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Chiral β-Amino Acid Derivatives via Asymmetric Hydrogenation

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Abstract:

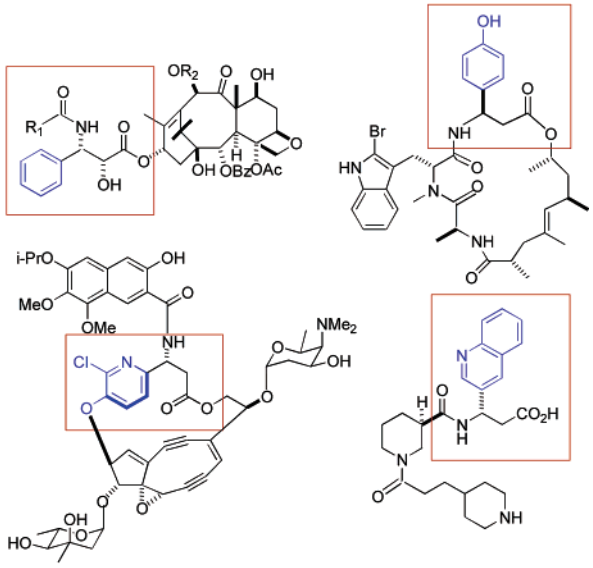
This contribution gives an overview of the synthesis of chiral β-amino acids via asymmetric hydrogenation of the corresponding dehydroamino derivatives. Literature results are discussed regarding substrate synthesis and catalyst performance and how it is affected by substrate and catalyst structure as well as experimental parameters. A tentative mechanistic concept for the hydrogenation step is also presented.

Introduction

Enantiomerically pure β-amino acids and their derivatives not only exhibit broad biological activity but are also the building blocks for the synthesis of β-peptides. The latter are characterized by a high enzymatic stability and show interesting three-dimensional structures.[1] The cyclization of β-amino acids leads to the important family of the β-lactams. Scheme 1 shows examples of pharmaceutically interesting structures containing a β-aryl-substituted β-amino acid as a common structural component.[2]

Methods for the preparation of optically enriched β-amino acids are predominantly based on stoichiometric reactions with chiral auxiliary agents and to a clearly smaller extent on stereoselective catalytic reactions.[2d,e,3] One of the most promising methodologies, also regarding industrial application, is the asymmetric hydrogenation of the appropriate β-dehydroamino acid precursors catalyzed by homogeneous Rh or Ru complexes containing chiral phosphane ligands. In contrast to the synthesis of α-amino acid precursors where it is a standard method with many industrial applications,[4] the asymmetric hydrogenation of β-dehydroamino acid derivatives is hardly established. In recent years, however, a rapid development has taken place, and the most important results are summarized and discussed in this contribution.

Scheme 1. **Biologically active compounds with β-amino acid units**[a]



[a] Top left: Taxol (R_1 = Ph, R_2 = Ac), a cancer chemotherapeutic agent; top right: Jasplakinolide with anthelminthic, insecticidal, and antifungal properties; bottom left: Kedarcidin, an antitumor antibiotic; bottom right: Elarobifan (RWJ-53033), an integrin antagonist.

Results and Discussion

1. Substrates. The prochiral starting compounds for the asymmetric hydrogenation are easily obtained by the reaction of β-ketocarboxylates with ammonium acetate followed by acylation (Scheme 2).[5,6] As a rule *Z*/*E* mixtures are obtained with the more stable *Z*-enamides predominating due to the stabilizing hydrogen bond. This was already proposed by Noyori,[5] and an example is shown in the X-ray crystal structure of *Z*-**3** (Figure 1 left). Whether such a hydrogen bond is present in protic solvents and whether it has an influence on the substrate binding to the transition metal complex and thus on the enantioselectivity is not yet clear.

In the case of β-alkyl-substituted β-acylaminoacrylates (R_2 = alkyl) the separation of the *Z*/*E* isomers (e.g. by column chromatography) is easy. Thus far β-aryl-substituted

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(1) (a) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905−925. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (c) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V. *Helv. Chim. Acta* **1998**, *81*, 932−982. (d) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022.

(2) (a) Bull, S. D.; Davies, S. G.; Fox, D. J.; Gianotti, M.; Kelly, P. M.; Pierres, C.; Savory, E. D.; Smith, A. D. *J. Chem. Soc., Perkin Trans 1* **2002**, 1858−1868. (b) Wehner, V.; Blum, H.; Kurz, M.; Stilz, H. U. *Synthesis* **2002**, *14*, 2032−2036. (c) Ojima, I.; Lin, S.; Wang, T. *Curr. Med. Chem.* **1999**, *6*, 927−954. (d) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983−1004. (e) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117−128.

(3) (a) Liu, M.; M. Sibi, M. P. *Tetrahedron* **2002**, 7991−8035. (b) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197−2199. (c) *Enantioselective Synthesis of β-Amino Acids*, Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (d) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582.

(4) (a) Blaser, H.-U.; Spindler, F.; Studer, M. *Appl. Catal., A* **2001**, 119−143. (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H. Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103−151.

(5) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543−554.

(6) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907−6910.

