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

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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.

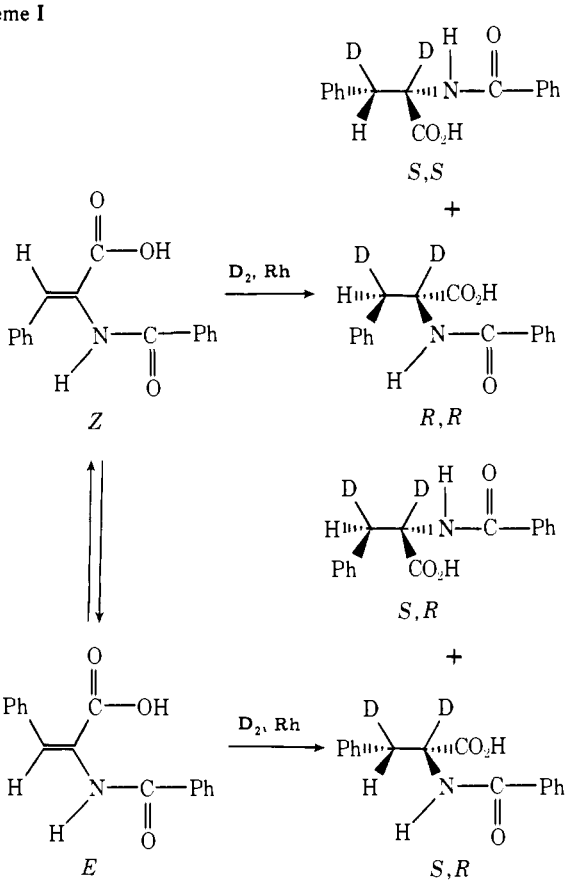
These results indicate that either no isomerization is occurring or that the rate of hydrogenation of one of the isomers is much faster than the isomerization. These two alternatives can be differentiated by using deuterium instead of hydrogen (Scheme I).

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



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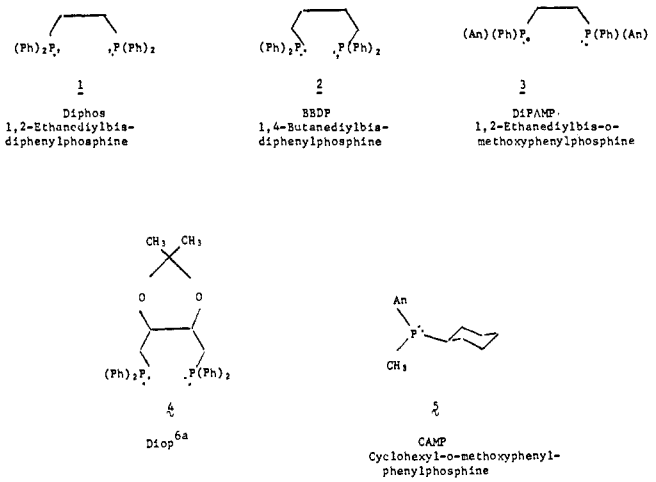


Figure 1. The catalysts formed from bisphosphines **1–4** have a 1/1 ratio with rhodium, whereas the monophosphine **5** has a 2/1 ratio.

Table I. Hydrogenation of (*E*)-α-Benzamidocinnamic Acid

	% isomerization		
	THF	ethanol	benzene
diphos (**1**)	23	28	0
BBDP (**2**)	20	28	0
(*R,R*)-DIOP (**4**)	20	33	0[a]
(*R,R*)-diPAMP (**3**)	0	6	0
(*R*)-CAMP (**5**)	0	4	0

[a] Based on 60% conversion.

