ORGANIC LETTERS

2001
Vol. 3, No. 11
1701−1704

Highly Enantioselective Hydrogenation of (*E*)-*β*-(Acylamino)acrylates Catalyzed by Rh(I)-Complexes of Electron-Rich P-Chirogenic Diphosphines

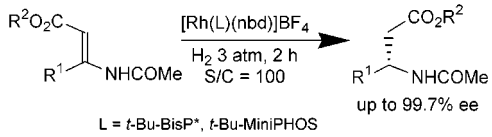
Masaya Yasutake, Ilya D. Gridnev,* Natsuka Higashi, and Tsuneo Imamoto*

Department of Chemistry, Faculty of Science, Chiba University, Chiba 263-8522, Japan

imamoto@scichem.s.chiba-u.ac.jp

Received March 27, 2001

ABSTRACT



Excellent enantioselectivities up to 99.7% were achieved in the hydrogenation of (*E*)-*β*-(acylamino)acrylates by the use of Rh(I)-complexes of electron-rich diphosphines, *t*-Bu-BisP* and *t*-Bu-MiniPHOS. Low-temperature NMR experiments testify that monohydrides with *β*-carbon atom of the substrate bound to rhodium are involved in the catalytic cycle.

Catalytic asymmetric hydrogenation has become one of the most powerful tools for synthesis of enantiomerically pure compounds.[1] Amino acids are especially attractive objects for the enantioselective synthesis due to their vital importance for biochemical and medicinal applications. Numerous studies in the field of asymmetric catalysis dealt with the synthesis of optically active α-amino acids. Natural and unnatural α-amino acids were obtained with excellent ee's in many cases. However, the synthesis of *β*-amino acids via catalytic asymmetric hydrogenation is much less studied. These compounds are synthetic precursors of *β*-lactams[2] and *β*-peptides[3] and are components of some medicinally important natural products.[4]

Most known synthetic approaches to optically pure *β*-amino acids use chiral protocols for C−C[5] or C−N[6] bond formation. Catalytic asymmetric hydrogenation is the most straightforward way to *β*-amino acids, but the early trials of this reaction gave only modest enantioselectivity.[7] More recently Noyori[8] and Zhang[9] reported good to excellent optical yields of *β*-amino acids in Ru−BINAP, Rh-DuPHOS, and Rh−BICP catalyzed hydrogenation of the corresponding prochiral substrates.

Recently, we demonstrated that (*S*,*S*)-1,2-bis(alkylmethylphosphino)ethanes **1** (abbreviated as BisP*) and (*R*,*R*)-1,1-bis(alkylmethylphosphino)methanes **2** (abbreviated as MiniPHOS) gave excellent enantioselectivities in the rhodium-

(1) (a) Noyori, R. *Asymmetric Catalysys in Organic Synthesis*; John Wiley & Sons: New York, 1994. (b) Brown, J. M. *Hydrogenation of Functionalized Carbon−Carbon Double Bonds*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 119−182. (c) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley: New York, 2000.

(2) (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

(3) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Cole, D. C. *Tetrahedron*. **1994**, *50*, 9517. (c) Hart, D. J.; Ha, D.-C. *Chem. Rev*. **1989**, *89*, 1447.

(4) (a) Deng, Li.; Jacobsen, E. N. *J. Org. Chem*. **1992**, *57*, 4320. (b) Wang, Z.-M.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem*. **1994**, *59*, 5104. (c) Guenard, D.; Voegelein, F. G.; Potier, P. *Acc. Chem. Res*. **1993**, *26*, 160.

(5) (a) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151.

(6) (a) Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455. (b) Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396. (c) Seebach, D.; Overhand, M.; Kühnle, Martinonni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913. (d) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc*. **1998**, *120*, 6615.

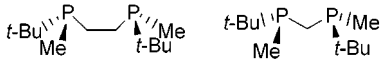
(7) (a) Achiwa, K.; Soga, T. *Tetrahedron Lett.* **1978**, *13*, 1119. (b) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 2223.

