Enantioselective hydrogenation of β-keto esters catalyzed by chiral binaphthylbisphosphine ruthenium complexes

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The catalytic activity and the enantioselectivity manifested by cationic chiral binaphthylbisphosphine ruthenium complexes in asymmetric hydrogenation of β-keto esters were studied. The effects of the nature of the solvent, the reaction temperature, the pressure, addition of acids, and the reagent ratio on the yield and the degree of enantiomeric enrichment of the reaction products were examined. For hydrogenation of ethyl 4-chloroacetoacetate to form (*R*)- or (*S*)-enantiomers of ethyl 4-chloro-3-hydroxybutyrate, conditions were found which allow one to quantitatively prepare this valuable synthon with high enantiomeric purity (97—99%) at a low concentration of the catalyst (the ratio substrate : Ru = 10000).

Key words: hydrogenation, asymmetric catalysis, chiral bisphosphine ruthenium complexes, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, β-keto esters, ethyl 4-chloro-3-hydroxybutyrate.

In the past few years, considerable progress has been achieved in the field of asymmetric catalytic hydrogenation of carbonyl compounds in the presence of ruthenium complexes with atropoisomeric bisphosphine ligands, such as 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) or (6,6′-dimethylbiphenyl-2,2′-diyl)bis(diphenylphosphine) (BIPHEMP).[1—4] Such simple β-keto esters as methyl and ethyl acetoacetates are the substrates which have been well studied in these reactions. However, less attention has been given to asymmetric hydrogenation of esters of functionalized β-keto acids, for example, of 4-chloroacetoacetic esters (chloroacetoacetic acid is a precursor of carnitine, which is a physiologically and pharmaceutically important compound), in the presence of ruthenium complexes.[5] Previously, the (BINAP)RuX_2 (X = Cl,[5,6] Br,[5,7] OAc,[5] or allyl[7]) and (BIPHEMP)RuBr_2 complexes[7] were used as catalysts in these reactions. The highest enantioselectivity of hydrogenation (*ee* 93—97%) was observed with the (BINAP)Ru$(OAc)_2$ catalyst (MeOH or EtOH as the solvent; the substrate : Ru ratio was 2000).[5]

This work is devoted to the use of π-arene ruthenium complexes **1** and **2** in asymmetric catalytic hydrogenation of derivatives of keto acids **3**—**6**. Hydrogenation of substrates **3** and **4** yielding hydroxy esters **7** and **8**, respectively, was studied in most detail (Scheme 1).

Catalyst **1** was prepared *in situ* using the $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ complex as a precursor. The latter readily adds BINAP with displacement of one of the chlorine atoms to the outer coordination sphere.[4,8]

Previously,[4] it has been noted that complex **2** is inactive in hydrogenation of methyl acetoacetate. We found that both complex **1** prepared *in situ* and complex **2** are effective in asymmetric catalytic hydrogenation of β-keto esters (Tables 1 and 2).

It is essential that the rate of catalytic hydrogenation of methyl acetoacetate is substantially increased in the presence of small amounts of HCl (*cf.* Ref. 9). Owing to this effect (see Table 1), we succeeded in performing enantioselective hydrogenation of this compound in a methanolic solution in the presence of very small amounts of a catalyst (the substrate : Ru ratio reached 70000). We also observed the effect of the addition of HCl when the reaction was carried out in THF. However, the addition of HCl had no noticeable effect on the rate of hydrogenation of keto ester **4**. Hydrogenation of **4** in the presence of catalyst **1** or **2** (see Table 1) proceeded quantitatively and enantioselectively in the absence of HCl at 75—100 °C and p_{H_2} = 20—100 atm in 0.5—2 h at the ratio substrate : Ru = 10000—20000. It is remarkable that there is a definite dependence of the enantioselectivity of hydrogenation of substrates **3** and **4** on the duration of the reaction in the presence of catalysts **1** and **2** (see Tables 1 and 2), *viz.*, the lower the reaction time the higher the *ee* value.

