced in humans, other higher animals, microorganisms, marine organisms and plants either in the free form or as components of peptides and depsipeptides. As components of peptidic natural compounds with antibiotic, antifungal and cytotoxic properties, their enantioselective synthesis is of increasing importance, in particular for synthetic pharmaceutical chemistry.

One of the most promising methods for the convenient preparation of β-amino acids on a large scale is the asymmetric hydrogenation of suitable unsaturated precursors such as β-acetamido acrylates with Rh^I catalysts bearing chiral phosphorus ligands. The requisite prochiral substrates are easily available by treatment of β-keto carboxylates with NH_4OAc and subsequent acetylation. However, while literally thousands of reports are concerned with the Rh-catalysed enantioselective hydrogenation of related prochiral α-acetamido acrylates, only a few devoted to the hydrogenation of β-analogues as substrates exist.[2] The reason for this is probably different behaviour in the asymmetric hydrogenation, which had for a long time been attributed to particular substrates such as the isomeric methyl 3-acetamido butenoates (*E*)-**1** and (*Z*)-**1**.

Both isomers are produced simultaneously in most synthetic procedures and their individual hydrogenation demands prior separation.[3] Moreover, most reports suggest that the hydrogenation of *Z*-enamides requires much higher H_2

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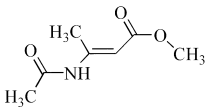
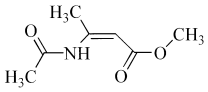
0947-6539/02/0822-5196 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 22



(*E*)-**1**

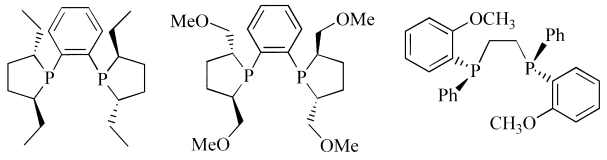


(*Z*)-**1**

pressures and longer reaction times than the reduction of their *E* analogues and gives inferior enantioselectivities.[2, 4] Recently, Zhang et al. showed for the first time that both isomeric substrates can be hydrogenated separately with good to excellent *ee* values, by use of the same Rh catalyst.[2c] Unfortunately, the reaction was sluggish when carried out in toluene as a solvent, in particular when *Z*-configured substrates were employed. However, as we showed recently, this feature is not necessarily associated with the hydrogenation of this particular substrate, but with the formation of catalytically inactive Rh-η^6-toluene complexes.[5] Obviously, the use of aromatic solvents for such hydrogenation reactions is not to be recommended.

In a preliminary communication we gave clear evidence that the asymmetric hydrogenation of (*E*)-**1** and (*Z*)-**1** with a Rh^I precatalyst and Et- or Me-DuPHOS[6] (see below) as chiral ligand can—surprisingly—proceed very rapidly and under mild conditions (1 bar H_2 pressure, room temperature) when the reaction is carried out in polar solvents such as alcohols, THF or methylene chloride.[7] In contrast to the hydrogenation of (*Z*)-**1** at high pressure, which affords only a moderate *ee*, a dramatic increase of the enantioselectivity resulted with decreasing pressure, finally approaching at 1 bar the high enantioselectivity commonly achieved with (*E*)-**1** as substrate. Interestingly, the excellent enantioselectivity in the hydrogenation of the latter isomer was fairly independent of the H_2 pressure. Fortunately, the same configuration was induced in the product independent of the substrate geometry. From these observations, the efficient and highly enantioselective hydrogenation of *E*/*Z*-substrate mixtures became feasible.

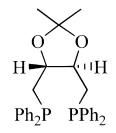
In order to understand this important catalytic transformation in more detail from the viewpoint of a practical application, we report here further systematic—especially kinetic—studies focused on the enantioselective hydrogenation of (*E*)-**1** and (*Z*)-**1** by chiral Rh^I complexes. As ligands, Et-DuPHOS, Me_4-BASPHOS,[8] DIPAMP,[9] DIOP,[10] HO-DIOP[11] and Et-FerroTANE[12] were investigated.