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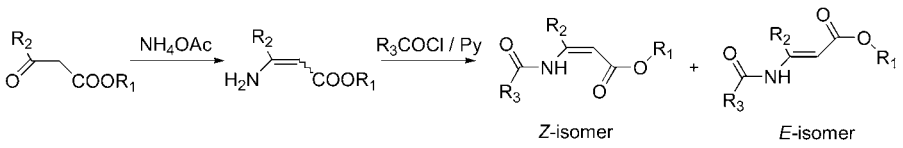
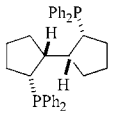
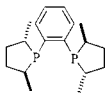
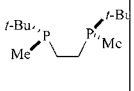
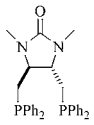
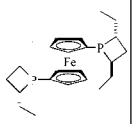
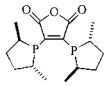
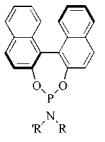
Scheme 2. **Synthesis of β-substituted β-acylamino acrylic acid derivatives**



R_1 = Me	R_2 = Me	R_3 = Me :	*Z*-**1**/*E*-**1**
R_1 = Et	R_2 = Me	R_3 = Me :	*Z*-**2**/*E*-**2**
R_1 = Me	R_2 = Ph	R_3 = Me :	*Z*-**3**/*E*-**3**
R_1 = Me	R_2 = Et	R_3 = Me :	*Z*-**4**/*E*-**4**
R_1 = Me	R_2 = Me	R_3 = BnO :	*Z*-**5**/*E*-**5**

Table 1. **Enantioselectivity for the Rh-complex-catalyzed hydrogenation of dehydroamino acid precursors**

BICP[6]	Me-DuPHOS[16]	*t*-Bu-BisP*[17]	BDPMI[8]	Et-Ferro-TANE[18]	MalPHOS[19]	MonoPHOS[10]
						
Z-**1**: 87 % ee	*Z*-**1**: 88 % ee	*Z*-**1**: 20 % ee	*Z*-**2**: 95 % ee	*Z*-**1**: 28 % ee	*Z*-**1**: 83 % ee	*Z*-**1**: 95 % ee
E-**1**: 96 % ee	*E*-**1**: 98 % ee	*E*-**1**: 99 % ee	*E*-**2**: 92 % ee	*E*-**1**: 99 % ee	*E*-**1**: 98 % ee	*E*-**1**: 99 % ee

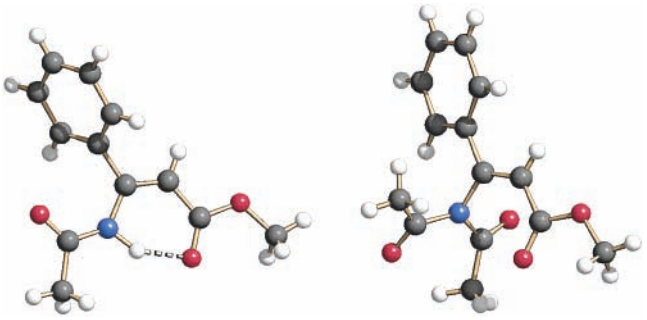


Figure 1. **X-ray crystal structure of Z-3[12] with the characteristic hydrogen bond (left) respective of 3-bisacetylamino-3-phenyl-acrylic acid methyl ester (on the right).**

dehydroamino acid precursors were problematic because the *Z*/*E* mixtures either could not be separated by the usual column chromatography[6−9] or only the unwanted *Z*-isomer was formed.[10] In an interesting aside, we could recently show that the compound described in the literature as (*E*)-3-acetylamino-3-phenyl-acrylic acid methyl ester (*E*-**3**) was actually the *N*,*N*-bisacetylated product (Figure 1 on the right shows the X-ray structure).[11] The desired *E*-**3** was produced in very low yield indicated by an additional spot in the thin-layer chromatogram. Under usual conditions, a *Z*-**3**/*E*-**3**-ratio of 14.5 is obtained, obviously insufficient for an economic preparation of *E*-**3**. This unfavorable *Z*/*E* ratio for β-aryl-substituted β-acylaminoacrylates is due to the reflux conditions applied for the acylation and a too-high concentration of the acylating agent; similar effects were already known for β-alkyl-substituted derivatives.[13] If the acylation is carried out at lower temperatures and with less acylating agent, the yield of *E*-isomer can be increased, and as an additional advantage, the *E*-isomer precipitates upon evaporation of the solvent due to its low solubility.[14]

2. Reaction conditions for the asymmetric hydrogenation. *Catalysts.* Even though some results on the asymmetric hydrogenation of β-dehydroamino acid derivatives have been published before,[15] an important breakthrough was made only recently by Zhang et al.[6] Table 1 summarizes selected literature results for the Rh-catalyzed hydrogenation of the β-alkyl-substituted β-acylaminoacrylates *Z*-**1** and *Z*-**2** or *E*-**1** and *E*-**2**, used as model substrates because of their easy preparation. The reaction conditions are very mild (1−20 bar hydrogen pressure, rt), usually with a substrate/catalyst ratio of 100 (1 mol %). Preferred are chiral, C_2 symmetrical diphosphanes forming five- or seven-membered Rh chelate

