(21) G. Herzberg, "Spectra of Diatomic Molecules", Van Nostrand, Princeton, N.J., 1950.
(22) S. V. O'Neil, H. F. Schaefer III and C. F. Bender, *J. Chem. Phys.*, **55**, 162 (1971).
(23) Strictly speaking, the GRHF orbital of the excited state is not orthogonal to the corresponding ground-state wave function of the same symmetry. Therefore, the actual $^1A'$ state of the singlet bent out of plane will have somewhat higher energy than that presented here.
(24) (a) K. Morokuma, *J. Chem. Phys.*, **55**, 1236 (1971); (b) S. Iwata and K. Morokuma, *J. Am. Chem. Soc.*, **95**, 7563 (1973); (c) K. Kitaura and K. Morokuma, *Int. J. Quantum Chem.*, **10**, 325 (1976).
(25) (a) K. Morokuma, *Acc. Chem. Res.*, **10**, 294 (1977); (b) S. Nagase and K. Morokuma, *J. Am. Chem. Soc.*, **100**, 1666 (1978).
(26) V. P. Zabransky and R. W. Carr, Jr., *J. Am. Chem. Soc.*, **98**, 1130 (1976).
(27) E. R. Davidson, *J. Am. Chem. Soc.*, **99**, 397 (1977).

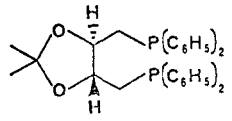
Asymmetric Catalysis with Chiral Complexes of Rhodium–*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane. 6. On the Mechanism of Reduction of (*E,Z*)-α-Acylaminocinnamic Acids with Homogeneous Rhodium Catalysts

Christian Detellier, Georges Gelbard, and Henri B. Kagan*

Contribution from The Laboratoire de Synthèse Asymétrique, LA CNRS No. 040-255-02, Université de Paris Sud, 91405 Orsay, France. *Received January 4, 1978*

Abstract: The stereochemistry of reduction of several α-acylaminocinnamic acids was investigated, in the presence of rhodium–*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) catalyst. Cis addition on the *Z* isomer was demonstrated by using deuterium. Catalytic deuteration of the *E* isomer gives a mixture of diastereoisomers d_2. This result was interpreted as an indication of some *E–Z* isomerization prior to reduction, allowing calculation of the actual optical yield. Tentative mechanisms for the *E–Z* isomerization which do not lead to d_3 species are discussed.

Asymmetric synthesis of α-amino acids was recently realized with great efficiency by using Wilkinson-type catalysts modified by chiral phosphines.[1-7] Several attempts were made to analyze the origin of the asymmetric induction with DIOP (**1**) as the chiral ligand.[8,9] Several pieces of information were

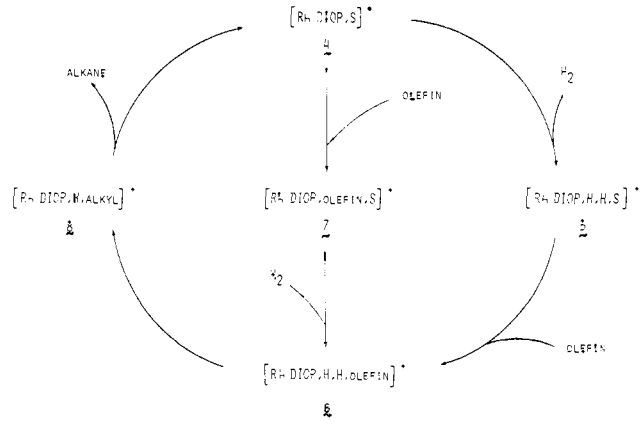


1

collected[9-11] but a detailed mechanism was still missing. It would be important to know the basic features of the catalytic cycle since α-amino acid precursors are very special substrates bearing two polar functions, and great care must be taken if they are to be compared with simple olefins such as cyclohexene. A better understanding of the mechanism would allow the synthesis of more efficient chiral ligands.

We examined the catalytic reduction of α-acylaminocinnamic acids **2** in experimental conditions used for asymmetric catalysis with Rh-DIOP catalysts, trying to demonstrate the stereochemistry of the reaction and eventually to detect a regiospecificity for the first hydrogen addition on the double bond. The catalyst was prepared as usual[1] in situ from $((RhCl(ethylene)_2)_2$ with 2 equiv of DIOP. A benzene–ethanol (1:3) mixture was used as solvent. Several catalytic species can coexist, the more likely RhClDIOP,S and $(RhDIOP,S)^+Cl$,[11] S being the solvent or a polar function of the substrate. We will arbitrarily adopt the formula $(RhDIOP,S)^+$ (**4**) to describe the initial species of the catalytic cycle (Scheme I) since cationic complexes give almost the same optical yields as the in situ catalyst.[11,12] The routes **4** → **5** → **6** and **4** → **7** → **6** are in competition; the former is preferred for the Wilkinson catalyst[13] but the latter fits better with recent results[14] on cationic rhodium complexes with chelating diphosphines.

Scheme I. Accepted Mechanism of Reduction by Wilkinson-Type Catalysts



Asymmetric reduction of various *E–Z* isomers frequently shows a great difference in stereospecificity.[7c] With α-amino acid precursors a faster reaction and a higher optical yield were observed for the *Z* isomer.[9] For example, with the Rh-(+)-DIOP catalyst **2a** (*Z* isomer) gives (*S*)-*N*-benzoylphenylalanine (**3a**) with 70% ee, while **2a** (*E* isomer) gives the *S* configuration also, with an optical yield of 25%. This result was taken as an argument that asymmetric induction does not occur after the formation of alkylrhodium complex **8**.[9] A fast equilibrium between **8** and **6** is also excluded since it will render unimportant the olefin stereochemistry. However, no quantitative information is available on the relative rate constants of the various elementary reactions involved in the catalysis.