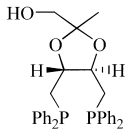
(*S*,*S*)-Et-DuPHOS

Me_4-BASPHOS

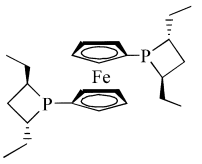
(*R*,*R*)-DIPAMP



(*R*,*R*)-DIOP



(*R*,*R*)-HO-DIOP



(*R*,*R*)-Et-FerroTANE

Results and Discussion

Catalyst versus precatalyst: Cationic Rh^I catalysts for enantioselective hydrogenation are frequently generated in situ by mixing $[Rh(diolefin)_2]^+$ with a stoichiometric amount of the chiral ligand. The application of such precatalysts, formed in situ, as well as of the precatalyst itself, intrinsically does not allow a reliable estimation of the "true" activity of the catalyst. In the enantioselective hydrogenation of related α-acetamido acrylates, recent reports provided evidence that the formation of the catalytically active species (in MeOH: $[Rh(P\text{-}P\text{-}ligand)(MeOH)_2]^+$) based on precatalysts containing cod (cyclooctadiene) as the stabilizing diolefin may require much more time than generally assumed.[13] Since the hydrogenation of the diolefin, proceeding in parallel to the enantioselective hydrogenation of the prochiral substrate, may take more time than the reduction of the latter, precious precatalyst is wasted. Moreover, because of the continually increasing concentration of the catalytically active species throughout the catalytic process, the rate of hydrogenation of the prochiral substrate cannot be determined.

In order to verify whether such effects also influence the hydrogenation of β-acetamido acrylates we tested different methods for the addition of the catalyst to the reaction mixture. The results for the hydrogenation of (*Z*)-**1** with the Rh(Et-DuPHOS) catalyst, prepared by different methods, are depicted in Figure 1. As is clearly to be seen, hydrogenation

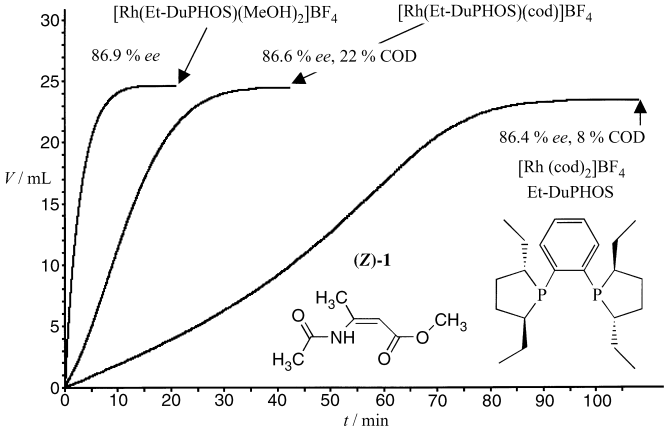


Figure 1. Hydrogenation of (*Z*)-**1** in the presence of Et-DuPHOS under standard conditions (1.0 mmol substrate, 0.01 mmol $[Rh(cod)_2]BF_4$ (+0.01 mmol Et-DuPHOS), $[Rh(Et\text{-}DuPHOS)(cod)]BF_4$ or $[Rh(Et\text{-}DuPHOS)(MeOH)_2]BF_4$ in 15.0 mL MeOH, 1.0 bar total pressure, 25 °C) for comparison of the solvent, the COD complex and the in situ technique.

by the in situ technique—$[Rh(cod)_2]BF_4$/ligand—takes the longest time to complete. After completion of the enantioselective hydrogenation a significant amount of COD could be observed in the reaction mixture. This corresponds to unconverted precatalyst.[13a] A reduction in the overall hydrogenation time can be achieved by employment of [Rh(Et-DuPHOS)(cod)]BF_4 as a precatalyst. Even on application of this method, however, unconverted precatalyst is left at the

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end; interestingly, the amount of remaining COD is higher than that observed on application of the in situ technique. This is obviously a result of the shorter reaction time. In contrast, after prior individual hydrogenation of the precatalyst for 90 min at 1 bar hydrogen pressure in MeOH and subsequent addition of the prochiral substrate, the reaction time is reduced to approximately 10 minutes compared with the application of the in situ precatalyst. Under these conditions, the catalytic reaction profits from the whole amount of the catalyst added at the beginning of the reaction. It should be noted that the enantioselectivity was not affected by the different methods used for the preparation of the catalyst.

Kinetics of the hydrogenation under normal pressure: Inspection of the H_2 consumption curves of the hydrogenation of (*Z*)-**1** or (*E*)-**1** with $[Rh(Et\text{-}DuPHOS)(MeOH)_2]BF_4$ revealed that the reaction follows first order kinetics.[14] For the hydrogenation of (*E*)-**1**, a comparison showing the experimentally obtained and the calculated values (curves are superimposed), together with the parameters of the nonlinear regression for a first order reaction, is depicted in Figure 2.