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

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

10.1021/ol0158967 CCC: $20.00 © 2001 American Chemical Society
Published on Web 05/10/2001

catalyzed hydrogenation of dehydro-α-amino acid derivatives and enamides.[10] The electron-rich character of these diphosphines results in the increased affinity of their rhodium complexes to dihydrogen and thus to the possibility of a dihydride pathway in the catalytic cycle of asymmetric hydrogenation.[11] Herein, we report the results of rhodium catalyzed asymmetric hydrogenation of β-(acylamino)acrylates using *t*-Bu-BisP* (**1**) and *t*-Bu-MiniPHOS (**2**) as the chiral ligands, as well as mechanistic studies clarifying the origin of different sense of enantioselection observed for hydrogenation of α- and β-dehydroamino acids.



t-Bu-BisP* *t*-Bu-MiniPHOS

1 **2**

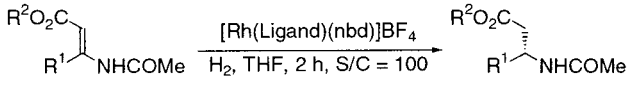
We first examined hydrogenation of methyl (*E*)-3-acetamido-2-butenoate (**3a**) in several common organic solvents. When the reaction using [Rh(*t*-Bu-BisP*)(nbd)]BF_4 as the catalyst was carried out at ambient temperature under 3 atm for 2 h, 100% conversion was obtained in all cases and the enantioselectivity did not largely depend on the solvents except for toluene: MeOH (92.7%), CH_2Cl_2 (98.2%), THF (98.7%), $C_6H_5CH_3$ (51.0%). The best result of hydrogenation of **3a** was achieved by the use of [Rh(*t*-Bu-BisP*)(nbd)]BF_4 in THF at room temperature and under 3 atm of H_2, leading to **4a** in 100% conversion and 98.7% ee.

Under similar conditions, a series of (*E*)-β-(acylamino)-acrylates **3a**−**d** were reduced using *t*-Bu-BisP*−Rh and *t*-Bu-MiniPHOS−Rh catalysts. The results are summarized in Table 1. The hydrogenation of **3a**−**d** proceeded in excellent to almost perfect enantioselectivity. Changing the ester groups and alkyl substituents of β-(acylamino)acrylates shows no distinct difference in both enantioselectivity and reactivity with *t*-Bu-BisP*−Rh and *t*-Bu-MiniPHOS−Rh catalysts. A remarkable feature of our catalysts is its high catalytic activity. The hydrogenation of **3a**−**d** in the presence of 1 mol % of [Rh(*t*-Bu-BisP*)(nbd)]BF_4 or [Rh(*t*-Bu-MiniPHOS)(nbd)]BF_4 was completed within 2 h under 3 atm of H_2. The fast hydrogenation is compared favorably with that obtained by the use of BICP or (*R*,*R*)-Me-DuPHOS ligand.[9] For example, the hydrogenation of **3a** with BICP catalyst (1 mol %) at room temperature under 3 atm of H_2 required 24 h for the complete conversion.

It is noted that the sense of enantioselection observed for (*E*)-β-dehydroamino acids is opposite to that found previously for α-dehydroamino acids with the use of the same catalysts.[10] To clarify origin of this effect we checked the structures of monohydride intermediates formed upon low-temperature reaction of **3a** with dihydride complex [RhH_2(BisP*)S_2]BF_4 (S = CD_3OD) (**5**).[11a]

Addition of a 2-fold excess (respective to the starting catalytic precursor) of compound **3a** to an equilibrium mixture of **5**, [Rh(BisP*)S_2]BF_4 (**6**), and dihydrogen[11a] at −100 °C resulted in immediate and quantitative conversion of **5** to three monohydride intermediates **7a**−**c** in ratio 1:0.7:0.1 (Figure 1a). When the temperature of the sample was gradually raised to −10 °C (Figures 1b−d), a new hydride species **7d** appeared, apparently due to the rearrangement

Table 1. Asymmetric Hydrogenation of (*E*)-β-(Acylamino)acrylates with *t*-Bu-BisP*−Rh and *t*-Bu-MiniPHOS−Rh Catalysts[12]



