Enantioselective hydrogenation of levulinic acid esters in the presence of the Ru^{II}—BINAP—HCl catalytic system

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The rate of hydrogenation of γ-ketoesters $MeCOCH_2CH_2COOR$ (R = Et, Pr^i, Bu^t) in the presence of the chiral Ru^{II}—BINAP catalyst (BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) greatly increases upon the addition of 5—10 equivalents of HCl with respect to ruthenium. In the hydrogenation of ethyl levulinate, the optically active γ-hydroxy ester initially formed would cyclize by ~95% to give γ-valerolactone with optical purity of 98—99% *ee*. When the $Ru(COD)(MA)_2$—BINAP—HCl catalytic system is used (COD is 1,5-cyclooctadiene, MA is 2-methylallyl), complete conversion of the ketoester (R = Et) in EtOH is attained in 5 h at 60 °C under an H_2 pressure of 60—70 atm.

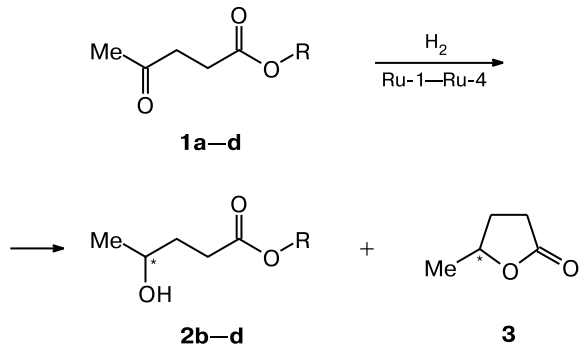
Key words: enantioselective catalytic hydrogenation, ruthenium(II), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), esters of levulinic acid, esters of γ-hydroxyvaleric acid, optically active γ-valerolactone.

The asymmetric catalytic hydrogenation of ketoesters is a highly efficient method for the preparation of optically active hydroxycarboxylic acids and their derivatives, valuable multi-purpose building blocks. The asymmetric hydrogenation of α- and β-ketoesters catalyzed by chiral ruthenium(II) complexes has been studied rather comprehensively in recent years.[1—5] However, little is known about the asymmetric hydrogenation of γ-ketoesters, which are much less reactive than α- and β-ketoesters. In the presence of the $RuCl_2$(BINAP) catalyst (BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), prepared *in situ* from $Ru(OAc)_2$(BINAP),[6] or the $[RuCl_2(BINAP)(DMF)]_n$,[7] $[RuCl_2(BINAP)]_2NEt_3$,[8,9] $[RuCl(p\text{-}MeC_6H_4Pr^i)(BINAP)]Cl$,[10] and $[Me_2NH_2]\{[RuCl(SEGPHOS)]_2(\mu\text{-}Cl)_3\}$[11] catalysts (SEGPHOS is 5,5′-bis(diphenylphosphino)-4,4′-bi(1,3-benzodioxolyl)), a high conversion of γ-ketoesters combined with a high hydrogenation enantioselectivity can be attained in 2 to 10 days at 30—65 °C and 50—100 atm H_2.

The purpose of this study is to search for a more efficient catalytic system for the enantioselective hydrogenation of γ-ketoesters. Esters of levulinic acid (**1a**), compounds **1b—d**, were chosen as model substrates. They were hydrogenated (Scheme 1) in the presence of the Ru-1—Ru-4 catalytic systems (Tables 1 and 2).

The plot shown in Fig. 1 indicates that in the presence of the Ru-1 catalytic system, containing only 2 equiv. of HCl (this amount of the acid is required for the formation of $RuCl_2$(BINAP)), the conversion of ketoester **1b** is less than 5% under the chosen hydrogenation conditions.

