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Ruthenium and rhodium complexes with chiral P-donor ligands as catalysts of enantioselective hydrogenation of ketoesters

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Abstract. The use of ruthenium(II) and rhodium(I) complexes with chiral P-donor ligands as catalysts of asymmetric hydrogenation of α-, β- and γ-ketoesters is considered. The attention is focused on highly enantioselective processes. The bibliography includes 79 references.

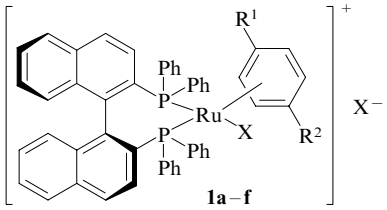
I. Introduction

There is a number of reviews on asymmetric catalytic hydrogenation of prochiral substrates, including ketoesters.[1–5] Asymmetric heterogeneous hydrogenation is usually carried out with surface complexes of such metals as nickel and platinum as catalysts.[6,7] At the same time, recent progress in homogeneous asymmetric hydrogenation is related to the development of chiral ruthenium and rhodium complexes. The Nobel Prize in chemistry in 2001 was awarded to W Knowles and R Noyori for the remarkable achievements in this particular area. There is virtually no information in literature about homogeneous asymmetric hydrogenation of ketoesters with catalysts based on other metals.

The literature data on highly enantioselective (*ee* not less than 80%) reactions of homogeneous asymmetric hydrogenation of α-, β- and γ-esters are summarised in present review. The lower *ee* values are given only for comparison.

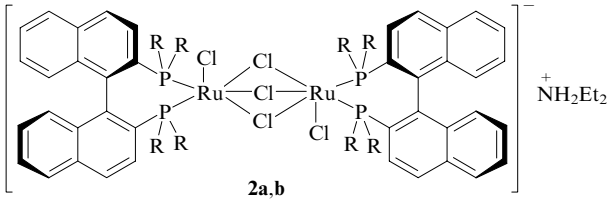
II. Synthesis of metal complex catalysts of asymmetric hydrogenation

For the reactions of asymmetric hydrogenation of ketoesters, either individual metal complexes are used or the catalyst is obtained *in situ* from a metal complex precursor. Particularly, individual Ru^{II} or Rh^{I} complexes with a chiral biphosphine ligand (P*P), for example 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), are used as catalysts of asymmetric hydrogenation of β-ketoesters. These include easily crystallisable anionic complexes **1** (Refs 8 and 9) or anionic complexes **2** (Ref. 10) studied by X-ray diffraction.



1a–f

$R^1 = R^2 = H$: X = Cl (**a**), Br (**b**), I (**c**);
$R^1 = Me$, $R^2 = Pr^i$: X = Cl (**d**), Br (**e**), I (**f**).



2a,b

R = Ph (**a**), 4-$MeOC_6H_4$ (**b**).

The formation of catalytically active dihalide ruthenium complex from inactive diacetate complex is an example of *in situ* generation of a catalyst in the hydrogenation of β-ketoesters [reaction (1)].[11,12]

$$[Ru(OAc)_2(BINAP)] + 2\,HX \longrightarrow [RuX_2(BINAP)] + 2\,AcOH, \quad (1)$$

X = Cl, Br.

The simplest and therefore most widely used method of *in situ* generation of ruthenium and rhodium catalysts is based on the ligand exchange in active achiral complexes $[RuCl_2(cod)]_n$

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[reactions (2) ($n = 1$) [12, 13] and (3) ($n = 2$) [14]], $[RuCl_2(C_6H_6)]_2$ [reactions (4) [15, 16] and (5) [8]], $[Ru(MA)_2(cod)]$ [reactions (6) [17] and (7) [18]] (cod is cycloocta-1,5-diene, MA is 2-methylallyl).

$$[RuCl_2(cod)] + P^*P \xrightarrow[140\ ^\circ C,\ 4\ h]{Et_3N,\ PhMe} [RuCl_2(P^*P)] + cod, \quad (2)$$

$$[RuCl(cod)]_2 + 2\,P^*P \xrightarrow[25\ ^\circ C,\ 15\ min]{C_6H_6} [RuCl(P^*P)]_2 + 2\,cod, \quad (3)$$

$$[RuCl_2(C_6H_6)]_2 + 2\,P^*P \xrightarrow[100\ ^\circ C,\ 10\ min]{DMF} 2\,[RuCl_2(P^*P)(DMF)_n] + 2\,C_6H_6, \quad (4)$$

$$[RuX_2(C_6H_6)]_2 + 2\,P^*P \xrightarrow[50\ ^\circ C,\ 1\ h]{EtOH-CH_2Cl_2} 2\,[RuX_2(C_6H_6)(P^*P)]^+X^-, \quad (5)$$

X = Cl, Br, I.

$$[Ru(MA)_2(cod)] + P^*P + 2\,HX \xrightarrow[25\ ^\circ C,\ 30\ min]{acetone} [RuX_2(P^*P)] + cod + 2\,C_4H_8, \quad (6)$$

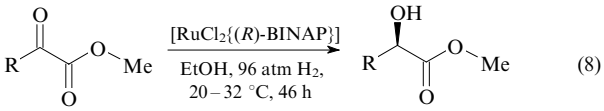
X = Cl, Br, I.

$$[Ru(MA)_2(cod)] + P^*P \xrightarrow[60\ ^\circ C,\ 5\ h]{hexane} [Ru(MA)_2(P^*P)] + cod. \quad (7)$$

Usually, a solid catalyst is first obtained *in situ* by vacuum removal of the solvent, however sometimes good results may be achieved by hydrogenation of ketoesters in the presence of a catalytic system containing achiral catalyst precursor and chiral ligand. This method may be applied if the same solvent is used both for the catalyst formation and for the hydrogenation reaction.[14, 19, 20]

III. Asymmetric hydrogenation of α-ketoesters catalysed by ruthenium(II) complexes

The pioneering paper by Noyori and co-workers [21] published in 1988 reported the application of catalytic system $[Ru(OAc)_2(BINAP)] + 2\,HCl$ for asymmetric hydrogenation of methyl 2-oxopropionate (**3a**) with substrate : catalyst (S : C) molar ratio equal to 780.



(8)

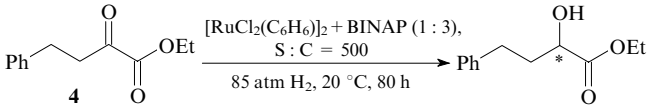
3a–f

R = Me (**a**), Ph (**b**), 4-$MeOC_6H_4$ (**c**), 4-MeC_6H_4 (**d**), 4-ClC_6H_4 (**e**), 4-$NO_2C_6H_4$ (**f**).

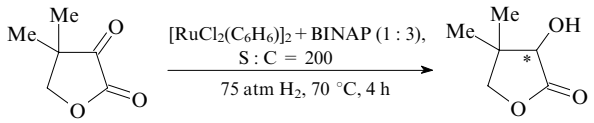
According to the authors, dichloride $[RuCl_2(BINAP)]$, formed from the acetate complex [reaction (1)], is a mixture of the dimer and higher molecular associates of unknown composition.

The yield of methyl (*R*)-α-hydroxypropionate was equal to 97%, the optical yield (enantiomeric excess *ee*) was 83%. Later, the cationic complex (*S*)-**1a** (configuration of the ligand is noted) was successfully used as catalyst for hydrogenation of the same α-ketoester.[8] In the presence of this catalyst and under conditions similar to those for reaction (8), the chiral α-hydroxyester was obtained in 100% yield and with *ee* equal to 88% (*S*-enantiomer). Similarly, hydrogenation of aryl-containing α-ketoesters **3b–f** catalysed by complex (*S*)-**1a** produced corresponding (*S*)-α-hydroxyesters in 82%–100% yields and with *ee* 86%–93%. In the hydrogenation of α-ketoester **3b** the effect of various additives in 10 to 1 equivalent ratio relative to complex **1a** was studied. While addition of water and Et_3N caused the decrease of both conversion and enantioselectivity of hydrogenation, addition of strong acids (HBF_4, $HClO_4$, *p*-TsOH) resulted in an increase in the optical yield. Thus, the optical yield in the hydrogenation of substrate **3b** in absence of acid was equal to 70%, while after addition of HBF_4 it increased up to 89%, the reaction rate being not affected by the presence of acid.[8]

The catalyst **1a** can be obtained *in situ* using the catalytic system $[RuCl_2(C_6H_6)]_2$ + BINAP. This was demonstrated [19] for model reactions of asymmetric hydrogenation of α-ketoester **4** and α-ketolactone **5** in the mixture MeOH–CH_2Cl_2 (1 : 1 in volume).

