Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 4, pp. 675-690, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $6.00+0.00

0957-4166(94)E0089-S

ENANTIOSELECTIVE HYDROGENATION REACTIONS WITH A FULL SET OF PREFORMED AND PREPARED *IN SITU* CHIRAL DIPHOSPHINE-RUTHENIUM (II) CATALYSTS.

J.P. Genêt*§, C. Pinel§,V. Ratovelomanana-Vidal§, S. Mallart§, X. Pfister§, L. Bischoff§, M.C. Caño De Andrade§, S. Darses§, C. Galopin§, J.A. Laffitte§§

§ Ecole Nationale Supérieure de Chimie de Paris, Laboratoire de Synthèse Organique, Associé au C.N.R.S., 11, rue Pierre et Marie Curie, 75231 Paris Cedex 05, France.

§ § Département Chimie Fine et Bioconversions, G.R.L. (Elf Aquitaine) 64170 Lacq, France.

Abstract: The new class of 2-methylallyl ruthenium chiral diphosphines **1** are efficient in asymmetric hydrogenation of α,β unsaturated acids and allylic alcohols.The related chiral halogen-containing ruthenium catalysts **2** are prepared from **1** or *in situ* from (COD)Ru(η^3-$(CH_2)_2CHCH_3)_2$ by ligand exchange with the chelating diphosphine followed by protonation (HX) in acetone. This procedure allows rapid screening of chiral phosphines, such as Diop, Chiraphos, Cbd, Bppm, Binap, β-glucophos, Biphemp, MeO-Biphep, Me-Duphos, in ruthenium mediated hydrogenations of prochiral substrates. A high efficiency is displayed by Ru-catalysts having atropisomeric ligands (e.e. up to 99%), and a C_2 symmetric bis(phospholane) has also emerged as a valuable ligand (Me-Duphos, e.e. up to 87% not optimized). Asymmetric hydrogenation of β-keto esters can be conducted under quite mild conditions (4 atm. of H_2, 50°C, e.e. up to 99%), β-keto esters having a disubstituted double bond are also hydrogenated chemoselectively to unsaturated chiral alcohols under controlled conditions with excellent optical purities.

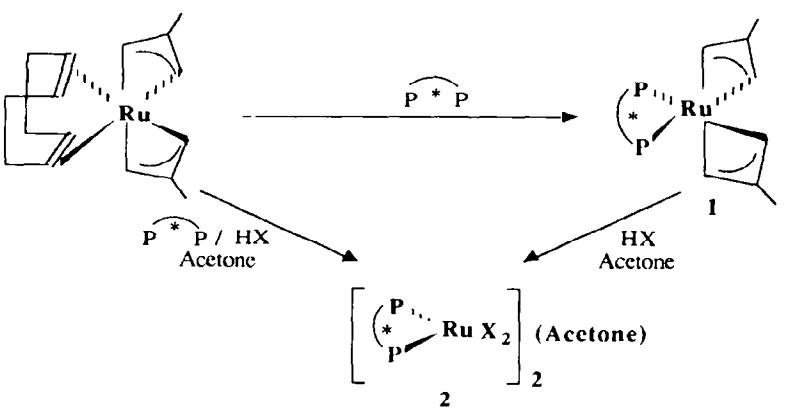
Introduction

Attempts to prepare optically active compounds by enantioselective hydrogenation with homogeneous catalysts emerged in the late 1960's and this methodology[1] has now become one of the most attractive synthetic approaches. Since the discovery of transition metals, a great number of chiral phosphines [2] has been prepared and used with transition metal catalysts. Such systems are of economic importance since a small amount of chiral material can transmit the chiral information to the substrate providing in theory a large amount of optically active product. Most of asymmetric hydrogenations have been accomplished using chiral rhodium complexes[3,4]. This method is used for commercial production of optically pure amino acids [5]. In contrast to those using rhodium catalytic hydrogenation, general methods using ruthenium complexes were limited. Noyori and Takaya[6-7] , Ikariya and Saburi [8] have initially shown that the Binap-ruthenium catalysts have remarkable chiral recognition ability. These catalysts are highly efficient for the asymmetric hydrogenation of various unsaturated substrates and the mechanism has been recently investigated [9].

We have demonstrated that a new class of chiral (P*P)$Ru^{II}(\eta^3$-$(CH_2)_2CHCH_3)_2$ [10] and related ruthenium (P*P) RuX_2 complexes served as catalyst for asymmetric hydrogenation [10b]. Our method allows screening of new chiral diphosphines having the phosphorus atom as stereogenic center such as Dipamp [11]. Thus, a significant advance in optically pure L and D threonine synthesis involves the powerful asymmetric dynamic hydrogenation of 2-acylamino 3-oxo butyrates, a reaction catalyzed by $BinapRuBr_2$ or $ChiraphosRuBr_2$ complexes [12]. The high efficiency of Ru-complexes having atropisomeric ligands such as Biphemp and MeO-Biphep has been shown by Heiser [13] and Cesarotti [14] in asymmetric hydrogenation of olefins and ketones. Other groups [15] using various Binap catalysts have also reported asymmetric hydrogenation with high levels of enantioselectivity . In the preceding paper, we described the synthesis of a large set of bidentate chiral complexes preformed and generated *in situ*. The ultimate interest in chiral diphosphine Ru^{II} chemistry is the development of catalysts for asymmetric reactions. We now wish to present their uses in asymmetric hydrogenation of a variety of prochiral substrates including alkenes and keto groups[16].