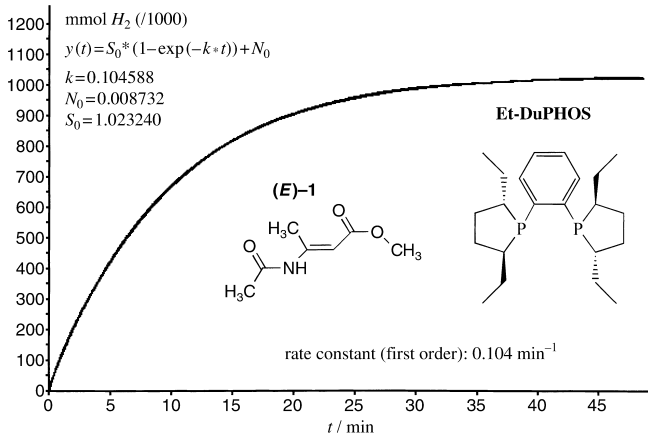

Figure 2. Kinetic analysis of the hydrogenation of (*E*)-**1** in the presence of $[Rh(Et\text{-}DuPHOS)(MeOH)_2]BF_4$ as a first order reaction (see Figure 1 for conditions; calculated and observed curves are superimposed).

Similar kinetic features were also observed with other chiral ligands (Table 1,[15]). It is remarkable that the enantioselectivities achieved varied over a huge range. Among the catalysts tested, those based on cyclic dialkylphosphanes gave excellent enantioselectivities in the hydrogenation of (*E*)-**1**. Good enantioselectivity was also observed with a catalyst derived from DIPAMP. Inferior enantioselectivities were in all cases achieved in the hydrogenation of (*Z*)-**1**. As listed in the table, $[Rh(Et\text{-}DuPHOS)(MeOH)_2]BF_4$ reduced (*Z*)-**1** approximately three times more rapidly than the corresponding isomer (*E*)-**1** at room temperature. The same tendency also holds for catalysts of DIOP. The incorporation of a remote HO group in this last catalyst (HO-DIOP) affected the hydrogenation of (*Z*)-**1**, whereas no effect on the *ee* was observed with (*E*)-**1**.

Interestingly, the MeO-functionalization of Et-DuPHOS, affording Me_4-BASPHOS, changed this order. Moreover, the rate of the hydrogenation was decreased, the *E* isomeric substrate now converting into the product more rapidly than the *Z* substrate.[15] The same also holds for the FerroTANE catalyst.

Table 1. First-order rate constants and enantioselectivities observed in the hydrogenation of (*Z*)-**1** and (*E*)-**1** with $(Rh(P\text{-}P\text{-}ligand)(MeOH)_2]^+$ in MeOH.[a]

Ligand	Substrate			
	Z-**1**		*E*-**1**	
	$k_{first\ order}$ [min^{-1}]	*ee* [%]	$k_{first\ order}$ [min^{-1}]	*ee* [%]
Et-DuPHOS	0.3	87	0.1	98
Me_4-BasPHOS	0.02	67	0.09	98
DIPAMP	zero-order reaction:			
	0.1 mL min^{-1}	68	0.02	90
DIOP	0.25	17	0.1	71
HO-DIOP	0.1	36	0.04	71
Et-FerroTANE	0.09	28	0.58[b]	99

[a] Rate constants indicated represent pseudo rate constants and also include gas solubilities under isobaric conditions: 0.01 mmol precatalyst, 1.0 mmol prochiral olefin, 15.0 mL MeOH, 25 °C, 1.0 bar total pressure. [b] 0.005 mmol precatalyst were used due to the high activity, in order to avoid diffusion influence.

Unexpectedly, while the hydrogenation of (*E*)-**1** in the presence of $[Rh(DIPAMP)(MeOH)_2]BF_4$ follows first-order kinetics, the hydrogenation of (*Z*)-**1** is of zero-order (compare Figure 3). Within the experimentally investigated substrate:-

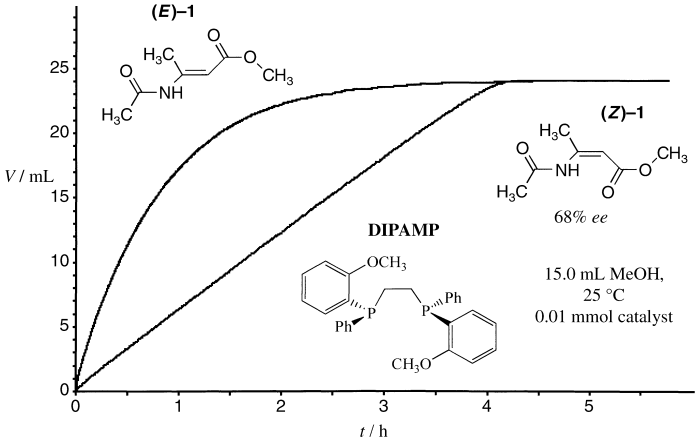

Figure 3. Reactions of zero- and first-order for the hydrogenations of (*Z*)-**1** and (*E*)-**1**, respectively, in the presence of $[Rh(DIPAMP)(MeOH)_2]BF_4$ (see Figure 1 for conditions).

catalyst ratio, ranging from 100 to 700, the rate remained constant.