(7) Zhou, Y. G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952−4953.
(8) Lee, S.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429−2431.
(9) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159−4161.
(10) Pena, D.; Minnaard, A. J.; deVries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14562−14563.
(11) You, J.; Drexler, H.-J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 913−916.
(12) Crystallographic data (excluding structure factors) for the structure of *Z*-**3** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-200716. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax: int. code + (1223) 336−033; e-mail: deposit@ccdc.cam.ac.uk; Internet: http://www.ccdc.cam.ac.uk).
(13) (a) Aberhardt, D. J.; Lin, H.-J. *J. Org. Chem.* **1981**, *46*, 3749−3751. (b) deMayo, P.; Weedon, A. C.; Zabel, R. W. *Can. J. Chem.* **1981**, *59*, 2328−2333 (c) Shabana, R.; Rasmussen, J. B.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1981**, *90*, 75−82. (d) Grob, C. A. *Helv. Chim. Acta* **1950**, *33*, 1787−1796.
(14) Further data for the synthesis and characterisation of the β-aryl-substituted β-acylaminoacrylates are in the supporting information of ref 11. Moreover, a comprehensive publication about the synthesis is in preparation.
(15) (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachmann, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946−5952. (b) Achiwa, K.; Soga, T. *Tetrahedron Lett.* **1978**, 1119−1120.

Table 2. **Hydrogenations of *E*-3 and *Z*-3 with different catalysts (0.01 mmol catalyst, 1.0 mmol substrate, 15.0 mL of MeOH, 1.0 bar, 25 °C)**

ligand in $[Rh(ligand)(MeOH)_2]^+$	*E*-**3** % ee	*Z*-**3** % ee
Et-FerroTANE	>99	76
Me-DuPHOS	96	81
Et-DuPHOS	89	85
CHIRAPHOS	55	56

complexes, but some unsymmetrical ligands[17b,20,21] and even a monodentate phosphorus ligand were also successful.[10] The results listed in Table 1 show that in most cases the hydrogenation of *E*-isomeric substrates proceeds with considerably higher enantioselectivities than with the analogous *Z*-isomers. This was also observed for *E*-**3** or *Z*-**3** with various catalysts under normal pressure (see Table 2). However, as already observed by Zhang,[6] there are exceptions such as the Rh−BDPMI-catalyzed hydrogenation of β-alkyl-substituted substrates giving somewhat higher enantioselectivity for the *Z*-isomers than the *E*-isomers.[8] Also remarkable is the very high enantioselectivity for the hydrogenation of *Z*-isomers with Rh−TangPhos.[9]

The use of Ru catalysts is thus far limited to two examples. *E*-enamides could be hydrogenated with up to 96% ee with a Ru−BINAP complex in MeOH. However, the same catalyst hydrogenated the corresponding *Z*-isomer with poor enantioselectivity, and sometimes even the product with the opposite configuration was obtained.[5] Ru−BINAPO catalysts were successfully used for the hydrogenation of β-acylaminoacrylates.[7] Depending on the ligand and the substrate, ee values of up to 99% could be obtained (Table 3). Since *Z*/*E* mixtures do not have to be separated (for different β-aryl-substituted compounds *Z*/*E* ratios from 95/5 to 60/40 were used), this is an obvious advantage. However, the substrate/catalyst ratio of 25 is insufficient for practical applications. Table 3 shows that it is also possible to achieve comparable enantioselectivities both for *Z*/*E* mixtures and for *E*-isomers of β-aryl-substituted β-acylaminoacrylates with Rh catalysts. Remarkable is the high ee of Rh−FerroTANE for the *o*-methoxy-phenyl derivative.[9,11]

The comparison of activity data is difficult because differing reaction conditions or catalyst preparations used by the various groups. By determining pseudo-first-order rate constants for *Z*-**1** and *E*-**1** in MeOH we[18] could show that the *E*-isomers are not generally hydrogenated faster than the *Z*-isomers, as claimed by some authors. Rh complexes of

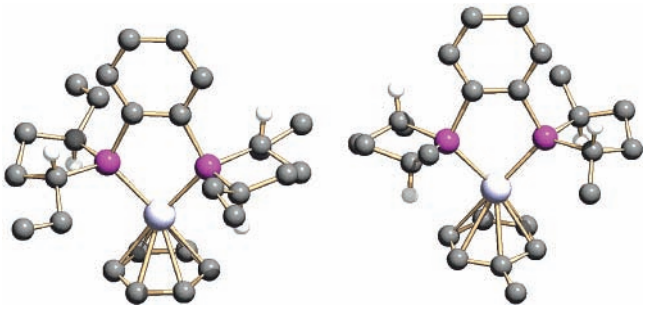


Figure 2. **X-ray crystal structures of the Rh−η^6-arene complexes [Rh((*R*,*R*)-Et-DuPHOS)(benzene)]BF_4 and [Rh(*S*,*S*)-(Me-DuPHOS)(toluene)]BF_4.**