Results and discussion

The full set of preformed and isolated hexacoordinate mononuclear ruthenium complexes (P*P)Ru^{II}(2-methylallyl)$_2$ **1** were effective catalysts in hydrogenation reactions .The related halogen containing complexes of type (P*P)$Ru^{II}X_2$ **2** prepared by mixing in acetone the chiral (P*P)$Ru^{II}(\eta^3$-$(CH_2)_2CHCH_3)_2$ **1** and HBr in a 1 : 2 ratio also have good catalytic efficiency. These preformed catalysts of type **2** (scheme 1) are used without purification and have a particularly good activity. We also found that the hydrogenation reactions were possible with catalysts (P*P)RuX_2 easily prepared *in situ* under one pot conditions from (COD)$Ru(\eta^3$-$(CH_2)_2CHCH_3)_2$by adding at room temperature in acetone 1 to 1.3 equiv. of the appropriate chiral ligand in presence of HBr (2 equiv.) After 30 min. of stirring and removal of the solvent, the resulting complex was directly used in the asymmetric hydrogenation of alkenes and ketones.

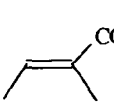
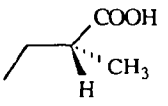
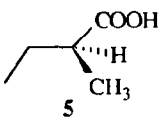


Scheme 1

The results listed in the following tables concerned the asymmetric hydrogenation of various chiral substrates including α, β unsaturated acids, α and β-keto esters. Reactions were generally carried out using different kinds of chiral catalysts, namely (P*P)$Ru(\eta^3$-$(CH_2)_2CHCH_3)_2$ **1** and $[P^*PRuX_2]_2$(acetone) **2** catalysts either preformed or prepared *in situ* . Results were not optimized for every substrate and phosphine.

Asymmetric hydrogenation of tiglic acid **3** chosen as standard substrate was firstly tested employing several chiral (P*P)$Ru^{II}(\eta^3\text{-}(CH_2)_2CHCH_3)_2$ **1** complexes as catalysts. The results obtained are listed in table 1. Under 3-4 atm. of hydrogen pressure at room temperature the hydrogenation proceeded smoothly to afford 2- methyl butyric acid **4** (R) or **5** (S) in quantitative yield. The enantiomeric excesses were in the range of 1 to 98%. The Bppm, Deguphos, Dimpc, Prophos, Bdpp, Chiraphos ligands and the phosphines having chirality at the phosphorus atom such as DipampSi, Dipamp gave poor results (1-25% e.e., entries 1, 2, 3 ,4, 10, 12, 5 and 11 respectively). The Diop ligand and the Cbd diphosphine gave encouraging asymmetric induction (51 and 70 % e.e. respectively, entries 6, 13).

Table 1 Asymmetric hydrogenation of tiglic acid

Entry	Substrate	Catalyst [a]	Product	Yield	e.e.[b]
1	 **3**	(S,S)-BppmRu(all)$_2$ [c]	 **4**	100	17
2		(-)-DeguphosRu(all)$_2$		100	20
3		(R,R)-DimpcRu(all)$_2$		100	19
4		(S)-ProphosRu(all)$_2$		100	17
5		(R,R)-DipampSiRu(all)$_2$		100	15
6		(R,R)-DiopRu(all)$_2$		100	51
7		(R,R)Me-DuphosRu(all)$_2$ [d]		100	80
8		(R)-BinapRu(all)$_2$		100	90
9		*in situ* (R)MeO-BiphepRuBr$_2$		100	92
10		(S,S)-BdppRu(all)$_2$	 **5**	100	1
11		(R,R)DipampRu(all)$_2$		100	25
12		(R,R)-ChiraphosRu(all)$_2$		100	30
13		(R,R)-CbdRu(all)$_2$		100	70
14		(S)-BiphempRu(all)$_2$		100	90
15		$[RuCl_2(S)Biphemp]_2,NEt_3$ [e]		100	98

(a) Reactions were carried out in 0.5-1 M solution of the substrate in MeOH under 4 atm of hydrogen at 20°C for 24h in the presence of 1 mol% of catalyst ; (b) Asymmetric inductions were determined after conversion to the corresponding amide with (R)-(+)-α-(1-Naphthyl)ethylamine) and HPLC analysis of the formed diastereoisomer (Zorbax column). (c) all = 2- methylallyl ; (d) This complex was prepared as developed in the preceding paper and used as crude material.(e)This Biphemp Ru complex was obtained by the same procedure described by Ikariya and Saburi for the related $[RuCl_2(S)Binap]_2NEt_3$[8a].