Scheme 1



R = H (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**)

Ru-1: $Ru(COD)(MA)_2$—BINAP—HCl
Ru-2: $[RuCl_2(C_6H_6)]_2$—BINAP—HCl
Ru-3: $[RuCl_2(COD)]_n$—BINAP—HCl
Ru-4: $[RuCl(p\text{-}MeC_6H_4Pr^i)(BINAP)]Cl$—HCl
COD is 1,5-cyclooctadiene, MA is 2-methylallyl

When HCl is added up to 5 equiv. with respect to ruthenium, hydrogenation occurs much faster and gives γ-hydroxy ester **2b**, which would cyclize into lactone **3** by ~95% under the reaction conditions. Further increase in the amount of HCl induces a gradual increase in the conversion of ketoester, which reaches 100% for the ratio [HCl]/[Ru] = 10. This ratio was chosen as the standard one in the subsequent experiments. It is significant that the growth of the medium acidity does not influence the

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Table 1. Asymmetric catalytic hydrogenation of ketoester **1b**[a]

Run	Catalytic system	BINAP	Procedure	[**1b**]/[Ru]	*T*/°C	τ/h	Substrate conversion (%)	Composition of the reaction products (mol.%)		*ee* (%)	TOF[b]
								2b	**3**		
1	Ru-1	(*S*)	*A*	1000[c]	60	5	54	20	80	98.5 (*S*)	110
2	Ru-1	(*R*)	*A*	200	60	5	100	5	95	99 (*R*)	—
3	Ru-1	(*R*)	*A*	300	40	5	79	10	90	99 (*R*)	—
4	Ru-1	(*R*)	*A*	200	25	18	100	15	85	99.5 (*R*)	—
5	Ru-2	(*S*)	*B*	200	60	7	41	5	95	98.5 (*S*)	12
6	Ru-2	(*S*)	*B*	300	80	18	95	8	92	98.5 (*S*)	—
7	Ru-3	(*S*)	*B*	200	70	8	54	20	80	98 (*S*)	21
8	Ru-4	(*S*)	*B*	500	65	20	17	25	75	—	4

[a] [HCl]/[Ru] = 10, anhydrous EtOH, [**1b**] = 1.7—2.6 mol L^{-1}, 60—70 atm H_2.
[b] Here and in Table 2, the catalytic activity TOF = [**2b** + **3**] $[Ru]^{-1}$ h^{-1}.
[c] [**1b**] = 12.3 mol L^{-1}.

Table 2. Asymmetric hydrogenation of levulinic acid (**1a**) and its esters **1b—d** in the presence of the Ru-1 catalytic system containing (*S*)-BINAP[a]

Run	Substrate	[HCl]/[Ru]	Solvent	τ/h	Substrate conversion (%)	Composition of the reaction products (mol.%)		*ee* (%)	TOF
						2	**3**		
1	**1a**	10	EtOH	5	69[b]	5	95	98.5 (*S*)	28
2	**1b**	10	EtOH	5	100[c]	5	95	99 (*S*)	—
3	**1c**	10	Pr^iOH	5	38	4	96	92 (*S*)	15
4	**1c**	10	Pr^iOH	8.5	75	4	96	92.5 (*S*)	18
5	**1c**	10	EtOH	5	84	5	95	95 (*S*)	34
6	**1d**	2	EtOH	6.5	11[d]	50	50	—	4
7	**1d**	6	EtOH	6.5	57[d]	50	50	96 (*S*)	16
8	**1d**	8	EtOH	6.5	65[d]	45	55	96 (*S*)	20
9	**1d**	10	EtOH	6.5	66[d]	45	55	98 (*S*)	20

[a] Procedure *A*, [**1**]/[Ru] = 200, [**1**] = 1.7—2.0 mol L^{-1}, 60 atm H_2, 60 °C.
[b] The reaction mixture contained esters **1b**, **2b** and lactone **3**.
[c] Procedure *B*.
[d] The reaction mixture contained 10—25% of ester **1b** with respect to ester **1d**.

hydrogenation enantioselectivity, which remains high (98—99% *ee*) over the whole range of [HCl]/[Ru] values.

In the case of the Ru-1 catalytic system, the $RuCl_2$(BINAP) catalyst was prepared in an acetone solution from the Ru(COD)$(MA)_2$ precursor (COD is 1,5-cyclooctadiene; MA is 2-methylallyl) and the solvent was subsequently removed (procedure *A*), as described for the synthesis of a similar bromine-containing catalyst.[12] In addition, we found that isolation of solid $RuCl_2$(BINAP) by the typical procedure[12] is not obligatory: similar results are obtained on mixing the catalyst precursor, the ligand, and γ-ketoester with the solvent (usually EtOH) that is used in hydrogenation (procedure *B*; see Table 2, run *2*).