3 **4**

entry[a]	ligand	substrate	R^1	R^2	ee %[b]	config.
1	**1**	**3a**	Me	Me	98.7	*R*
2	**2**				96.4	*R*
3	**1**	**3b**	Me	Et	99.7	*R*
4	**2**				99.3	*R*
5	**1**	**3c**	Et	Me	97.2	*R*
6	**2**				95.6	*R*
7	**1**	**3d**	Pr	Et	98.5	*R*
8	**2**				98.7	*R*

[a] Reactions were carried out at room temperature and an initial H_2 pressure of 3 atm for 2 h. [b] Enantiomeric excesses were determined by HPLC or GC analysis using chiral columns. **4a**: GC, Chiral Select 1000 (30 m), 130 °C, isothermal, carrier gas N_2, flow rate 20 cm/sec, t1 = 25.6 min, t2 = 26.9 min. **4b**: GC, Chiral Select 1000 (30 m), 135 °C, isothermal, carrier gas: N_2, flow rate 10 cm/sec, t1 = 55.9 min, t2 = 58.1 min. **4c**: GC, Chirasil DEX-CB (30 m), 130 °C, isothermal, carrier gas: N_2, flow rate 20 cm/sec, t1 = 16.0 min, t2 = 16.8 min. **4d**: HPLC, Daicel Chiralcel OC, hexane/2-propanol = 9/1, UV = 210 nm, flow rate 0.5 mL/min., t1 = 13.0 min, t2 = 17.0 min.

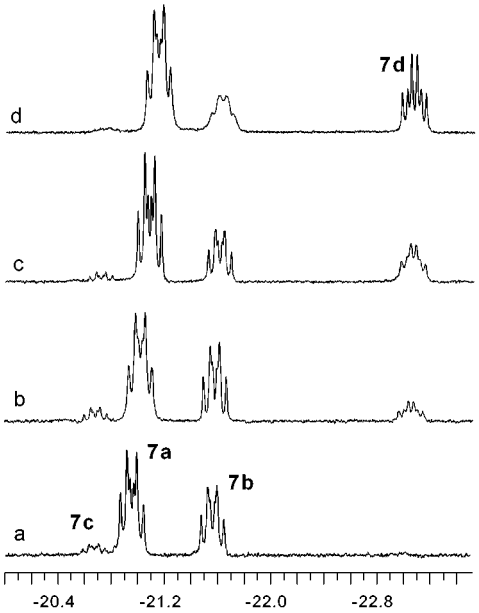


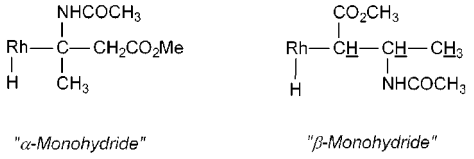
Figure 1. Evolution of the hydride region of the ^1H NMR spectrum (400 MHz, CD_3OD) of the sample obtained by the low-temperature reaction of **3a** and **5**: (a) spectrum taken immediately after mixing the reagents at −100 °C and placing it to a precooled probe of NMR spectrometer, −90 °C; (b) after raising temperature to −50 °C; (c) after raising temperature to −30 °C; (d) after raising temperature to −10 °C.

of **7b** as follows from the change in resonance intensities in Figure 1. At higher temperatures, hydrides **7a**−**d** decomposed producing the hydrogenation product **4a** (98% ee) and solvate complex **5**. When an equimolar mixture of **3a** and **6** was hydrogenated for 10 min at −80 °C, complete conversion of the substrate to monohydrides **7a**−**d** was achieved. Enantiomeric excess of **4a** obtained after quenching of the sample was the same as in the previous experiment (98%).