The stereochemistry of hydrogen addition has been established in several cases.[13a,15] From these results it is usually assumed that all other reductions are cis additions. More recently cis reduction of (*Z*)-**2a** catalyzed by $RhCl(PPh_3)_3$ was demonstrated by Kirby.[16] Since the Rh–DIOP system is very

0002-7863/78/1500-7556$01.00/0

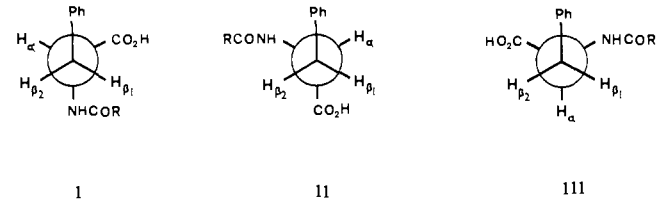
Table I. ^1H NMR Data of *N*-Acylphenylalanines[a]

compd	chemical shifts, δ ppm					coupling constants, Hz			
	NH	H_α	H_{β_1}	H_{β_2}	CH_3	$J_{H_{\beta_1}-H_{\beta_2}}$	$J_{H_{\beta_1}-H_\alpha}$	$J_{H_{\beta_2}-H_\alpha}$	J_{NH-H_α}
3a	8.75	4.65	3.18	3.05		14.17	3.84	10.84	8.0
3b	8.19	4.43	3.06	2.85	1.79	13.97	5.06	9.64	8.09

[a] Spectra run in Me_2SO-d_6 at 250 MHz, T = 298 K with Me_4Si as an internal standard. The chemical shifts and the coupling constants are calculated using the classfcal formulas for an ABX case.

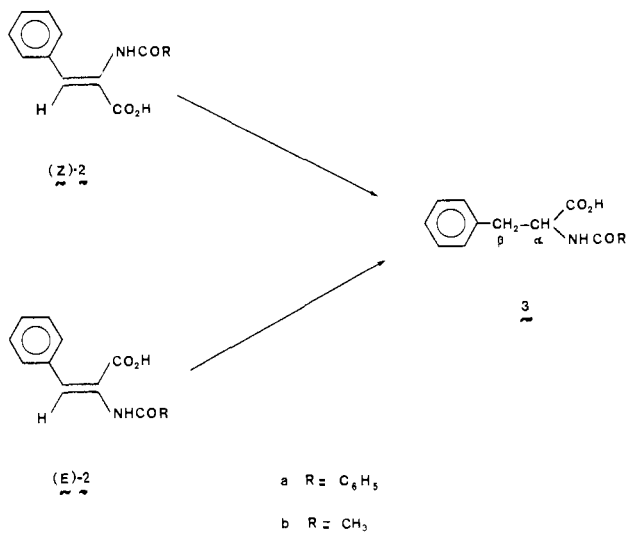
Table II. Rotamer Populations (*P*) of *N*-Acylphenylalanines (Conformers I, II, and III of Figure 1)

compd	P_I	P_{II}	P_{III}
3a	0.11	0.75	0.14
3b	0.22	0.64	0.14
phenylalanine in D_2O[17]	0.24	0.48	0.28



I II III

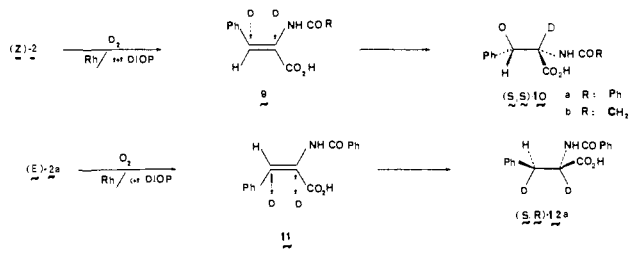
Figure 1. Rotamer population of **3**.



different from the Wilkinson catalyst, it was interesting to elucidate the behavior of a *E*-*Z* pair of olefins such as **2** which is representative of useful prochiral precursors in the asymmetric synthesis of α-amino acids. For that purpose we used D_2 instead of H_2 and determined the structure of deuterated products.

NMR Analysis of *N*-Acylphenylalanine. The determination of the stereochemistry of *N*-acylphenylalanine-d_2 diastereomers **10** and **12** necessitates the assignment of the signals of β protons in *N*-acylphenylalanine (**3**). This unequivocal assignment and the fractional populations for all three rotamers can be obtained either by specific labeling of amino acids[17] or by using vicinal ^{13}C–H coupling constants between $^1H_\beta$ and $^{13}COOH$, in conjunction with ^1H–^1H coupling constants as was shown by Feeney et al.[18,19] We chose this latter method to obtain the assignments and the populations of the preferred rotamers I–III of *N*-acylphenylalanine (Figure 1). ^1H spectra of *N*-benzoylphenylalanine (**3a**) (Figure 3) and *N*-acetylphenylalanine (**3b**) were registered in Me_2SO-d_6 at 250 MHz. A complete analysis of the ABX system was carried out, giving the chemical shifts and coupling constants of protons α and β. The results are listed in Table I. In accordance with the method of Feeney et al., the sum of the vicinal coupling constants $^{13}COOH$–$^1H_\beta$ was measured. The values are 3.2 ± 0.8 and 4.7 ± 0.3 Hz for **3a** and **3b**, respectively. These values permit us to calculate[20] the rotamer populations given in Table II where we have made the usual[21,22] and acceptable[23] assumption that J_g = 2.56 Hz and J_t = 13.6 Hz in all of the three rotamers. These results are consistent with studies of the conformation of phenylalanine itself in D_2O[23] which shows a predominance of conformation II in which the phenyl ring and the carboxylic function are in a trans conformation. Monodeuterated or monotritiated aromatic amino acids labeled stereoselectively at C_β have been prepared previously.[16,24-26] Tritiated phenylalanine or tyrosine at C_α and C_β had also been stereospecifically synthesized.[27] Agreement is good between our conclusions and those obtained from previous experiments. For example, Kirby[16] obtained one diastereoisomer of *dl*-*N*-benzoylphenylalanine-d_1 (monodeuteration at C_β) which shows an AX spectrum (spectra run in alkaline solution) with J_{AX} = 4.8 Hz. The relative configuration was established by degradation to *threo*-monodeuterioaspartic acid. This means that the remaining hydrogen is H_{β_1}, which is characterized by a small J_{AX} coupling constant as we found for **3a** and **3b** (Table I). Both the optically active diastereoisomers of *N*-acetylphenylalanine-d_1 (deuterium at C_β) were recently synthetized by an enzymatic method which allows the deduction of the absolute configuration at each center.[25] The mixture of the same d_1 diastereomers was obtained by asymmetric deuteration followed by epimerization at C_α[6] without NMR assignments of the H_β signals. The method described here is quite direct and needs neither enzymatic nor degradative reactions.

