Chiral Sulfonated Phosphines. 9.[1] Role of Water in the Hydrogenation of Dehydro Amino Acids

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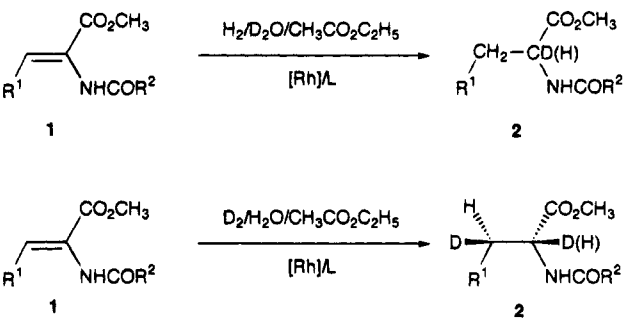
Homogeneous reduction of (*Z*)-α-acetamido- and (*Z*)-α-benzamidodocinnamic acid methyl ester and α-acetamidoacrylic acid methyl ester in an organic–water medium in the presence of a soluble catalyst obtained by mixing $[Rh(COD)Cl]_2$ and a phosphine occurred with regiospecific incorporation of a deuterium atom at the position α to the acetamido and the ester group. When the reduction was performed under a deuterium atmosphere in the presence of water, hydrogen incorporation occurred at the same position and the overall reaction was a *cis* addition of HD. The amount of incorporation of deuterium depends on the nature of the phosphine, the solvent, and the amount of water. A mechanism involving a hydrogen–deuterium exchange on a σ-rhodium monohydride intermediate is proposed.

Introduction

Considerable attention has been devoted during the last years to reactions catalyzed by organometallic complexes in aqueous or in biphasic aqueous–organic media.[2-5] Using a biphasic aqueous–organic phase system, the catalyst being soluble in the aqueous phase and the reactants and products in the organic phase, allowed a very easy separation of the catalyst by decantation and separation of the two phases. This technology has been developed industrially in the hydroformylation process.[6] On the other hand, catalysis in water could also modify the kinetics and the regio- and stereoselectivity of a reaction.[7-10] During our studies on the asymmetric hydrogenation of amino acids precursors in a two-phase system using rhodium complexes in association with chiral sulfonated phosphines,[11] we reported that water acted not only as a solvent but also as a reactant.[12] We notice in the reduction of the methyl ester of α-acetamidocinnamic acid with hydrogen in the presence of deuterium oxide a regiospecific incorporation of deuterium at the position α to the acetamido and the ester group. Some participations of water in organometallic reactions were described in the literature,[13-18] but generally most of these reactions are not truly homogeneous. In the case of the reduction of unsaturated esters and acids by rhodium or ruthenium complexes, incorporation of hydrogen from the solvent CD_3OD was also observed.[19-21]

We described in this paper a detailed investigation on this peculiar reaction in the reduction of amino acid precursors using deuterium in the presence of water or hydrogen in the presence of deuterium oxide.

Scheme 1



a $R^1 = C_6H_5$, $R^2 = CH_3$; **b** $R^1 = R^2 = C_6H_5$; **c** $R^1 = H$; $R^2 = CH_3$

Results and Discussion

The reduction of (*Z*)-α-acetamidocinnamic acid methyl ester (**1a**) (Scheme 1) was carried out in a two-phase