Finally, among the new chiral diphosphines Ru (2-methylallyl)$_2$ investigated, the Ru^{II} complexes possessing atropisomeric ligands (e.g. Binap and Biphemp) served as catalysts precursors for a highly selective hydrogenation giving enantioselectivity of up to 90 % e.e. (entries 8 and 14). Using C_2-symmetric bis (phospholanes) such as the (R,R)-Me-Duphos[17] $Ru(\eta^3\text{-}(CH_2)_2CHCH_3)_2$ complex led to **4** and the enantiomeric excess reached 80% (entry 7). Interestingly, the (R)-MeOBiphepRuBr$_2$ prepared *in situ* provided **4** with higher selectivity (92% e.e., entry 9).We also found that Ru_2Cl_4(S)-Biphemp$_2$,NEt_3 was an excellent catalyst with high chiral recognition giving up to 98% e.e (entry 15), it should be noted that this binuclear complex exhibited a slightly better selectivity than our mononuclear chiral Ru(allyl)$_2$ catalyst (compare entries 14 and 15).

This study was extended to various prochiral unsaturated substrates (table 2).

Table 2 Asymmetric hydrogenation of 2,2 disubstituted α,β unsaturated acids

Entry	Substrate	Catalyst	Conditions		Product	Yield	e.e
			Press. atm.	Temp. °C			
1		(S,S)-ChiraphosRu(all)$_2$	40	25[a]		84	18[b]
2		(S,S)-ChiraphosRuBr$_2$	20	25		80	33
3	MeCONH CO_2H	(S,S)-DiopRuBr$_2$	10	25	MeCONH CO_2H	89	36
4	**6**	(R)-ProphosRuBr$_2$	20	25	**7**	65	23
5		(S)-BinapRuBr$_2$	20	25		70	75
6		(S)-BiphempRuBr$_2$	20	25		80	77
7		(R,R)-DiopRuBr$_2$	60	25		92	49
8		(R,R)-DipampRu(all)$_2$	40	25	MeCONH CO_2H	75	25
9		(R,R)-DipampRuBr$_2$	10	25	**8**	75	38
10		(R,R)-ChdRuBr$_2$	4	35[c]		99	57[d]
11		(S)-BinapRu(all)$_2$	4	35		100	69
12	HO_2C CO_2H	(S)-BiphempRu(all)$_2$	4	35	HO_2C CO_2H	100	50
13	**9**	(S)-BinapRuBr$_2$	4	35	**10**	100	93
14		*in situ* (R)-BinapRuBr$_2$	3	50		100	98
15		*in situ* (R)-BinapRuBr$_2$/Et$_3$N	3	50		100	63
16		*in situ* (R)MeO-BiphepRuBr$_2$	3	50	HO_2C CO_2H **11**	100	93
17	MeO CO_2H	(R,R)-DipampRu(all)$_2$	30	25[e]	MeO CO_2H	100	49
18	**12**	(R,R)-DipampRuBr$_2$	30	25	**13**	100	55
19		(R,R)-DiopRu(all)$_2$	70	25[f]		100	18[g]
20		(S)-BinapRu(all)$_2$	70	25	MeO CO_2H **14**	100	85

(a) Hydrogenations were conducted in a mixture of THF/Ethanol (1/1) at room temperature for 48-72h in the presence of 1mol% of catalyst; (b) Asymmetric inductions were based on the rotation value of N-Acetyl-(R)-alanine $[\alpha]_D^{26}$ +66 (c 2, H_2O) ; (c) Reductions were performed at 3-4 atm for 24 h in THF in the presence of 1mol% of catalys; (d) Asymmetric inductions were based on the rotation value of (R)-methyl-succinic acid : $[\alpha]_D^{20}$+16.88 (c 2.2, EtOH); (e) Reactions were carried out in THF for 64h in the presence of 1mol% of catalyst ; (f) Toluene was used as solvent and he reaction time was 24h ; (g) Enantiomeric excesses were determined by H. P.L.C. analysis (chiral AGP column, 10 x 4.0 mm).

Several prochiral 2,2-disubstituted α,β unsaturated acids (e.g.N-acetyl-dehydroalanine, itaconic acid and naproxen precursor) were reduced with complexes **1** and **2** (table 2) in order to compare the effectiveness of our different catalysts. Hydrogenation was investigated with N-acetyl-dehydroalanine (table 2).