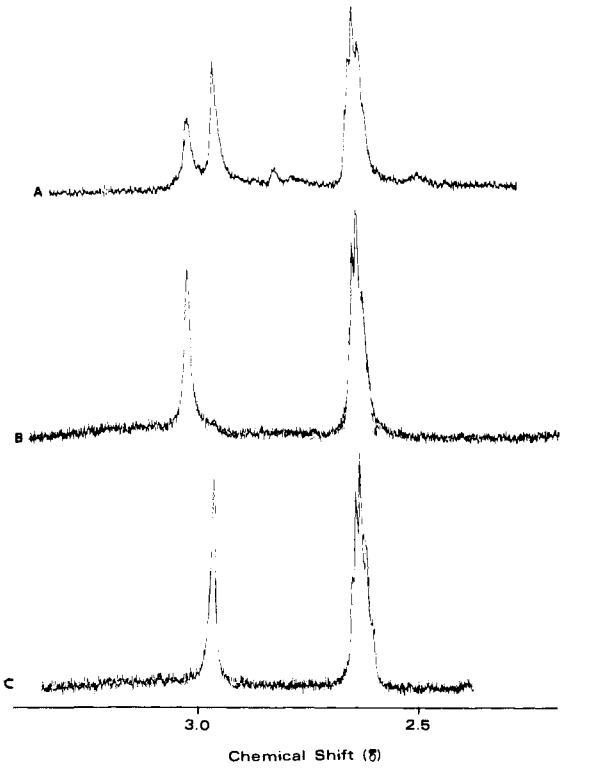


Figure 2. The benzylic region including Me_2SO-d_6 is shown for (A) *N*-benzoyl-2,3-dideuteriophenylalanine resulting from deuteration of 50/50 (*E/Z*)-α-benzamidocinnamic acid with diphos (**1**), (B) pure (*R,S*)-*N*-benzoyl-2,3-dideuteriophenylalanine, and (C) pure (*S,S*)-*N*-benzoyl-2,3-dideuteriophenylalanine.

PAMP (**3**) have similar structures, there is considerable difference in amounts of isomerization.

Large changes also occur with variation in solvent (Table I). THF and ethanol behave similarly, but when benzene was used no isomerization was observed. The reductions were quantitative in all cases except for (−)-(*R,R*)-DIOP (**4**), where the rate was appreciably slower, giving only 60% reduction after 71 h. Carbon tetrachloride and cyclohexane were also tried as solvents, but the reduction did not occur, probably owing to the insolubility of the reactants in such nonpolar solvents. In benzene, the rates of reduction were similar for diphos (**1**) and BBDP (**2**), with (*R,R*)-diPAMP (**3**) being slightly slower and (*R*)-CAMP (**5**) being eight to ten times faster than any of the diphosphine catalysts. (−)-(*R,R*)-DIOP (**4**) was, on the other hand, the slowest catalyst observed. The fact that (*R*)-CAMP (**5**) was appreciably faster than the bisphosphines may be attributed either to the ability of the monophosphines to dissociate or to the capability of the ligands to be situated trans to each other on the rhodium. Either factor would reduce steric inhibition and increase the rate of reaction.

When we consider the subtleties of asymmetric induction, geometric isomers are ideal for such a study since the electronic factors for each isomer are the same. Previous data[3] have been confusing because of inability to detect isomerization. With the help of the deuteration technique, unambiguous results have been obtained. In ethanol, (*Z*)-α-benzamidocinnamic acid reduces quickly with (*R,R*)-diPAMP (**3**) with no isomerization (40 min at 1 g substrate/4 mg catalyst) and gives 94% (*S*) ee.[3,11] In contrast, the *E* isomer reduces at $^1/_{20}$ the rate and gives only 30% (*S*) ee after the correction for 6% isomerization. In both cases the catalyst is attacking the re[12] face of the α carbon preferentially. The low enantiomeric excess for the *E* isomer may be caused by the steric hindrance between the phenyl on the substrate and the edge of the phenyl on the catalyst which indicates that the conformation in solution is similar to that observed for the rhodium (I) precursor by X-ray analysis.[3]

Table II. Asymmetric Induction Results for (*E*)-α-Benzamidocinnamic Acid in Benzene

	% conversion	% ee
(*R,R*)-DIOP (**4**)	60	62(*R*)
(*R,R*)-diPAMP (**3**)	100	85(*S*)
(*R*)-CAMP (**5**)	100	15(*S*)