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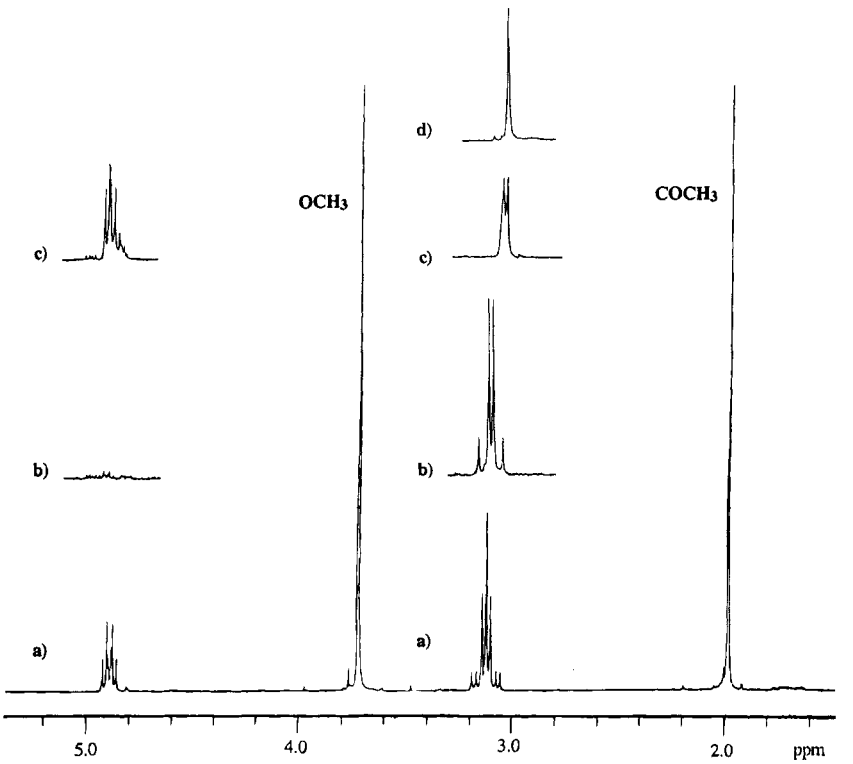
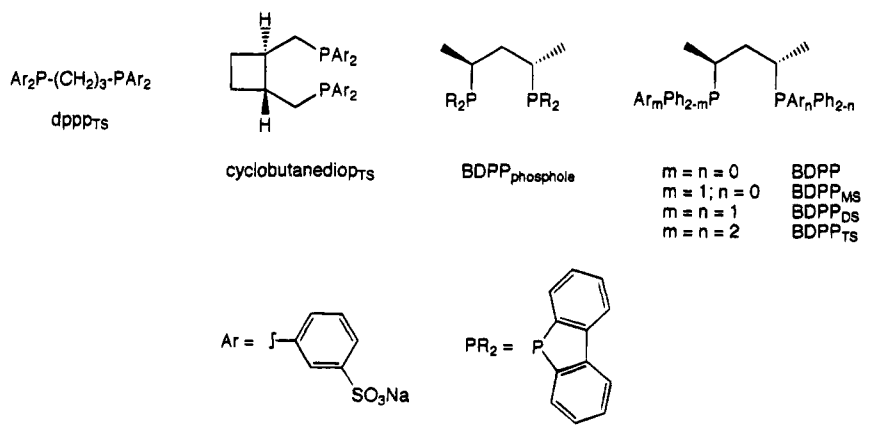


Figure 1. ^1H NMR spectra of the product obtained by hydrogenation of **1a**: (a) by H_2 in C_2H_5OH; (b) by H_2 in $D_2O/CH_3CO_2C_2H_5$; (c) by D_2 in $H_2O/CH_3CO_2C_2H_5$; (d) by D_2 in THF.

Chart 1



system of deuterium oxide–ethyl acetate at 25 °C under 1 atm of hydrogen with $[Rh(COD)Cl]_2$ in association with $dppp_{TS}$ (Chart 1) as the catalyst. The reduced sample was analyzed by NMR.

^1H NMR of the sample shows incorporation of deuterium at the position α to the acetamido and the ester groups: the two doublets at δ 3.15 and 3.06 ppm ($^2J_{H-H}$ = 13.9 Hz) correspond to the two diastereotopic protons of the $-CH_2-$ group of the labeled ester (Figure 1), whereas a small signal corresponding to the $-CH<$ group of the unlabeled substrate appears at δ 4.87 ppm as a multiplet. The quantitative determination of the deuterium content and the regioselectivity of the incorporation are performed on the basis of the analysis of this proton spectrum; since no labeling occurs at the acetamido or the ester groups, these resonance peaks are used as an internal standard. By comparison of their areas to those of the $-CH<$ and $-CH_2<$ resonances, the amounts of deuterium incorporation on the carbons α and β to the acetamido and the ester group are 75% and 0%, respectively. The deuterium NMR spectrum of this sample in CCl_4 (C_6D_6 as an internal standard) also shows only a unique signal at δ 4.86 ppm corresponding to the $-CD<$ group. The $^{13}C\{^1H\}$ NMR spectra of the compound show two singlets at δ 37.8 and 53.2 ppm for the $-CH_2-$ and $-CH<$ groups, respectively and a triplet at δ 52.9 ppm ($^1J_{C-D}$ = 20 Hz) for the $-CD<$ group.

The extent of deuterium incorporation was also confirmed by mass spectrometry (electronic impact). The peaks $[M + 1]^{\bullet+}$ at *m/z* 222 and $[M]^{\bullet+}$ at *m/z* 221 allow the determination of the content of deuterium atom in the molecule. Moreover the presence of a unique peak at *m/z* 91 corresponding to $[C_7H_7]^{\bullet+}$ confirms the regiospecificity of the introduction of deuterium.

The analysis of the proton NMR spectrum of the product **2b** obtained by reduction of (*Z*)-α-benzamidocinnamic acid methyl ester (**1b**) under the same conditions revealed also the incorporation of deuterium (66%) at the position α to the benzamido and ester groups.