The structure of the monohydrides **7a,b,d** was elucidated from NMR data (the concentration of **7c** was too low for an accurate structural assignment). Most of the monohydride intermediates in the Rh-catalyzed asymmetric hydrogenation characterized so far[11,13] had an α-carbon atom bound to rhodium. Only hydrogenation of *t*-Bu and 1-adamantyl-substituted enamides proceeded via monohydrides with a *β*-carbon bound to rhodium which corresponded to an opposite sense of enantioselection observed for these substrates.[11b]

Monohydrides arising in the course of hydrogenation of *β*-(acylamino)acrylates with α- or *β*-bound carbons can be distinguished relatively easily, since in the former case a CH_2 group is expected to have no coupling partners, whereas in a monohydride with a *β*-bound carbon atom two CH protons should be coupled and the coupling of one of them with a methyl group should be observed (Scheme 1). A portion of

Scheme 1



the COSY spectrum of the mixture of monohydride intermediates **7a**−**d** is shown in Figure 2. Monohydrides **7a** and **7b** exhibit both expected cross-peaks for a *β*-monohydride each, and **7d** gives a cross-peak between CH and CH_3. We conclude that all three monohydrides have $CHCO_2Me$ moiety bound to rhodium, and in the case of **7d** the vicinal coupling is not observed due to geometric reasons.

This conclusion was further proven by ^1H-^{31}P and ^1H-^{13}C HMQC spectra. The correlations obtained in these experiments unequivocally prove the existence of a CH−CH−CH_3 fragment in monohydrides **7a,b,d**.[14] The chemical shifts of the hydride protons indicate that hydrides are located at the *trans*-position to the electronegative oxygen atom. The 98% ee of **4a** obtained after reductive elimination indicates that all three major components of the reaction mixture have *R*-configuration at the α-carbon atom.

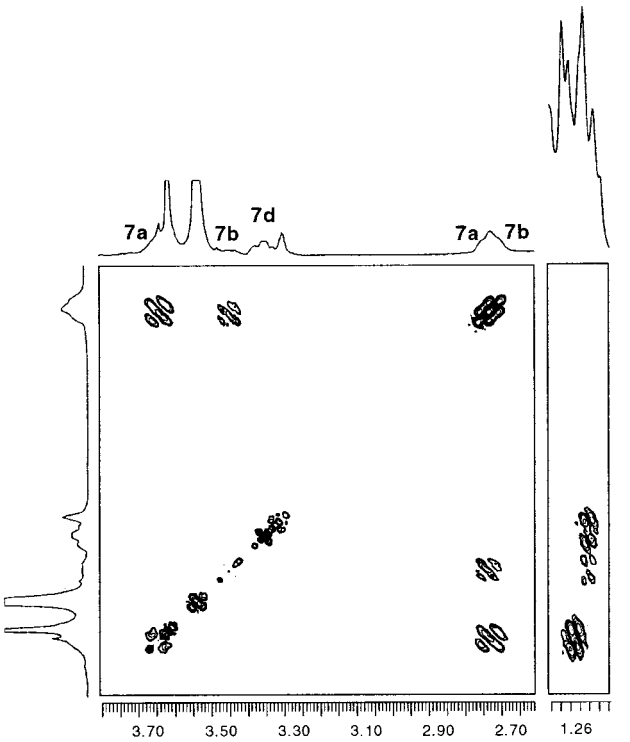


Figure 2. Portion of the phase-sensitive double quantum-filtered ^1H-^1H COSY spectrum (400 MHz, CD_3OD, −60 °C) of the mixture of monohydride intermediates **7a**−**d**.

(10) (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (b) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988. (c) Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118.

(11) (a) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183. (b) Gridnev, I. D.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 10486. (c) Gridnev, I. D.; Imamoto, T. *Organometallics* **2001**, *20*, 545−549. (d) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.*, in press.

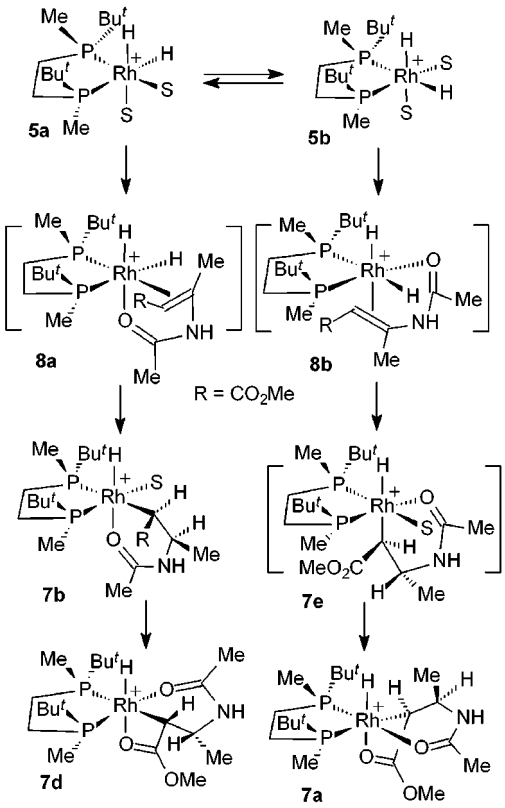
(12) We tried the hydrogenation of several *Z*-isomers with the same catalysts. The complete reduction required 18 h at 20 atm of H_2 to result in low to moderate *S*-enantioselection.