For the discussion of these unrefined kinetic results a model for the reaction sequence is desirable. Unfortunately, no such model for the hydrogenation of β-dehydroacylamino acids is yet available (compare, however, ref. [2d]). In the related case of the enantioselective hydrogenation of α-dehydroacylamino acids, several pieces of evidence that the formation of diastereomeric catalyst-substrate complexes and the subsequent oxidative addition of hydrogen represent the rate-determining step of the catalytic reaction ("unsaturated route", Scheme 1) have been accumulated.[16] By this model, in the first step, the catalyst (solvent complex) reacts with the

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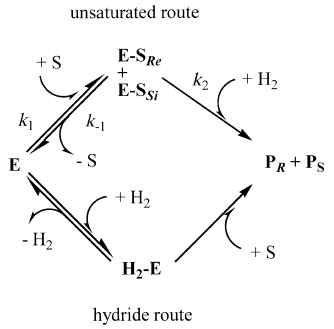

Scheme 1. Unsaturated route and hydride route as alternative pathways in the enantioselective hydrogenation of a prochiral olefin with C_2-symmetric Rh-catalysts (E = catalyst, S = prochiral substrate, P = product).

prochiral substrate to form diastereomeric catalyst–substrate complexes (E-S_{Re} and E-S_{Si}). Subsequently, hydrogen adds to the metal centre and the chiral products P_R and P_S are delivered after the saturation of the double bond.

For this model (Michaelis–Menten kinetics), reactions of zero-order and first-order represent borderline cases. The reaction order is dependent upon the shift of the preequilibrium consisting of the solvent complex [Rh(ligand)(-MeOH)$_2$]BF_4 and diastereomeric substrate-catalyst complexes. In the hydrogenation of α-amino acid precursors, five-membered ring chelates, such as the DIPAMP-Rh catalyst, form stable substrate-catalyst complexes ($k_1 \gg k_{-1}$, reaction of zero order). With seven-membered chelate rings these substrate–catalyst complexes are significantly less stable ($k_{-1} > k_1$, reaction of first order).[14] In the latter case, Rh employed under the experimental conditions is mainly present in the solvent complex. Consequently, structure elucidation of corresponding substrate–catalyst complexes by analytical methods is not possible.

Whether or not a pressure dependency of the enantioselectivity can be observed under isobaric conditions is determined by the magnitude of the pseudo rate constant $k_2[H_2]$. When the pseudo rate constant is larger than k_{-1} the preequilibria are disturbed, and the enantioselectivity decreases with increasing H_2 pressure. An example has been given by Halpern et al., for the DIPAMP/methyl (*Z*)-α-acetamidocinnamate catalytic system, in which stable substrate–catalyst complexes have been found.[16a] Since all required rate constants are known for this reaction, the relevant differential equation system can be calculated numerically.[17] Thus, the full set of concentration/time data for different pressures is available (this is illustratively shown for 1 and 100 bar as graphics in the Supporting Information).

In the case of unstable substrate–catalyst complexes, a similar dependency of the enantioselectivity on the H_2 pressure can in principle be expected. In order to illustrate this feature, the k_1 values derived from Halpern's work have been multiplied by 1×10^{-6}. All other constants correspond to the original data. This simulation shifts the equilibrium from the substrate–catalyst complexes towards the solvent complex. The calculation of all concentration/time data at 1 and 100 bar, respectively, confirms the expected behaviour (relevant graphics can be seen in the Supporting Information). Thus, a pressure dependency of the enantioselectivity can also be found for weakly binding substrates. Moreover, this simulation provides evidence that high enantioselectivity is not necessarily associated with high stability of substrate–catalyst complexes, as is frequently stated in the literature.

An alternative pathway involves the addition of hydrogen to the catalyst prior to the coordination of the prochiral substrate ("hydride route").[18, 19] With this last pathway, under isobaric, stationary conditions a constant concentration of the hydrido complex (H_2-E) can be expected. The hydrido complex subsequently reacts with the substrate to form the products. An increase in the H_2 pressure would cause an increase in the stationary concentration of the hydrido complex, indicated macroscopically by an enhancement of the activity. However, since the prochiral substrate is not engaged in this early stage of the reaction (which means that the ratio of the subsequently formed diastereomeric substrate complexes is not influenced by the H_2 pressure), the enantioselectivity should not be affected. Moreover, it is important to remark that in the case of the hydride route according to Scheme 1 in general, a first order reaction should be observed. The formal kinetic derivation can be found in the Supporting Information.

The principal conclusions based on the two mechanisms depicted in Scheme 1 are summarised in Table 2.

Table 2. Kinetics for the unsaturated and the hydride route according to Scheme 1.