The best results were obtained with the use of an EtOH—CH_2Cl_2 mixture as the solvent. The dependence of the degree of enantiomeric enrichment of hydroxy

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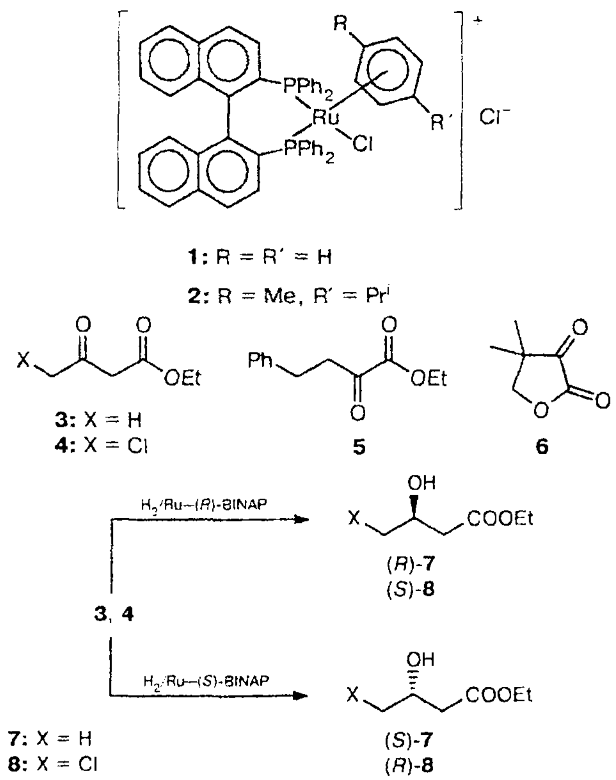
Scheme 1



ester **8** on the composition of the solvent is shown in Fig. 1. It can be seen that the enantioselectivity of hydrogenation of keto ester **4** increases as the proportion of CH_2Cl_2 in the solvent increases up to the ratio CH_2Cl_2 : EtOH = 1 : 1 (v/v), and then the *ee* values remain unchanged (97—99%) up to the ratio CH_2Cl_2 : EtOH = 9 : 1. In pure CH_2Cl_2, the reaction proceeded very slowly under the chosen conditions.

With the aim of improving the reliability of the quantitative estimate of the stereoselectivity of hydrogenation of keto esters in the presence of catalysts **1** and **2**, the enantiomeric compositions of hydroxy esters **7** and **8** were determined by different methods with the use of polarimetry, GLC, HPLC, and NMR spectroscopy in the presence of a shift reagent. As can be seen from Tables 1 and 2 as well as from Fig. 1, different methods gave similar quantitative characteristics of the degree of enantiomeric enrichment of the products.

Hydrogenation of substrates **5** and **6** under similar conditions proceeded with a somewhat lower enantioselectivity than that of β-keto esters **3** and **4** (see Table 2). This fact correlates with the data reported previously on asymmetric hydrogenation of other 1,2-dicarbonyl compounds in the presence of BINAP-containing ruthenium catalysts.[4]

The optimum conditions found for the asymmetric hydrogenation of β-keto esters in the presence of BINAP-containing cationic π-arene ruthenium complexes can be recommended for the preparative synthesis of chiral multipurpose synthons **7** and **8**.

Experimental

The polarimetric measurements were carried out on a Jasco DIP-360 instrument in a 1-cm cell. Below are given the following data: the reduction product, the literature $[\alpha]_D$ value, which we used for calculating the *ee* values, the optical purity of the product (% *ee*) to which this value corresponds, and the

Table 1. Asymmetric hydrogenation of β-keto esters **3** and **4** and methyl acetoacetate catalyzed by $[RuCl(\eta^6\text{-}p\text{-cymene})((R)\text{-BINAP})]Cl^a$