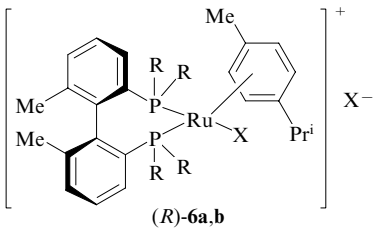


Conversion 99%. (*ee* 83%)



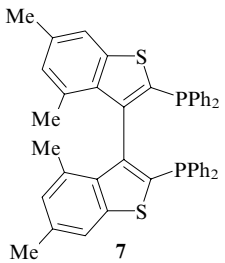
Conversion 100%. (*ee* 56%)

Hydrogenation of both α-ketoesters and β-ketoesters (see Section V) is very sensitive to the type of halide ligands in arene complexes of Ru^{II} with atropisomeric bisphosphines. Thus, complex **6a** with (*R*)-BIPHEP (X = I) ligand was several times more catalytically active in hydrogenation of ketoester **3b** than analogous Cl-containing complex **6b**. The enantioselectivity of hydrogenation of substrate **3b** in the presence of 1 mol % of cationic complex (*R*)-**6a** (EtOH, 5 atm H_2, 25 °C, < 10 h) was > 99% (*S*).[22] For comparison, the optical yield of hydrogenation of ketoester **3b** in the presence of similar complex **1f**, containing (*S*)-BINAP (MeOH, 100 atm H_2, 30 °C, 95 h) was only 45%.

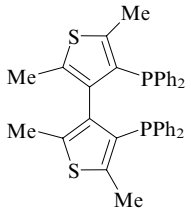


(*R*)-**6a,b**

X = I (**a**), Cl (**b**); R = cyclo-C_6H_{11}.

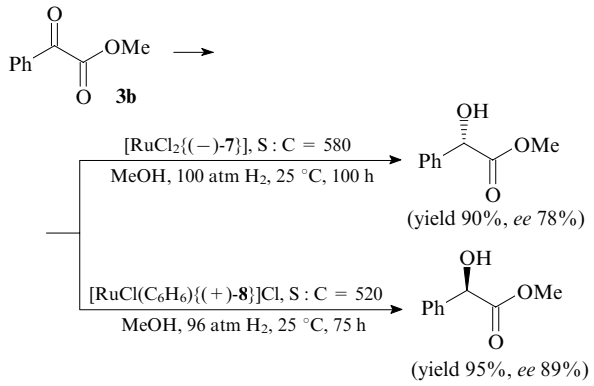


7
tetra-Me-BITIANP



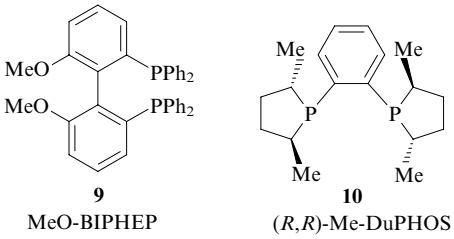
8
tetra-Me-BITIOP

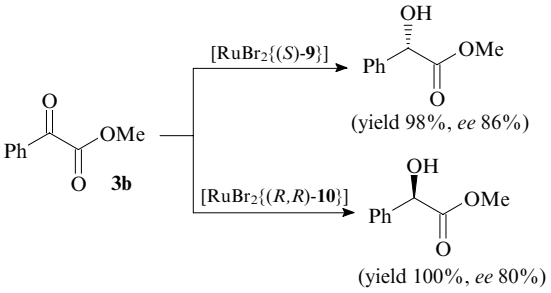
Hydrogenation of substrate **3b** is also catalysed by Ru^{II} complexes with heterocyclic atropisomeric ligands tetra-Me-BITIANP (**7**) (Refs 23 and 24) and tetra-Me-BITIOP (**8**).[25]



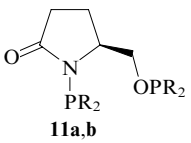
The diphenylphosphine groups of ligand **8** are located at β-positions of thiophene rings where the charge density is maximum; this increases the donor properties of this ligand and probably enhances asymmetric induction. The hydrogenation catalysts containing ligands **7** and **8** were obtained *in situ* according to reactions (4) and (5), respectively.

Highly active ruthenium catalysts of asymmetric hydrogenation of α-ketoester **3b** were obtained *in situ* from achiral catalyst precursor $[Ru(MA)_2(cod)]$ and chiral ligands (*S*)-**9** or **10** [reaction (6)], both reactions take place under H_2 pressure not exceeding 20 atm (S : C = 100, toluene, 50 °C, 48 h).[18]





At the same time more drastic conditions (50 atm H_2, 60 °C) were required for asymmetric hydrogenation of ketolactone **5** in the presence of a catalyst formed from the same precursor and aminophosphine phosphinite ligand **11a**. Hydrogenation of substrate **5** with this catalyst in CH_2Cl_2 reached full conversion in 20 h with stereoselectivity of 79% (*R*).[26]

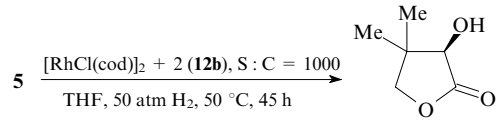


R = Ph ((*S*)-Ph,Ph-oxo-ProNOP, **a**), cyclo-C_5H_9 (**b**).

Generally, ruthenium complexes with chiral biphosphines and other P-donor ligands catalyse asymmetric hydrogenation of α-ketoesters with enantioselectivity of 80% – 90% in most cases, except complex **6a**. In the presence of this complex the enantioselectivity of hydrogenation of α-ketoester **3b** was higher than 99%.

IV. Asymmetric hydrogenation of α-ketoesters catalysed by rhodium(I) complexes

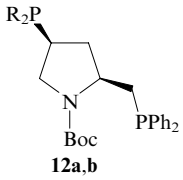
One of the first examples of asymmetric hydrogenation of α-ketoesters was hydrogenation of lactone **5** [reaction (9)],



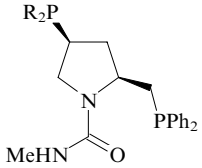
(9)

Conversion 100%. (*ee* 91%)

catalysed by Rh^I complexes with chiral biphosphine ligands **12**, which were synthesised from (*S*,*S*)-4-hydroxyproline. The catalysts were obtained by reaction (3).[27, 28]



R = Ph (BPPM) (**a**),
cyclo-C_6H_{11} (BPCM) (**b**).

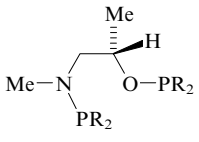


R = cyclo-C_6H_{11} (MCCPM).

The choice of substituents R in ligand **12** is crucial for attaining high level of asymmetric induction.[14, 29] The ligand **12b** exhibits the highest enantioselectivity **12b** (*ee* 91%). Substitution of (cyclo-C_6H_{11})$_2$P group in ligand **12b** for Ph_2P group causes the decrease of optical yield from 91% to 61%, and reversal of the mutual positions of donor groups Ph_2P and (cyclo-C_6H_{11})$_2$P results in decrease of *ee* down to 9%. At the same time the character of acyl group in ligands **12** and **13** probably does not affect noticeably the result of asymmetric hydrogenation of α-ketoesters. Thus, hydrogenation of ketoester **3a** catalysed by Rh^I complexes with ligand **13** under conditions similar to those for the reaction (9), furnishes (*R*)-α-hydroxyester in 100% yield and 87% optical yield.[30]

The papers [31 – 44] describe synthesis of a series of amino- and amidophosphine-phosphinite ligands (AMPP) and their rhodium complexes, which are highly active and enantioselective in hydrogenation under mild conditions: the H_2 pressure up to 1 atm and reaction temperature of about 25 °C.

