Pressure Dependent Highly Enantioselective Hydrogenation of Unsaturated β-Amino Acid Precursors

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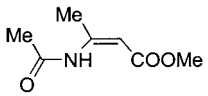
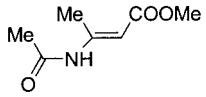
The synthesis of chiral β-amino acids is a challenging goal for academic research with an increasing potential for pharmaceutical application.[1] Enantiomerically pure β-amino acids and their derivatives are useful building blocks for the synthesis of β-peptides and β-lactam antibiotics with high stability to enzymatic hydrolysis. Peptides derived from β-amino acids exhibit interesting folding properties.[2] In the past, several methods using stoichiometric chiral auxiliaries and catalytic methods have been developed for the synthesis of the target compounds, however, only a few of them might be useful for large scale preparation.[1,3,4] One of the most promising methods seems to be the enantioselective hydrogenation of prochiral 3-aminoacrylic acid derivatives with homogeneous metal catalysts. However, in striking contrast to the application of this methodology for the synthesis of α-amino acids, which was developed in the last three decades to a standard procedure in organic chemistry, the asymmetric hydrogenation of β-acylamino acrylates is far from being mature. The crucial problem consists of the different catalytic behaviors hitherto attributed to isomeric substrates, such as *Z*-**1** and *E*-**1**.



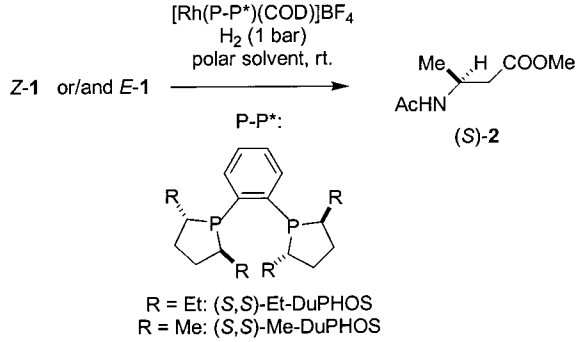
Z-**1**



E-**1**

In most synthetic protocols, both of these isomeric substrates are formed simultaneously. Frequently, a large excess of the *Z*-enamide is obtained. Single *E*-enamides could be easily reduced by up to 96% ee using a Ru−BINAP complex in MeOH.[5] However, the same catalyst hydrogenated the corresponding *Z*-isomer with poor enantioselectivity. Sometimes even the product with the opposite configuration was obtained. Therefore, up to now, prior to the asymmetric hydrogenation, separation by crystallization or chromatography is required. Low enantioselectivity in the hydrogenation of *Z*-**1** was also observed by employment of a Rh complex bearing BPPM as ancillary ligand.[6] The inferior enantioselectivity achieved in general with *Z*-β-acylamino acrylates was rationalized by the assumption of an intramolecular hydrogen bond between amido and ester group, which prevents the desired bidentate coordination of the substrate at the metal center.[5] These disappointing results stimulated attempts for the selective double bond isomerization of the *Z*- into the *E*-isomer, but this tedious procedure seems not to be efficient.[5]

Scheme 1. Enantioselective Hydrogenation of Isomeric Methyl β-*N*-Acetylamino Acrylates



Recently, Zhang and co-workers reported a breakthrough by application of a Rh−BICP catalyst.[7] In the reduction of *E*-**1** and *Z*-**1**, 96% ee and 87% ee, respectively, were observed in toluene as solvent. The hydrogenation of *E*-**1** with a Rh complex based on Me−DuPHOS as chiral ligand gave an even higher enantioselectivity. Unfortunately, when *Z*-**1** was used as substrate, the latter afforded only moderate ee's. It is important to note that the hydrogenation of *E*-**1** proceeded fast at 3 bar, whereas the hydrogenation of *Z*-**1** required 20 bar in order to achieve complete conversion within 24 h. A single trial in MeOH with the Rh−BICP complex and *E*-**1** as substrate gave a lower ee in the product, therefore this solvent was not recommended.