The reaction was first carried out with chiral (P*P)Ru(η^3-$(CH_2)_2CHCH_3)_2$ complexes **1** and preformed (P*P)$RuBr_2$ complexes **2** .Thus, (S,S)-ChiraphosRu(η^3-$(CH_2)_2CHCH_3)_2$ is less efficient than the corresponding dibromo analog (18% and 33% e.e. respectively at 40 atm and 20 atm, entries 1 and 2). This result was also confirmed using DipampRu(2-methylallyl)$_2$ and Dipamp$RuBr_2$ (25% and 38% e.e. respectively at 40 and 10 atm of hydrogen, entries 8 and 9). In the case of Diop$RuBr_2$, an increase of pressure resulted in better enantioselectivity (36% and 49% ee respectively at 10 to 60 atm., entries 3 and 7). Prophos is less efficient than Diop even at higher pressure : enantioselectivity and yield were lower (e.e. 23%, yield 65%, compare entries 3 and 4). Again as we have previously found in the case of tiglic acid, the atropisomeric ligands such as Binap and Biphemp gave the best enantioselectivities (up to 77% e.e.) with acceptable chemical yields (75 and 77%, entries 5 and 6).

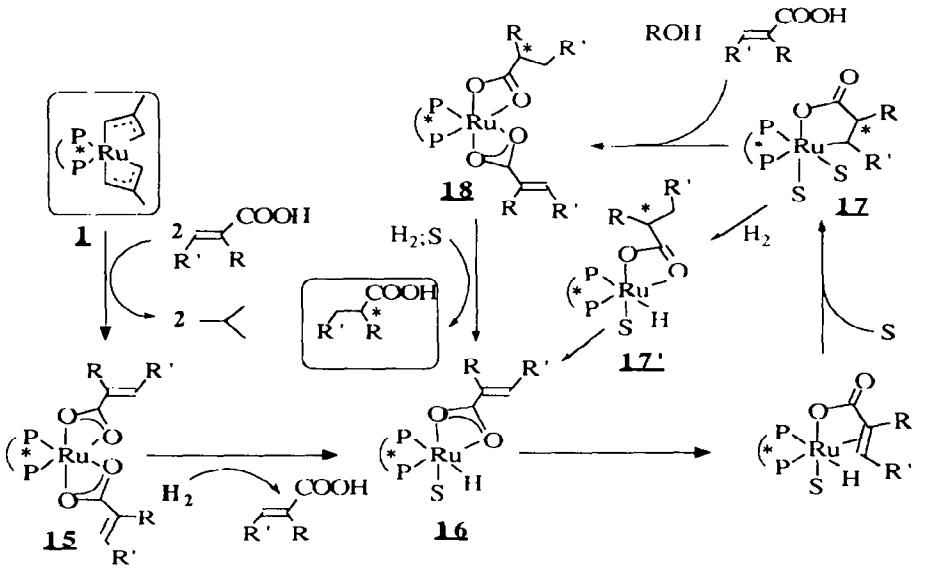
Similarly, hydrogenation of itaconic acid (table 2), confirmed the activity of our preformed or prepared *in situ* chiral (P*P)$RuBr_2$ **2**. As previously pointed out, complexes **1** (P*P)Ru(η^3-$(CH_2)_2CHCH_3)_2$ were less efficient than their corresponding dibromo analogs (P*P)$RuBr_2$ **2** for Binap and Biphemp ligands (93% and 69% e.e. entries 11 and 14). Once again, Binap gave the best e.e. with the dibromo catalysts **2** either preformed or prepared *in situ* (93% and 98% e.e. entries 13 and 14). Surprisingly, the addition of triethylamine to Binap$RuBr_2$ prepared *in situ* resulted in a non negligible decrease of the enantiomeric excess (compare entries 14 and 15). Under the same conditions with (R)-MeO-Biphep$RuBr_2$, itaconic acid **9** was reduced to **10** in 93 % e.e. (entry 16).

Finally, this study was extended to a precursor of naproxen **12** (table 2). As expected and according to the above mentioned results, chiral catalysts **2** were more effective than complexes **1** under the same reaction conditions with Dipamp ligand (49% and 55% e.e. entries 17 and 18). Binap Ru(η^3-$(CH_2)_2CHCH_3)_2$ complex exhibited relatively good enantiomeric excess (e.e. 85%, entry 20) in comparison with the very low selectivity obtained with Diop (e.e. 18 %, entry 19).

The mechanism of catalysis of the asymmetric hydrogenation of α,β-unsaturated carboxylic acids has been investigated by Halpern[9a,b] and Noyori-Takaya[9c] with [Binap$Ru^{II}(O_2CR)_2$]. A plausible mechanism of reduction of α,β-unsaturated carboxylic acids with our (P*P)Ru(η^3-$(CH_2)_2CHCH_3)_2$ catalyst is shown in scheme 2.