The above NMR analysis shows unambiguously that the diastereotopic protons H_{β_1} and H_{β_2} resonate at low field and high field, respectively (Table I). When dideuteration, catalyzed by the DIOP–Rh catalyst, is effected on (*Z*)-**2b** the spectrum is modified (Figure 2); H_{β_1} completely disappears, which demonstrates the stereospecific formation of the diastereomer **10b**. The same result is obtained with (*Z*)-**2a**; **10a**



is the only product. In both cases the diastereomer **10** has predominantly (*S*,*S*) stereochemistry,[28] as shown by the sign of its optical rotation. The (*S*,*S*) stereochemistry for **10** indicates that (*Z*)-**2** *reacts exclusively by a cis addition* as described in **9**. This conclusion is in agreement with various results in the literature for the Wilkinson catalyst especially on some (*Z*)-acylaminocinnamic acids.[16] When a 1:1 mixture of

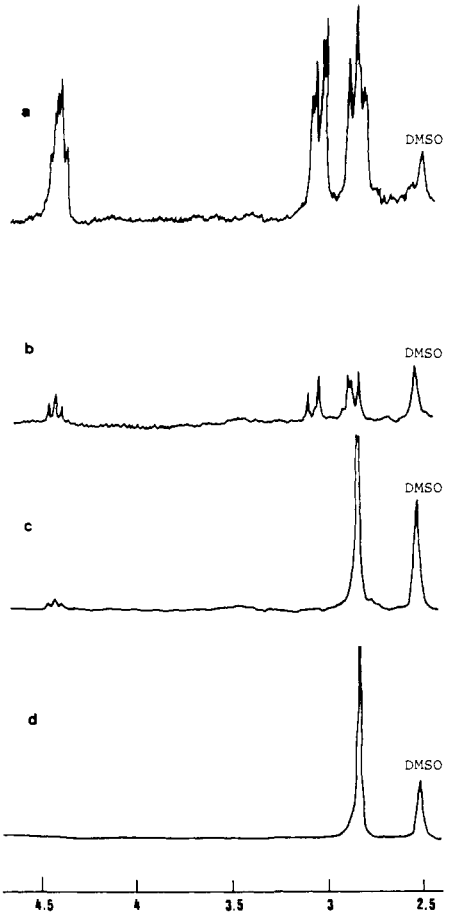


Figure 2. NMR spectra (see footnote of Table I) of *N*-acetylphenylalanine (**3b**) prepared by reduction of (*Z*)-**2b**: (a) in EtOH with H_2; (b) in EtOH with HD; superposition of the AB and the AX system of a 1:1 mixture of **15** and **3** (D at C_α); (c) in EtOH with D_2; (d) in EtOD with D_2.

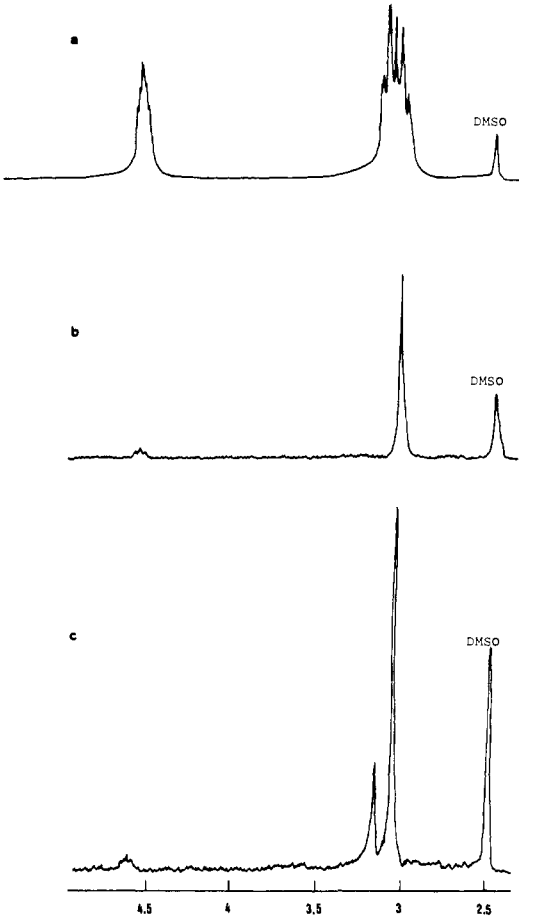
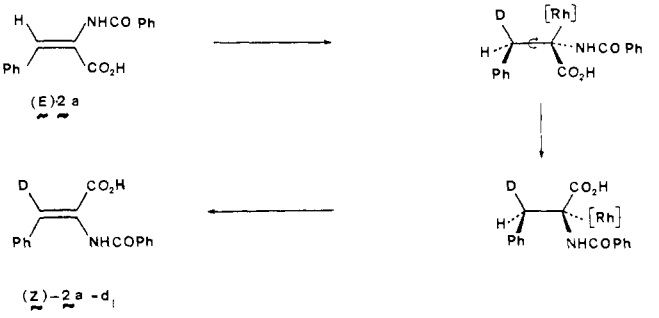


Figure 3. NMR spectra of *N*-benzoylphenylalanine (**3a**) prepared by reduction of (a) (*Z*)-**2a** in EtOH with H_2; (b) (*Z*)-**2a** in EtOH with D_2; (c) 1:1 mixture of (*E*)- and (*Z*)-**2a** in EtOH with D_2.