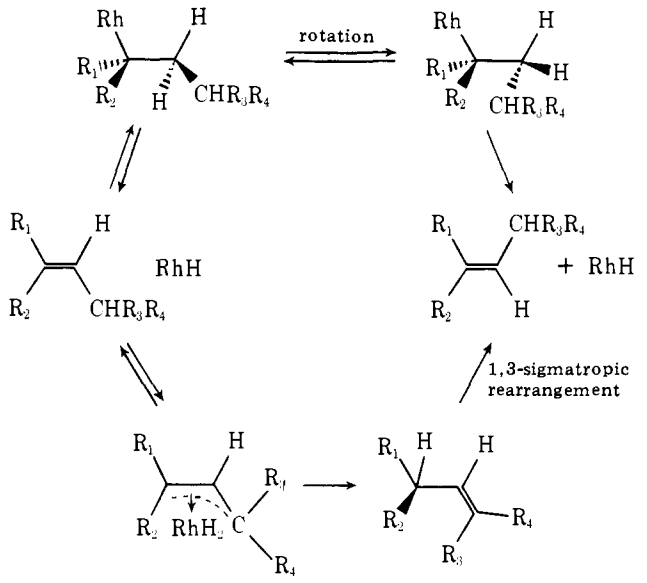
When the solvent was changed to benzene, however, the roles reversed. The *E* isomer gave an 84% (*S*) ee, while the *Z* isomer gave only a 16% (*S*) ee—still the same enantiomer is in excess and with virtually no isomerization in either case. Also, in benzene, the reduction rates for *E* and *Z* are similar and about one-tenth as fast as the *Z* isomer was in ethanol. Since benzene had such a large effect, other chiral catalysts were studied.

In comparison, (*R,R*)-diPAMP (**3**) gave the highest induction, 85% (*S*) ee. This is the first example of an (*E*)-α-benzamidocinnamic acid being reduced in high enantiomeric excess with an asymmetric rhodium catalyst. The change of solvent from ethanol or ethanol/benzene to pure benzene at least doubled the induction for the *E* isomer and gave the same isomer in excess. It should also be noted that even though (*R*)-CAMP (**5**) was extremely fast, the amount of induction was very low, which is consistent with the lack of steric interaction between the catalyst and the substrate.

Discussion

Possible reasons for the variable isomerization of the *E* isomer were explored. It could be induced thermally, photo-

Scheme II



chemically, by impurities in the rhodium catalyst, or by the rhodium species itself. In order to identify the nature of the catalysis, the following control experiments were performed. The *E* isomer was heated at 50 °C in 100% ethanol for 24 h under 50 psi of hydrogen. No isomerization occurred. In order to eliminate the possibility that impurities such as free phosphines, HF, or $HClO_4$[13] are the cause, diphos (**1**) catalyst was added to a solution of *E* isomer in 25 mL of ethanol at 50 °C under 30 psi of nitrogen for 24 h. Again no isomerization occurred, indicating that a rhodium species is definitely responsible for the *E/Z* isomerization.

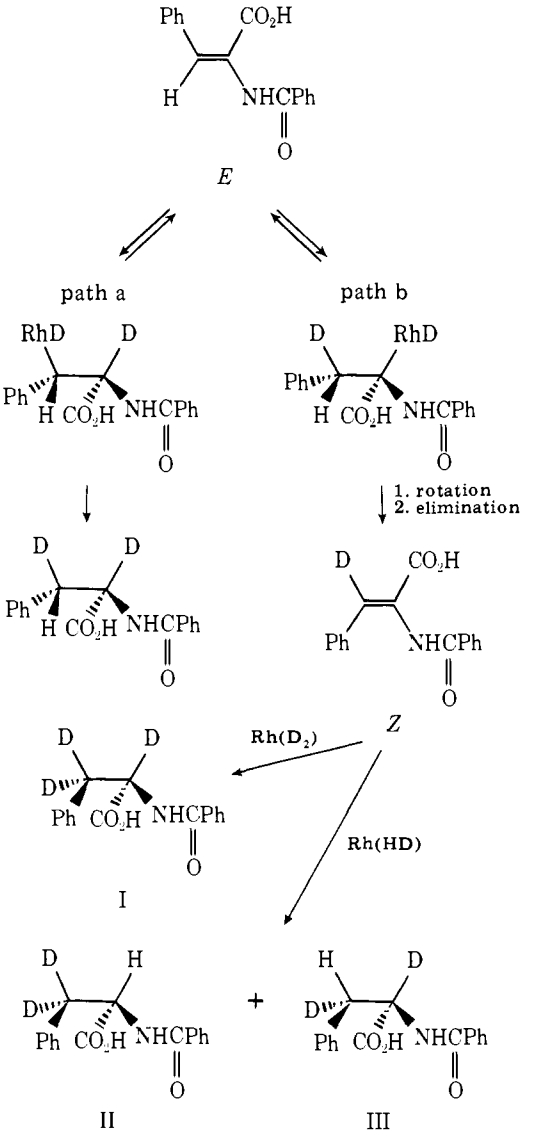
In order to differentiate whether a Rh(I) or Rh(III) species is involved, a Rh(I)[14] complex was placed in 25 mL of ethanol at 50 °C under 3 atm of hydrogen for 1 h to remove the strongly coordinating cyclooctadiene. The hydrogen was removed and the solution thoroughly degassed with nitrogen. An ethanol solution of the *E* isomer was syringed in and the solution held at 50 °C for 24 h. This gives virtually no Rh(III) catalyst since the hydrogen is quickly transferred to a small amount of the *E* isomer (<3% of the isomer being hydrogenated). Still, no isomerization was observed in contrast to Osborn's studies on simple olefins.[15] Apparently hydrogen is required to induce isomerization and a Rh(III) species is involved.