The bis(2-methylallyl)Ru^{II} diphosphine complexes **1** are acting as catalyst precursors. The rapid exchange between the allyl ligands and the α,β unsaturated acid substrate leads to the dicarboxylate complex **15** and eliminates 2-methylpropane. Afterwards, the course of the asymmetric hydrogenation is essentially the same described by Noyori and Takaya. The reaction at low pressure (4atm.) of hydrogen generates a monohydride ruthenium species **16**. After ligand exchange and insertion of the double bond into the Ru-H bond, a five-membered chelated complex **17** is formed. The ruthenium-carbon bond is cleaved by either the solvent (ROH) or acid, subsequent ligand exchange with the α,β unsaturated acid leading to **18**. Reaction of **18** and hydrogen affords the hydrogenated product and **16**, completing the catalytic cycle. Alternatively, under higher pressure of hydrogen, intermediate **17** may suffer hydrogenolysis to give **17'** which reacts with the starting α,β-unsaturated acid to give **16** [9c].

Plausible scheme for the asymmetric hydrogenation with (P*P)Ru(η^3-$(CH_2)_2CHCH_3)_2$

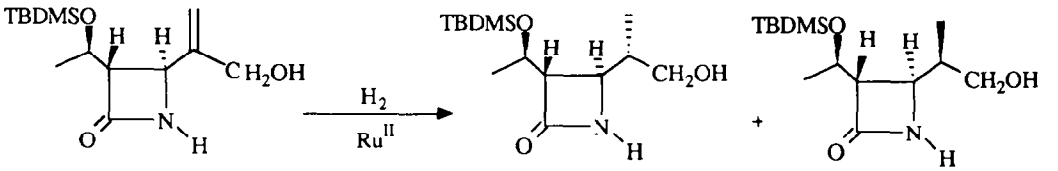


Scheme 2

Next, we envisaged the asymmetric hydrogenation of the allylic alcohol **19**, an interesting solution to the preparation of 1β-methylcarbapenem (table 3). The hydrogenation reaction was performed in methanol containing 1% of ruthenium catalysts. In the presence of (S)-BiphempRu(η^3-$(CH_2)_2CHCH_3)_2$ the allylic alcohol containing chiral azetidinone moiety was hydrogenated under 15 atm of hydrogen pressure to give **20** and **21** in a 78:22 ratio (entry 1).

The related (S)-BiphempRuBr_2 provided lower diasteroselectivity (entry 2). The (P*P)Ru(η^3-$(CH_2)_2CHCH_3)_2$ bearing (R)-Binap produced a high diastereoselectivity **21/20** = 96.5:3.5. Such high diastereoselectivity [18] is the result of two factors as pointed out by Noyori : chiral Ru^{II} catalysts first transfer the chirality to the olefinic face of **19** and environment of the chiral azetidinone backbone favors the formation of compound **21** having the 1β-methyl substituent.

Table 3 Asymmetric hydrogenation of a methyl carbapenem intermediate



19 [c] **20** **21**

Entry	Catalyst	Conditions [a]			Yield	d.e [b]	product
		Press. atm	Temp. °C	Time h			
1	(S)-BiphempRu(all)$_2$	15	25	48	80	56	**20**
2	(S)-BiphempRuBr$_2$	15	25	48	100	36	**20**
3	(S)-BiphempRuBr$_2$	15	30	48	100	38	**20**
4	(R)-BinapRu(all)$_2$	15	25	48	100	93	**21**

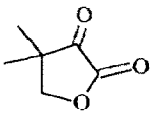
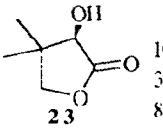
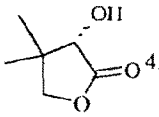
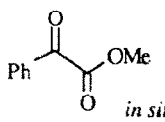
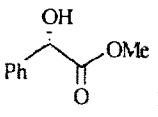
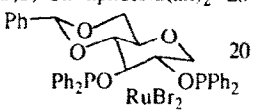
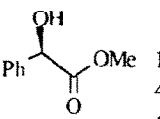
(a) Hydrogenations were carried out in methanol under 15 atm. of hydrogen at 25-30°C for 48h.in the presence of 1mol% of catalyst ; (b) The diastereoisomeric excesses were determined by GC analysis (column DB 1701) ; (c) The unsaturated allylic alcohol was prepared from acetoxy azetidinone (3 S, 4R-3-[(R)-1-[t-butyldimethylsilyl) oxy] ethyl-4--acetoxy-2-azetidinone[19] ; e) all=2 methylallyl.

Another important part of our study was the asymmetric hydrogenation of carbonyl groups of α and β -keto esters, affording the α and β -hydroxyesters. We first attempted the reduction of cyclic and acyclic α-keto esters (table 4). We were pleased to observe that our chiral catalysts (P*P)Ru(η^3-$(CH_2)_2CHCH_3)_2$ **1** and (P*P)RuBr$_2$ **2** preformed or prepared *in situ* were active for the reduction of keto groups.

In the case of α-keto esters, the precursor of the pantolactone (table 4), dihydro-4,4-dimethyl-2,3-furandione **22**, required severe reaction conditions (pressure and temperature) to achieve the reductions, the chemical yields were in the range 33-100% (entries 1-4). In all cases, a pressure of 100 atm of hydrogen and 50°C were necessary to perform the reactions into **23** and **24**. Enantiomeric excesses were moderate (14-35% e.e., entries 1, 3 and 4). Surprisingly and in contrast with previous results concerning hydrogenation of α,β-unsaturated acids, Binap gave a lower enantioselectivity than Dipamp (compare entries 2 and 3, respectively 78 and 35% e.e.) [20].