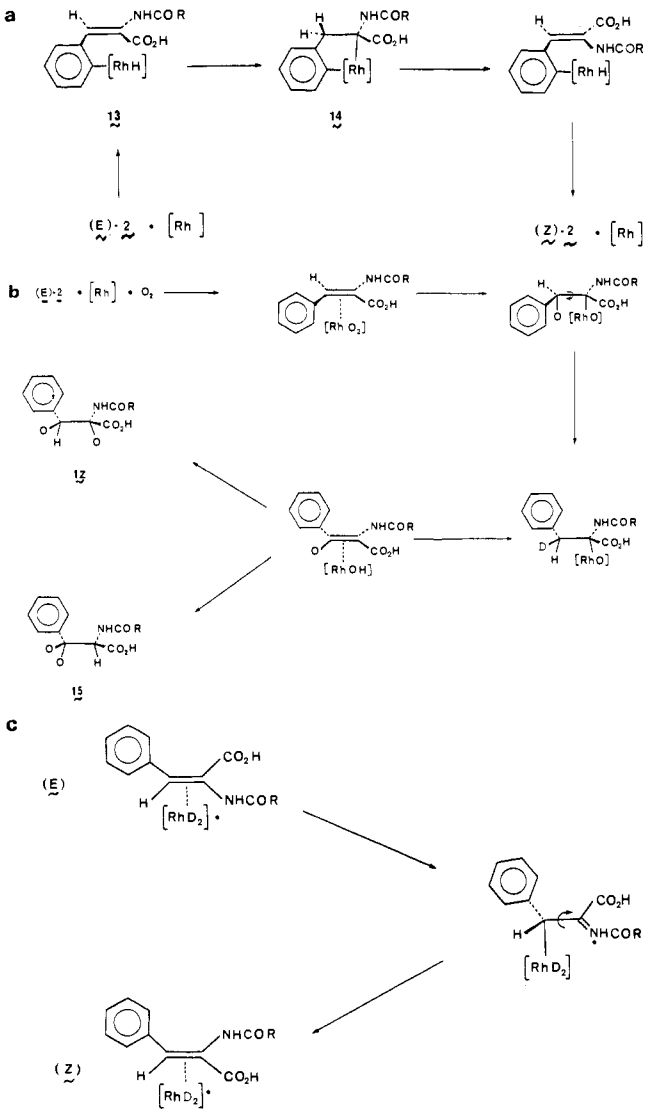
(*E*)- and (*Z*)-**2a** is reduced two singlets are observed (H_{β_1} and H_{β_2} protons) in the NMR spectrum of **3a**-d_2 (Figure 3c). This is indicative of the simultaneous presence of diastereoisomers (*S,S* or *R,R*)-**10a** and (*R,S* or *S,R*)-**12a.** Taking into account the fact that (*Z*)-**2a** gives only one signal at 3.05 ppm (Figure 3b) under the same conditions, it can be estimated that pure (*E*)-**2a** should give rise to a 1:1 mixture of **10a** and **12a.** We previously demonstrated[28] that (*E*)-**2a** is reduced into **3a** with *S* configuration at C_α. The presence of **10a** would mean that a 50% reduction of (*E*)-**2a** would result in a trans addition.[29] We prefer an alternate explanation with the formation of **10a** by a partial isomerization of (*E*)-**2a** into (*Z*)-**2a** during the reduction.[30] This seems reasonable in view of the slow reduction rate of (*E*)-**2a** compared to (*Z*)-**2a** (initial uptake rate of hydrogen in the ratio of 1:13). We can now compute the actual optical yield when (*E*)-**2a** is reduced (with cis addition). The observed value is 25% ee *S*. Since 50% of the *N*-benzoylphenylalanine came from cis addition on (*Z*)-**2a** with 70% ee *S*, it turns out that the remaining part is the result of a cis addition on (*E*)-**2a** with 20% ee *R*.

The absolute configurations are opposite, as is often observed in asymmetric reduction of *E*–*Z* pairs.[7c] However, a major difficulty has to be overcome to adopt this hypothesis. The mechanism of $E \rightarrow Z$ isomerization must involve the rhodium-DIOP complex. The migration of a double bond during reduction of an olefin catalyzed by the Wilkinson catalyst is the result of a reversibility at the first step of hydrogen transfer.[31] We can expect, too, a mechanism where addition of deuterium and rhodium(III) on (*E*)-**2** will be reversible (Scheme II): if the rhodium atom binds to C_α and D to C_β the reverse cis elimination (after rotation around the central bond) will produce (*E*)-**2** with one deuterium atom at C_β. Deuteration of this d_1 species will necessarily give an amino acid-d_3, which is not the case. Mass spectrometry and NMR analysis of the crude product demonstrate the absence of significant amounts of d_3 species. To gain some insight into the $E \rightarrow Z$ isomerization mechanism we did some control experiments under nitrogen, in the solvent system (benzene–EtOH, 1:3) of the reaction, on a mixture of (*E*)- and (*Z*)-**2a** (53:47). In the absence of the Rh–DIOP catalyst the *E*/*Z* ratio remains unchanged, even after 15 h. The same is true if 0.2% DIOP (with respect to **2a**) is added in absence of the catalyst. Addition of a benzene solution of the prehydrogenated catalyst does not affect the *E*/*Z* composition. A partial reduction of the previous *E*/*Z* mixture of **2a** confirms the high reaction rate of the *Z* isomer.[9]

Scheme II. Mechanism of $E \rightarrow Z$ Isomerization of **2a** Involving Deuterium Incorporation



Scheme III. Suggested Mechanisms of $E \rightarrow Z$ Isomerization of **2** without Incorporation of Deuterium (Equilibria Not Represented)



After 57% reaction completion the remaining **2a** has an E/Z composition of 39:4.