(13) (a) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838. (b) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344.

(14) **7a**: ^1H NMR (400 MHz, CD_3OD, −60 °C): −21.03 (ddd, $^1J_{Rh-H}$ = 21 Hz, $^2J_{P-H}$ = 19, 31 Hz), 1.27 (C*H*$_3$CHN), 2.75 (m, 1H, CH−Rh), 3.65 (m, 1H, CHN), alkyl groups of the diphosphine unresolved. ^{13}C NMR (100 MHz, CD_3OD, −60 °C): 7.7 (d, CH_3, $^1J_{P-C}$ = 27 Hz), 12.6 7 (d, CH_3, $^1J_{P-C}$ = 20 Hz), 21.6 (d, CH_2, $^1J_{P-C}$ = 27 Hz), 22.6 (*C*H$_3$CHN), 24.4 (CH_3CON), 26.8 and 27.4 (6 CH_3), 29.2 (dm, CH_2, $^1J_{P-C}$ = 14 Hz), 31.0 (d, C^{tert}, $^1J_{P-C}$ = 22 Hz), 33.2 (d, C^{tert}, $^1J_{P-C}$ = 16 Hz), 36.3 (dm, CH═, $^1J_{P-C}$ approximately 70 Hz), 47.5 (d, CH═, $^2J_{P-C}$ = 3 Hz), 50.9 (OCH_3), 176.5 (C═O), 182.9 (C═O). ^{31}P NMR (162 MHz, CD_3OD, −50 °C): 55.3 (dd, $^1J_{Rh-P}$ = 95 Hz, $^2J_{P-P}$ = 11 Hz), 83.9 (dd, $^1J_{Rh-P}$ = 148 Hz, $^2J_{P-P}$ = 11 Hz). **7b:** ^1H NMR (400 MHz, CD_3OD, −60 °C): −21.60 (ddd, $^1J_{Rh-H}$ = 21 Hz, $^2J_{P-H}$ = 19, 23 Hz), 1.26 (C*H*$_3$CHN), 2.74 (m, 1H, CH−Rh), 3.44 (m, 1H, CHN), alkyl groups of the diphosphine unresolved. ^{13}C NMR (100 MHz, CD_3OD, −60 °C): 7.5 (d, CH_3, $^1J_{P-C}$ = 34 Hz), 12.1 (d, CH_3, $^1J_{P-C}$ = 22 Hz), 24.9 (*C*H$_3$CN), 27.0 and 27.2 (6 CH_3), 47.8 (d, CH═, $^2J_{P-C}$ = 3 Hz), 51.6 (OCH_3), 176.3 (C═O), 184.7 (C═O). ^{31}P NMR (162 MHz, CD_3OD, −50 °C): 60.9 (dd, $^1J_{Rh-P}$ = 98 Hz, $^2J_{P-P}$ = 12 Hz), 82.3 (dd, $^1J_{Rh-P}$ = 153 Hz, $^2J_{P-P}$ = 12 Hz). **7c:** ^1H NMR (400 MHz, CD_3OD, −60 °C): −20.65 (ddd, $^1J_{Rh-H}$ = 19 Hz, $^2J_{P-H}$ = 20, 24 Hz), other signals not found. ^{31}P NMR (162 MHz, CD_3OD, −50 °C): 54.6 (dd, $^1J_{Rh-P}$ = 95 Hz, $^2J_{P-P}$ = 8 Hz), 82.0 (dd, $^1J_{Rh-P}$ = 148 Hz, $^2J_{P-P}$ = 8 Hz). **7d:** ^1H NMR (400 MHz, CD_3OD, −60 °C): −23.05 (ddd, $^1J_{Rh-H}$ = 28 Hz, $^2J_{P-H}$ = 16, 28 Hz), 1.26 (C*H*$_3$CHN), 3.35 (m, 2H, CH−Rh and CHN). ^{13}C NMR (100 MHz, CD_3OD, −60 °C): 5.8 (d, CH_3, $^1J_{P-C}$ = 13 Hz), 14.7 (d, CH_3, $^1J_{P-C}$ = 35 Hz), 21.4 (d, CH_2, $^1J_{P-C}$ = 22 Hz), 23.8 (CH_3CON), 23.9 (*C*H$_3$CN), 26.4 and 26.5 (6 CH_3), 28.8 (dd, $^1J_{P-C}$ = 16 Hz, $^2J_{P-C}$ = 6 Hz), 33.7 (d, C^{tert}, $^1J_{P-C}$ = 21 Hz), 34.1 (d, C^{tert}, $^1J_{P-C}$ = 30 Hz), 36.1 (dm, CH═, $^1J_{P-C}$ approximately 70 Hz), 50.0 (d, CH═, $^2J_{P-C}$ = 3 Hz), 50.5 (OCH_3), 172.4 (C═O), 184.0 (C═O).^{31}P NMR (162 MHz, CD_3OD, −10 °C): 54.6 (dd, $^1J_{Rh-P}$ = 95 Hz, $^2J_{P-P}$ = 12 Hz), 82.0 (dd, $^1J_{Rh-P}$ = 142 Hz, $^2J_{P-P}$ = 12 Hz).