Substrate (S)	S : Ru molar ratio	Solvent	p_{H_2}/atm	*T*/°C	*t*/h	Conversion of the substrate (%)	*ee* (%)[b]	Configuration of the hydroxy ester
MAA[c]	1800	MeOH	75	55	13	0	—	—
	1800	MeOH	120	55	11	92	92[d]	*R*
	1800	MeOH—HCl[e]	105	55	10	100	92	*R*
	70000	MeOH—HCl[e]	90	60	50	88	89	*R*
3	1800	CH_2Cl_2	115	55	2.7	61	93	*R*
	1800	THF	115	55	20	17	39	*R*
	6000	THF—HCl[e]	100	25	120	100	86	*R*
	1800	—	115	55	13	22	60	*R*
4	4500	EtOH	75	100	2	100	93 (91)	*S*
	4500	EtOH—HCl[e]	75	100	4	100	88 (86)	*S*
	10000	EtOH	90	100	1	100	96 (95)	*S*
	20000	EtOH	90	100	1.5	100	93 (93)	*S*
	10000	EtOH—CH_2Cl_2 (1 : 1)	100	95	0.5	100	99 (98)	*S*
	10000	CH_2Cl_2	90	105	27	50	(95)	*S*
	10000	THF	90	100	4	100	(93)	*S*

[a] In the experiments, 15—20 mmol of the substrate and 10 mL of the solvent were used.
[b] The *ee* values were determined by polarimetry (the *ee* values determined by GLC are given in parentheses).
[c] Methyl acetoacetate.
[d] The same *ee* value was determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$.
[e] A 1 *M* HCl solution (10 vol.%) was added to the solvent.

Table 2. Asymmetric hydrogenation of compounds **4—6** in the presence of the $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$—BINAP catalytic system[a]

Substrate (S)	Molar ratio S : Ru	Molar ratio BINAP : Ru	Configuration of BINAP	Solvent	p_{H_2} /atm	*T*/°C	*t*/h	Conversion of the substrate (%)	*ee* (%)[b]	Configuration of the product
4	2000	1.05	*S*	EtOH	20	105	7.5	91	95 (91)	*R*
	2000	1.05	*S*	EtOH	50	105	3	76	93	*R*
	2000	1.05	*S*	EtOH	80	105	1.5	96	90	*R*
	2000	1.5	*S*	EtOH	20	75	1.3	98	93	*R*
	2000	1.5	*S*	EtOH	80	85	0.7	100	95	*R*
	2000	1.5	*S*	EtOH	20	90	0.7	98	96	*R*
	2000	1.5	*S*	EtOH—CH_2Cl_2 (1 : 1)	20	75	0.7	100	99	*R*
	2000	1.5	*R*	EtOH—CH_2Cl_2 (1 : 1)	20	75	0.7	100	99 (98)	*S*
	10000	1.5	*S*	EtOH—CH_2Cl_2 (1 : 1)	25	90	2	93	98	*R*
5	500	1.5	*R*	EtOH—CH_2Cl_2 (1 : 1)	85	20	80	99	(83)	*R*
6	200	1.5	*R*	EtOH—CH_2Cl_2 (1 : 1)	75	70	4	100	(56)	*R*

[a,b] See notes[a,b] in Table 1.

conditions of its determination, *viz.*, the solvent, the concentration (g (100 mL)$^{-1}$), and the temperature (°C): (*S*)-**7**, +43°, 100, $CHCl_3$, 0.93, 25[10]; methyl (*S*)-3-hydroxybutyrate, +50°, 100, neat, 20[11]; and (*R*)-**8**, +20.9°, 97, $CHCl_3$, 7.71, 21.[5] The GLC analysis was carried out on a Biokhrom-21 instrument equipped with a quartz capillary column (30 m×0.25 mm×0.25 µm) coated with β-DEX™ (Supelco). He (1 mL min^{-1}) was used as the carrier gas, and methane was used as the nonretainable component. To determine the enantiomeric compositions of hydroxy ester **8** and ethyl 3-hydroxy-4-phenylbutyrate (the product of hydrogenation of α-keto ester **5**), these compounds were preliminarily derivatized with acetic anhydride according to a standard procedure to form *O*-acetyl derivatives.