In order to detect some $E \rightarrow Z$ isomerization during the course of deuteration of (Z)-**2** several experiments were stopped at half reaction, and products and olefins analyzed for their deuterium content. No (E)-**2** was formed; (Z)-**2a** or (Z)-**2b** as well as **3a** and **3b** were treated by diazomethane and recovered by preparative thin layer chromatography. At the accuracy of our mass spectral measurement (<5%) it was not possible to detect deuteration in recovered (Z)-**2** nor d_3 species in the reduced products. The same set of experiments was repeated on $(Z) + (E)$-**2a.**

Additional experiments were performed in order to see if the reduced product is capable of undergoing an exchange reaction at the C_α or C_β position. Optically pure *N*-acetylphenylalanine was kept in contact for several days with deuterium gas in the conditions of reduction (benzene-EtOH (1:3), 0.01 equiv of RhClDIOP). We did not observe deuterium incorporation or decrease in the specific rotation of the amino acid.

Several conclusions can now be drawn: (1) The cis deuteration of (Z)-**2** does not involve a H/D exchange reaction at the vinylic position or $Z \rightarrow E$ isomerization. (2) The Z isomer is reduced much faster than the E isomer, even in a mixture of both. (3) There is no H/D exchange at C_α or C_β in the *N*-acylamino acid **3** which is produced. (4) Some $E \rightarrow Z$ isomerization occurs when (E)-**2a** is reduced. The Rh-DIOP catalyst is responsible for this isomerization which is not accompanied by deuterium incorporation at the vinylic position.

Mechanism of $E \rightarrow Z$ Isomerization. The mechanism outlined in Scheme II has to be ruled out. Several alternatives can be proposed involving participation of a rhodium complex. Mechanism a in Scheme III is based on the hypothesis of an ortho metalation of the benzene ring; this is not unrealistic when an aromatic ring is part of a ligand.[32] An internal hydride addition will lead to a metallocycle. The reverse reactions, which are β-eliminations, will take place with different rates because of the diastereotopic character of the two hydrogens. Z and E isomers free of deuterium will then be formed. The large amounts of a pathway through reduction of (Z)-**2** when (E)-**2** is the starting material could be explained by a preferred decomposition of **14** into (Z)-**2** and by its higher reactivity compared to (E)-**2.** The ortho-metalation mechanism is in competition with the direct reduction. It is then predicted that increasing the hydrogen pressure will decrease the $E \rightarrow Z$ isomerization. In order to accommodate all the experimental data it is necessary to assume that there is no H/D exchange in **13** since no deuterium is incorporated on the vinylic and ortho positions of (E)-**2** and (Z)-**2** recovered after partial reaction; though it is known[13d] that cationic hydridorhodium complexes can reversibly loose a proton, this phenomenom seems to be very slow in this case. Another alternative is presented in Scheme IIIb. As in the mechanism of Scheme II there is addition of deuterium at C_β and rhodium at C_α. After internal rotation and reductive elimination the deuterated olefin is formed. The key hypothesis is that the complex stays on the same face of the double bond which will receive H and D (for a similar hypothesis in hydroformylation see ref 33). The rhodium atom is regioselectively fixed at C_α if an isotope effect favors the formation of **12** over **15** (because H will be transferred first). The formation of d_3 species is then avoided. This mechanism seems less probable than the previous one because an appreciable amount of **15** should accumulate but was not detected. To evaluate the relative amounts of **12** and **15** when HD is the reagent, HD was used for catalytic reduction of (Z)-**2b.** Almost 50% of both isomers (D at C_α or C_β) was obtained (Figure 2b). Until now we only envisaged attachment of rhodium at the C_α position in the first step of the reaction. Another tentative mechanism to explain the $E \rightarrow Z$ isomerization would place rhodium and deuterium at C_β and C_α, respectively. A reversible σ-π rearrangement involving the aromatic ring[34] could give geometrical isomerization and subsequent formation of nondeuterated Z isomer. So does formation of an immonium intermediate (Scheme IIIc). Of the four aforementioned mechanisms we can reject mechanism b (Scheme III); more experiments are needed to decide if mechanism a or c (Scheme III) are the actual routes to the observed deuterium-free geometrical isomerization.

Deuteration in Presence of Ethanol. When the standard experiments of deuteration of (Z)-**2b** were performed in benzene-ethanol (1:3), a small but reproducible signal at 4.42 ppm (doublet of doublets) which corresponds to a C_α proton was always observed (Figure 2c). This signal, which is only 6% of the H_{β_2} signal, disappeared if ethanol-d_1 replaced ethanol in the solvent (Figure 2d). The two coupling constants are very similar (Figure 4) and close to 9 Hz. They correspond to $^3J_{H_{B_2}-H_\alpha}$ and $^3J_{H_{NH}-H_\alpha}$ and not to $^3J_{H_{\beta 1}-H_\alpha}$ (see Table I). This means that formally there was a cis addition of a deuterium atom at C_β and of a H atom at C_α. The same results were obtained when starting from (Z)-**2a** (Figure 3b) or (E)-**2a**.