Et-DuPHOS or DIOP, for example, reduced *Z*-**1** about 2.5−3 times faster than *E*-**1**. Generally, Ru catalysts are less active than Rh complexes where, depending on reaction conditions, complete conversion can be obtained in 10 min.[11] As a consequence, the substrate/catalyst ratio can be increased without problems to 1000 as for example for *E*-**3** or with the Rh−TangPHOS catalyst.[9,11]

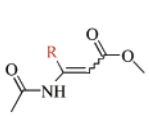
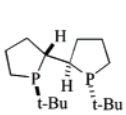
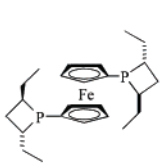
Solvents. Protic solvents such as alcohols, but also THF and CH_2Cl_2, are particularly suitable for the asymmetric hydrogenation of β-dehydroamino acid precursors. A systematic investigation of the hydrogenation of *E*-**1** with Rh−BICP gave the following sequence of enantioselectivities: toluene (96% ee) = benzene (96% ee) > THF (94% ee) > CH_2Cl_2 (93% ee) > MeOH (85% ee).[6] For alcohols, the following results were reported for the hydrogenation of *Z*-**1** with Rh−Et-DuPHOS: MeOH 87% ee, *i*-PrOH 82% ee and *n*-BuOH 78% ee.[16] Some authors differentiate between the two isomers and recommend CH_2Cl_2 for *E*-isomers and MeOH or *i*-PrOH for *Z*-isomers.[8,10,21b] Also reported was that toluene can lead to comparatively low enantioselectivities,[17a] and that with certain catalyst−solvent systems complete substrate conversion can be a problem.[8,9]

Particularly for *Z*-isomers, rates are often lower in aromatic solvents. As shown for other systems,[23] this is not necessarily due to an inherently low activity of these substrates but rather to the formation of rather stable Rh(I)−arene complexes. Figure 2 shows the crystal structures of such complexes with DuPHOS.[24]

The complexed arene presumably blocks free coordination sites leading to decreased activity as shown for hydrogenation of β-amino acid precursors in Figure 3. The left curve shows the hydrogen uptake for *Z*-**1** with the cationic Rh−DIPAMP catalyst in pure MeOH, on the right in a MeOH/*p*-xylene mixture. The MeOH/*p*-xylene and *p*-xylene/Rh ratios were 650 and 57, respectively. While the enantioselectivity was the same, already a very small concentration of xylene (0.5 volume % related to MeOH) led to a significantly lower activity. Using initial rate data, it was estimated that ca. 50%

(16) Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem.* **2001**, *66*, 6816−6817.
(17) (a) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701−1704. (b) Ohashi, A.; Kikuchi, S.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, 2535−2546.
(18) Heller, D.; Drexler, H.-J.; You, J.; Baumann, W.; Drauz, K.; Krimmer, H.-P.; Börner, A. *Chem. Eur. J.* **2002**, *8*, 5196−5202.
(19) Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701−1707.
(20) Demay, S.; Lotz, M.; Polborn, K.; Knochel, P. *Tetrahedron: Asymmetry* **2001**, *12*, 909−914.
(21) (a) Komarow, I. V.; Monsees, A.; Kadyrov, R.; Fischer, C.; Schmidt, U.; Börner, A. *Tetrahedron: Asymmetry* **2002**, 1615−1620. (b) Komarow, I. V.; Monsees, A.; Spannenberg, A.; Baumann, W.; Schmidt, U.; Fischer, C.; Börner, A. *Eur. J. Org. Chem.* **2002**, 138−150.
(22) The hydrogenation of the corresponding *Z*-isomers with the Et-FerroTANE catalyst leads, as expected, only to enantioselectivities of about 25−80%.
(23) (a) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 8055−8057; (b) Landis, C. R.; Halpern, J. *Organometallics* **1983**, *2*, 840−842. (c) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345−4353. (d) Burk, M. J.; Bienewald, F.; Challenger, S.; Derrick, A.; Ramsden, J. A. *J. Org. Chem.* **1999**, *64*, 3290−3298.
(24) Heller, D.; Drexler, H.-J.; Spannenberg, A.; Heller, B.; You, J.; Baumann, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 777−780.

Table 3. **Comparison of Ru or Rh catalysts for the hydrogenation of β-aryl-substituted β-acylaminoacrylates**

	Ru-BINAPO[7,a]	Rh-TangPHOS[9,b]	Rh-Et-Ferrotane[11,c]
			
phenyl	*Z*/*E* (86/14): 99 % ee	*Z*/*E*: 94 % ee	*E*-isomer[22]: > 99 % ee
p-methoxy-phenyl	*Z*/*E* (95/5): 99 % ee	*Z*/*E*: 98 % ee	*E*-isomer: 98 % ee
p-chloro-phenyl	*Z*/*E* (85/15): 97 % ee	*Z*/*E*: 92 % ee	*E*-isomer: 98 % ee
o-methoxy-phenyl	*Z*/*E* (95/5): 80 % ee	*Z*/*E*: 83 % ee	*E*-isomer: 98 % ee
m-nitro-phenyl (ethylester)	-	-	*E*-isomer: 99 % ee

[a] 5 bar, 50 °C, EtOH as solvent, 20 h reaction time, substrate/catalyst = 25. [b] 1.3 bar, room temperature, THF as solvent, 24 h reaction time, substrate/catalyst = 200. [c] 1 bar, 25 °C, MeOH as solvent, max. 10 min reaction time, substrate/catalyst = 100.