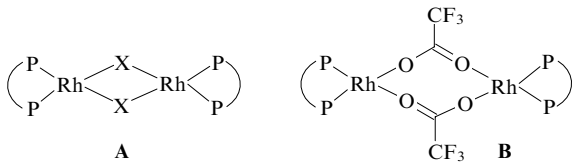
The complexes of Rh^I with ligands **11b**, **14**, which are derivatives of (*S*)-prolinol and (*S*)-isoalaninol, are among the most active in this series.[31 – 35] These ligands as well as biphosphine ligands **12** contain cycloalkyl groups, which are distinctive electron donors.



(*S*)-R-iso-AlaNOP

R = cyclo-C_5H_9.

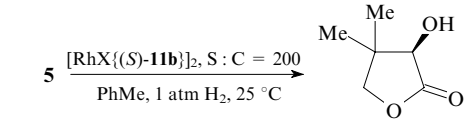
The catalysts of hydrogenation were obtained by the reaction of ligands **11b**, **14** or their analogues with complexes $[RhX(cod)]_2$ (X = Cl, I, AcO, CF_3CO_2 or n-$C_3F_7CO_2$). According to ^{31}P NMR data the formed complexes are binuclear with bridging halogen (structure **A**) or carboxylate (structure **B**) groups.[33, 34]



A **B**

P P is biphosphine ligand.

As in the case of catalytic hydrogenation of α-ketoesters with mononuclear cationic complexes $[RuX(C_6H_6)(BINAP)]X$ (X = Cl or I) (see Section III), the character of halogen or carboxylate ligand in rhodium complexes of **A** and **B** types significantly affects their catalytic activity. That was demonstrated in the following reaction (*t* is time required for the reaction completion):

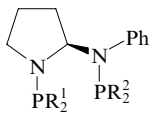


(10)

X	*t*/min	*ee* (%) (*R*)
I	1080	98
Cl	72	96
$MeCO_2$	90	98
CF_3CO_2	6	99
n-$C_3F_7CO_2$	5	98

These data show that complexes of **A** type with chloride bridges are several times more active than those with iodide ligands and replacement of chloride ligands by perfluorocarboxylate ones increases the rate of catalytic hydrogenation of lactone **5** [reaction (10)] by an order of magnitude, high enantioselectivity being retained.[34]

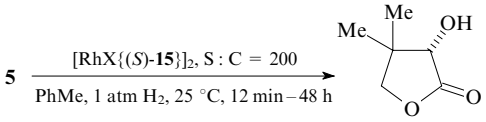
It is interesting to compare the catalytic activity of rhodium complexes with AMPP ligands containing R_2PO group with that of structurally related complexes with bis(aminophosphine) ligands **15a**–**f** (BAMP).



15a–**f**
(BAMP)

Compound **15**	R^1	R^2	X
a	Ph	Ph	Cl
b	cyclo-C_5H_9	cyclo-C_5H_9	Cl
c	cyclo-C_6H_{11}	cyclo-C_6H_{11}	Cl
d	cyclo-C_5H_9	Ph	Cl
e	cyclo-C_6H_{11}	Ph	Cl
f	cyclo-C_5H_9	Ph	CF_3CO_2

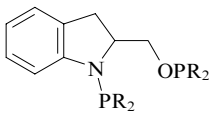
The complexes of rhodium with ligands **15a**–**f** were tested in the asymmetric hydrogenation of α-ketolactone **5**.[36]



[yield 100%,
ee 62%–83% (*S*)]

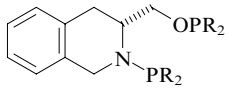
It was found that Rh^I complexes with BAMP ligands **15b** and **15c** are rather active, but the level of asymmetric induction did not exceed 83%, *i.e.* was significantly lower than in the case of the same reaction catalysed by complexes with AMPP ligands [reaction (10)].

The activity of rhodium catalysts, containing indoline[38] and tetrahydroisoquinoline[39, 43] AMPP ligands **16b** and **17a**,**b** with bis(cycloalkyl)phosphite groups,



16a,**b** (IndoNOP)

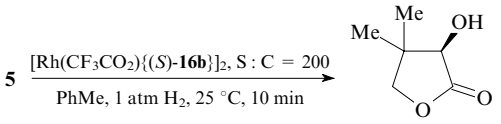
R = Ph (**a**), cyclo-C_5H_9 (**b**).



17a,**b** (QuinoNOP)

R = cyclo-C_6H_{11} (**a**), cyclo-C_5H_9 (**b**).

is much higher than that of similar catalysts with Ph_2PO groups.

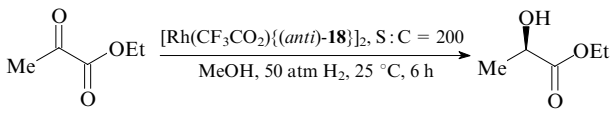


Conversion 100%. [*ee* >99% (*R*)]

Indeed, 81% conversion of substrate **5** at 50 atm H_2 pressure and temperature of 50 °C in this reaction was achieved in 66 h when the highly active catalyst with ligand **16b** was replaced by the catalyst with ligand **16a**. Under the same conditions hydrogenation was completed in 1 h when the catalyst with ligand **16b** was replaced by similarly active Rh^I catalyst **17a**.

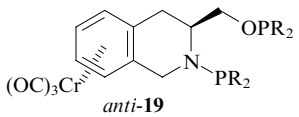
An original method of QuinoNOP ligand modification by complexation of their benzene fragment by chromium carbonyl was suggested;[43] this significantly affects enantioselectivity of hydrogenation.

Enantioselectivity of hydrogenation of ethyl 2-oxopropionate (**18**) in the presence of catalyst with ligand **17b** is equal to 83% (*R*), while the catalyst with the same ligand coordinated by chromium carbonyl (*anti*-**19**) increases enantioselectivity up to 95%.

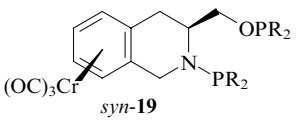


18 (*ee* 95%)

Conversion 100%.



anti-**19**

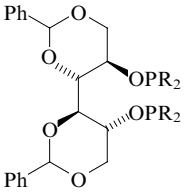


syn-**19**

R = cyclo-C_5H_9.

On the contrary, application of a catalyst based on ligand **19** with *syn*-coordinated $Cr(CO)_3$ fragment, decreases the optical yield to 78%.

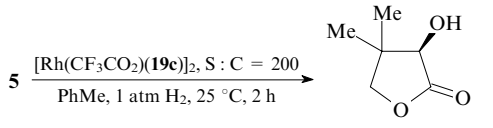
Three chiral atropisomeric bisphosphinite ligands **20a–c** were synthesised on the basis of polyatomic alcohol mannitol;



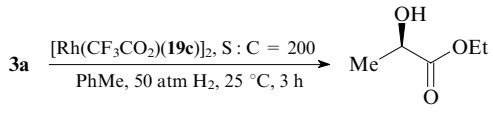
20a–c (MannOP)

R = Ph (**a**), cyclo-C_5H_9 (**b**), cyclo-C_6H_{11} (**c**).

they were tested as chiral inductors of Rh-catalysed hydrogenation of lactone **5** and ketoester **3a**.



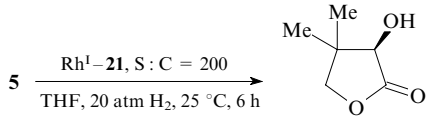
Conversion 100%. (*ee* 84%)



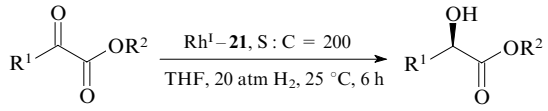
Conversion 100%. (*ee* 86%)

As in the case of catalytic systems Rh^I–AMPP, the catalysts Rh^I–**20b,c** with ligands containing electron-donating groups (cyclo-Alk)$_2$PO are 5–10 times more active than the catalyst Rh^I–**20a** with the ligand containing Ph_2PO fragment.[40]

The complex Rh^I with chiral ferrocene derivative **21** is quite effective in the reactions of asymmetric catalytic

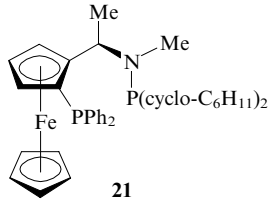


Conversion 100%. (*ee* 97%)



Conversion >95%. (*ee* 88%–92%)

hydrogenation of lactone **5** and α-keto esters **3a**, **4**, **18**.[41,45]



21

Thus, the catalytic efficiency of rhodium complexes depends not only on the structure of chiral P-donor ligand, but also on the character of other ligands bound to rhodium atom. Among the abovementioned rhodium catalysts of hydrogenation of α-ketoesters and α-ketolactones, the binuclear complexes with AMPP ligands **11b**, **14** and bridging perfluorocarboxylate groups, which show simultaneously high activity and enantioselectivity, seem preferable.