It is possible to assume that some HD is formed by exchange reaction between ethanol and D_2; generally this exchange is slow[35] with respect to reduction.[36] This hypothesis cannot be retained since it would imply that HD is regiospecifically added (with deuterium at C_β). We demonstrated (vide supra) that in HD addition the distribution of D is statistical on the two

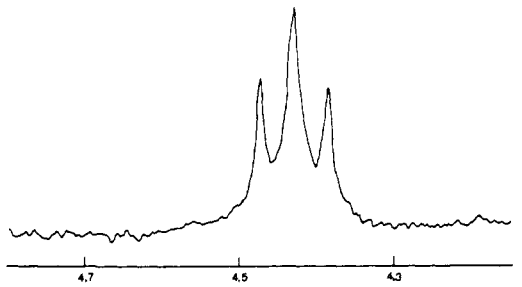


Figure 4. NMR spectra of **3a** in H_α region by reduction of (*Z*)-**2a** in EtOH with D_2.

Scheme **IV.** Tentative Mechanisms of H–D Exchange by Rhodium Complexes[35]

olefinic carbon atoms. Another explanation of the formation of a small amount of d_1 species could be a cis deuteration followed by a stereospecific replacement of D_α by a hydrogen atom in the final product **3**. We did control experiments which show that there is no significant and reproducible H/D exchange at C_α of *N*-acylamino acids under the condition of the reaction or during the workup (vide supra). The presence of the d_1 species seems related to an exchange reaction occurring during one step of the catalytic cycle. This suggests the participation of ethanol at the second stage of the deuterium addition (Scheme **I**, **8** in which D is taken in place of H) by the exchange mechanisms proposed[35] (Scheme IV). A Rh–H bond is formed and leads to stereospecific introduction of hydrogen at the C_α position. If this interpretation is correct it gives an important piece of information; the rhodium is specifically bound at C_α in the intermediate **8** (at least for the pathway involving H/D exchange and formation of the *N*-acylamino acid-d_1). A minute amount of **3b**-d_1 where deuterium is at C_α was also detected and identified by its ^2J coupling constant (<2% of the H_{β_2} signal). It must be emphasized that to obtain a complete picture and full interpretation of the asymmetric reduction of a dissymmetric double bond we need to know the structure of the alkylrhodium intermediate **8.** This problem was recently discussed in asymmetric hydroformylation[37] of styrene-d_1. Consequently detailed studies need to be made on *E* and *Z* isomers since is not obvious that rhodium atom will be fixed in the same position in both cases.[38]

Experimental Section

Starting materials, reduction procedure, and workup of the products are essentially those described previously.[1,9]

The experiment with HD was run by filling the reaction vessel with gas obtained by the careful addition of a THF solution of $LiAlH_4$ in a mixture of D_2O and THF.

^1H NMR spectra were run on a 250-MHz Cameca spectrometer in Me_2SO-d_6 as solvent; ^{13}C data were obtained on a Bruker HX90 apparatus with gated decoupling.

Samples for mass spectral measurements were obtained by treating the crude products with diazomethane and purified by preparative layer chromatography on silica gel with a 1:1 mixture of methylene chloride and hexane to separate **2a** from **3a** and chloroform to separate **2b** from **3b.**

Mass spectra were run on a CH-5 Varian MAT apparatus at 70 eV (source temperature 150 °C) with slow recording.

Acknowledgments. One of us (C.D) thanks the Institut Français du Pétrole for a fellowship. We thank CNRS for financial support, Compagnie des Métaux Précieux for a loan of rhodium chloride, Mr. C. Merienne for performing some ^1H and ^{13}C NMR spectra, and Dr. J. C. Tabet for the mass spectra.