Herein, we report that by application of polar solvents, the rate of the hydrogenation of *Z*-enamides is dramatically accelerated. (Scheme 1). Simultaneously, a considerable gain of enantioselectivity can be achieved when the reaction is run at ambient H_2 pressure.

In a preliminary trial, *Z*-**1** was reduced using MeOH as the solvent and applying [Rh((*S*,*S*)-Et-DuPHOS)(COD)]BF_4[8] as precatalyst under the conditions suggested by Zhang et al. for the reduction in toluene. Unexpectedly, at 20 bar the reaction was finished within a few minutes. Careful inspection of the hydrogen consumption revealed that in MeOH enhanced H_2 pressure is not required for rapid and full conversion of the substrate. Indeed, the reaction is also complete at 1 bar after 40

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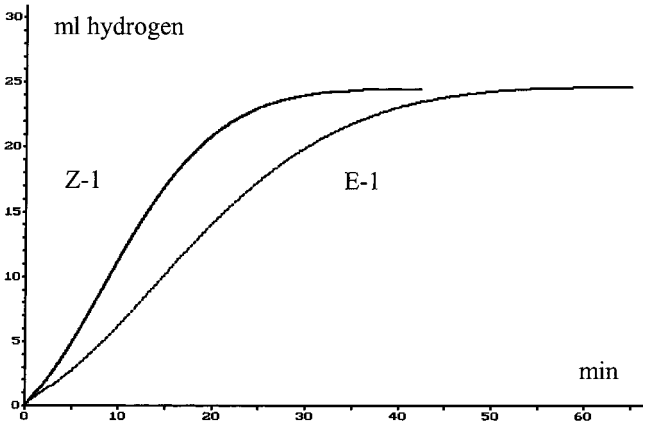

Figure 1. Hydrogen consumption curves of the hydrogenation of *E*-**1** and *Z*-**1** with [Rh((*S*,*S*)-Et-DuPHOS)(COD)]BF_4 in MeOH at 1 bar H_2 pressure.

Table 1. Dependence of the % ee on the H_2 Pressure and Solvent Employed in the Hydrogenation of Isomeric Enamides[a]

run	complex	solvent	substrate	*p* [bar]	ee [%][b]
1	(*S*,*S*)-Et-DuPHOS	MeOH	*Z*−1	45	35.0
2	(*S*,*S*)-Et-DuPHOS	MeOH	*Z*−1	30	47.0
3	(*S*,*S*)-Et-DuPHOS	MeOH	*Z*−1	1	86.7
4	(*S*,*S*)-Et-DuPHOS	*i*-PrOH	Z−1	38	12.8
5	(*S*,*S*)-Et-DuPHOS	*i*-PrOH	Z−1	1	82.4
6	(*S*,*S*)-Et-DuPHOS	*n*-BuOH	Z−1	37	12.9
7	(*S*,*S*)-Et-DuPHOS	*n*-BuOH	Z−1	1	78.4
8	(*S*,*S*)-Et-DuPHOS	CH_2Cl_2	Z−1	38	60.3
9	(*S*,*S*)-Et-DuPHOS	CH_2Cl_2	Z−1	1	87.2
10	(*S*,*S*)-Et-DuPHOS	THF	Z−1	37	20.4
11	(*S*,*S*)-Et-DuPHOS	THF	Z−1	1	85.0
12	(*S*,*S*)-Me-DuPHOS	MeOH	*Z*−1	1	87.8
13	(*S*,*S*)-Et-DuPHOS	MeOH	*E*−1	45	96.0
14	(*S*,*S*)-Et-DuPHOS	MeOH	*E*−1	30	96.0
15	(*S*,*S*)-Et-DuPHOS	MeOH	*E*−1	1	97.0
16	(*S*,*S*)-Me-DuPHOS	MeOH	*E*−1	1	98.2
17	(*S*,*S*)-Et-DuPHOS	MeOH	*E*−1/*Z*−1	35	67.0[c]
18	(*S*,*S*)-Et-DuPHOS	MeOH	*E*−1/*Z*−1	1	91.8[d]