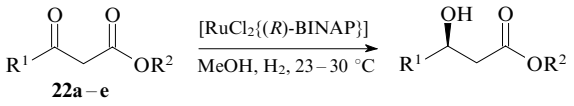
V. Asymmetric hydrogenation of β-ketoesters catalysed by ruthenium(II) complexes

In contrast to homogeneous asymmetric hydrogenation of α-ketoesters for which Rh^I complexes are the most effective catalysts (Section IV), these complexes are not used in the asymmetric hydrogenation of β-ketoesters. In the case of hydrogenation of β-ketoesters, the most important results related to the enantioselective hydrogenation of the C=O bond were obtained with the help of chiral complexes of Ru^{II}. These studies were started by Japanese scientists in the late 1980s–early 1990s.[8,11,16,21,46] The catalysis of asymmetric hydrogenation of β-ketoesters by metal complexes is undoubtedly more favourable than that by enzymes: during enzyme catalysis the concentration of initial substrate should be less than 1 g litre^{-1} (*i.e.* less than 0.1%), while in the case of Rh-catalysed hydrogenation it reaches 50% (*i.e.* 500 times higher).[11]

The complexes of Ru^{II} with atropisomeric biphosphines of BINAP type as well as their derivatives and analogues, including heterocyclic biphosphines, are among the most efficient and versatile catalysts.

1. Catalysis by neutral complexes, obtained *in situ* from ruthenium(II) dicarboxylates

The dicarboxylate complexes [Ru(O$_2$CR)$_2$(BINAP)] are effective catalysts of C=C bond hydrogenation,[42] while the attempts to apply these complexes as catalysts of the C=O bond hydrogenation failed. However, *in situ* replacement of carboxylate ligands by halide ones [reaction (1)] yielded effective catalysts of asymmetric hydrogenation of β-ketoesters.[11] Their composition corresponded to the empirical formula [RuX$_2$(BINAP)]$_n$ (X = Cl, Br, I; $n \geqslant 2$). It should be noted that in the presence of these catalysts enantioselectivity of hydrogenation of aliphatic β-ketoesters **22** [reaction (11), Table 1] is significantly higher than that for the same catalysts in the hydrogenation of aliphatic α-ketoesters [reaction (8), Table 1].



(11)

22a–e

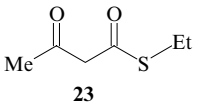
R^1 = Me: R^2 = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**);
R^1 = Ph, R^2 = Et (**e**).

Table 1. The results of catalytic hydrogenation of some β-ketoesters.

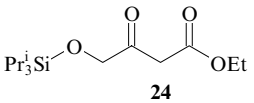
Substrate	Pressure H_2 /atm	S : C	Reaction time /h	Substrate conversion (%)	*ee* (%)[a]
22a	100	2000	36	99	>99 (*R*)
22b	103	1000	58	99	>99 (*R*)
22c (see[b])	73	1100	34	93	98 (*R*)
22d	70	1000	34	98	98 (*R*)
22e	91	760	106	>99	85 (*S*)

[a] The obtained enantiomer is shown in parentheses; [b] in this particular case [RuBr$_2$(BINAP)] was used as a catalyst.

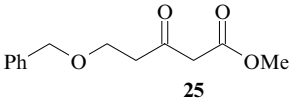
The presented data show that the bulk of ester fragment CO_2R^2 does not affect the rate and enantioselectivity of hydrogenation of aliphatic β-ketoesters (*ee* ⩾ 98%). The hydrogenation rate decreases when the methyl group (R^1) is replaced by a phenyl one; the optical yield also decreases to 85%. The substituted chiral β-hydroxyesters where obtained from β-ketothioester **23** and β-ketoesters **24**, **25** under similar conditions in 42%, 100%, 94% yields and with enantioselectivity of 93%, 95%, 99%, respectively.[21]



23

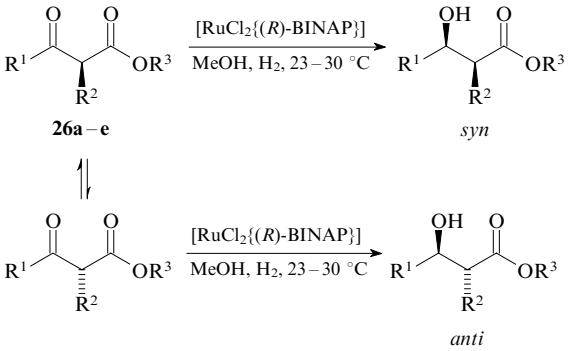


24



25

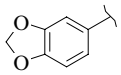
In the presence of Ru^{II}–BINAP catalyst obtained *in situ* according to the reaction (1) the dynamic kinetic resolution of racemic α-substituted β-ketoesters **26** by their asymmetric hydrogenation in CH_2Cl_2 was performed [47] (S : C = 230–270, 100 atm H_2, 5–50 °C, 50–120 h).



26a–e *syn* *anti*

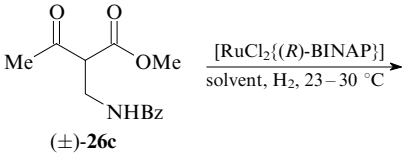
R^1 = Me: R^2 = Me, R^3 = Et (**a**); R^2 = NHAc, R^3 = Me (**b**);

R^2 = CH_2NHBz, R^3 = Me (**c**);

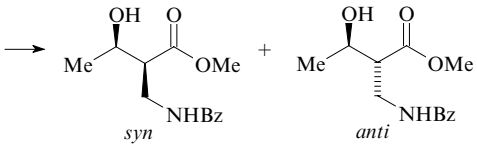
R^1 = , R^3 = Me: R^2 = NHAc (**d**), $NHCO_2Bn$ (**e**).

If the α-position of the starting β-ketoester is occupied by a normal alkyl substituent (ketoester **26a**), then the ratio of obtained *syn*- and *anti*-diasteromeres of β-hydroxyesters is almost equimolar and each isomer is formed with high enantioselectivity. However, in the case of amidoketoesters **26b–e** hydrogenation proceeds with high both diastereo- and enantioselectivity (the ratio *syn* : *anti* = 99 : 1 and *ee* 92%–98%).[47] The 100% conversion of the substrates into chiral β-hydroxyesters in high optical yields at both α- and β-carbon atoms is achieved because the enantiomers of starting racemic β-ketoester are in equilibrium due to easy enolisation.

The character of the solvent strongly affects stereochemistry of hydrogenation of α-substituted β-ketoesters. It may be demonstrated with the following reaction as an example [48] (only the structures of predominant *syn*- and *anti*-enantiomers are shown):



(±)-**26c** (12)

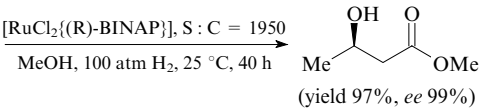


syn *anti*

Solvent	*syn* : *anti*	*ee*, %	
		syn	*anti*
MeOH	49 : 51	93	97
CH_2Cl_2	94 : 6	99	97

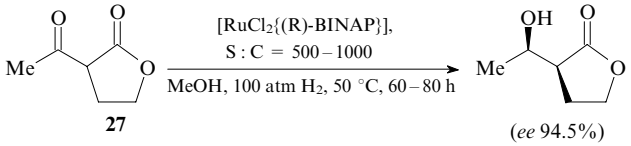
2. Catalysis by neutral complexes obtained *in situ* from ruthenium(II) halide arene complexes

This method of generation of catalysts [reaction (4)], which does not require application of chiral dicarboxylate precursor (see above), is based on the commercially available arene complex and because of that, it is widely used in catalytic asymmetric hydrogenation.[15,16,23–25,48–53] Thus the reaction of $[RuCl_2(C_6H_6)]_2$ with two equivalents of chiral biphosphine BINAP in DMF at 150 °C for 10 min followed by the removal of solvent in vacuum yields (according to the ^{31}P NMR data) a mixture of Ru^{II} complexes, probably $[RuCl_2(BINAP)(DMF)_2]$ and $[RuCl_2(BINAP)(DMF)_n]$. Low electrical condutivity of this mixture in CH_2Cl_2 (0.4 Ω cm^2 mol^{-1}) indicates its neutrality.[15,16] The obtained catalyst is directly used in hydrogenation reactions. The activity and the level of asymmetric induction of catalyst Ru^{II}–BINAP generated by described method in the model reaction (13) were comparable with the results of hydrogenation of the same substrate in the presence of catalytic system $[Ru(O_2CR)_2(BINAP)] + 2\,HCl$ [reaction (11)].