References and Notes

(1) H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972).
(2) T. P. Dang, J. C. Poulin, and H. B. Kagan, *J. Organomet. Chem.*, **91**, 39 (1975).
(3) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *J. Am. Chem. Soc.*, **97**, 2567 (1975).
(4) T. Hayashi, T. Mise, S. Mitachi, K. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, 1133 (1976).
(5) M. Fiorini, G. M. Giongo, F. Marcati, and W. Marconi, *J. Mol. Catal.*, **1**, 451 (1975–1976).
(6) M. D. Frysuk and B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6262 (1977).
(7) For some review articles on asymmetric catalysis see inter alia (a) B. Bogdanovic, *Angew. Chem., Int. Ed. Engl.*, **12**, 954 (1973); (b) J. W. Scott and D. Valentine, *Science*, **184**, 943 (1974); (c) J. D. Morrison, W. F. Masler, and S. Hathaway, "Catalysis In Organic Synthesis", P. N. Rylander and H. Garfield, Ed., Academic Press, New York, N.Y., 1976, p 203; (d) H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, **10**, 175 (1978).
(8) R. Glaser, *Tetrahedron Lett.*, 2127 (1975).
(9) G. Gelbard, H. B. Kagan, and R. Stern, *Tetrahedron*, **32**, 233 (1976).
(10) S. Brunie, J. Mazan, N. Langlois, and H. B. Kagan, *J. Organomet. Chem.*, **114**, 225 (1976).
(11) D. Sinou and H. B. Kagan, *J. Organomet. Chem.*, **114**, 325 (1976).
(12) R. Glaser, S. Geresh, and J. Blumenfeld, *J. Organomet. Chem.*, **112**, 355 (1976).
(13) (a) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966). (b) J. Halpern and C. S. Wong, *J. Chem. Soc., Chem. Commun.*, 629 (1973); (c) C. A. Tolman, P. Z. Meakin, D. L. Lindner, and J. P. Jesson, *J. Am. Chem. Soc.*, **96**, 2762 (1974); (d) R. R. Schrock and J. A. Osborn, *ibid.*, **98**, 2134 (1976).
(14) J. Halpern, D. P. Riley, A. S. C. Chan, and J. J. Pluth, *J. Am. Chem. Soc.*, **99**, 8055 (1977).
(15) A. J. Birch and K. A. M. Walker *Tetrahedron Lett.*, 647 (1962); D. Gagnaire and P. Vottero *Bull. Soc. Chim. Fr.*, 164 (1970).
(16) G. W. Kirby and J. Michael, *Chem. Commun.*, 415 (1971); G. W. Kirby and J. Michael, *J. Chem. Soc., Perkin Trans. 1*, 115 (1973).
(17) M. Kainosho and K. Ajisaka *J. Am. Chem. Soc.*, **97**, 5630 (1975).
(18) J. Feeney, P. E. Hansen, and G. C. K. Roberts, *J. Chem. Soc., Chem. Commun.*, 465 (1974).
(19) P. E. Hansen, J. Feeney, and G. C. K. Roberts, *J. Magn. Reson.*, **17**, 249 (1975).
(20) Making the reasonable assumption that the reference value $J(^{13}C_{COOH}-^1H_\beta)$ in alanine is applicable here, we calculate 12.6 (**3a**) and 12.3 Hz (**3b**) for $J_\delta(^{13}C_{COOH}-^1H_\beta)$, and 0.0 (**3a**) and 0.2 Hz (**3b**) for $J_\theta(^{13}C_{COOH}-^1H_\beta)$. We did not detect any $^{13}C-O-^1H$ coupling in Me_2SO solution (see C. J. Chang, *J. Org. Chem.*, **41**, 1881 (1976), for the same observation in the case of phenol in Me_2SO).
(21) K. G. R. Pachler, *Spectrochim. Acta*, **19**, 2085 (1963).
(22) K. G. R. Pachler, *Spectrochim. Acta*, **20**, 581 (1964).
(23) J. Feeney, *J. Magn. Reson.*, **21**, 473 (1976).
(24) P. G. Strange, J. Staunton, H. R. Wilshire, A. R. Battersby, K. R. Hanson, and E. A. Havir, *J. Chem. Soc., Perkin Trans. 1*, 2364 (1972).
(25) U. Nagai and J. Kobayashi, *Tetrahedron Lett.*, 2873 (1976); 1803 (1977).
(26) G. W. Kirby, J. Michael, and S. Narayanaswami, *J. Chem. Soc., Perkin Trans. 1*, 203 (1972).
(27) G. W. Kirby, S. Narayanaswami, and P. S. Rao, *J. Chem. Soc., Perkin Trans. 1*, 645 (1975).
(28) This result was of course previously obtained in the hydrogenation reaction.[9] When deuterium replaces hydrogen two minor effects can be envisaged: an isotopic effect modifying the optical yield and a change in the specific rotation of **10a** and **10b** compared to **3a** or **3b.** By repeated crystallization of **10b** (prepared by asymmetric reduction) we could improve the specific rotation up to a limit. Taking the specific rotation of recovered **10b** the optical yield of the reaction (*Z*)-**2** → **10** could be evaluated; it is a little higher than in the corresponding hydrogenation reaction (84% ee instead of 80%).
(29) (a) Trans addition in homogeneous catalytic reduction is unusual but not unprecedented.[29b] (b) A. P. G. Kieboom and F. Van Rantwijk in "Hydrogenation and Hydrogenolysis in Synthetic Organic Chemistry," Delft Chemistry Press, 1977, p 36, and references cited therein.
(30) (a) Similar studies on *E–Z* isomerization of **2a** during catalyzed hydrogenation were made independently by Koenig and Knowles.[39] (b) It is interesting to mention that catalytic (Pd/C) hydrogenation of (*E*)-**3a** monodeuterated at C_β gives a mixture of diastereoisomers.[16] This was explained by an isomerization of the double bond during reduction, as a consequence of stepwise addition of the two hydrogen atoms. (*Z*)-**3a** leads to only one diastereoisomer. (c) *Z–E* isomerization was recently observed[30d] during reduction of several esters of (*Z*)-**2b** with a neutral Rh–DIOP complex. (d) R. Glaser and J. Blumenfeld, *Tetrahedron Lett.*, 2525 (1977).
(31) J. F. Biellman and M. J. Jung, *J. Am. Chem. Soc.*, **90**, 1673 (1968); A. S. Hussey and Y. Takeuchi, *ibid.*, **91**, 672 (1969); J. G. Atkinson and M. O. Luke, *Can. J. Chem.*, **48**, 3580 (1970).
(32) G. W. Parshall, *Acc. Chem. Res.*, **8**, 113 (1975).
(33) A. Stefani, G. Consiglio, C. Botteghi, and P. Pino, *J. Am. Chem. Soc.*, **99**, 1058 (1977).
(34) R. R. Stevens and G. D. Shier, *J. Organomet. Chem.*, **21**, 495 (1970).
(35) G. Strathdee and R. Given, *Can. J. Chem.*, **52**, 2216, 2226 (1974).
(36) (a) This is no longer true when using $HRh(PPh_3)_4$[36b] as catalyst: reduction of (*Z*)-**2b** in EtOH solution with D_2 gave exclusively **3b** without incorporation of deuterium. Then according to the relative amounts of EtOH and D_2 in the reaction vessel, a fast exchange gave first an atmosphere of H_2 at the early stage of reduction. (b) N. Ahmad, S. D. Robinson, and M. F. Uttley, *J. Chem. Soc., Dalton Trans.*, 843 (1972).
(37) A. Stefani and D. Tatone, *Helv. Chim. Acta*, **60**, 518 (1977).

