The role of protic solvent in asymmetric hydrogenation of methyl levulinate in the presence of a ruthenium-containing catalyst

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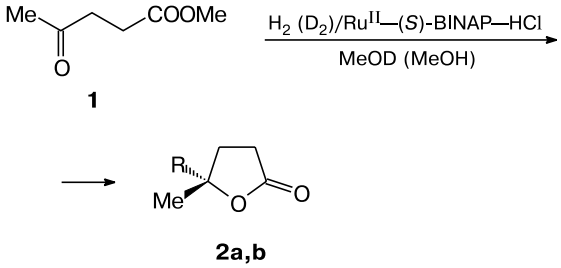
A comparative study of asymmetric hydrogenation and deuteration of methyl levulinate catalyzed by the Ru^{II}—(*S*)-BINAP—HCl system (BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) in MeOH and MeOD was carried out. The results obtained suggest an important role of the protic solvent in the formation of catalytically active ruthenium complexes.

Key words: asymmetric catalytic hydrogenation, deuteration, hydrogen heterolysis, H/D exchange, ruthenium complexes, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), levulinic acid ester, chiral γ-valerolactone.

Earlier,[1] we have investigated asymmetric hydrogenation of levulinic acid esters catalyzed by the Ru^{II}—(*S*)-BINAP—HCl system (BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl). The resulting (*S*)-γ-hydroxy esters underwent *in situ* transformation into (*S*)-γ-valerolactone with up to 99% *ee*.

Here we studied the role of solvent in the aforementioned reactions with methyl levulinate (**1**) as a model substrate (Scheme 1).

Scheme 1



R = H (**a**), D (**b**)

Experimental

Commercial (*S*)-BINAP, (COD)Ru($H_2C(Me)C=CH_2)_2$ (COD is cycloocta-1,5-diene) (Acros), and D_2 and MeOD (pilot plant Prikladnaya Khimiya, St.-Petersburg) were used. Methyl levulinate was prepared from levulinic acid (Acros) according to a standard procedure.[2] Gaseous H_2 and D_2 were purified by passing through columns with a nickel—chromium catalyst and molecular sieves. All solvents were dehydrated before use. Catalytic hydrogenation of oxo ester **1** and analysis of the reaction products were carried out as described in the preceding paper.[1] Here the catalyst for the asymmetric hydrogenation and deuteration of oxo ester **1** was prepared *in situ* without isolating the intermediate complex [((*S*)-BINAP)$RuCl_2$].

Results and Discussion

Our experiments showed (Table 1) that the solvent nature strongly influences the rate and enantioselectivity of the catalytic hydrogenation of oxo ester **1**.

The highest conversion and enantioselectivity were reached when the hydrogenation was carried out in water-free MeOH and EtOH (see Table 1, entries *1*—*3*); the rate of the catalytic reaction in MeOH was appreciably

Table 1. Asymmetric catalytic hydrogenation of compound **1** in protic and aprotic media[a]

Entry	Solvent	*t*/h	Conversion of compound **1**	*ee* (*S*)
			%	
1	MeOH	3	100	99
2[b]	EtOH	3	90	99
3[b]	EtOH	5	100	99
4[b]	Pr^iOH	5	38	92
5	THF	5	<5	—
6	THF—H_2O (9 : 1)	9[c]	74	67
7	CH_2Cl_2	5	<5	—

[a] Ru^{II}—(*S*)-BINAP—HCl; [**1**]/[Ru] = 200, [HCl]/[Ru] = 10, [**1**] = 1.7 mol L^{-1}, 60 atm (H_2), 60 °C.
[b] Previous data[1] on the hydrogenation of ethyl levulinate in EtOH and isopropyl levulinate in Pr^iOH.
[c] At 75 °C.

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higher than in EtOH and Pr^iOH. In water-free aprotic solvents such as THF and CH_2Cl_2 (entries *5*, *7*), the reaction virtually did not occur under the same conditions. In aqueous THF (entry *6*), the conversion of oxo ester **1** hydrogenated at 75 °C for 9 h was 74%. However, the reaction in this solvent was substantially less enantioselective (67% *ee*) than in alcohols, which is attributable to a change in the composition of the catalytic system in the presence of water. Earlier,[3] we have found that water deactivates the ruthenium catalyst in the deuteration of oxo ester **1** in aqueous 90% MeOH at 60 °C before complete conversion of oxo ester **1** into lactone **2** (at ~70% conversion).

The considerable acceleration of the reaction in protic solvents can be due to their role in the formation of catalytically active ruthenium complexes. To elucidate this issue, we performed a comparative study of Ru-catalyzed hydrogenation and deuteration of oxo ester **1** in MeOH, MeOD, and MeOH—MeOD.

A comparison of the kinetic curves in Fig. 1 shows that the catalytic hydrogenation with hydrogen in MeOH (curve *1*) and with deuterium in MeOD (curve *2*) have very close initial rates. This suggests that the kinetic isotopic effect of this reaction is absent or insignificant.

At the same time, one can assume that the heterolysis[4,5] of D_2 (H_2) is substantially facilitated in such a polar solvent as methanol. This is indicated by the data on the isotopic enrichment dynamics for lactone **2** during the catalytic reduction of oxo ester **1** with deuterium in MeOH and with hydrogen in MeOD (Fig. 2).