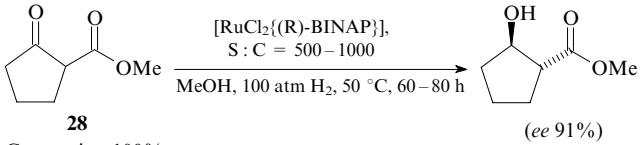
22a (yield 97%, *ee* 99%) (13)

Asymmetric hydrogenation of racemic β-ketoesters **27** and **28** in the presence of the same catalyst was studied.[53]



27 (*ee* 94.5%)

Conversion 100%.



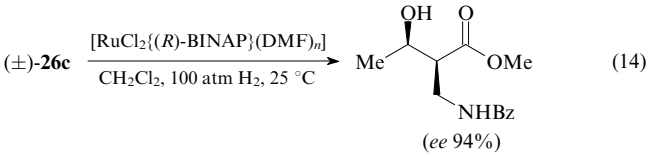
28 (*ee* 91%)

Conversion 100%.

In both cases hydrogenation shows high diastereo- and enantioselectivity: the hydrogenation of ketoester **27** results in the formation of diastereomeric hydroxyesters with the ratio *syn* : *anti* = 98 : 2, and in the case of ketoester **28** the ratio *anti* : *syn* = 80 : 20. For both reactions diastereoselectivity is higher in CH_2Cl_2, and the highest enantioselectivity of the predominant enantiomer formation was observed in MeOH.

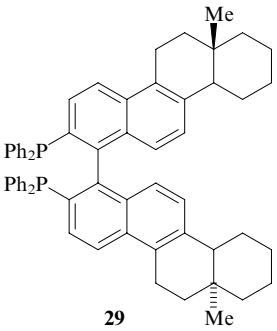
The catalyst obtained from $[RuCl_2(C_6H_6)]_2$ and BINAP turned out to be as selective in hydrogenation of β-ketoester **26c** (the diastereomer ratio *syn* : *anti* = 94 : 6) [13,48] as an analogous catalyst obtained form diacetate complex

[Ru(OAc)$_2$(BINAP)]; however, in the former case, enantioselectivity was slightly lower [*cf.* reactions (14) and (12)].

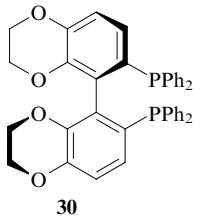


Series of catalysts containing atropoisomeric analogues of BINAP were synthesised *in situ* by reaction of [RuCl$_2$(C$_6$H$_6$)]$_2$ with chiral biphosphines in DMF [reaction (4)]. Among them is the Ru^{II} complex with steroid-like biphosphine **29**. This catalyst shows the same activity and stereodifferential ability as the ruthenium complex with BINAP. Hydrogenation of β-ketoester **22a** in the presence of [RuCl$_2${(*S*)-**29**}(DMF)$_2$] complex (100 atm H$_2$, 100 °C, 1 h) furnishes methyl (*S*)-3-hydroxybutanoate in 99% (*S*) optical yield and with full conversion of ketoester.[50]

The complex [RuCl$_2${(*R*)-**30**}(DMF)$_n$] containing heterocyclic chiral biphosphine **30** catalyses asymmetric hydrogenation of series of aliphatic β-ketoesters (3.5 atm H$_2$, 80–90 °C) with quantitative yield and enantioselectivity of 97%–99.5%.[49]



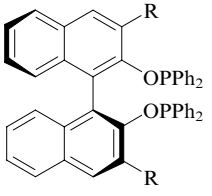
29



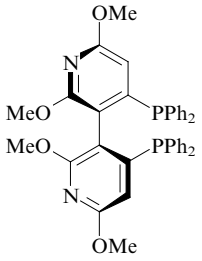
30
(*R*)-BisbenzodioxanPhos

Similarly to hydrogenation of α-ketoesters, good results in hydrogenation of β-ketoesters were obtained when neutral dichloride Ru^{II} complexes with chiral atropoisomeric ligands [thiophene (**8**) and benzothiophene (**7**) derivatives] were used as catalysts (up to *ee* 99% with 95% substrate conversion).[23–25]

A comparative study of the catalysts obtained *in situ* from [RuCl$_2$(*p*-Cym)]$_2$ (*p*-Cym is *p*-cymene) according to reaction (4) and various atropoisomeric ligands in the reaction of asymmetric hydrogenation of β-phenyl-β-ketoester **22e** was performed [S : C = 200, EtOH–CH$_2$Cl$_2$ (3 : 1), 5.4 atm H$_2$, 50 °C, 20 h]. According to the level of asymmmetric induction (*ee*, %), the ligands were arranged in the following order: **31a** (29), **31b** (29) < BINAP (80) < **9** (88) < **31c** (94) < **31d** (99).



31a–d
R = H (**a**), Me (**b**), Ph (**c**), 3,5-Me$_2$C$_6$H$_3$ (**d**).



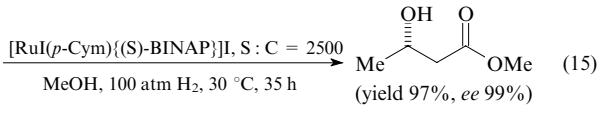
32
(*S*)-P-Phos

These data and the results of asymmetric hydrogenation of other β-aryl-β-ketoesters show that the Ru^{II} complex with bisphosphinite ligand **31d** provides the highest enantioselectivity of the reaction for this type of substrates and this may be explained by steric factors. In this process the Ru^{II} complex with methoxy-substituted bipyridylbiphosphine ligand **32** is just slightly inferior to the complex of Ru^{II} with ligand **31d**. Hydrogenation of β-ketoester **22e** catalysed by this complex proceeds with optical yield of 95.2% and full conversion of the substrate [S : C = 2400, MeOH–CH$_2$Cl$_2$ (1 : 1) or EtOH–CH$_2$Cl$_2$ (1 : 1), 90 °C, 12–36 h].[52]

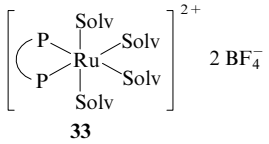
3. Catalysis by cationic complexes obtained from halide arene ruthenium(II) complexes

The binuclear arene complexes [RuX$_2$(C$_6$H$_6$)]$_2$ (X = Cl, Br) in which the metal atoms are linked by two bridging Ru–X···Ru bonds are precursors of not only neutral catalysts discussed in the previous Section but also of catalysts with an ionic structure. The reaction of [RuX$_2$Ar]$_2$ with biphosphines in the mixture EtOH–CH$_2$Cl$_2$ at 50 °C [reaction (5)] yields mononuclear cationic complexes **1**. Due to low stability of complexes [RuI(C$_6$H$_6$)(P*P)]I, more stable complexes [RuI(*p*-Cym)(P*P)I obtained from the precursor [RuI$_2$(*p*-Cym)]$_2$ are used as catalysts instead.[8,9,46]

The highest enantioselectivity (*ee* 99%) of the asymmetric hydrogenation of methyl 3-oxobutanoate (**22a**) was achieved when iodide complexes **1c** and **1f** were used as catalysts.[8,46]



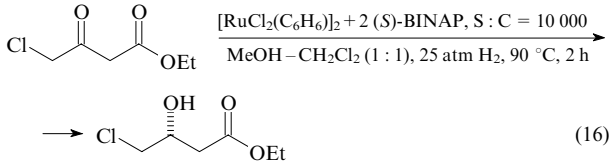
The same reaction catalysed by similar chloride cationic complex **1d** proceeds only by 0.4% in 22 h at 60 °C.[8] However later it was shown[19] that the same chloride complex with BINAP ligand is active in the reaction (15) at the S : C ratios of up to 70 000 under slightly different conditions than those used in paper.[8] Remarkably that the cationic complex **33**, containing in its inner coordination sphere only BINAP and acetonitrile molecules, is not catalytically active; only the complexes containing Ru–Hal bonds are catalytically active.[9]



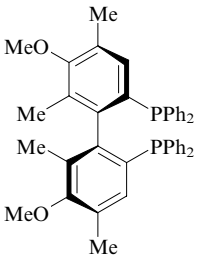
33

P⌒P = BINAP, Solv = MeCN.