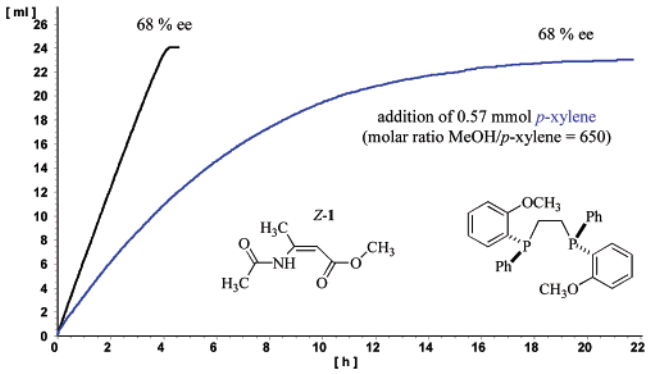


Figure 3. **Hydrogenation of *Z*-1 with $[Rh(DIPAMP)(MeOH)_2]^+$ in MeOH and in MeOH/*p*-xylene = 650, respectively. (0.01 mmol catalyst, 1.0 mmol substrate, 1.0 bar pressure, 15.0 mL of solvent, 25 °C).**

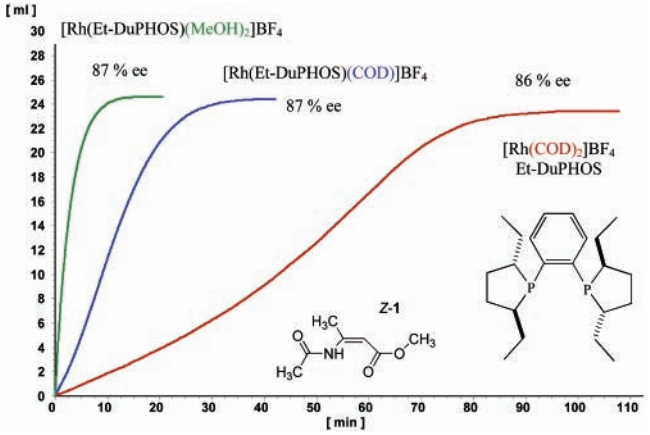


Figure 4. **Effect of preparation methods for the hydrogenation of *Z*-1 with Rh−Et-DuPHOS. From right to left, in situ technique ($[Rh(COD)_2]BF_4$ + Et-DuPHOS), COD containing precatalyst ($[Rh(Et\text{-}DuPHOS)(COD)]BF_4$), solvent complex ($[Rh(Et\text{-}DuPHOS)(MeOH)_2]BF_4$) (0.01 mmol catalyst, 1.0 mmol substrate, 1.0 bar pressure, 15.0 mL of MeOH, 25 °C).[18]**

inactive *p*-xylene complex was formed; this complex can be detected by ^{31}P NMR spectroscopy and was definitely identified with ^{103}Rh NMR spectroscopy.[24]

Catalyst Preparation−Induction Period. Since Zhang et al.[6] found that neutral Rh complexes achieve lower conversion and enantioselectivity than the cationic complexes of the general type $[Rh(PP^*)(diolefin)]^+$ (PP* = chiral ligand), these are now used exclusively. An alternative to the preformed Rh−diphosphane complex is the so-called "in situ" method, where the catalyst is prepared in situ from a suitable precursor such as $[Rh(COD)_2]^+$ and the chiral ligand. To get the active species the diene has to be removed via hydrogenation. For the hydrogenation of α-amino acid precursors it is well-known that for COD this step is comparatively slow, especially for ligands forming five-membered chelates, resulting in substantial induction periods and increasing rates with reaction time.[25] As Figure 4 shows for the hydrogenation of *Z*-**1** with Rh−Et-DuPHOS this makes meaningful activity comparisons or kinetic measurements difficult. A similar effect was also described for a monodentate phosphoramidite where a "preformed solution of both catalyst precursor and ligand" led to a substantial improvement in both the activity and the selectivity.[10]

Pressure Dependence. Zhang et al.[6] reported higher rates for the hydrogenation of the *E*-isomer β-alkyl-substituted substrates than for the *Z*-isomers. Therefore, higher hydrogen pressures were necessary for the latter. It was also shown that the enantioselectivity for the *E*-isomers was practically pressure-independent.[6] The results listed in Table 4 confirm this outcome which applies also to solvents other than MeOH and for other catalyst systems.[8,10] For the hydrogenation of *Z*-**1** we showed that the enantioselectivity increases strongly with decreasing hydrogen pressure; this finding is not limited to MeOH as solvent and was also confirmed for other β-alkyl-substituted substrates and catalyst systems (Table 4).[9,16,26,27] Note that this behavior is well-known and well understood for the hydrogenation of α-dehydroamino acid

(25) (a) Drexler, H.-J.; Baumann, W.; Spannenberg, A.; Heller, D. *J. Organomet. Chem.* **2001**, *621*, 89−102. (b) Börner, A.; Heller, D. *Tetrahedron Lett.* **2001**, *42*, 223−225. (c) Cobley, C. J.; Lennon, I. C.; McCague, R.; Ramsden, J. A.; Zanotti-Gerosa, A. *Tetrahedron Lett.* **2001**, *42*, 7481−7483.