The dependences obtained suggest that the change in the isotopic composition of lactone **2** (ratio **2a**/**2b**) is determined by the isotopic composition of the solvent (ratio MeOH/MeOD), regardless of whether hydrogen or deuterium is used as the reducing agent. For instance, in the reduction of oxo ester **1** with deuterium in MeOH (see

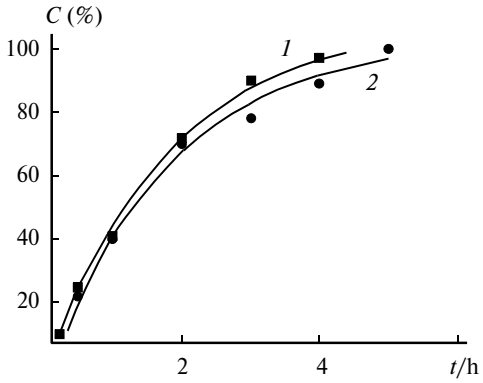


Fig. 1. Plots of the conversion (*C*) of methyl levulinate **1** *vs.* the hydrogenation time in MeOH (*1*) and the deuteration time in MeOD (*2*). The catalytic system is (COD)Ru($H_2C(Me)C=CH_2)_2$—(*S*)-BINAP—HCl; [**1**] = 1.7 mol L^{-1}; [**1**] : [Ru] : [HCl] = 200 : 1 : 10; 60 atm H_2 (D_2); 40 °C.

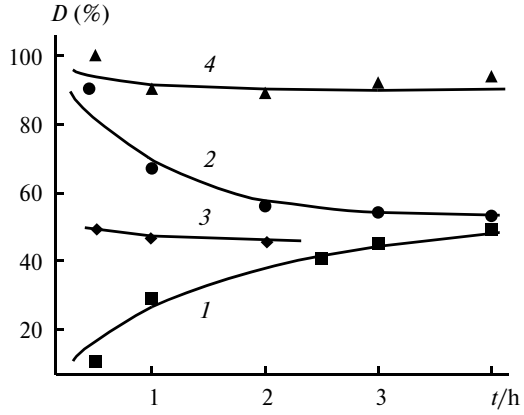
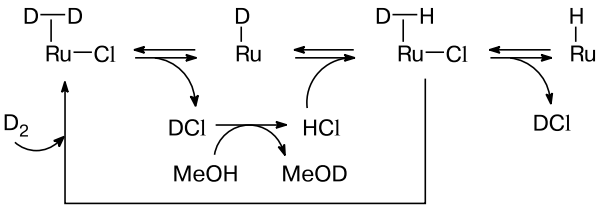


Fig. 2. Plots of the content of lactone **2b** in the mixture of compounds **2a** and **2b** (*D*) vs. the reduction time in the reaction of methyl levulinate **1** with deuterium in MeOH (*1*), hydrogen in MeOD (*2*), hydrogen in MeOH—MeOD (1 : 1) (*3*), and deuterium in MeOD (*4*). The catalytic system is (COD)Ru($H_2C(Me)C=CH_2)_2$—(*S*)-BINAP—HCl; [**1**] = 1.7 mol L^{-1}; [**1**] : [Ru] : [HCl] = 200 : 1 : 10; 60 atm D_2 (H_2); 40 °C.

Fig. 2, curve *1*), lactone **2** contained ~10% deuterium in the γ-position 30 min after the reaction started (which corresponds to a ~20% conversion of compound **1**) and ~50% deuterium after 4 h (90% conversion). When D_2 was replaced by H_2 and MeOH was replaced by MeOD, the dependence became opposite (see Fig. 2, curve *2*): the deuterium content of the reaction product decreased from 100 to ~50% over the same period of time. In the reduction of oxo ester **1** by hydrogen in MeOH—MeOD (1 : 1), the contents of lactones **2a** and **2b** in the initial period of the reaction were also equal (see Fig. 2, curve *3*). As expected, during the reduction of oxo ester **1** by deuterium in MeOD, the isotopic enrichment of product **2** in the γ-position changed only slightly (see Fig. 2, curve *4*). Some decrease in it (from 100 to 90%) was due to the formation of MeOH as the result of partial H/D exchange between oxo ester **1** and MeOD.

The data obtained (see Fig. 2) can be explained by ruthenium-catalyzed H/D exchange[6] between the reducing agent (D_2 or H_2) and the solvent (MeOH or MeOD) (Scheme 2), which occurs in parallel with the hydrogenation of oxo ester **1** and is much more rapid than the major hydrogenation (deuteration) reaction.

Scheme 2



In this case, a change in the MeOH/MeOD ratio during the catalytic reduction should correspondingly change the deuterium content of the catalytically active Ru-containing intermediates, which are in rapid equilibrium; in turn, their isotopic composition determines the ratio of lactones **2a** and **2b**. As noted above, the initial amounts of lactones **2a** and **2b** are equal at MeOH : MeOD = 1 : 1 (see Fig. 1, curve *3*). This can be due to equal steady-state concentrations of hydrogen- and deuterium-containing ruthenium complexes. This fact is consistent with the absence of the kinetic isotopic effect in the catalytic reduction of compound **1** (see Fig. 1). Earlier,[7,8] intermediates of the types $Ru(H_2)$ and Ru—H in equilibrium have been thought to participate in Ru-catalyzed hydrogenation of strongly enolized 1,3-diketones.

Based on the results obtained, one can assume that the Ru-catalyzed asymmetric hydrogenation of γ-oxo esters in protic organic solvents involves heterolysis of molecular hydrogen; a protic solvent facilitates this process and takes an active part in the formation of catalytically active ruthenium complexes that are in rapid equilibrium.

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