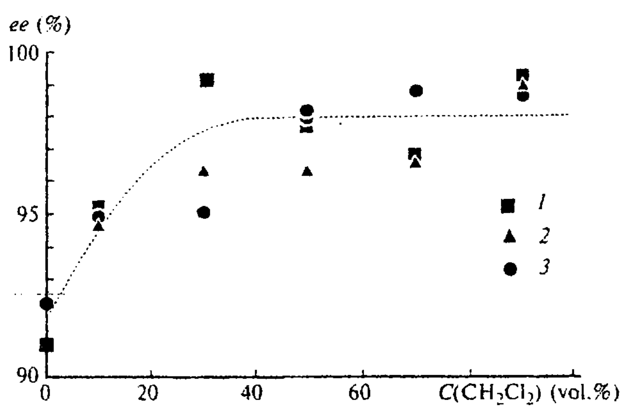


Fig. 1. Dependence of the enantioselectivity of asymmetric hydrogenation of compound **4** in the presence of complex **1** on the concentration of CH_2Cl_2 in an EtOH—CH_2Cl_2 mixture. The experimental conditions: 15.8 mmol of **4**, 8 µmol of $0.5[RuCl_2(C_6H_6)]_2$, 12 µmol of (*R*)-BINAP, and 10 mL of the solvent; H_2 pressure, 22 atm, 75→90 °C, 2 h. The optical purity of the product was determined by GLC (*1*), HPLC (*2*), and polarimetry (*3*).

Below are given the column temperatures (*T*) and the retention times (τ) of the compounds under study.

T/°C	Compound	τ/min
145	CH_4	1.9
	4	45.2
	O-Acetyl-(*R*)-**8**	48.9
	O-Acetyl-(*S*)-**8**	50.1
	5	39.8
	Ethyl *O*-acetyl-(*R*)-3-hydroxy-4-phenylbutyrate	43.1
	Ethyl *O*-acetyl-(*S*)-3-hydroxy-4-phenylbutyrate	44.0
135	CH_4	3.1
	6	15.1
	(*S*)-Pantolactone	20.7
	(*R*)-Pantolactone	21.2

HPLC was carried out on a Laboratorny Pristroje Praha Chromatograph instrument (a UV detector, λ = 254 nm, a 25×0.46-cm column, Chiralcel OD (Daicel), a 9 : 1 hexane—propan-2-ol mixture as the eluent, 1 mL min^{-1}). The optical purity of hydroxy ester **8** was determined for its *O*-benzoyl derivative, which was prepared by the reaction of compound **8** with BzCl in Py. The retention times of *O*-benzoyl (*S*)-**8** and *O*-benzoyl (*R*)-**8** were 5.66 and 6.33 min, respectively. The ^{1}H NMR spectra were recorded on a Bruker AM-300 instrument in $CDCl_3$. The chemical shifts (δ) of the protons of the CH_3 group of the enantiomers of hydroxy ester **7** in the presence of 15 mol.% Eu(hfc$_3$) are as follows: 2.1 d (*S*) and 2.2 d (*R*).

$[((R)\text{-BINAP})RuCl(\eta^6\text{-}p\text{-cymene})]Cl$ (**2**), (*S*)-BINAP, (*R*)-BINAP, ethyl 4-chloroacetoacetate, and Eu(hfc)$_3$ were purchased from Fluka; $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ was synthesized[12] from $RuCl_3$ and 1,3-cyclohexadiene (both initial reagents were purchased from Fluka).

Asymmetric catalytic hydrogenation (general procedure). ***A. Hydrogenation in MeOH.*** The solvent and the freshly distilled substrate were placed into a glass tube under argon, cooled with liquid N_2, and evacuated. Then the mixture was thawed and the tube was filled with argon. The freezing—thawing procedure was repeated three times. Then catalyst **2** or the components from which catalyst **1** was prepared *in situ* were added to the reaction mixture and the mixture was degassed as described above, after which the tube was placed into a rotating (120 rpm) stainless steel autoclave (30 mL) and the autoclave was filled with purified hydrogen. After completion of hydrogenation, the solvent was evaporated and the product was isolated by distillation *in vacuo*.

B. Hydrogenation in EtOH, THF, or CH_2Cl_2. The solvent and the freshly distilled substrate were placed into a glass flask. The solution was degassed as described above and transferred under Ar into a glass tube containing the catalyst. Subsequent operations were carried out as described in procedure *A*.

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