We next sought to evaluate the effectiveness of the Ru-catalysts **1** and **2** in the asymmetric hydrogenation of an acyclic α-ketoester (table 4, e.g. phenylglyoxylic methyl ester **25**). The reaction conditions were not so drastic as those previously described (5 to 20 atm of hydrogen were required to carry out the reduction in almost quantitative yields 95-100%, entries 5 to 11) and enantioselectivities ranged from 27 to 86% e.e. Relatively moderate enantioselectivities were observed in the reduction of **25** to **26** or **27** (table 4) with catalysts derived from Chiraphos and β-glucophos (27 and 30% enantiomeric excesses, entries 5 and 6). However, high chiral recognition was found using *in situ* prepared dibromide Ru complexes bearing (R,R)-McDuphos, (S)-Binap and (S)-MeO-Biphep (80, 82, 86% enantiomeric excesses, respectively entries 11, 7, 8).

Table 4 Asymmetric hydrogenation of pantolactone and phenylpyruvate

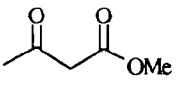
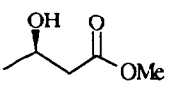
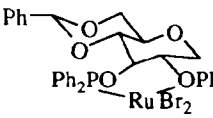
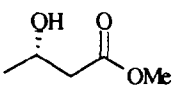
Entry	Substrate	Catalyst	Conditions			Product	Yield	e.e.
			Press. atm.	Temp. °C	Time h			
1	 **22**	(R,R)-DipampRu(all)$_2$	100	50	64 (a)	 **23**	100	14 (b)
2		(R,R)-DipampRuBr$_2$	100	50	64		33	78
3		(R)-BinapRuBr$_2$	100	50	64		85	35
4		(R,R)-DiopRuBr$_2$	100	50	64	 **24**	43	30
5	 **25**	(S,S)-ChiraphosRu(all)$_2$	20	50	70 (c)	 **26**	100	27 (d)
6	*in situ*		20	50	48		100	30
7	*in situ*	(S)-BinapRuBr$_2$	20	50	48		98	82
8	*in situ*	(S)-MeO-BiphepRuBr$_2$	20	50	48		100	86
9	*in situ*	(R,R)-DiopRuBr$_2$	5	50	65	 **27**	100	30
10		(R,R)-DiopRuBr$_2$	10	80	1		40	50
11	*in situ*	(R,R)-Me-DuphosRuBr$_2$	20	50	48		100	80

(a) Reactions were carried out in toluene with 1% mol of catalyst ; (b) Enantiomeric excesses were determined by HPLC (Chiracel O. A. column) ; (c) Hydrogenations were conducted in MeOH with 1% mol of catalyst ; (d) Enantiomeric excesses, determined by G.C. (chiral Lipodex A column). (R)-methyl mandelate $[\alpha]_D^{20}$-144 (c=1; MeOH).

In view of the excellent ability of our (P*P)Ru(η^3-$(CH_2)_2CHCH_3)_2$ **1** or (P*P)RuBr$_2$ **2** complexes to catalyze asymmetric hydrogenation and with the aim of exploring a wider range of such complexes, we screened catalysts having new chiral phosphines for the hydrogenation of methylacetoacetate **28**, methyl-3 oxopentanoate **31** and methyl 3-oxooctadecanoate **34**. The results obtained are listed in table 5-1 and 5-2.

The BinapRu(2-methylallyl)$_2$ catalyst was not efficient at all for the hydrogenation of such carbonyl groups even at 100 atm. of hydrogen (entry 1). However, under more drastic conditions (100 atm of H_2, 50°C, 48 h., table 5-2) with CBDRu(η^3-$(CH_2)_2CHCH_3)_2$ complex, we observed high conversions of **34** to **35** (10% e.e., entry 21) with a poor enantioselectivity. All other reductions were then performed with chiral (P*P)RuBr$_2$ **2** preformed or prepared *in situ*. Under 5 to 20 atm. hydrogen at 50 to 80°C, the hydrogenation proceeded smoothly to give 3- hydroxybutyrate **29** (R) or **30** (S) in 80-100% yield (table 5-1).

Table 5-1 Asymmetric hydrogenation of β-keto esters.