Conditions: [a] In general, precatalysts of the type [Rh(DuPHOS)(diolefin)]BF_4 (diolefin = COD or NBD) were employed, 0.01 mmol precatalyst, 1.0 mmol prochiral olefin, 15.0 mL solvent, and 25.0 °C. [b] GC-analysis: 5890 Hewlett-Packard, Chiraldex *β*-PM 50m × 0.25 mm (astec), and temperature 130 °C. [c] Mean value of the invidual hydrogenations: 70% ee. [d] Mean value of the invidual hydrogenations: 91.9% ee.

min, Figure 1. It is important to note that a decreasing H_2 pressure resulted in a dramatic increase of the enantioselectivity. Obviously, this feature is not only restricted to the use of MeOH. In Table 1 , typical results obtained by application of different H_2 pressures and solvents are listed. The highest enantioselectivity of 86.7% was obtained in MeOH at 1 bar (run 3), whereas with increasing pressure, the ee's dropped seriously (runs 1, 2). The most striking difference of about 70% ee were observed in *i*-PrOH at 38 and 1 bar, respectively (runs 4, 5). The reactions in *n*-BuOH, CH_2Cl_2, and THF followed the same tendency (runs 6−11), but, in general the stereoselectivity is lower compared to the reaction in MeOH. By applying Me−DuPHOS as the ancillary ligand, the ee was slightly improved (run 12).

In contrast to the hydrogenation of *Z*-**1**, the enantioselectivity obtained in the reduction of the corresponding *E*-isomer in MeOH is less dependent on the H_2 pressure (runs 13−15). This result matches results obtained with other catalysts.[5,7] Under all conditions tested, extremely high ee values were produced. The enantioselective production of (*S*)-**2** was independent of the substrate geometry. As shown in Figure 1, and in striking contrast to the reaction in toluene, the hydrogenation of *E*-**1** proceeds in MeOH more slowly than the reduction of *Z*-**1**. Preliminary investigations gave evidence that the asymmetric hydrogenation of the substrates may proceed even up to four-fold faster when the solvent complex ([Rh((*S*,*S*)-Et-DuPHOS)$(MeOH)_2$]BF_4) was applied instead of the commercially available [Rh((*S*,*S*)-Et-DuPHOS)(COD)]-BF_4 precatalyst.[9] The former can be easily generated by the prehydrogenation of COD in the precatalyst using MeOH as solvent.[10]

Our results show, for the first time, that individual hydrogenation of *E*-**1** and *Z*-**1** can be performed under identical catalytic conditions with the same catalysts, affording *β*-amino acid derivatives with the same configuration and high enantioselectivity. These findings open up the opportunity to hydrogenate substrate mixtures. Indeed, as indicated in runs 17 and 18, a 1:1 mixture of isomeric substrates can be conveniently hydrogenated in MeOH by application of [Rh((*S*,*S*)-Et-DuPHOS)$(MeOH)_2$]-BF_4. Similar to the results shown in the individual trials, decreasing pressure gave rise to an enhancement of the ee. At 1 bar H_2 pressure, 91.8% ee was observed (run 18). This corresponds to the mean value of the individual hydrogenations of *E*-**1** and *Z*-**1**.

In conclusion, Rh(DuPHOS) complexes represent efficient homogeneous catalysts for the highly enantioselective hydrogenation of *β*-dehydroamino acid derivatives independent of their *E*/*Z* geometry, provided that polar solvents and low pressures are used for the catalytic reaction. It should be noted that pressure dependence of the enantioselectivity is well known for the hydrogenation of α-dehydroamino acid and methyl succinic acid precursors.[11,12] This has been rationalized according to the major−minor concept of Halpern and Brown by pressure dependent disturbance of the pre-equilibrium to the minor substrate complex.[13] Work is in progress to broaden the scope of the reaction to other substrates and to elucidate the superiority of polar solvents for the hydrogenation.[14] Preliminary results indicate that, besides the problem of the removal of coordinated COD as discussed above, in aromatic solvents, stable arene complexes are formed, also blocking parts of the catalyst.[15]

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