Two pathways are reported for Rh(III)-catalyzed isomerization of olefins: (1) an addition-elimination reaction which is the more documented pathway, and (2) the π-allyl mechanism (Scheme II).[16]

For the isomerization of the α-benzamidocinnamic acids, if the addition-elimination mechanisms were involved, the reaction sequence shown in Scheme III would occur.

Path (a) cannot lead to isomerization. If path (b) is operative, then amide I and/or II must be formed along with the observed amide III. The presence of amide I or II can easily be detected since the NMR integration of the benzyl region would account for appreciably less than one proton when compared to the aromatic region. In all the hydrogenations studied, the benzyl region integrated for one proton, therefore eliminating the presence of amide I or II which, in turn, eliminates path (b) as a route for isomerization. This unequivocally proves that the addition-elimination pathway which is widely invoked for rhodium-catalyzed isomerizations[17] is not operative in this case. The isomerization must occur along a secondary pathway which is consistent with the lack of isomerization observed in benzene for which good reduction and induction data have been obtained.

Scheme III



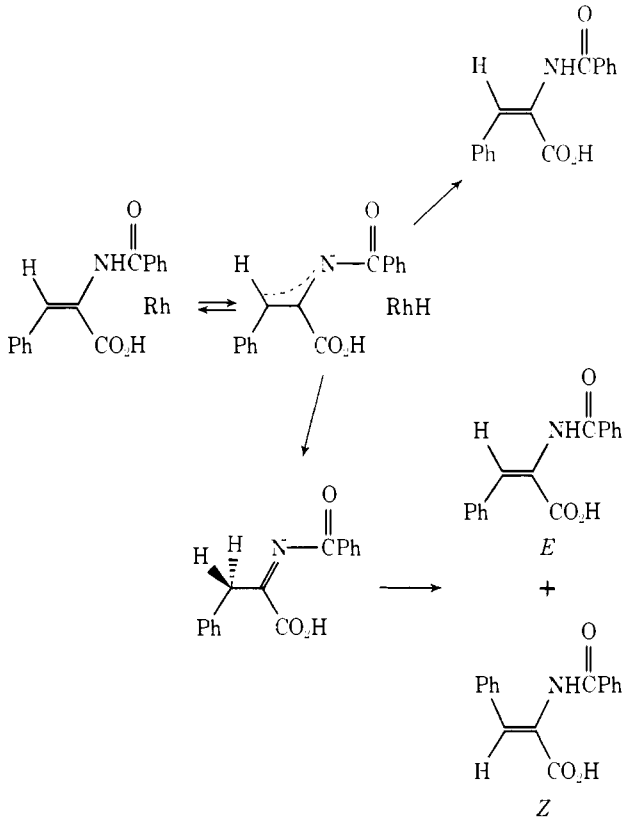
The π-allyl mechanism is consistent with all the data accumulated and would allow for isomerization as shown in Scheme IV.