Entry	Substrate	Catalyst	Conditions			Product	Yield	e.e
			Press. atm.	Temp. ℃	Time h			
1	 **28**	(R)-BinapRu(all)$_2$	100	25	48[a]	 **29**	0	
2		(R,R)-DiopRuBr$_2$	10	80	1		99	5[b]
3		(S,S)-Cbd RuBr$_2$	10	80	1		98	14
4		(R)-ProphosRuBr$_2$	10	80	1		80	56
5		(R)-BinapRuBr$_2$	10	80	1		100	98
6		[RuCl$_2$(R)-Binap]$_2$NEt$_3$	20	50	48		100	96
7		*in situ* (R,R)-Me-DuphosRuBr$_2$	20	50	48		86	87
8		*in situ* (R)-MeO-BiphepRuBr$_2$	20	50	48		100	>99
9			5	50	20	 **30**	100	21
10		(R,R)-BdppRuBr$_2$	20	80	1		100	22
11		(S,S)-ChiraphosRuBr$_2$	5	50	24		100	60
12		*in situ* (S,S)-ChiraphosRuBr$_2$	20	50	48		100	66
13		(S)-BiphempRuBr$_2$	10	80	1		100	>99
14		(S)-BiphempRuBr$_2$	5	50	60		100	>99
15		(S)-BinapRuBr$_2$	20	40	12		100	>99
16		*in situ* (S)-BinapRuBr$_2$	20	50	48		100	>99

(a) Reactions were carried out in MeOH in presence of 1 mol% of catalyst except entry 14 (0.5 mol% of catalyst) ; (b) The asymmetric inductions were determined by GC analysis (Lipodex A column).

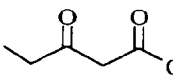
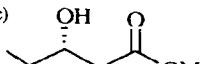
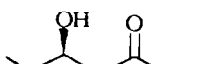
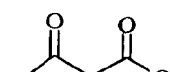
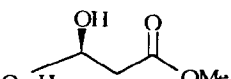
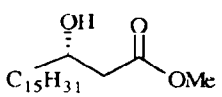
The enantiomeric excesses were in the range of 5 to 99%. The Diop, Cbd, Bdpp gave poor results (5-22% e.e., entries 2, 3 and 10). Under the same conditions a better selectivity was observed with Prophos (56% e.e., entry 4). We compare the efficiency of our chiral ruthenium dibromide (P*P)RuBr2 preformed and prepared *in situ* having (-)-chiraphos as chelating phosphine for the homogeneous hydrogenation of methylacetoacetate **28**. The preformed chiraphosRuBr2 afforded methyl (S)-3-hydroxybutyrate **30** in quantitative yield and moderate excess (5atm , 50°C, 60% e.e., entry 11). Similar results were obtained using the same catalyst prepared *in situ* (20atm, 50°C, 66% e.e., entry 12). We were pleased to find that it was possible to effect ketone reduction with our catalysts 2 prepared *in situ* at a relatively low pressure : the dibromo Ru^{II} complex containing the glucose phosphinite ligand produced at 5atm. of hydrogen pressure the β-hydroxyester **30** from **28** in quantitative yield but with a poor enantioselectivity (21% e.e., entry 9).

Using this *in situ* preparation of complexes **2**, we also were gratified to find that the crude dibromo ruthenium complex bearing C_2 symmetric bis(phospholane) (R,R)-Me-Duphos as chelating phosphine afforded the conversion of **28** to **29** in 86% yield and high enantioselectivity (up to 87% e.e.) under 20atm of hydrogen at 50°C for 48h (entry 7). The dibromide Ru^{II} complexes either preformed or prepared *in situ* containing atropisomeric ligands (e.g. Biphemp, MeO-Biphep, Binap) gave very high level of enantioselectivity (up to 99%) for the reduction of β-ketoesters (entries 8, 13, 14 , 15 and 16). The reduction were generally conducted

at 20atm. of hydrogen pressure, 40-50°C in 16 to 60h reaction time. However, it was possible to effect ketone reduction under lower pressure without a decrease of enantioselectivity. For example, (S)-BiphempRuBr$_2$ (0.5%) complex was an excellent chiral catalyst affording at 5 atm. hydrogen pressure (50°C, 60h) a quantitative yield of (S)-3-hydroxybutyrate **30** (99% e.e., entry 14).

Similarly, hydrogenation of **31** to **32** or **33** (table 5-2) under the same conditions using Br$_2$RuBinap or Biphemp preformed or prepared *in situ* as catalysts proceeded with extremely high enantioselectivity (up to 99%) and quantitative chemical yields (entries 17, 18, 19, 20). Again, the β-ketoester **34** (table 5-2) having a long alkyl chain was reduced quantitatively to **35** or **36** with in *situ* or preformed Biphemp and BinapRuBr$_2$ complexes (50 atm, 30-50°C, entries 22, 23 and 24) in 48h reaction time and with high enantioselectivity (up to 96% e.e.).