We observed two doublets at δ 3.17 and 3.26 ppm ($^2J_{H-H}$ = 13.8 Hz) for the $-CH_2-$ group of the labeled saturated product and a small signal at δ 5.10 ppm for the $-CH<$ group of the unlabeled product. In the $^{13}C\{^1H\}$ spectrum, the following signals are easily recognized: a singlet at δ 53.7 ppm and a triplet at δ 53.3 ppm ($^1J_{C-D}$ = 21.6 Hz) for respectively the $-CH<$ group of the unlabeled product and the $-CD<$ group of the labeled product and a singlet at δ 37.8 ppm for the methine group. The introduction of only one deuterium atom was again confirmed by mass spectrometry with two peaks at *m/z* 284 ($[M + 1]^{\bullet+}$) and *m/z* 283 ($[M]^{\bullet+}$).

(*Z*)-α-Acetamidocinnamic acid methyl ester (**1a**) was also reduced under a deuterium atmosphere in a two-phase system of water−ethyl acetate. As expected, the ^1H NMR spectrum of the reduced product **2a** (Figure 1) consists of a doublet at δ 3.05 ppm for the $-CHD-$ group ($^3J_{H-H}$ = 6 Hz) and a doublet of doublets at δ 4.87 ppm for the $-CH<$ group by coupling with $-CHD-$ and $-NH-$. The amount of hydrogen incorporation at the carbon α to the acetamido and ester groups was about 94%, with no hydrogen incorporation into the methine group. This regiospecific incorporation was confirmed by the deuterium NMR spectrum which shows one very important signal at δ 3.13 ($-CHD-$ group) and by the $^{13}C\{^1H\}$ NMR spectrum with a singlet at δ 53.2 ppm ($-CH<$ group) and a triplet at δ 37.6 ($-CHD-$ group, $^1J_{C-D}$ = 20 Hz).

The reaction product of the reduction of **1a** under a deuterium atmosphere in a two-phase system of water−ethyl acetate showing only a unique signal for the $-CHD-$ group, the addition of HD to the unsaturated substrate is stereospecific. In order to know the relative configuration of the obtained product (*cis* or *trans* addition of HD), the reduction of compound **1a** was carried out under a deuterium atmosphere in tetrahydrofuran catalyzed by $RhCl(PPh_3)_3$; the dideuterated product resulting from a *cis* addition shows in its ^1H NMR spectrum a singlet slightly broadened owing to coupling to deuterium at δ 3.04 ppm for the $-CHD-$ signal. So we can assume that the addition of HD or DH is stereospecifically *cis*.

The reduction of α-acetamidoacrylic acid methyl ester (**1c**) was also performed under a hydrogen atmosphere in a two-phase system of deuterium oxide−ethyl acetate. The ^1H NMR spectrum indicates again that deuterium incorporation up to 66% occurred only at the position α to the acetamido and ester groups. The spectrum consists of a doublet at δ 1.37 ppm and a broadened singlet at δ 1.35 for the unlabeled and the labeled products, respectively, and a signal at δ 4.57 ppm for the $-CH<$ group. The deuterium NMR spectrum shows only one signal at δ 4.60 for the $-CD<$ group. The $^{13}C\{^1H\}$ NMR is also consistent with this monodeuteration with a singlet at δ 48.0 ppm for the $-CH<$ group and a triplet at δ 47.8 ppm for the $-CD<$ group ($^1J_{C-D}$ = 19 Hz). The mass spectrum of the crude mixture shows also the two peaks at *m/z* 146 for $[M + 1]^{\bullet+}$ and *m/z* 145 for $[M]^{\bullet+}$ in the ratio 66/34.

The reduction of unsaturated substrate **1c** was also carried out in a two-phase system of water−ethyl acetate under a deuterium atmosphere. The extent of hydrogen incorporation at the position α to the acetamido and ester groups was determined by ^1H NMR. The spectrum shows effectively a broad singlet at δ 1.35 ppm for the DCH_2- group of the dideuterated product and a doublet at δ 1.36 ppm for the monodeuterated product obtained by the incorporation of the $-CH<$ group. The ratio of 33/67 between the dideuterated and monodeuterated compounds was again easily determined from the areas of the signals corresponding to these protons, the signals of the ester and the acetamido groups being used as internal standards. The mass spectrum of this compound shows also two peaks at *m/z* 88 for $[M + 2]^{\bullet+}$ and *m/z* 87 for $[M + 1]^{\bullet+}$ in a ratio 35/65. Finally, the $^{13}C\{^1H\}$ NMR spectrum shows the characteristic signals at δ 48.1 ppm (s) for the $-CH<$ group and at δ 18.1 (t, $^1J_{C-D}$ 20 Hz) for the $-CH_2D$ group.