A number of facts lend further support to this mechanism. For example, not only have π-allylrhodium diphosphines been observed experimentally and shown to be dynamic,[18] but it has also been shown that unsymmetrically coordinated π-allyl groups on rhodium give mixtures of isomeric olefins upon disruption of the complex. Such an isomerization would yield the original olefin plus the imine shown in Scheme IV. Similar imines were prepared by Poisel and Schmidt[19] but could not be isolated, even under mild conditions, owing to their facile rearrangement to the more stable vinyl acetamides. Such rearrangement in our case would result in a mixture of (*E*)- and (*Z*)-α-benzamidocinnamic acids giving the olefin isomerization observed experimentally with no deuterium scrambling or trideuterated materials being formed.[20]

Conclusion

The use of deuterium for the hydrogenation of prochiral trisubstituted olefins has been shown to be extremely useful in quantifying the amount of *E/Z* isomerization. This technique has shown a wide variation in isomerization for benzaminocinnamic acids depending on the type of catalyst and the solvent system employed. Benzene was shown not only to eliminate the unwanted isomerization reaction, but in most of

Scheme IV



the cases studied to appreciably increase the enantiomeric excesses for the *E* isomer over those obtained with traditional protic solvents. In fact, this is the first case of such an *E* isomer undergoing hydrogenation to give enantiomeric excesses greater than 80%.

The fact that the isomerization pathway can be eliminated while obtaining good reduction yields and high enantiomeric excesses indicates that the isomerization does not occur on the reaction path. It was also proven that the traditional addition-elimination mechanism is not involved and that the Rh(III) species is the active isomerization catalyst. These data, along with solvent effects and other experimental data, lend strong support for a π-allyl mechanism.

Experimental Section

NMR spectra were recorded on Varian T-60 and Bruker HX-90-E spectrometers. Ultraviolet spectra were recorded on a Cary 118 spectrophotometer. The mass spectra were obtained on a Hewlett-Packard 5980 by methane-induced chemical ionization with a direct insertion probe. Commercial-grade solvents were used without further purification except for THF, which was freshly distilled from sodium ketyl. All hydrogenations and deuterations were conducted at 50 psi and 50 °C unless otherwise noted.

Typical Deuteration Experiment. Ethanol (25 mL) was thoroughly degassed by bubbling dry nitrogen through the solution for 10 min immediately prior to use. (*E*)-α-Benzamidocinnamic acid[3] (100 mg, 0.37 mmol) and 4.5 mg (0.0059 mmol) of $Rh^+(COD)(R,R)$-diPAMP BF_4^- were placed in a 50-mL hydrogenation bottle containing a magnetic stirring bar. The solvent was then quickly added to the hydrogenation bottle and immediately placed in a 50 °C bath, evacuated, then charged with nitrogen to 30 psi. This vacuum/N_2 degassing procedure was repeated ten times. The bottle was then pressurized with 3 atm of deuterium or hydrogen. The completion of the reduction was monitored by gas uptake. Upon completion, the solvent was removed under reduced pressure and the residue taken up in 10 mL of 95% methanol at 20 °C to obtain an accurate rotation. The methanol was then removed under reduced pressure, the residue diluted with CH_3NO_2, and the CH_3NO_2 removed under reduced pressure.[21] The NMR was then taken in 1 mL of Me_2SO-d_6 with 1% Me_4Si to measure the amount of isomerization. (*Z*)-α-Benzamidocinnamic acid reacted with deuterium to give solely the *SS* product, which had the following spectral properties: NMR (Me_2SO-d_6) δ 8.48 (1 H, singlet, NH), 7.9-6.9 (10 H, multiplet, aromatic), 2.95 (1 H, singlet, benzylic). (*E*)-α-Benzamidocinnamic acid reacted with deuterium in ethanol with (*R,R*)-diPAMP catalyst to give the following spectral properties: NMR (Me_2SO-d_6) δ 8.48 (1 H, singlet, NH), 7.9-6.93 (10 H, multiplet, aromatic), 3.07 (1 H, singlet, benzylic).

Acknowledgments. We would like to thank Professor Jack Halpern and Professor Peter Beak for their helpful discussions. We are deeply indebted to Dr. Robert Kaley, who conducted the mass spectra studies, and to Mrs. Claudette Deatherage for her assistance with the NMR data.

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