Table 4. **Enantioselectivities as function of the hydrogen pressure for the hydrogenation of β-alkyl-substituted β-acylaminoacrylates in MeOH with different catalyst systems[16,27]**

ligand	substrate	*Z*-isomer pressure, bar/% ee	*E*-isomer pressure, bar/% ee
Et-DuPHOS	*Z*-**1**/*E*-**1**	45 bar: 35% ee 30 bar: 47% ee 1 bar: 87% ee	45 bar: 96% ee 30 bar: 96% ee 1 bar: 98% ee
Me-BasPHOS	*Z*-**1**/*E*-**1**	30 bar: 56% ee 1 bar: 67% ee	30 bar: 98% ee 1 bar: 98% ee
Et-DuPHOS	*Z*-**4**/*E*-**4**	30 bar: 28% ee 1 bar: 68% ee	30 bar: 97% ee 1 bar: 98% ee
Et-DuPHOS	*Z*-**5**	30 bar: 38% ee 1 bar: 80% ee	
Et-FerroTane	*E*-**5**		15 bar: 74% ee
DIOP	*Z*-**1**/*E*-**1**	30 bar: 26% ee 1 bar: 17% ee	30 bar: 70% ee 1 bar: 71% ee

derivatives.[28a] However, there are also exceptions as the example of Rh−DIOP for *Z*-**1** in Table 4 shows where the enantioselectivity is higher at 30 bar than at 1 bar. Similar results were described for the hydrogenation of *Z*-**1** with an unsymmetrical P-chiral ligand and for monodentate phosphoramidite ligands as well.[17b,10]

A remarkable pressure effect was observed for the hydrogenation of *Z*-**4** with Rh−Et-DuPHOS: the enantioselectivity not only decreased with increasing pressure, but the configuration of the product was inverse! Such a pressure-dependent inversion of the enantioselectivity was also found for other substrates;[27] it is of importance because it shows that within certain pressure ranges *Z*/*E* mixtures cannot be hydrogenated effectively.

Hydrogenation of Z/E Mixtures. With the exceptions mentioned above, the same sense of chirality is induced in the product regardless of the double bond configuration in the substrate, allowing, in principle, the hydrogenation of the Z/*E* mixtures. Figure 5 shows the hydrogen uptake curve for the hydrogenation of *Z*-**1** and *E*-**1** and of a 1:1-mixture of *Z*-**1**/*E*-**1** with the Rh−Et-DuPHOS system. For the mixture, both activities and enantioselectivities were found to be between the results for the individual isomers which was confirmed by other authors.[8,9] Table 5 shows that similar results will be obtained under higher hydrogen pressure. This means that in favorable cases, the costly separation of the isomers can be avoided, solving one of the central problems of the asymmetric hydrogenation of β-amino acid precursors.

Temperature Dependence of the Hydrogenation. All results described until now were obtained at room temperature. The temperature dependence of the hydrogenation of

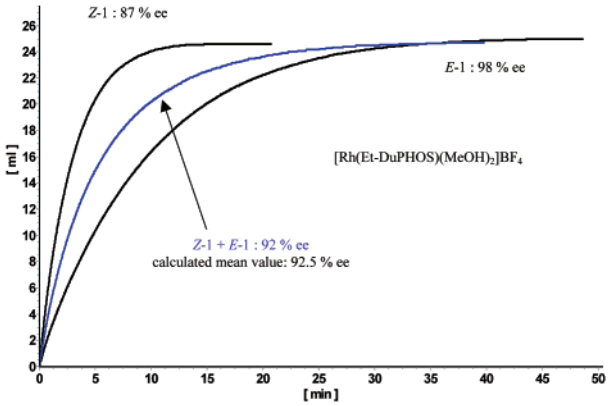


Figure 5. **Hydrogenation of a 1/1 mixture of *Z*-1/*E*-1 with [Rh-(Et-DuPHOS)(MeOH)$_2$]BF$_4$ in comparison to the hydrogenation of the individual isomers *Z*-1 and *E*-1. (0.01 mmol catalyst, 1.0 mmol substrate, 1.0 bar pressure, 15.0 mL of MeOH, 25 °C)**

Table 5. **Comparison of enantioselectivities under elevated hydrogen pressure for *Z*-1, *E*-1 and 1/1 mixtures of *Z*-1/*E*-1 with [Rh(ligand)(MeOH$_2$)]BF$_4$[27]**

[Rh(ligand)(MeOH$_2$)]$^+$	*Z*-**1** (% ee)	*E*-**1** (% ee)	*Z*-**1**/*E*-**1** (1:1)
Et-DuPHOS (35 bar)	44	96	mean value 70% ee, observed 67% ee
Me-BasPHOS (35 bar)	56	97	mean value 76.5% ee, observed 76% ee
DIOP (30 bar)	26	70	mean value 48% ee, observed 48% ee

Z-**1** and *E*-**1** with the Rh−Et-DuPHOS catalyst was investigated in more detail, and the resulting ee's are shown in Figure 6.[18] In both cases, a maximum was observed for the enantioselectivities between 0 °C and ambient temperature. Over a temperature range of 70 °C the ee's for *Z*-**1** change only from approximately 85 to 87.5%, for *E*-**1** from 90 to ca. 99%.