All these results clearly show that a hydrogen atom from gaseous hydrogen (or a deuterium atom from deuterium) is introduced to the β position and deuterium from deuterium oxide (or a hydrogen atom from water) mainly to the α position. The mechanism of this isotopic incorporation was further investigated by reducing (*Z*)-α-acetamidocinnamic acid methyl ester (**1a**) by hydrogen in methanol-d_4 using $RhCl(PPh_3)_3$, $[Rh(COD)Cl]_2$ + BDPP, or $[Rh(COD)Cl]_2$ + $BDPP_{TS}$ as the catalyst. In agreement with the preceding result of Kagan,[22] no deuterium incorporation was observed, although some exchange processes were observed by Wilkinson[23] on stirring alcohol solutions of catalyst $RhCl(PPh_3)_3$ or $[Rh(NBD)(PPh_3)_2]PF_6$ under a deuterium atmosphere and by Schrock[24] during ketone hydrogenation. Furthermore, *N*-acetylphenylalanine methyl ester (**2a**) did not undergo any detectable deuterium incorporation after 1 day in a two-phase system of deuterium oxide−ethyl acetate in the presence or not of $dpppp_{TS}$. These experiments show that isotopic exchange occurs during the catalytic cycle.

A possible mechanism for this deuterium incorporation could be a H/D exchange reaction between deuterium oxide and hydrogen (or water and deuterium) in the presence of the rhodium complex, leading to the formation of HD. However the lack of deuterium scrambling rules out this possibility; moreover such an exchange process has been shown to be slow with respect to reduction.[25] The other possibility is a deuterium incorporation occurring after the formation of the enamido complex. According to the hydrogenation mechanism,[26] the association of the unsaturated substrate to the organometallic complex gives the enamido complex (Scheme 2). The next step is the oxidative addition of hydrogen (or deuterium) to the rhodium followed by a hydrogen insertion, leading to the σ-rhodium alkyl intermediate with the introduction of a hydrogen atom (or deuterium atom) at the β position. The following step could be either an external protonation by H^+ (or D^+) of the solvent (water or deuterium) of the rhodium alkyl intermediate or an isotopic exchange [Rh]−H ⇄ [Rh]−D followed by a reductive elimination, leading to the saturated substrate with deuterium (or hydrogen) incorporation at the α position.

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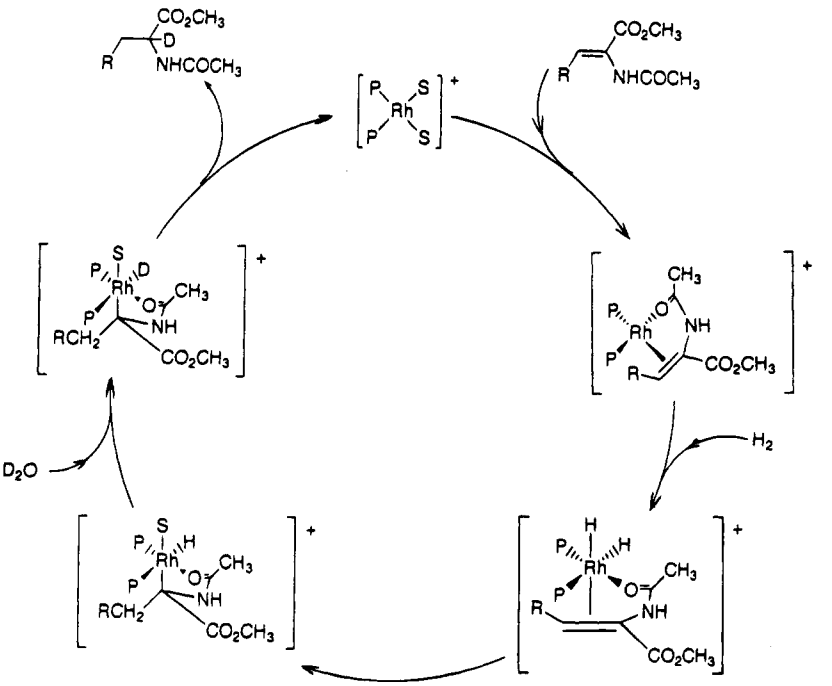
Scheme 2



An exchange process between the dihydro complex and deuterium oxide could again be ruled out due to the lack of deuterium scrambling. Although it is difficult at this time to determine the exact mechanism, the observed *cis* addition of HD seems more compatible with the H/D exchange at the rhodium than an external protonation; we expected that such an external protonation of the σ-rhodium alkyl complex, which was recently postulated by Joo *et al.*,[27] would give the other stereochemistry, or at least would not give a stereospecific *cis* addition.[19] Moreover, such a protonation would also probably occur in an alcoholic solution, the values of the acidities of methanol, ethanol, propanol, butanol, and water, in solution, being very similar.[28] The [Rh]—H $\rightleftarrows$ [Rh]—D exchange, which did not occur in ethanol, is probably possible in water or in mixtures of water and organic solvent due to the higher lifetime of the rhodium monohydride intermediate in water than in an organic solvent, and such a mechanism is in agreement with the observed stereochemistry.

