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Enantioselective hydrogenation of ethyl 4-chloro-3-oxobutyrate in solutions of organic salts with recycling of the catalyst Ru-BINAP

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Enantioselective hydrogenation of ethyl 4-chloro-3-oxobutyrate in ionic liquid systems containing tetraethylammonium bromide, 1-butyl-3-methylimidazolium hexafluorophosphate, or 1-butyl-3-methylimidazolium trifluoromethanesulfonate in the presence of the chiral catalyst Ru-BINAP ensures a high level of asymmetric induction after at least threefold recycling of the catalyst.

Key words: enantioselective hydrogenation, ethyl 4-chloro-3-oxobutyrate, ethyl 4-chloro-3-hydroxybutyrate, chiral ruthenium complexes, (*R*)- and (*S*)-BINAP, ionic liquid, tetraethylammonium bromide, recycling of the catalyst.

In recent years, considerable progress has been achieved in metal complex catalysis. An important line in this area is catalyzed asymmetric hydrogenation of prochiral C=C, C=O, and C=N bonds in the presence of Rh and Ru complexes with chiral bisphosphine ligands. The high efficiency and enantioselectivity of asymmetric hydrogenation was attained with such chiral ligands as 2,2´-bis(diphenylphosphino)-1,1´-binaphthyl (BINAP), 1,2-bis(2,5-dimethylphospholan-1-yl)benzene, 1,2-bis(2,5-dimethylphospholan-1-yl)ethane, and their structural analogs.[1—5] However, asymmetric catalysis by metal complexes is still practically unfeasible since noble metals and chiral ligands are expensive and the catalysts are difficult to separate from reaction products. The latter circumstance is especially important in the synthesis of medicinal preparations because of stringent requirements for the heavy metal content.

The above problems can be solved by, *e.g.*, heterogenization of metal complex catalysts through binding them chemically to the surface of a mineral or polymeric support.[1,6—10] Partial leaching of the metal from its complex with a support to the liquid phase is a drawback of such heterogenized catalysts. A significantly lower rate of the catalyzed reaction compared to homogeneous systems is another drawback. This is especially pronounced in processes with gaseous reagents (*e.g.*, hydrogen), which necessitates raising the pressure and, consequently, imposes more stringent requirements on the equipment of the process. It should also be noted that heterogenization of chiral metal complexes on the support surface sometimes lowers the level of asymmetric induction compared to homogeneous systems.

In the last ten years, the attention of the researchers has been attracted by reactions catalyzed by metal complexes in liquid (at room temperature) organic salts called ionic liquids (IL). Most frequently, alkylimidazolium salts are used for this purpose. The use of a chiral metal complex catalyst dissolved in IL makes it possible to combine the advantages of homogeneous catalysis (high reaction rate and enantioselectivity) with those of heterogeneous systems (possibility of recycling the catalyst separated from reaction products). After completion of the reaction, the products can be separated from the solution of the catalyst in IL by simple separation of the layers (for biphasic systems) or extraction with a non-polar solvent (*e.g.*, hexane) in which both the catalyst and IL are virtually insoluble.

Recently, IL have successfully been used in asymmetric hydrogenation catalyzed by chiral rhodium and ruthenium complexes. The published data[11—15] mainly refer to the asymmetric hydrogenation of the C=C bond. Only very recently, this approach has been applied to asymmetric hydrogenation of the C=O bond.[16,17]

Earlier,[5] arene ruthenium complexes with the chiral ligand BINAP were found to be highly active and enantioselective in the catalyzed asymmetric hydrogenation of oxo esters. In the present work, we studied the possibility of recycling a catalyst in the catalyzed asymmetric hydrogenation of ethyl 4-chloro-3-oxobutyrate (**1**) into ethyl 4-chloro-3-hydroxybutyrate (**2**), which is a precursor of carnitine (vitamin B_T)[18] (Scheme 1). The catalysts $[RuCl((S)\text{-BINAP})(p\text{-MeC}_6H_4Pr^i)]Cl$ ((*S*)-**3**), $[RuCl_2(C_6H_6)]_2/(S)$-BINAP ((*S*)-**4**), and $[RuCl_2(C_6H_6)]_2/(R)$-BINAP ((*R*)-**4**) were used as solu-

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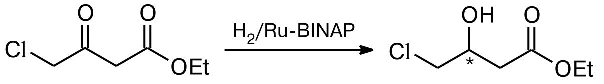
tions in IL and IL—co-solvent or tetraalkylammonium salt—solvent systems (Tables 1, 2).