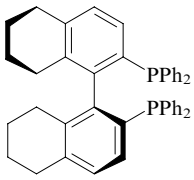
Good results in the catalytic hydrogenation of β-ketoesters were also achieved in the cases where the cationic arene complex was obtained *in situ*, *e.g.* in reaction (16).[19] Carrying out of this reaction in the ionic liquid (trifluoromethyl sulfonate or 1-butyl-3-methylimidazolium hexafluorophosphate) or in an alcohol solution of Bu$^n_4$NBr makes possible a multiple use of metal complex catalyst without deterioration of enantioselectivity of the process, which remained at the level of *ee* 95%–96% at least after three cycles.[54]



Hydrogenation of the model substrate **22a** in the presence of catalytic system $[RuI_2(p\text{-Cym})]_2 + 2[(R)\text{-}\mathbf{34}]$ [S : C = 2000, MeOH – CH_2Cl_2 (1 : 1), 10 atm H_2, 30 – 40 °C, 20 h] yields (*S*)-β-hydroxyester with 100% optical purity and complete conversion of the starting compound.[55]



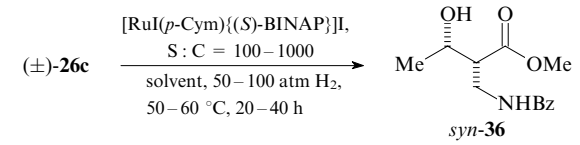
(*R*)-**34**
BIMOP



35
(*S*)-H_8-BINAP

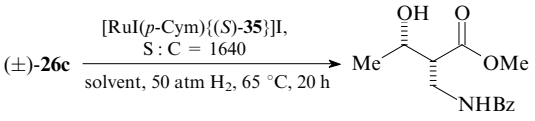
The rate of hydrogenation of β-ketoesters in alcohol solutions is usually higher than that in aprotic solvents. For example, the rate of hydrogenation of ketoester **22a** catalysed by cationic complex **6b** is several times higher in anhydrous MeOH than in CH_2Cl_2.[56] At the same time hydrogenation in aqueous MeOH results in decrease of the catalytic activity and the optical yield of the product in comparison with those for the reaction in anhydrous alcohol.[56 – 58]

As was mentioned above, the character of solvent considerably affects stereochemistry of the dynamic kinetic resolution of racemic β-ketoesters catalysed by neutral complexes of Ru^{II} with BINAP ligand [reactions (12), (14)]. The solvent effect is also significant in catalysis of hydrogenation of the same substrate by cationic complexes of Ru^{II} with BINAP[6] and H_8-BINAP (**35**).[59] In both cases the predominant product is *syn*-diastereomer of hydroxyamidoester **36**.



syn-**36**

Solvent	Substrate conversion (%)	*de* (%)	*ee* (%)
MeOH	100	51	97
CH_2Cl_2 – MeOH (7 : 1)	91	84	99

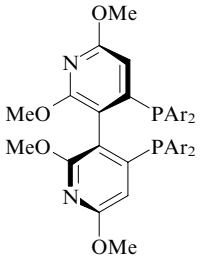


syn-**36**

Solvent	Substrate conversion (%)	*de* (%)	*ee* (%)
MeOH	53	71	93
CH_2Cl_2 – MeOH (7 : 1)	80	92	99

The highest rate as well as diastereo- and enantioselectivity in the same reaction of asymmetric hydrogenation of racemic substrate **26f** (R^1 = Me, R^2 = CH_2NHBz, R^3 = Et) was observed during the catalysis by cationic complex [RuI(*p*-Cym){(−)-**8**}]I in the presence of acidic co-catalyst (RSO_3H) (S : C = 200, CH_2Cl_2, 100 atm H_2, 50 °C, 20 min). Under these conditions the convesion of β-ketoester **26f** was 95% with the values of *de* 94% (*syn*) and *ee* 99% (2*R*,3*S*), respectively.[25]

As compared with the catalytic complex containing 3,3-bithienyl biphosphine **8**, which catalyses asymmetric hydrogenation of β-ketoesters at room temperature, the 3,3-bipyridinyl biphosphine ligand **37** is catalytically active under more drastic conditions (80 – 90 °C), providing 95% – 97% enantioselectivity of hydrogenation of a series of β-ketoesters.[60]

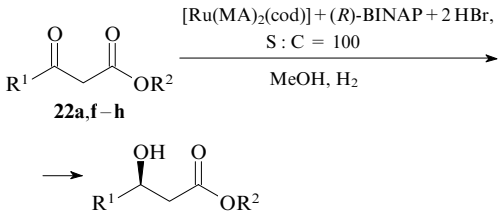


(*R*)-**37** (Xyl-P-Phos)

Ar = 3,5-$Me_2C_6H_3$.

4. Catalysis by neutral complexes obtained *in situ* from ruthenium(II) compounds with allyl ligands

The Ru^{II} compounds with allyl ligands, such as $[Ru(MA)_2(cod)]$ or $[RuCl(Cp)(PPh_3)_2]$, have some advantages in comparison with other precursors of chiral catalysts. In contrast to $RuCl_2$ and $RuBr_2$ derivatives, they are mononuclear complexes and therefore readily soluble in common solvents. Besides, during the synthesis of chiral catalysts from these compounds it is possible to substitute under mild conditions not only the π-bonded diene by chiral biphosphine but also the ligands MA or Cp by halide or carboxylate ligands; both substitution reactions can proceed simultaneously.[17, 18, 61 – 63] Thus the catalyst $[RuBr_2\{(R)\text{-BINAP}\}]$ in reaction (17) was obtained *in situ* in one step from $[Ru(MA)_2(cod)]$, (*R*)-BINAP and HBr. The reaction proceeds with high enantioselectivity and was performed under H_2 pressure of 10 – 70 atm and temperature of 40 – 80 °C.[18]

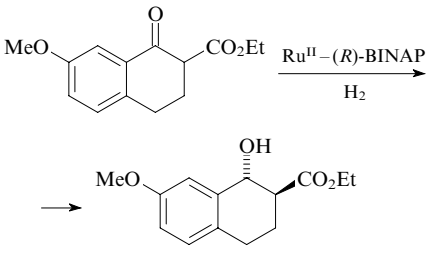


(17)

R^2 = Me: R^1 = Me (**a**), Et (**f**), n-$C_{15}H_{31}$ (**g**);
R^1 = $ClCH_2$, R^2 = Et (**h**).

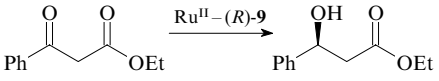
Substrate	S : C	Pressure H_2 /atm	*T* /°C	Reaction time /h	Yield (%)	*ee* (%)
22a	100	10	80	1	100	98
22f	1000	20	40	16	100	> 99
22g	100	50	50	48	100	96
22h	1700	70	93	1	100	89

The kinetic dynamic resolution of racemic β-ketoester, the derivative of tetraline, was performed in the presence of $[RuBr_2\{(R)\text{-BINAP}\}]$ catalyst, obtained *in situ* by the above-mentioned method (S : C = 30 – 100, CH_2Cl_2, 10 atm H_2, 80 °C, 48 h).[62]



[yield 95%,
de 97% (*trans*), *ee* 87%]

The catalyst [$RuBr_2$\{(*R*)-MeO-BIPHEP\}] synthesised *in situ* from [$Ru(MA)_2$(cod)], chiral biphosphine (*R*)-**9** and HBr shows high activity in the asymmetric hydrogenation of ketoester **22e**.