In order to have more important knowledge concerning the factors influencing the deuterium incorporation in the case of hydrogenation in the presence of deuterium oxide, we undertook a systematic study of this reaction.

In Table 1 are summarized the results concerning the reduction of some (*Z*) dehydro amino acid methyl esters in a biphasic deuterium oxide—ethyl acetate medium (1/1) using rhodium complexes associated with various sulfonated phosphines, chiral or achiral. It is obvious that an increase in the degree of sulfonation of the ligand significantly increases the extent of incorporation of deuterium (entries 1, 2, 10, 12, and 13). This is due to the fact that the hydrogenation reaction occurs only in the aqueous phase using tppts (entry 2) or $BDPP_{TS}$ (entry 10). We noticed also that the highest deuterium

Table 1. Hydrogenation of (Z) Dehydro Amino Acids in a Biphasic Deuterium Oxide—Ethyl Acetate Medium[a]

				D incorporation (%)[b]	
entry	substrate	phosphine	P_{H_2} (atm)	by ^{1}H NMR	by MS
1	**1a**	$2Ph_2P(m\text{-}C_6H_4SO_3Na)$	1	29	
2	**1a**	$2P(m\text{-}C_6H_4SO_3Na)_3$	1	45	
3	**1a**	$dppp_{TS}$	1	75	80
4	**1a**	$dppp_{TS}$	10	70	
5	**1a**	$dppp_{TS}$	40	66	
6	**1a**	(cyclobutane)$diop_{TS}$	1	46	
7	**1a**	(cyclobutane)$diop_{TS}$	15	32	
8	**1a**	(cyclobutane)$diop_{TS}$	40	20	
9	**1a**	$BDPP_{TS}$	10	54	53
10	**1a**	$BDPP_{TS}$	20	54	53
11	**1a**	$BDPP_{TS}$	50	54	53
12	**1a**	$BDPP_{DS}$	20	35	29
13	**1a**	$BDPP_{MS}$	20	23	
14	**1a**	$BDPP_{MS}$	50	23	
15	**1b**	$dppp_{TS}$	1	66	
16	**1c**	$dppp_{TS}$	1	65	

[a] A 2.5-mL solution of deuterium oxide containing 10^{-2} mmol of $[Rh(COD)Cl]_2$ + phosphine and a 2.5-mL solution of ethyl acetate containing 1 mmol of the unsaturated substrate; 25 °C; 24 h; quantitative conversion. [b] Determined on the crude product.

incorporation occurs using $dppp_{TS}$ or $BDPP_{TS}$, which form a six-membered chelate ring with the metal, as the ligand. Increasing the hydrogen pressure in the case of (cyclobutane)$diop_{TS}$ from 1 to 40 atm (entries 6–8) decreases the extent of incorporation from 46% to 20%. This decrease in deuterium incorporation is not significantly changed in the case of $dppp_{TS}$ (entries 3–5) or $BDPP_{TS}$ (entries 9–11). According to Halpern's work[26a] the influence of the pressure of hydrogen on the kinetics of hydrogenation is more important in the case of ligands leading to a seven-membered ring with the metal than ligands leading to a five- or six-membered ring.

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Table 2. Hydrogenation of (Z)-α-Acetamidocinnamic Acid Methyl Ester (1a) in a Deuterium Oxide–Tetrahydrofuran Medium[a]

entry	catalyst	P_{H_2} (atm)	D incorporation (%)[b] by ^{1}H NMR	D incorporation (%)[b] by MS
1	$[Rh(COD)_2]PF_6 + 2PPh_3$	1	33	
2	$[Rh(COD)Cl]_2 + Ph_2P(CH_2)_2PPh_2$	1	47	40
3	$[Rh(COD)Ph_2P(CH_2)_2PPh_2]ClO_4$	1	40	47
4	$[Rh(COD)Ph_2P(CH_2)_3PPh_2]ClO_4$	1	67	
5	$[Rh(COD)Cl]_2$ + BDPP	1	40	40
6	$[Rh(COD)Cl]_2 + BDPP_{phosphole}$	10	59	46
7	$[Rh(COD)Cl]_2 + BDPP_{TS}$	10	70	72
8	$[Rh(COD)Cl]_2 + Ph_2P(CH_2)_4PPh_2$	1	23	19
9	$[Rh(COD)Cl]_2 + s\text{-}Bu_2P(CH_2)_3Ps\text{-}Bu_2$	10	22	25