Comparison of the catalytic activities of the Ru-1—Ru-4 systems, which was defined as TOF = [**2b** + **3**] $[Ru]^{-1}$ h^{-1}, in the hydrogenation of ketoester **1b** for a conversion not exceeding 55% (see Table 1) allows one to arrange the systems in the following series: Ru-1 ≫ Ru-3 > Ru-2 > Ru-4; the Ru-1 system proved to be almost 30 times as active as Ru-4. The data given in Table 1 also show that the enantioselectivity of hydrogenation in the presence of Ru-1 depends only slightly on the reaction temperature in the range of 25—60 °C and remains about 98.5—99.5% *ee* (runs *1—4*).

With the Ru-1 catalytic system ([**1b**]/[Ru] = 200), complete conversion of the substrate at 60 °C in EtOH is attained in 5 h (Fig. 2). The S-shape of the kinetic curve *1*

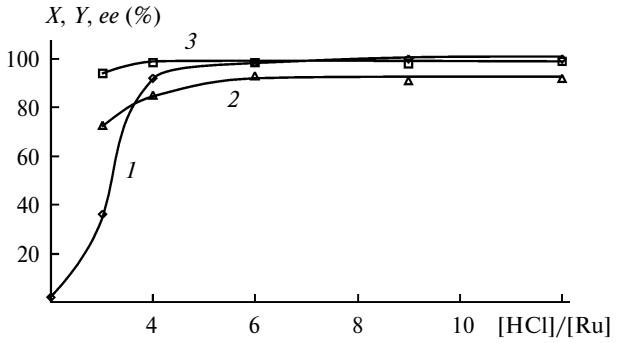


Fig. 1. Conversion of ketoester **1b** (*X*) (*1*), content of lactone **3** in a mixture of **2b** and **3** (*Y*) (*2*), and hydrogenation enantioselectivity (*ee*) (*3*) *vs.* HCl content in the Ru-1 catalytic system (EtOH, [**1b**] = 1.75 mol L^{-1}, [**1b**]/[Ru] = 200, 60—65 atm H_2, 60 °C, 5 h).

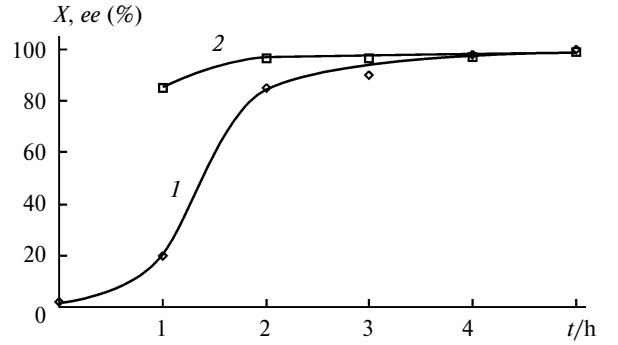


Fig. 2. Conversion of ketoester **1b** (*X*) (*1*) and hydrogenation enantioselectivity (*ee*) (*2*) *vs.* reaction duration in the presence of the Ru-1 catalytic system (EtOH, [**1b**] = 1.75 mol L^{-1}, [**1b**]/[Ru] = 200, [HCl]/[Ru] = 10, 60 atm H_2, 60 °C).

(see Fig. 2) can be attributed to the fact that the initial reaction period involves the formation of catalytically active species (this period is characterized by lowered enantioselectivity, curve *2*); this is followed by acceleration of the hydrogenation where the highest level of enantioselectivity is attained. At the final stage, the substrate conversion gradually increases to 100%.

Using asymmetric hydrogenation of ketoester **1b** as an example, we tested, under similar conditions, a number of catalytic systems with chiral biphosphine ligands other than BINAP, namely, $Ru(COD)(MA)_2$—Pr^i-DuPHOS—HCl (Pr^i-DuPHOS is 1,2-bis[(*R*,*R*)-*trans*-2,5-diisopropyl-1-phospholano]benzene), $Ru(COD)(MA)_2$—(*S*,*S*)-Me-BPE—HCl (Me-BPE is 1,2-bis[(*R*,*R*)-*trans*-2,5-dimethyl-1-phospholano]ethane), and $Ru(COD)(MA)_2$—(*R*)-Prophos—HCl (Prophos is 1,2-bis(diphenylphosphino)propane). However, these systems exhibited low activity under the chosen conditions.