3. Mechanism of the Asymmetric Hydrogenation

As depicted in Figure 7, two basic mechanisms can be distinguished: the "unsaturated route" where two diastereomeric substrate complexes (major/minor) with the prochiral olefin are formed followed by the rate-determining oxidative addition of hydrogen. For the hydrogenation of α-dehydroamino acids, this mechanism is generally favored.[28] An alternative catalytic cycle is the so-called "hydride route" where a dihydride complex is formed which then reacts with the prochiral olefin.[29] In support of this idea, Gridnev/Imamoto could detect monohydride intermediates (hydrido alkyl complexes) after addition of *E*-**1** to the dihydride solvent complex [RhH$_2$(BisP*)(MeOH)$_2$]BF$_4$,[17a] using NMR spectroscopy at −100 °C. It is, however, questionable whether such species are also stable enough during the hydrogenation at ambient temperature.

(26) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Börner, A. *Eur. J. Org. Chem.* **2001**, 4615−4624.
(27) Heller, D.; Holz, J.; Komarov, I.; Drexler, H.-J.; You, J.; Drauz, K.; Börner, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2735−2741.
(28) (a) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746−1754. (b) Brown, J. M. Hydrogenation of functionalized carbon−carbon double bonds. In *Comprehensive asymmetric catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Chapter 5.1, pp 121−182. (c) Feldgus, S.; Landis, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 12714−12727.
(29) (a) Giernoth, R.; Heinrich, H.; Adams, N. J.; Deeth, R. J.; Bargon, J.; Brown, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 12381−12382. (b) Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118−136. (c) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268−5276.

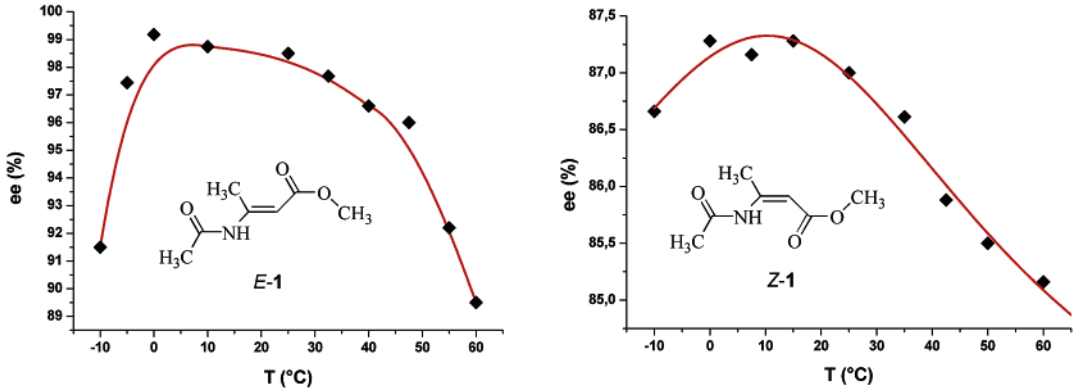


Figure 6. **Enantioselectivities for the hydrogenation of *E*-1 (left) and *Z*-1 (right) with the Et-DuPHOS system as function of the temperature.**

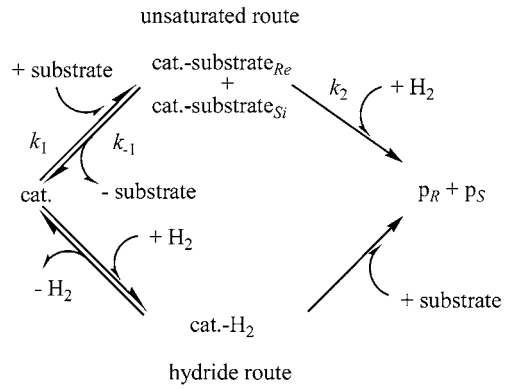


Figure 7. **Unsaturated route and hydride route as alternative pathways in the enantioselective hydrogenation of a prochiral olefin with chiral, C_2-symmetric Rh catalysts (cat. = catalyst, p = product).**

For the "hydride route" under isobaric, stationary conditions a constant concentration of the hydride species would be expected. An increase of the hydrogen partial pressure would raise the concentration of the hydride species, and thus the macroscopic activity, but should not change the enantioselectivity. In addition, a first-order dependence on olefin results (a formal kinetic derivation can be found in the Supporting Information of ref 18). Kinetic investigations of the hydrogenation of *Z*-**1** and *E*-**1** with different Rh catalysts under normal pressure showed that the rate of hydrogen uptake can usually be described quantitatively in terms of a Michaelis−Menten model, with first- and zero-order olefin dependencies as the two limiting situations.[18] The considerable pressure dependence of the enantioselectivity for most *Z*-isomers (Table 4) and the observation of zero-order agree better with the "unsaturated route" than with the "hydride route".