Scheme 1



1 2

The catalytic hydrogenation of oxo ester **1** in IL without a solvent or in IL + aprotic solvent (*e.g.*, CH_2Cl_2) proceeds very slowly. Therefore, the substrate was hydrogenated in ionic media containing a protic solvent (anhydrous or aqueous EtOH) to ensure a high degree of its conversion.

The same catalyst Ru-BINAP dissolved in the above ionic systems was used in a number of successive cycles. As follows from the data in Tables 1 and 2, the asymmetric hydrogenation of oxo ester **1** is highly enantioselective in all the tested ionic media. In most cases, the enantioselectivity of the hydrogenation decreases slightly with an increase in the number of cycles (see Table 1, entries I—IV). However, under optimum conditions (see Table 2, entry I), the asymmetric induction remains high (94—96% *ee*) for at least three successive cycles.

Table 1. Asymmetric hydrogenation[a] of oxo ester **1** in the ionic liquid—co-solvent system containing the catalyst Ru-BINAP

Entry	Cycle	Conversion of **1**	Selectivity	*ee* (GLC)
		%		
		(S)-**3**—$BMIm^+PF_6^-$—EtOH[b]		
I	*1*	62	100	90 (*R*)
	2	29	95	88 (*R*)
	3	25	88	87 (*R*)
		(R)-**4**—$BMIm^+PF_6^-$—95% EtOH—CH_2Cl_2[c]		
II	*1*	100	100	95 (94)[d] (*S*)
	2	100	100	81 (*S*)
	3	45	100	78 (*S*)
		(S)-**3**—$BMIm^+OTf^-$—EtOH[c]		
III	*1*	100	100	88 (*R*)
	2	100	100	86 (*R*)
	3	92	100	82 (*R*)
	4	89	94	78 (*R*)
	5	59	93	77 (*R*)
		(R)-**4**—$BMIm^+OTf^-$—95% EtOH—CH_2Cl_2[c]		
IV	*1*	100	100	92 (*S*)
	2	91	100	87 (*S*)
	3	46	100	85 (*S*)

[a] Hydrogenation conditions: substrate **1** (0.7 mmol), the catalyst (1 mol. %), the ionic liquid (0.5 mL), the co-solvent (2 mL), P = 12 atm (H_2), 70 °C. The reaction time was 1 h in the first cycle and 6 h in the next ones.

[b] Hereinafter, BMIm stands for 1-butyl-3-methylimidazolium.

[c] 95% EtOH—CH_2Cl_2 (1 : 1).

[d] In the absence of IL.

Table 2. Asymmetric hydrogenation of oxo ester **1** in the $Et_4N^+Br^-$—EtOH—CH_2Cl_2 system containing the catalyst Ru-(S)-BINAP ((S)-**4**)*

Entry	Cycle	T/°C	τ/h	Conversion of **1**	Selectivity %	*ee* (*R*) (GLC)
				%		
I	*1*	70	2	100	100	96
	2	70	2	100	97	95
	3	70	2	76	92	94
II	*1*	30	7	0	—	—
	2	60	2	100	93	96
	3	30	5	50	80	83
III	*1*	70	1	100	100	96
	2	50	1	98	97	85
	3	30	5	42	93	85

* Hydrogenation conditions: the substrate (0.7 mmol), the catalyst (1 mol. %), $[Et_4N^+Br^-]$ = 0.65 mol L^{-1} in anhydrous EtOH—CH_2Cl_2 (1 : 1, v/v), 2 mL.

Data on the effect of the temperature on the conversion of oxo ester **1** and the enantioselectivity of its hydrogenation before and after the recycling of the catalyst are given in Table 2. At 30 °C in the presence of a freshly prepared catalyst, no hydrogenation occurs (entry II, cycle *1*); however, the reaction at 60 °C in the next cycle was completed in 2 h. Apparently, the complex formed at this temperature is catalytically active and can, in contrast to the initial system, catalyze the hydrogenation of compound **1** even at 30 °C, although the conversion and *ee* are lower (entry II, cycle *3*). The reduction in both the catalyst activity and the hydrogenation enantioselectivity with a decrease in the reaction temperature was confirmed in entry III (see Table 2).