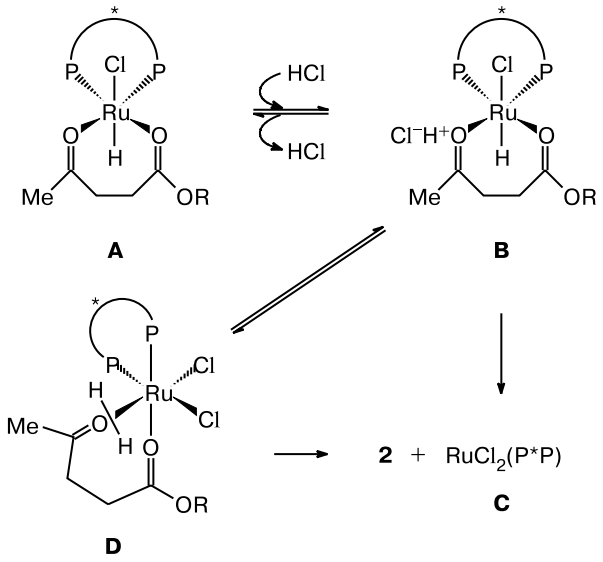
The data presented in Table 2 indicate that the rate of asymmetric hydrogenation of ketoesters **1** is affected by the structure of the alkoxy fragment at the ester moiety, the degree of substrate conversion markedly decreasing in the sequence **1b** > **1c** > **1d** under similar reaction conditions. As was to be expected, cyclization of hydroxy ester **2d**, formed upon hydrogenation of *tert*-butyl ester **1d**, proceeds to a much lesser extent than that of hydroxy esters **2b,c**: ester **2d** and lactone **3** are present in the reaction mixture in approximately equimolar amounts irrespective of medium acidity (see Table 2, runs *6*—*9*).

It is of interest that levulinic acid (**1a**) itself is apparently hydrogenated more slowly than its ethyl ester. Most likely, it is first esterified with the solvent (EtOH), as indicated by the absence of free acids **1a** or **2a** in the reaction mixture on incomplete hydrogenation: the mixture contains only esters **1b**, **2b** and lactone **3** (see Table 2, run *1*). This assumption is also supported by the approximately equal *ee* values in the catalytic hydrogenation of the acid and its ethyl ester in EtOH (runs *1* and *2*).

The acceleration of the reaction upon the addition of HCl to the ruthenium phosphine catalyst was discovered by King[13] in relation to catalytic hydrogenation of β-ketoesters and subsequently confirmed in other studies.[14,15] However, this was not observed for all substrates.[15] To our knowledge, the effect of HCl or another acid on the rate and enantioselectivity of asymmetric hydrogenation of γ-ketoesters has not been studied previously.

The effect of HCl can be attributed to the involvement of the acid in the activation of the keto group of the coordinated substrate (Scheme 2). The putative mechanism includes the formation of the intermediate complex [HRu(P*P)Cl] upon heterolysis of molecular hydrogen (H^+/H^-) in its reaction with the $[Ru(P^*P)Cl_2]$ catalyst. Presumably, in the reaction we study here, the arising

Scheme 2



monohydride complex, [HRu(P*P)Cl], coordinates a γ-ketoester molecule to give intermediate complex **A**. In the presence of HCl, complex **A** is in equilibrium with complex **B**, in which protonation of the keto group facilitates the subsequent hydride transfer giving rise to hydroxy ester and to coordinatively unsaturated complex **C**, which returns to the catalytic cycle. Apparently, due to the small amounts and low concentrations of both complex **A** and HCl, the **A** $\rightleftharpoons$ **B** equilibrium in the absence of excess HCl is substantially shifted to the left. In this case, an increase in the medium acidity would shift this equilibrium toward the formation of complex **B** and, as a consequence, increase the hydrogenation rate. The heterolysis of the η^2-coordinated hydrogen molecule and hydrogenation of the acid-activated keto group can take place synchronously in the coordination sphere of ruthenium complex **D**, which is equilibrated with the reaction complex **B**. The formation of intermediates of types **B** and **D** has been assumed previously[16,17] for analogous Ru^{II}-catalyzed hydrogenation of 1,3-dicarbonyl compounds.

In addition to the foregoing, the coordinatively unsaturated complex **C** involved in the catalytic cycle is in equilibrium in solution with its low-activity linear or ring associates[18,19] containing Ru...Cl bridging bonds. An increase in the degree of the acid-catalyzed dissociation of these associates can induce an additional acceleration of hydrogenation.