We suggest the following mechanism accounting for the experimental data (Scheme 2). Two isomers of solvate

Scheme 2. Plausible Mechanism of the Formation of Monohydride Intermediates **7a,b,d**.



dihydride **5** are capable to produce eight diastereomeric dihydrides **8**. Only two of them, viz **8a** and **8b** are precursors of β-monohydrides with *R*-configuration at the α-carbon atom. Migratory insertion in these dihydrides yields monohydride intermediates **7b** and **7e**. The latter complex has *trans*-disposed Rh−C and Rh−H bonds that is energetically unfavorable, so it isomerizes immediately to a more stable compound **7a** via *pseudo*-rotation. Calculations predict very low activation barriers for similar isomerizations.[15]

The complex **7b** isomerizes at elevated temperatures to monohydride **7d** via rotation around the Rh−C bond, since in the latter compound additional stabilization can be achieved via terdentate coordination involving the carboxymethyl group (Scheme 2).

Thus, the opposite sense of enantioselection in the BisP*−Rh catalyzed hydrogenation of α- and β- dehydro amino acids is explained by different reaction pathways: in the former case the first hydrogen atom is transferred to the β-position yielding monohydrides with an α-carbon atom bound to rhodium, whereas in the latter case the reaction takes place in the opposite manner. These experimental facts are in accord with recent computational data, which predict preferential binding of β-carbon atom to rhodium in the case of substrates with an electron-withdrawing substituents in β-position.[15a,16]

In conclusion, excellent *R*-enantioselectivity is observed in asymmetric hydrogenation of (*E*)-β-(acylamino)acrylates catalyzed by *t*-Bu-BisP*−Rh and *t*-BuMiniPHOS−Rh complexes. The opposite sense of stereoselection compared to the hydrogenation of α-dehydroamino acids is explained by different reaction pathways: in the case of β-dehydroamino acids the reaction proceeds via monohydrides with β-carbon atom bound to rhodium.

Acknowledgment. This work was supported by the "Research for the Future" Program (Grant JSPS-RFTF96P00304), The Japan Society for the Promotion of Science, The Ministry of Education, Culture, Sports, Science and Technology, Japan.

OL0158967

(15) (a) Landis, C. R.; Feldgus, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2863. (b) Feldgus, S.; Landis, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 12714.

(16) Feldgus, S.; Landis, C. R. *Organometallics* **2001**, in press; we gratefully acknowledge Professor Clark Landis' kind sharing of information prior to publication.