	Unsaturated route	Hydride route
zero-order reaction	possible, mainly substrate complex in solution during hydrogenation	impossible[a]
first-order reaction	possible, mainly solvent complex in solution during hydrogenation	possible, mainly dihydride complex in solution during hydrogenation
pressure dependency of *ee*	possible	impossible

[a] Theoretically a reaction of zero-order should be possible if a dihydrido-substrate or hydrido-alkyl complex is dominant during the hydrogenation. However, such complexes have yet to be observed under (room temperature) hydrogenation conditions. Therefore, this case was not considered.

Since, by the hydride route, neither a reaction of zero order (DIPAMP/(*Z*)-**1**), nor a pressure dependency of the enantioselectivity[2c, 7, 8] can be expected, our obtained values correlate best with the assumption of the unsaturated route. The generality of this assumption for other catalytic systems still has to be proven.[20]

This hypothesis is lent additional support by the fact that, in all systems that follow first-order kinetics, both for (*Z*)-**1** and for (*E*)-**1**, only the solvent complex could be found in solution (^{31}P NMR spectrum of Et-DuPHOS[15]). For the DIPAMP/(*Z*)-**1** system, on the other hand, only one substrate complex (probably the major complex) was observed (compare

ref. [5]). In this case, resonances of the relevant solvent complex were not visible.[15]

It should additionally be noted that, for a reaction of first order, there is an opportunity to improve the space/time yield by increasing the initial concentration of the substrate. Figure 4 gives the experimental confirmation for this hypothesis. Thus, the time for the conversion of 1 and 5 mmol of substrate, respectively, under the same conditions is approximately the same (10–15 min). A further increase in the concentration of the substrate should give similar results.[21]

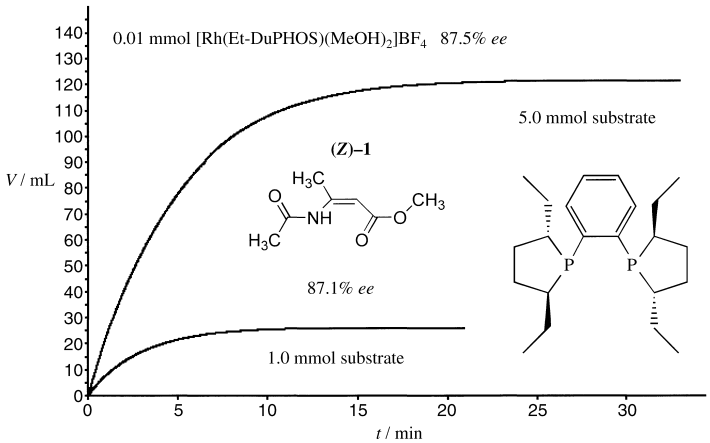

Figure 4. Variation of the concentration of (*Z*)-**1** with [Rh(Et-DuPHOS)(MeOH)$_2$]BF$_4$ (variable amount of substrate, other conditions see Figure 1).

As shown in our recent paper,[7] the negligible differences in the hydrogenation rates of (*E*)-**1** and (*Z*)-**1** in MeOH and the formation of the product with the same configuration gave the opportunity to reduce both substrates simultaneously in one pot. Figure 5 shows the relevant curves in the presence of [Rh(Et-DuPHOS)(MeOH)$_2$]BF$_4$. The enantioselectivities observed in the hydrogenation of the 1:1 mixture of the isomeric substrates correspond to the mean values of the individual hydrogenations. Similar behaviour can also be found in the presence of other catalysts (e.g. the Rh-catalyst derived from Me$_4$-BASPHOS).[15]

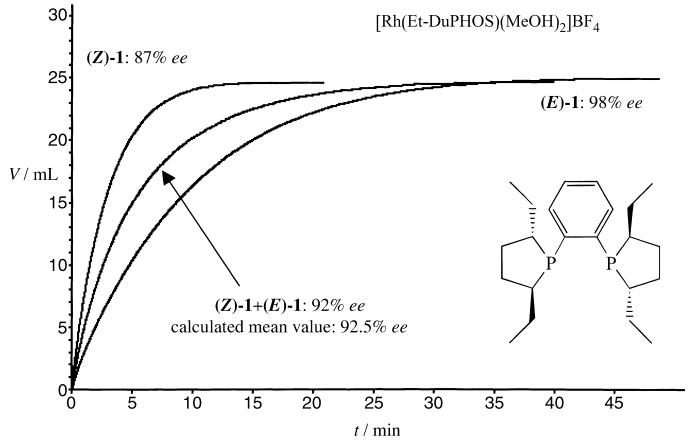

Figure 5. Hydrogenation of a (*Z*)-**1**/(*E*)-**1** 1:1 mixture in the presence of [Rh(Et-DuPHOS)(MeOH)$_2$]BF$_4$, in comparison to the individual hydrogenation of (*Z*)-**1** and (*E*)-**1** (1.0 mmol) only; 0.5 mmol of each substrate were applied; standard conditions.