[a] A 5-mL solution of deuterium oxide/tetrahydrofuran (1/1) containing 2×10^{-2} mmol of the rhodium complex and 1 mmol of the unsaturated substrate; 25 °C; 24 h; quantitative conversion. [b] Determined on the crude product.

Table 2 shows the results obtained in the reduction of (Z)-α-acetamidocinnamic acid methyl ester in a deuterium oxide–tetrahydrofuran medium in the presence of various catalysts. It is obvious from these results that the presence of sulfonated ligands is not necessary for the incorporation of deuterium. The ligand forming a six-membered chelating ring with the metal gives again the highest incorporation of deuterium (compare entries 1, 2, 4, and 8). There is practically no difference between a cationic and a neutral complex (entries 2 and 3). The extent of incorporation is also decreasing with increasing basicity of the ligand (compare entries 5–7 and 9).

To define the role of the cosolvent on the extent of incorporation of deuterium, we studied the reaction of (Z)-α-acetamidocinnamic acid methyl ester (**1a**) in various aqueous media using $[Rh(COD)Cl]_2$ in association with BDPP or $BDPP_{TS}$ as the catalyst (Table 3).

Using BDPP as the ligand a higher incorporation of deuterium was observed in tetrahydrofuran–deuterium oxide (entry 3) than in protic solvent–deuterium oxide (entries 1 and 2). The same trend was found using dimethyl sulfoxide or ethyl acetate as the cosolvent. This could be easily explained by an exchange process between methanol or isopropyl alcohol and deuterium oxide leading to a lower concentration in deuterium oxide in the mixture. This was confirmed by using $BDPP_{TS}$ as the ligand and mixture of methanol-*d*–deuterium oxide (entries 6 and 7) and methanol–deuterium oxide (entries 11 and 12), where higher deuterium incorporation was obtained under the former conditions; an important trend is the higher deuterium incorporation with increasing amounts of deuterium oxide (entries 6 and 7). We noticed also that incorporation increases with increasing chain length of the cosolvent; this could be related to the decreasing dielectric constant of the solvent or to a lower deuterium–proton exchange.

The temperature of the reaction seems to have little influence on the extent of the incorporation (entries 8–10). When the reaction was performed in tetrahydrofuran–deuterium oxide, a higher incorporation was observed than in protic solvent–deuterium oxide and increasing pressure of hydrogen increases the extent of incorporation (compare entries 18 and 21).

Table 3. Hydrogenation of (Z)-α-Acetamidocinnamic Acid Methyl Ester (1a) in Various Deuterium Oxide Media Catalyzed by $[Rh(COD)Cl]_2$ + BDPP or $BDPP_{TS}$[a]

entry	ligand	solvent	P_{H_2} (atm)	D incorporation (%)[b] by ^{1}H NMR	D incorporation (%)[b] by MS
1	BDPP	CH_3OH/D_2O (1/1)	10	8	0
2		$n\text{-}C_3H_7OH/D_2O$ (1/1)	10	11	4
3		THF/D_2O (1/1)	1	40	40
4		$DMSO/D_2O$ (3/1)	10	35	
5		$CH_3CO_2C_2H_5/D_2O$ (1/1)[c]	1	38	
6	$BDPP_{TS}$	CH_3OD/D_2O (14.4/1)	10	24	32
7		CH_3OD/D_2O (1.74/1)	10	49	50
8		D_2O	10 (5 °C)	76	
9		D_2O	10 (25 °C)	70	70
10		D_2O	10 (50 °C)	75	
11		CH_3OH/D_2O (1/1)	1	28	20
12		CH_3OH/D_2O (1/1)	10	31	27
13		C_2H_5OH/D_2O (1/1)	1	36	36
14		C_2H_5OH/D_2O (1/1)	10	38	37
15		$n\text{-}C_3H_7OH/D_2O$ (1/1)	1	44	46
16		$i\text{-}PrOH/D_2O$ (1/1)	1	36	36
17		$n\text{-}BuOH/D_2O$ (1/1)	1	45	
18		THF/D_2O (1/1)	1	59	57
19		THF/D_2O (1/1)	10	70 (54%)[d]	
20		THF/D_2O (1/1)	10	70 (90%)[d]	
21		THF/D_2O (1/1)	10	70	72
22		$DMSO/D_2O$ (3/1)	10	63	

[a] A 5-mL solution of deuterium oxide/organic solvent containing 10^{-2} mmol of the catalyst and 1 mmol of the unsaturated substrate; 25 °C; 24 h; quantitative conversion. [b] Determined on the crude product. [c] Lauryl sulfate added. [d] Value in brackets corresponds to the conversion.