Within this framework, the reported kinetic findings can be well-arranged. A first-order reaction means that the stability constants of the substrate complexes are small. Therefore, under hydrogenating conditions only the solvent complex [Rh(ligand)$(MeOH)_2$]BF_4 is to be expected. In fact, for all systems which follow first-order kinetics, independent of the substrate geometry, only the solvent complex could be found in solution under argon (the left part of Figure 8). A zero-order reaction, in turn order of zero, points to stable substrate complexes, and only substrate complexes should be detected. For the system DIPAMP/*Z*-**1** as an example only one substrate complex (probably the major complex) is observable, signals of a solvent complex are not visible (see right part of Figure 8). These first interpretations of the reaction sequence have, however, only a tentative character and have to be confirmed by further studies.

Summary

Findings from the literature can be summarized as follows:

The hydrogenation of β-substituted β-acylaminoacrylates is possible under mild reaction conditions (normal pressure and ambient temperature) using Rh and Ru complexes with various chiral diphosphanes.

MeOH, THF, and CH_2Cl_2 are preferred solvents. The choice of the right solvent (exclusive of deactivating arene complexes) and an optimal catalyst preparation (avoidance of induction periods) increase the efficiency of the catalysis.

The hydrogenation of the *E*-isomers usually occurs with higher enantioselectivity and is practically pressure independent. The hydrogenation of the *Z*-isomers is frequently pressure dependent; usually the enantioselectivity increases with decreasing pressure; however, there are exceptions.

With suitable catalysts, *Z*/*E*-mixtures can be hydrogenated with high enantioselectivity without isomer separation. With some substrates, caution is required because of a possible pressure-dependent inversion of the product chirality for the *Z*-isomer.

The industrial application depends on the general acceptance of the homogeneous hydrogenation technology in general. For the β-amino acid derivatives the central problem is rather the substrate synthesis than the catalytic step because of the impressive results reported in the past few years, particularly for the Rh complexes. An alternative method for the preparation of chiral β-amino acid derivatives is (dynamic) kinetic resolution.[31] The necessary racemic β-amino acids seem partly efficiently available very recently.[32]

(30) For a detailed discussion of the overall kinetics of asymmetric hydrogenations, see, e.g.: Heller, D.; Thede, R.; Haberland, D. *J. Mol. Catal. A: Chem.* **1997**, *115*, 273−281.

(31) Boesch, H.; Cesco-Cancian, S.; Hecker, L. R.; Hoekstra, W. J.; Justus, M.; Maryanoff, C. A.; Scott, L.; Shah, R. D.; Solms, G.; Sorgi, K. L.; Stafanick, S. M.; Thurnheer, U.; Villani, F. J.; Walker, D. G. *Org. Process Res. Dev.* **2001**, *5*, 23−27.

(32) Tan, C. Y. K.; Weaver, D. F. *Tetrahedron* **2002**, *58*, 7449−7461.

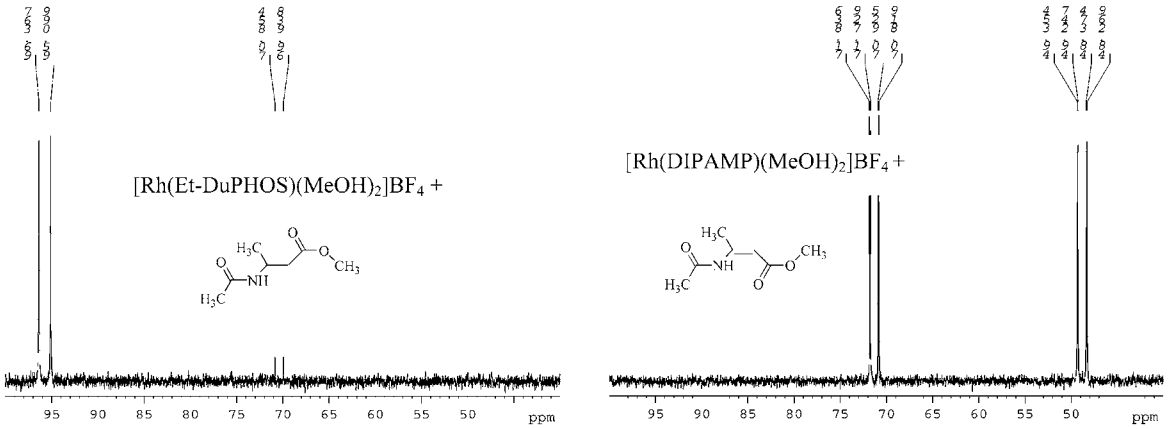


Figure 8. **^{31}P NMR spectra of a solution of 0.01 mmol [Rh(Et-DuPHOS)(MeOH)$_2$]BF$_4$ + 0.1 mmol *E*-1 (left) and of a solution of 0.01 mmol [Rh(DIPAMP)(MeOH)$_2$]BF$_4$ + 0.05 mmol *Z*-1 (right).**

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