Temperature dependency of the hydrogenation of (*Z*)-1 and (*E*)-1: According to the work of Halpern and others[16] concerning the hydrogenation of α-dehydroamino acids, reduction of the H_2 pressure gives rise to an enhancement of the enantioselectivity.[22] Obviously the same effect also holds for the hydrogenation of (*Z*)-**1**.[7] Moreover, as Halpern showed, an increase in the temperature improves the enantioselectivity. Since the partial pressure of hydrogen also decreases with increasing temperature under isobaric conditions, there should be a further opportunity to improve the enantioselectivity through enhancement of the temperature.

The hydrogenation of (*Z*)-**1** and (*E*)-**1** in the presence of the Et-DuPHOS catalyst could easily be quantified as a first order reaction, so we chose this system. The results are summarized in Table 3 and a graphical overview is given in Figures 6 and 7. At first, both the activity and the enantioselectivity increased with increasing temperature. At higher temperatures, however, both the activity and the enantioselectivity dropped. A comparison of the activities of the hydrogenations of (*Z*)-**1** and (*E*)-**1** reveals that both hydrogenation processes show distinct maxima: at 40–50 °C for (*E*)-**1** and at 30–40 °C for (*Z*)-**1**. It is remarkable that the ratio of the rate constants for (*Z*)-**1**/(*E*)-**1** increases with decreasing temperature. At 25 °C the *Z* isomer is hydrogenated approximately 3.5 times more rapidly than the *E* isomer, while at −10 °C the *E* substrate is hydrogenated 10 times more slowly. This observation indicates stepwise hydrogenation of isomers when a mixture of *E* and *Z* isomers is employed.

Table 3. First-order rate constants and enantioselectivities for the hydrogenation of (*Z*)-**1** and (*E*)-**1** in the presence of the Et-DuPHOS catalyst and dependence on the temperature.

T	Substrate (*E*)-**1**		Substrate (*Z*)-**1**	
[°C]	$k_{\text{first order}}$ [min^{-1}]	*ee* [%]	$k_{\text{first order}}$ [min^{-1}]	*ee* [%]
−10.0	0.0011	91.5	0.0914	86.7
−5.0	0.0028	97.4	–	–
0.0	0.012	99.2	0.175	87.3
7.5	–	–	0.177	87.2
10.0	0.044	98.7	–	–
15.0	–	–	0.259	87.3
25.0	0.111	98.5	0.340	87.0
32.5	0.147	97.8	–	–
35.0	–	–	0.398	86.6
40.0	0.175	96.6	–	–
42.5	–	–	0.367	85.9
47.5	0.178	96.0	–	–
50.0	–	–	0.355	85.5
55.0	0.142	92.2	–	–
60.0	0.112	89.5	0.144	85.2

For (*Z*)-**1**, the enantioselectivity changed only from 85.0 % *ee* to 87.5 % *ee* over the measured temperature region (70 °C range: −10 to +60 °C), whereas for (*E*)-**1** it changed from 90.0 to 99.0 % *ee*. The enantioselectivity maxima can also be shown to be dependent on the temperature; however, they are less

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pronounced than the activity differences found. For (*Z*)-**1** the enantioselectivity maximum lies between 0 and 15 °C, and for (*E*)-**1** the maximum enantioselectivity can be achieved between 0 °C and room temperature.

The interpretation of the nonlinear dependence of the enantiomeric ratio as a function of the reciprocal temperature has been discussed in detail in the literature. This phenomenon is known as the "isoinversion principle".[23] Since the temperature-dependent enantioselectivities for the hydrogenations of (*E*)-**1** and (*Z*)-**1** are characterized by typical maxima (Figures 6 and 7), it also holds for the plot of the logarithmic ratios of enantiomers as a function of the reciprocal temperature.[15]

In general, a linear temperature dependency of the modified Eyring plots can be expected for use of catalysts based on C_2-symmetric chiral ligands such as DuPHOS for the selection processes considered here, under the condition that pre-equilibria affording diastereomeric substrate complexes are established.[24] One indication is derived from the dependence of the enantioselectivity on pressure. In the case of pressure independence, the pre-equilibrium is established and the temperature dependence of the enantioselectivity as a ratio of products according to Eyring is linear.[25] Obviously, this does not hold for the hydrogenation of (*E*)-**1** and (*Z*)-**1**. The reason for this behaviour is not yet clear; however some possible explanations can be found in ref. [26]

Under isobaric conditions, as mentioned above, an increase in temperature lowers the partial pressure of hydrogen.[27] This effect is caused by the temperature-dependent increase of the vapour pressure of the solvent, here MeOH.[15] Since the overall pressure remains constant, the partial pressure of hydrogen must decrease. As a result, in accordance with Henry's law, the concentration of the hydrogen in the liquid phase will also decrease.