Finally, two experiments using $dpppp_{TS}$ and $BDPP_{TS}$ as the ligand in a deuterium oxide–ethyl acetate and deuterium oxide–tetrahydrofuran medium respectively showed that under our conditions there was no change in the isotope incorporation during the hydrogenation of compound **1a** (entries 19–21 for $BDPP_{TS}$); this behavior is easily explained by the fact that the amount of HDO or H_2O formed during the reaction, even in increasing amounts, is very small compared to the solvent D_2O.

Conclusion

In conclusion, our studies on the reduction of dehydro amino acids in deuterium oxide showed that the incorporation of deuterium occurred regiospecifically at the position α to the acetamido and ester groups and is only due to the presence of water. However the nature of the cosolvent and the phosphine used have a great influence on the extent of incorporation. The crucial step for this incorporation is probably a [Rh]–H ⇄ [Rh]–D exchange on the σ-rhodium monohydride intermediate, although protonation by H^+ (or D^+) of the intermediate σ-rhodium complex could not be completely ruled out. This is also a potentially useful methodology in the regiospecific synthesis of isotopically labeled compounds, by using deuterium oxide in the presence of hydrogen which does not require expensive deuterium and which could be applicable to the synthesis of tritiated compounds.

Experimental Section

General Methods. All manipulations were performed under a nitrogen atmosphere using standard Schlenk techniques. Distilled deionized water was used. The following commercial products were used without further purification:

D_2O (99.8% D, Spectrometric Spin et Techniques), D_2 (99.8% D, Alphagaz), CH_3OD (99.5% D,), PBu_3, PPh_3, dppe [1,2-bis(diphenylphosphino)ethane], dppp [1,3-bis(diphenylphosphino)propane], and dppb [1,4-bis(diphenylphosphino)butane]. (*Z*)-α-Acetamidocinnamic acid methyl ester (**1a**),[29] (*Z*)-α-benzamidocinnamic acid methyl ester (**1b**),[29] α-acetamidoacrylic acid methyl ester (**1c**),[30] $Ph_2P(m\text{-}C_6H_4SO_3Na)$,[31] $dppp_{TS}$ or the sodium salt of 1,3-bis[bis(*m*-sulfophenyl)phosphino]propane,[10a] (cyclobutane)$diop_{TS}$ or the sodium salt of (*S,S*)-1,2-bis{[bis(*m*-sulfophenyl)phosphino]methyl}cyclobutane,[10a] (*S,S*)-BDPP or (*S,S*)-2,4-bis(diphenylphosphino)pentane,[32] (*S,S*)-$BDPP_{TS}$ or the sodium salt of (*S,S*)-2,4-bis[bis(*m*-sulfophenyl)phosphino]pentane,[10a] $BDPP_{phosphole}$ or (*S,S*)-pentane-2,4-diylbis((5*H*)-benzo[*b*]phosphindole)[33] and complexes $[Rh(COD)Cl]_2$,[34] $[Rh(COD)Ph_2P(CH_2)_2PPh_2]^+ClO_4^-$, and $[Rh(COD)Ph_2P(CH_2)_3PPh_2]^+ClO_4^-$ [35] were prepared according to literature procedures. (*S,S*)-(Cyclobutane)diop or (*S,S*)-1,2-bis[(diphenylphosphino)methyl]-cyclobutane and $P(m\text{-}C_6H_4SO_3Na)_3$ or tppts were gifts from Rhône-Poulenc Recherches. ^1H, ^2H, and ^{13}C NMR spectra were recorded on a Brüker AM 300 spectrometer, TMS being used as an internal standard. Mass spectra (EI, 70 eV) were measured with a Nermag R 1010M spectrometer coupled with an OV1 (25-m) silica capillary column.

General Procedure for Hydrogenation. A solution of 2×10^{-3} mmol of the catalyst was prepared in 2.5 mL of deuterium oxide (or water) in a Schlenk tube. This solution was injected into a hydrogenation apparatus containing the unsaturated substrate (1 mmol) in the organic solvent and placed under hydrogen (or deuterium). The catalytic reaction was carried out at room temperature. At the end of the reaction, the solvents were evaporated, the substrate was dissolved in dichloromethane (5 mL), and the solution was stirred twice with 10 mL of water. After removal of the solvent in vacuo, the crude product was analyzed.