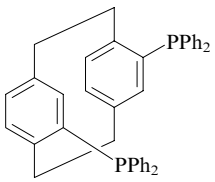


22e [yield 82%, *ee* 96%)

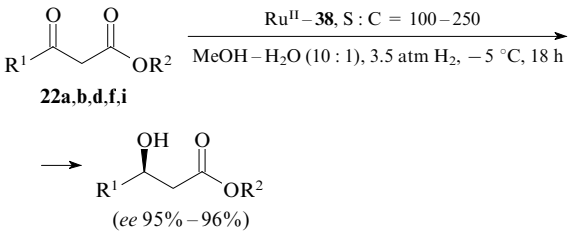
This reaction proceeds in MeOH or EtOH at a reasonably high rate and enantioselectivity even under the H_2 pressure of 1 atm.[17] It should be noted that in the presence of chiral catalysts obtained from [$Ru(MA)_2$(cod)] almost 100% enantioselectivity can be achieved using the chiral biphosphine ligands of optical purity 80%–90% if hydrogenation of β-ketoeters takes place under mild conditions (1 atm H_2, 20 °C).[63]

Hydrogenation of ketoester **22e** in the presence of a catalyst obtained *in situ* from [$Ru(MA)_2$(cod)] and heterocyclic biphosphine **8** (S : C = 1000, EtOH, 100 atm H_2, 70 °C, 1 h) proceeds with high enantioselectivity (*ee* 98% with 100% conversion).

The biphosphine ligand **38** with planar chirality was used in asymmetric Ru-catalysed hydrogenation of β-ketoesters.[64]



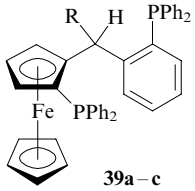
38
(*S*)-[2,2]PHANEPHOS



R^1 = Pr^i, R^2 = Et (**i**).
Conversion 100%.

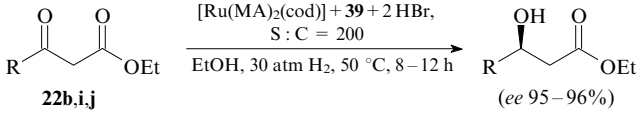
The hydrogenation was performed in aqueous MeOH in order to inhibit the side acetalisation of the keto group. The catalyst was obtained *in situ* in acetone from the precursor [$Ru(MA)_2$(cod)] using HBr or CF_3CO_2H as acidic components (in the latter case with the addition of Bu^n_4NI, which increases the catalyst activity). The [$RuBr_2$(**38**)] catalyst was inactive and did not provide reproducible results, while significantly more stable [$Ru(CF_3CO_2)_2$(**38**)] makes possible to perform enantioselective hydrogenation of ketoesters **22** even at –5 °C.

The *in situ* synthesised catalysts with chiral ligands **39a**–**c**, based on ferrocene, show good results in hydrogenation of β-ketoesters **22**.[65]



39a–**c**

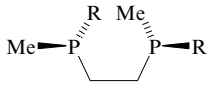
R = Me (**a**), Pr^i (**b**), NMe_2 (**c**).



22b,**i**,**j** (*ee* 95–96%)

R = Me (**b**), Pr^i (**i**), Pr^n (**j**).
Conversion 100%.

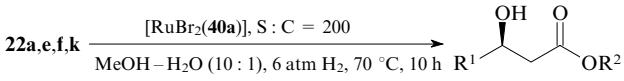
Similarly to hydrogenation in the presence of ruthenium catalyst with ligand **8**, the catalysts containing P-stereogenic biphosphines **40** are significantly more effective in reactions of β-ketoesters than in those of α-ketoesters (γ- and δ-ketoesters were not tested in the presence of these catalysts).[66]



40a,**b**

R = Bu^t (**a**), adamant-1-yl (**b**).

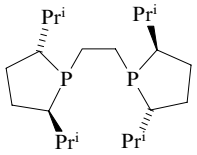
The precursor [$Ru(MA)_2$(cod)] was used for *in situ* synthesis of ruthenium catalysts containing P-stereogenic biphosphines. Of the two tested biphosphines **40a** and **40b**, the first one formed a considerably more efficient catalyst.



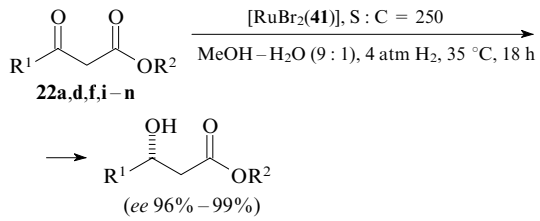
[yield 80%–96%,
ee 97%–98%]

R^1 = $MeOCH_2$, R^2 = Me (**k**).

Good results were obtained when the catalytic system formed from [$Ru(MA)_2$(cod)], chiral biphosphine **41** and HBr was used for hydrogenation of β-ketoesters.[67]



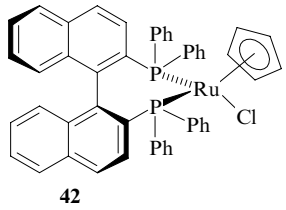
41
(*R*,*R*)-Pr^i-BPE



R^2 = Me: R^1 = $MeOCH_2$ (**k**), n-$C_{11}H_{23}$ (**l**), $ClCH_2$ (**m**), cyclo-C_6H_{11} (**n**). Conversion 100%.

It should be noted that the increase of H_2 pressure (up to 50 atm) results in the decrease of enantioselectivity to *ee* 78% (for ketoester **22a**).

The cyclopentadienyl complex **42**, which is stable in ambient conditions for several months, may be used as a catalyst of asymmetric hydrogenation of β-ketoesters. However its activity is low: there is an induction period (2 h) in the hydrogenation of ketoester **22** at 60 °C and H_2 pressure of 70 atm, and 90 h is required to complete the reaction.[68] In contrast to neutral complex **42**, the cationic complex $[Ru(Cp)(BINAP)]PF_6$ was catalytically inactive, which was explained by the absence of chloride ligand.

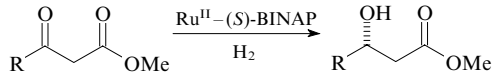


42

5. Catalysis by anionic biphosphine ruthenium(II) complexes

One of the first ruthenium complex catalysts effective in the reaction of asymmetric hydrogenation of C=O bond was initially described[69] as a neutral binuclear complex $[RuCl_2(BINAP)]_2 \cdot Et_3N$. This complex, obtained by heating of $[RuCl_2(cod)]_n$ with BINAP and Et_3N in boiling toluene followed by removal of solvent, is highly active and enantioselective in asymmetric hydrogenation of β-ketoesters.[10, 12, 70, 71] Later, it was found that under used conditions not neutral but anionic binuclear complex **2** is formed from $[RuCl_2(cod)]_n$. The structure of the complex was determined by X-ray crystallography (compound **2b**).[10, 70, 72]

A series of chiral β-hydroxyesters were synthesised by asymmetric hydrogenation of β-ketoesters (MeOH, 3 atm H_2, 80 °C, 6 h) using catalyst **2a** obtained *in situ* from $[RuCl_2(cod)]_n$, (*S*)-BINAP and Et_3N.[71]



R	Yield (%)	*ee* (%)
Pr^n	86	98
Bu^n	90	97
$MeCH{=}CHCH_2$	73	98
$Me_2C{=}CHCH_2$	96	98

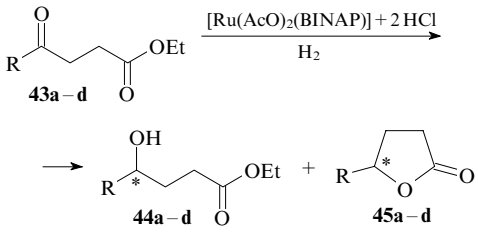
It was found[12] that the rate of hydrogenation of β-ketoesters in the presence of this catalyst increases drastically when a strong acid (HCl or H_2SO_4) is added.

VI. Asymmetric hydrogenation of γ-ketoesters catalysed by biphosphine ruthenium(II) complexes

Only highly enantioselective reactions of asymmetric hydrogenation of α- and β-ketoesters were discussed in the previous Sections. There are very few data on asymmetric hydrogenation of γ-ketoesters in literature, so in the present Section all available information is presented. In all cases the chiral ruthenium complexes were used as catalysts, there are no records in literature about homogenious catalysis of asymmetric hydrogenation of γ-ketoesters by complexes of other metals.