Thus, of the catalytic systems tested, the Ru-1 system ([HCl]/[Ru] = 10) exhibited the highest activity accompanied by a high enantioselectivity in the asymmetric hydrogenation of γ-ketoesters derived from levulinic acid. Currently, we are investigating other γ-ketoesters as substrates in order to develop a convenient general method for the preparation of enaniomerically pure γ-alkyl-γ-butyrolactones.

Experimental

Commercial levulinic acid (Acros) was used. Ethyl and isopropyl levulinates were prepared by a standard procedure and *tert*-butyl levulinate by a published procedure.[20] Commercial (*S*)- and (*R*)-BINAP, $[RuCl_2(COD)]_n$, [RuCl((*R*)-BINAP)(*p*-$MeC_6H_4Pr^i$)]Cl (Fluka); $Ru(COD)(MA)_2$ (Acros); (*R*,*R*)-Pr^i-DuPHOS, (*S*,*S*)-BPE, and (*R*)-Prophos (Strem) were used. The complex $[RuCl_2(C_6H_6)]_2$ was synthesized from $RuCl_3$ and 1,3-cyclohexadiene (Fluka) by a reported procedure.[21] Prior to use, all solvents were dehydrated and distilled in an argon flow, which was purified by passing through columns containing a nickel-chromium catalyst, copper supported on Kieselguhr (80 °C), and molecular sieves (4A). Hydrogen was purified by passing through columns with the nickel-chromium catalyst and molecular sieves.

The composition of the products was determined by NMR on a Bruker AM-300 instrument. The enantiomeric analysis of lactone **3** was carried out on a Biochrom-21 chromatograph (30 m × 0.2 mm × 0.25 μm quartz capillary column, 2,6-dipentyl-3-(trifluoroacetyl)-β-cyclodextrin as the stationary phase, a column temperature of 130 °C). Retention times/min: CH_4 (non-sorbable component), 3.5; **1b**, 6.5; (*R*)-**3**, 12; (*S*)-**3**, 15.3. The absolute configuration of the lactone was determined on the basis of the known $[\alpha]_D$ value for the predominant enantiomer.[22] The sign of the optical rotation was determined on a PU-09 spectropolarimeter (State Research Center for Scientific Instrument Making at the Bauman Moscow State Technical University).

Asymmetric catalytic hydrogenation (general procedure). ***A.*** The BINAP ligand (12 mg, 0.019 mmol) and $Ru(COD)(MA)_2$ (6 mg, 0.019 mmol) were placed in a glass tube for hydrogenation, the tube was three times evacuated and filled with argon. A 2 *M* solution of HCl in MeOH (19 μL, 0.038 mmol) was added to anhydrous acetone (2 mL) and the resulting solution was degassed through three cycles including liquid nitrogen freezing, evacuation, thawing, and argon filling and then injected into the hydrogenation tube containing the ligand and the ruthenium complex. The mixture was stirred for 0.5 h; during this period, a yellow- or orange-colored precipitate was formed. After evaporation of acetone *in vacuo*, a solution of ketoester **1b** (519 mg, 3.6 mmol) in a mixture of EtOH (2 mL) and 2 *M* HCl in MeOH (95 μL, 0.19 mmol), pre-degassed three times, was added to the residual solid complex. Then the tube was placed into a stainless-steel autoclave (50 mL) pre-filled with argon, the autoclave was purged with purified hydrogen, and the H_2 pressure was adjusted to 60—70 atm. The reaction mixture was magnetically stirred. After completion of the experiment, the reaction mixture was passed through a 1 cm-thick silica gel layer (elution with hexane—ethyl acetate, 9 : 1) to separate the catalyst. The solvent was evaporated at 40 °C on a rotary evaporator, and the residue was analyzed by NMR and GLC.

B. The BINAP ligand (12 mg, 0.019 mmol) and $Ru(COD)(MA)_2$ (6 mg, 0.019 mmol) were placed into a glass tube for hydrogenation, three times evacuated and filled with argon, and a pre-degassed solution of ketoester **1b** (519 mg, 3.6 mmol) in EtOH (2 mL) and 2 *M* HCl in MeOH (95 μL, 0.19 mmol) were added. Further operations were as described in procedure *A*.

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