Because of this correlation, an increasing temperature gives rise to a lower hydrogen concentration in the solution. In other words, less hydrogen is available for the hydrogenation process. Since, with decreasing hydrogen pressure in the hydrogenation of (*Z*)-**1**, an increase in the *ee* was found, as shown above, we did not expect a disadvantageous effect on the *ee* with an increase in the temperature. Indeed, as shown in Figure 7 the enantioselectivity is not significantly affected over a broad temperature range of 70 K, giving confirmation of our hypothesis. Evidence can similarly be derived by consideration of the analogous behaviour seen in the hydrogenation of (*E*)-**1** (Figure 6).

Thanks to the isobaric conditions applied, the formal kinetic relationships became much simpler, but on the other hand pseudo rate constants result, additionally containing a concentration of hydrogen (gas solubilities) under the reaction conditions. Since different solubilities of hydrogen in MeOH are reported in the literature,[28] and rate constants cannot be directly compared because of different hydrogen partial pressures, we have standardised the pseudo first-order rate constants to a partial pressure of 760 Torr (Table 4).

Now, by use of the Eyring plot of the temperature-dependent pseudo rate constants, the apparent activation values can be calculated. As shown in Figure 8 for the hydrogenation of (*Z*)-**1**, a linear correlation is obtained. This does not hold for the hydrogenation of (*E*)-**1**.

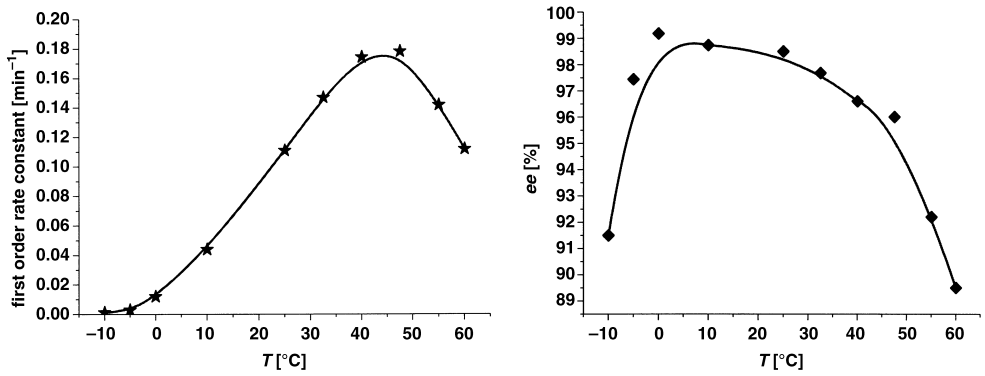

Figure 6. Rate constants (left) and enantioselectivities (right) for the hydrogenation of (*E*)-**1** in the presence of [Rh(Et-DuPHOS)(MeOH)$_2$]BF$_4$ and dependence on the temperature; standard conditions.

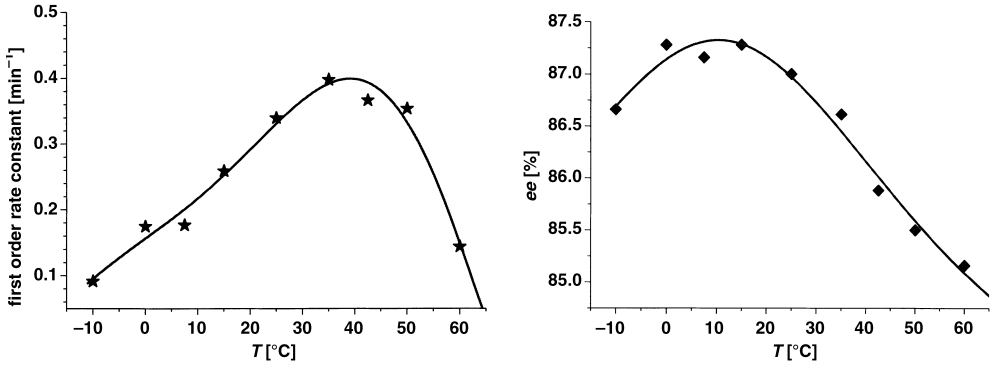

Figure 7. Rate constants (left) and enantioselectivities (right) for the hydrogenation of (*Z*)-**1** in the presence of [Rh(Et-DuPHOS)(MeOH)$_2$]BF$_4$ and dependence on the temperature; standard conditions.