(38) (a) For one example *in* homogeneous reduction where there is a change in regiospecificity (at the stage of the formation of an alkylcobalt species) with the *E* or *Z* stereochemistry see ref 38b. (b) J. Basters, C. J. Groenvenboom, H. Van Bekkum, and L. L. Van Reijen, *Recl. Trav. Chim. Pays-Bas*, **92**, 219 (1973).
(39) K. E. Koenig and W. S. Knowles, Abstracts, 175th National Meeting of the American Chemical Society, Anaheim, Calif., March 1978; *J. Am. Chem. Soc.*, in press.

Use of Deuterium to Investigate *E–Z* Isomerizations during Rhodium-Catalyzed Reduction. Asymmetric Induction and Mechanistic Implications[1]

Karl E. Koenig* and William S. Knowles

Contribution from Monsanto Company, Corporate Research Laboratories, St. Louis, Missouri 63166. *Received April 24, 1978*

Abstract: Treatment of (*E*)- and (*Z*)-α-benzamidocinnamic acids with deuterium in the presence of various Rh(I) catalysts gives (*R,R*)- and (*S,S*)-*N*-benzoyl-2,3-dideuterio-3-phenylalanine from the *Z* isomer and the corresponding *R,S* and *S,R* products from the *E* isomer. Since these products are diastereomeric, the degree of isomerization during hydrogenation can be measured by NMR. Isomerization was indeed observed in many cases in this study, and the mechanistic implications are discussed.

In the last 10 years, asymmetric induction has burgeoned as a technique for the synthesis of optically active compounds, especially in the area of catalytic asymmetric hydrogenations.[2] By using optically active rhodium catalysts, enantiomeric excesses as high as 96% have been observed for the hydrogenation of α-acetyl- or α-benzoylaminocinnamic acids.[3] Many studies have been conducted altering substituents on both the catalyst and the substrate to obtain an optimum fit and to gain an insight into the mechanism of reduction.[3-8] Even though it was well known that geometric isomers have a profound effect[3] on the rate and the induction observed, no conclusive study has been done because of the inability to measure the amount of isomerization prior to hydrogenation. In this paper, a technique is described to measure this isomerization and obtain exact induction data for both isomers with various chiral catalysts and solvent systems.[9]

Results

In order to assess the stereochemistry of the hydrogenation of (*E*)- and (*Z*)-α-benzamidocinnamic acids, any possible isomerization between the reactants must be accurately determined. This task is difficult since identical products are obtained from each isomer. The first approach was to stop the reaction prior to completion and examine the unreacted starting materials. This was done for diphos (**1**), BBDP (**2**), and (*R,R*)-diPAMP (**3**) in 100% ethanol (Figure 1) and in each case none of the opposite isomer was observed by NMR.

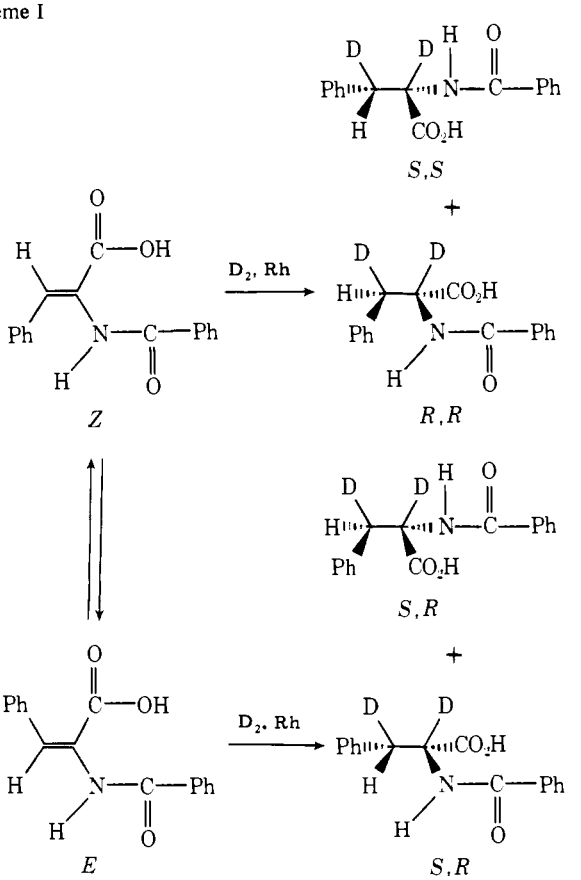
These results indicate that either no isomerization is occurring or that the rate of hydrogenation of one of the isomers is much faster than the isomerization. These two alternatives can be differentiated by using deuterium instead of hydrogen (Scheme I).

Since Wilkinson-type catalysts are known to hydrogenate via a cis addition,[10] the *Z* isomer will give only *R,R* and/or *S,S* products, whereas the *E* isomer will give *R,S* and/or *S,R* compounds. Since these two sets of products are diastereomeric, they can be differentiated by NMR. When a 50/50 mixture of (*E*)- and (*Z*)-α-benzamidocinnamic acids is reduced by diphos (**1**), two singlets are observed for the benzylic proton in a 35/65 ratio of diastereoisomers; hence, approximately 30% isomerization has occurred (Figure 2).

Pure *E* and *Z* isomers were then reduced separately under identical conditions, and the results agreed exactly with the mixed experiment: *E* gave a diastereomeric ratio of 72:28, while the *Z* isomer gave a ratio of 0:100. Hence, by reducing pure *E* and *Z* isomers, the amount of isomerization prior to hydrogenation can easily be detected within 3–5% error.

Table I lists some representative results using 100% ethanol as the solvent. As can be seen, all the ligands give some degree of isomerization with (*R,R*)-diPAMP (**3**) and (*R*)-CAMP (**5**) being the smallest. Even though diphos (**1**) and (*R,R*)-di-

Scheme I



0002-7863/78/1500-7561$01.00/0