With anhydrous EtOH as a co-solvent, the selectivity of the hydrogenation of oxo ester **1** in the first two cycles in all the tested ionic media equals or approaches 100%, yet slightly decreasing in the next cycles. This is explained by the fact that the recycled catalyst gradually becomes less effective in hydrogenation and prolonged heating is required to attain a high conversion of the substrate, which results in partial ketal formation from oxo ester **1**. The formation of diethyl ketal was completely prevented (in at least the first three cycles) by using 95% EtOH as a component of the solvent system. Moreover, addition of aqueous EtOH to the ionic liquid $BMIm^+PF_6^-$ makes the system homogeneous, while anhydrous EtOH and this IL are immiscible and hydrogenation in such a biphasic system proceeds substantially more slowly than in homogeneous media (see Table 1, entries I and II). In contrast, when the catalyst is "immobilized" in the ionic liquid $BMIm^+OTf^-$, the system remains homogeneous upon the addition of both anhydrous and aqueous EtOH. The presence of water inhibits the formation of ketal as a by-product from compound **1** but favors more rapid deactivation of the catalyst and reduction in the degree of conversion of the substrate (see Table 1, entries III and IV).

Thus, the catalyst Ru-BINAP used in the asymmetric hydrogenation of practically important structural block **1** in solutions of tetraethylammonium or 1-butyl-3-methylimidazolium salts can be recycled. For the reaction in the presence of $Et_4N^+Br^-$, the same high level of asymmetric induction is retained in at least three successive cycles.

Experimental

Ethyl 4-chloro-3-oxobutyrate, (*R*)- and (*S*)-BINAP, $[((S)\text{-BINAP})RuCl(p\text{-}MeC_6H_4Pr^i)]Cl$ (Fluka), 1-butyl-3-methylimidazolium hexafluorophosphate, and 1-butyl-3-methylimidazolium trifluoromethanesulfonate (Acros) were used. The complex $[RuCl_2(C_6H_6)]_2$ was synthesized according to a known procedure.[19] $Et_4N^+Br^-$ was purified by recrystallization from EtOH and dried *in vacuo* (1—2 Torr) at 50 °C for 24 h. Before use, 95% EtOH was purged with argon; other solvents were dried and distilled in a flow of argon. Argon was purified by passing through columns packed with a nickel—chromium catalyst, copper on Kieselguhr (80 °C), and molecular sieves (4A). Hydrogen was purified by passing through columns packed with a nickel—chromium catalyst and molecular sieves. All manipulations with catalyst recycling, including work-up of the reaction mixture between cycles, were carried out under purified argon.

The degree of conversion of the starting oxo ester and the selectivity of its hydrogenation (relative to diethyl ketal as a by-product) were determined by ^1H NMR spectroscopy on a Bruker AM-300 instrument; the *ee* of the hydrogenation product **2** were determined by GLC as described earlier.[5]

Catalyzed asymmetric hydrogenation (general procedure). A catalyst (or its components for the *in situ* formation) and IL or $Et_4N^+Br^-$ were placed in a glass tube, which was thrice evacuated and filled with argon. A solution of the substrate in an appropriate solvent was degassed by three freezing (in liquid nitrogen)—evacuation—thawing cycles under argon. Then the solution of the substrate was added to the solution of the catalyst in a tube with a magnetic stirring bar and the tube was placed in a 30-mL stainless-steel autoclave filled with argon. The autoclave was purged with purified hydrogen. After the pressure of hydrogen reached 12 atm, the reaction mixture was kept at a specified temperature. After the first cycle of hydrogenation was terminated, organic material was extracted three times with a triple volume of degassed hexane. The layer of the ionic liquid containing the catalyst or the solid residue, which represents a mixture of the tetraethylammonium salt and the catalyst, was evacuated, the tube was filled with argon, and the next hydrogenation cycle was carried out as described above. The extract obtained after each cycle was concentrated on a rotary evaporator and the residue was dried *in vacuo* and analyzed by ^1H NMR spectroscopy and GLC. The results obtained are given in Tables 1 and 2.

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