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Table 4. Standardised rate constants for the hydrogenation of (*Z*)-**1** and (*E*)-**1** in the presence of [Rh(Et-DuPHOS)(MeOH)$_2$]BF$_4$ in MeOH[a] at normal pressure (760 Torr).

T/(1/*T*) [°C]//[K^{-1}]	MeOH Vapour pressure [Torr]	H_2 Partial pressure [Torr]	Substrate (*E*)-**1** $k_{\text{first order}}$[b] [min^{-1}]	Substrate (*Z*)-**1** $k_{\text{first order}}$[b] [min^{-1}]
$-10.0/3.800\times10^{-3}$	15.7	744.3	0.001	0.093
$-5.0/3.73\times10^{-3}$	21.7	738.3	0.003	–
$0.0/3.66\times10^{-3}$	29.8	730.2	0.012	0.182
$7.5/3.56\times10^{-3}$	46.7	713.3	–	0.188
$10.0/3.53\times10^{-3}$	54.0	706.0	0.047	–
$15.0/3.47\times10^{-3}$	71.6	688.4	–	0.286
$25.0/3.35\times10^{-3}$	122.5	637.5	0.132	0.405
$32.5/3.27\times10^{-3}$	178.9	581.1	0.192	–
$35.0/3.24\times10^{-3}$	202.2	557.8	–	0.542
$40.0/3.19\times10^{-3}$	256.8	503.2	0.263	–
$42.5/3.17\times10^{-3}$	288.5	471.5	–	0.591
$47.5/3.12\times10^{-3}$	362.3	397.7	0.341	–
$50.0/3.09\times10^{-3}$	404.9	355.1	–	0.758
$55.0/3.05\times10^{-3}$	503.1	256.9	0.420	–
$60.0/3.00\times10^{-3}$	621.2	138.8	0.613	0.788

[a] Standard conditions. [b] Standardised to 760 Torr.

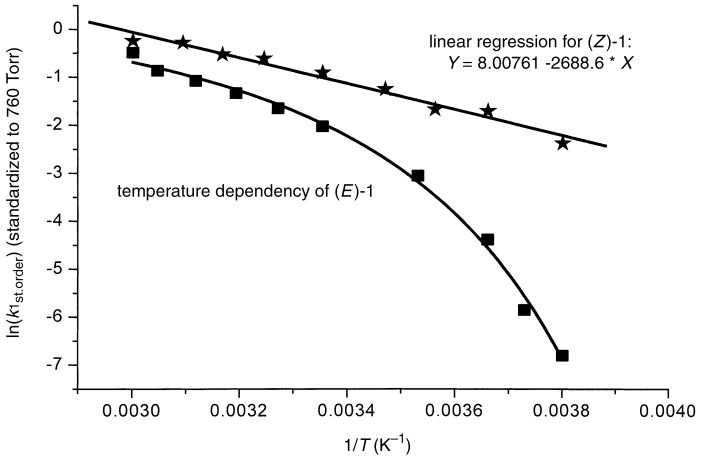

Figure 8. Eyring plot for standardised first order rate constants of the temperature-dependent hydrogenation of (*Z*)-**1** and (*E*)-**1** in the presence of the Et-DuPHOS catalyst in MeOH.

Conclusion

The enantioselective hydrogenation of the isomeric methyl 3-acetamidobutenoates (*E*)-**1** and (*Z*)-**1** in the presence of [Rh(ligand)(MeOH)$_2$]BF$_4$ (ligand: Et-DuPHOS, Me$_4$-BASPHOS, DIPAMP, DIOP, HO-DIOP and Et-FerroTANE) as a catalyst in MeOH has been investigated in detail. Our results indicate that the hydrogenation proceeds by the "unsaturated route", as has also been found for the hydrogenation of related unsaturated α-amino acid precursors. This hypothesis receives additional support from NMR spectroscopic investigations. Thus, in solutions containing solvent complex and prochiral olefin, either the solvent complex is present (and a reaction of first-order results, due to the low stability of the substrate complexes), or a relevant substrate complex (and a reaction of zero order results, due to the high stability of the substrate complexes). Moreover, it can be concluded that the highest enantioselectivities can be achieved for the hydrogenation of both isomeric substrates at room temperature and below, whereas the fastest conversion takes place at 30–50 °C.

Acknowledgements

The authors are grateful for the financial support provided by Degussa AG (Frankfurt), the BMBF and the Fonds der Chemischen Industrie. It is a pleasure for us to acknowledge skilled technical assistance by Mrs. C. Pribbenow. We thank ChiroTech (Dr. R. McCague, Dr. A. Zanotti-Gerosa) for a generous gift of Et-FerroTANE).

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Received: March 14, 2002 [F3953]

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