***N*-Acetyl[2-^{2}H]phenylalanine Methyl Ester.** ^1H NMR ($CDCl_3$): δ 1.96 (s, 3H, $COCH_3$), 3.06 (d, ^2J = 13.9 Hz, 1H, CH_2), 3.15 (d, ^2J = 13.9 Hz, 1H, CH_2), 3.73 (s, 3H, OCH_3), 6.16 (s, 1H, NH), 7.07–7.32 (m, 5H, C_6H_5–). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 23.1 (s, $COCH_3$), 37.8 (s, CH_2), 52.3 (s, OCH_3), 52.6 (t, $^1J_{C-D}$ = 24 Hz, –CD<), 126.6, 128.3, 129.2, and 135.9 (C_6H_5), 169.7 (s, CO), 172.1 (s, CO_2). $^2H\{^1H\}$ NMR (CCl_4/C_6D_6): δ 4.86.

***N*-Acetyl[3-^{2}H]phenylalanine Methyl Ester.** ^1H NMR ($CDCl_3$): δ 1.96 (s, 3H, $COCH_3$), 3.05 (d, ^3J = 6.1 Hz, 1H, CHD), 3.70 (s, 3H, OCH_3), 4.86 (d, ^3J = 6.1 Hz, 1H, –CH<), 6.31 (d, ^3J = 7.2 Hz, 1H, NH), 7.08–7.34 (m, 5H, C_6H_5–). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 23.0 (s, $COCH_3$), 37.5 (t, $^1J_{C-D}$ = 20 Hz, –CHD–), 52.3 (s, OCH_3), 53.2 (s, –CH<), 126.6, 128.5, 129.0, and 135.9 (C_6H_5), 169.9 (s, CO), 172.2 (s, CO_2). $^2H\{^1H\}$ NMR (CCl_4/C_6D_6): δ 3.14.

***N*-Acetyl[2-^{2}H,3-^{2}H]phenylalanine Methyl Ester.** ^1H NMR ($CDCl_3$): δ 1.96 (s, 3H, $COCH_3$), 3.05 (s, 1H, –CHD–), 3.73 (s, 3H, OCH_3), 6.16 (s, 1H, NH), 7.08–7.34 (m, 5H, C_6H_5–). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 23.0 (s, $COCH_3$), 37.4 (t, $^1J_{C-D}$ = 20.1 Hz, –CHD–), 52.3 (s, OCH_3), 53.0 (s, $^1J_{C-D}$ = 21.2 Hz, –CD<), 127.1, 128.6, 129.2, and 135.9 (C_6H_5), 170.0 (s, CO), 172.2 (s, CO_2).

***N*-Acetyl[2-^{2}H]Alanine Methyl Ester.** ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 2.05 (s, 3H, $COCH_3$), 3.88 (s, 3H, OCH_3), 6.36 (d, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 17.9 (s, CH_3), 22.8 (s, $COCH_3$), 47.8 (t, $^1J_{C-D}$ = 19 Hz, –CD<), 52.3 (s, OCH_3), 170.3 (s, CO), 173.7 (s, CO_2). $^2H\{^1H\}$ NMR (CCl_4/C_6D_6): δ 4.60.

***N*-Acetyl[3-^{2}H]alanine Methyl Ester.** ^1H NMR ($CDCl_3$): δ 1.36 (d, 2H, CH_2D), 2.02 (s, 3H, $COCH_3$), 3.76 (s, 3H, OCH_3), 4.65 (m, 1H, –CH<), 6.06 (d, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 18.1 (t, $^1J_{C-D}$ = 20 Hz, CH_2D), 23.0 (s, $COCH_3$), 47.9 (s, –CH<), 52.4 (s, OCH_3), 169.8 (s, CO), 173.7 (s, CO_2).

***N*-Benzoyl[2-^{2}H]phenylalanine Methyl Ester.** ^1H NMR ($CDCl_3$): δ 3.20 (d, ^2J = 13.8 Hz, 1H, CH_2), 3.27 (d, ^2J = 13.8 Hz, 1H, CH_2), 3.83 (s, 3H, OCH_3), 7.0–8.0 (m, 11H, NH and C_6H_5–). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 37.8 (s, CH_2), 52.8 (s, OCH_3), 52.3 (t, $^1J_{C-D}$ = 21.6 Hz, –CD<), 127.1–136.0 (m, C_6H_5), 167.1 (s, CO), 172.2 (s, CO_2).

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Supplementary Material Available: ^1H and $\{^1H\}^{13}C$ NMR spectra (2 pages). Ordering information is given on any current masthead page.

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