1. Catalysis by neutral ruthenium(II) complexes obtained *in situ*

The asymmetric hydrogenation of γ-ketoesters **43a – d** (S : C = 100, EtOH, 100 atm H_2, 30 °C) in the presence of catalytic system $[Ru(AcO)_2(BINAP)]$ and HCl results in the formation of γ-hydroxyesters **44a – d** and γ-lactones **45a – d**.[73]

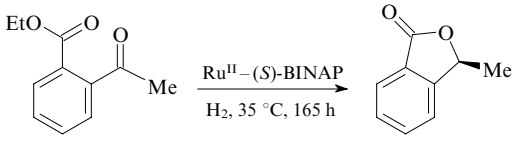


(18)

R = Me (**a**), Et (**b**), n-C_8H_{17} (**c**), Ph (**d**).

Substrate	BINAP configuration	Reaction time /h	Yield **44** + **45** (%)	*ee* (%)
43a	*S*	110	86	98
43b	*S*	110	90	97
43c	*S*	110	73	98
43d	*R*	258	30	97

The ketoester **43d** reacts with H_2 significantly slower than aliphatic ketoesters **43a – c**. At the same time the reactivity of ethyl 2-acetylbenzoate (**46**) under similar conditions of hydrogenation is higher than that of ketoester **43d**, probably due to the presence of electron-withdrawing group at the aromatic ring.[73]



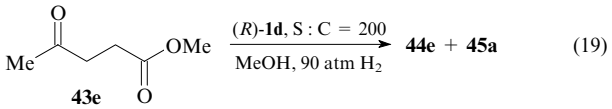
46 **47**

(yield 97%, *ee* 97%)

Hydrogenation of corresponding to ketoester **46** acid under similar conditions also yields the phthalide **47** but with lower enantioselectivity (*ee* 92%).[21]

2. Catalysis by cationic complex (*R*)-1d

The effect of temperature of asymmetric hydrogenation of γ-ketoester **43e** on the yield of hydrogenation products, their composition and optical yield was studied.[74]

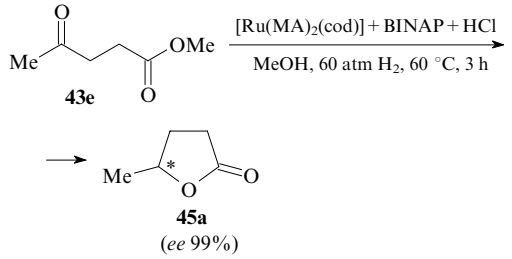


(19)

The highest yields of products (75%, the ratio **44e** : **45a** = 1 : 2) and enantioselectivity of hydrogenation [*ee* 98% (*R*)] were achieved at 65 °C and reaction time of 72 h.

3. Catalysis by anionic ruthenium(II) complexes

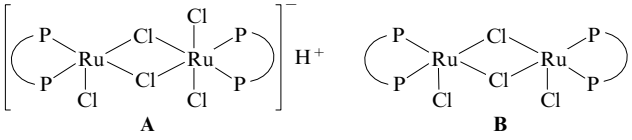
The effect of addition of HCl on the hydrogenation process was reported.[75] When the catalytic system $[Ru(MA)_2(cod)]$ + BINAP + HCl containing 2 equiv. of HCl relative to pre-catalyst {this amount of acid is necessary for the formation of complex $[RuCl_2(BINAP)]$ was used in the reaction (20), the conversion of methyl levulinate (**43e**) under chosen hydrogenation conditions was less than 5%, *i.e.* the formed *in situ* complex $[RuCl_2(BINAP)]$} shows low activity without excess of HCl. Further addition of HCl results in a sharp increase of hydrogenation rate and the formation of γ-hydroxyester, which undergoes ~95% cyclisation into chiral lactone **45a** under the reaction conditions. The character of solvent significantly affects the rate of methyl levulinate hydrogenation. The best results of hydrogenation were obtained in MeOH.[76]



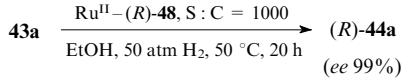
(20)

The catalytic systems based on other pre-catalysts, for example, $[RuCl_2(C_6H_6)]_2$ and $[RuCl_2(cod)]_n$, were less active in this reaction. Indeed, the replacement of $[Ru(MA)_2(cod)]$ by $[RuCl_2(cod)]_n$ caused the decrease of catalytic activity, represented by TOF value (TOF = $[\mathbf{45}]\cdot[Ru]^{-1}\ h^{-1}$), from 110 to 21, and in the presence of cationic complex **1d** the reaction rate decreased almost 30-fold.[75]

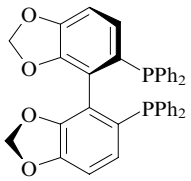
The study of mechanism of the reaction (20) by kinetic and isotopic methods and ^{31}P NMR spectroscopic analysis of ruthenium-containing intermediates indicate that binuclear anionic complex **A**, formed from binuclear neutral complex **B** in excess of HCl, is the catalytically active entity.[77]



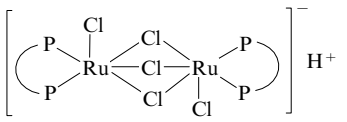
Other recently published data also confirm high catalytic activity of anionic binuclear ruthenium(II) complexes in asymmetric hydrogenation of γ-ketoesters.[78,79] Thus asymmetric hydrogenation of γ-ketoester **43a** catalysed by binuclear anionic Ru^{II} complex with ligand **48**, the structure of which is similar to that of complex **2a**, proceeds much faster than in the presence of catalytic system $Ru(AcO)_2$(BINAP) + 2 HCl [reaction (18)] or mononuclear cationic complex **1d** [reaction (19)] yielding γ-hydroxyester **44a** (predominant product).[78]



Conversion 100%.

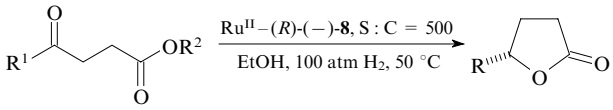


(*R*)-**48**
SEGPHOS



49
P*P = (*R*)-**8**

The anionic complex **49** was used as a catalyst of asymmetric hydrogenation of γ-ketoesters.[79] In the asymmetric hydrogenation this complex, the structure of which was determined by X-ray crystallography, was formed *in situ* by interaction between $[Ru(CF_3CO_2)_2\{(R)\text{-}(-)\text{-}\mathbf{8}\}]$ and excess of HCl.



43a,**f**,**g**,**h**,**i**

R^2 = Et, R^1 = Me (**a**); R^2 = Me: R^1 = Bu^n (**f**), n-C_8H_{17} (**g**), $Ph(CH_2)_2$ (**h**), $Ph(CH_2)_3$ (**i**).

Substrate	Reaction time /h	*ee* (%) (*R*)
43a	76	98
43f	168	97
43g	168	98
43h	168	98
43i	168	> 99.9

Thus, although γ-ketoesters are significantly less active under the conditions of asymmetric catalytic hydrogenation, highly effective ruthenium-containing catalytic systems were developed during the recent years, which make it possible to obtain chiral γ-hydroxyesters and γ-alkyl-substituted γ-lactones in preparative yield and high optical purity.

* * *

The data discussed in the present review show that up to date the most efficient catalysts of asymmetric hydrogenation are binuclear Rh(I) complexes with chiral AMPP-ligands and bridging perfluorocarboxylate groups. The chiral Ru(II) complexes significantly less effective in hydrogenation of α-ketoesters than rhodium catalysts. At the same time in catalytic asymmetric hydrogenation of β-ketoesters the ruthenium(II) complexes are used almost exclusively, the most effective in this process being the ruthenium complexes with chiral atropisomeric biphosphine ligands, such as BINAP and its analogues, including those containing heterocyclic fragments. It should be noted that the reaction proceeds much faster and with higher optical yield in alcohols (MeOH or EtOH) rather than in aprotic solvents. The best results in hydrogenation of γ-ketoesters, which are significantly less active than α- and β-ketoesters, were achieved when the catalytic systems consisting of ruthenium-containing precursor, atropisomeric biphosphine ligand and acidic promoter were applied.

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