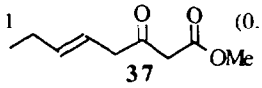
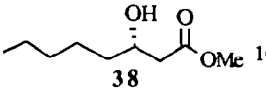
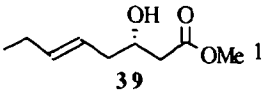
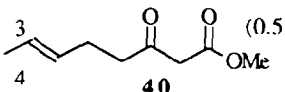
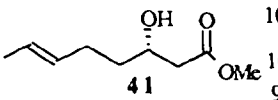
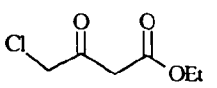
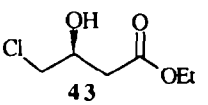
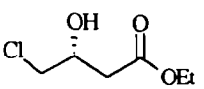
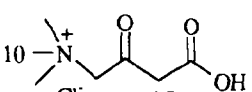
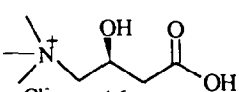
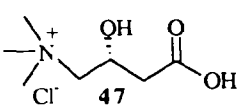
Table 5-2

Entry	Substrate	Catalyst	Conditions			Product	Yield	e.e
			Press. atm.	Temp. °C	Time h			
17	 **31**	(S) BiphempRuBr$_2$	20	40	65[c]	 **32**	100	>99
18		*in situ* (S)-BinapRuBr$_2$	20	40	16		100	>99
19		(R)-BinapRuBr$_2$	20	40	65	 **33**	100	>99
20		*in situ* (R)-BinapRuBr$_2$	20	40	16		100	>99
21	 **34**	(R,R)-CbdRu(all)$_2$	100	50	48[d]	 **35**	100	10[c]
22		(R)-BinapRuBr$_2$	50	50	48		100	94
23		*in situ* (R)-BinapRuBr$_2$	50	50	48		100	96
24		*in situ* (S)-BiphempRuBr$_2$	50	30	48	 **36**	100	95
25		*in situ* (S)-BiphempRuBr$_2$	15	30	48		19	94

(c) Hydrogenations in presence of 0.1%mol of catalyts ; (d) All the reactions were conducted in methylene chloride with 1% mol of catalyst ; (e) The enantiomeric excesses were determined by GC analysis of (S)-(O-acetyl)lactyl esters (column, DB 1701).

The enantioselective hydrogenation can be extended to olefin, halogen and ammonium salt-containing β-ketoesters. The results are shown in table 6. The alkene-containing β-ketoester **37** under 20atm of hydrogen pressure , 40°C in 65h reaction time was reduced to the fully saturated compound **38** in quantitative yield and with complete enantioselectivity (99%, entry 1). However, we were pleased to find that using our Biphemp or BinapRuBr$_2$ complexes (0.2 to 0.5%) either preformed or prepared *in situ*, the disubstituted alkene-containing β-ketoester can be reduced chemoselectively under controlled conditions.

Table 6 Asymmetric hydrogenation of functionalized β–keto esters:

Entry	Substrate	Catalyst	Conditions			Product	Yield	e.e
			Press. atm.	Temp. °C	Time h			
1	 **37**	(0.3%) (S)-BiphempRuBr$_2$	20	40	65 [a]	 **38**	100	99 [b]
2		(0.3%) (S)-BiphempRuBr$_2$ [d]	6	80	0.5 [c]	 **39**	100	99
3	 **40**	(0.5%) (S)-BiphempRuBr$_2$	6	80	0.5	 **41**	100 [e]	99
4			6	80	5 min		100 [f]	99
5		*in situ* (0.2%) (S)-BinapRuBr$_2$	4	80	0.25		95 [g]	99
6	 **42**	(S,S)-Chiraphos Ru(all)$_2$	100	80	1	 **43**	80	2 [h]
7		(S)-BinapRu(all)$_2$	100	80	75	 **44**	95	90
8		(0.06%) (S)-BiphempRuBr$_2$	70	93	1		100	81
9		*in situ* (0.06%) (S)-BinapRuBr$_2$	70	93	1		100	89
10	 **45**	[RuCl$_2$(R)-Binap]$_2$NEt$_3$	100	25	68	 **46**	75	96 [i]
11		(S)-BiphempRuBr$_2$	100	25	72	 **47**	90	80

(a) All reactions were carried out in methanol or ethanol, depending on the ester group ; (b) The enantiomeric excesses were determined by ^{1}H NMR in the presence of (+)-Eu(tfc)$_3$; (c) After 50 min. reaction time under these conditions, 10 % of fully hydrogenated product is observed ; (d) With 0.5 % of catalyst at 80°C within 15 min., the ß-hydroxyester was optically pure with 100 % yield.; (e) 20 % of the saturated ß-hydroxyester was observed ; (f) Under these conditions only traces (4 %) of the saturated ß-hydroxyester are seen ; (g) less than 5 % of saturated ß-hydroxyester ; (h) The asymmetric inductions were determined by GC analysis (Lipodex A column) ; (i) The enantiomeric excesses were respectively based on the optical rotation values of carnitine $[\alpha]_D^{26}$ -23.7 (c 1, H_2O).

The keto group was more rapidly reduced than the olefin moiety (entry 2). Thus, the ester **37** was cleanly reduced to **38** without olefin hydrogenation using 0.3% of (S)-BiphempRuBr$_2$ under 6 atm of hydrogen pressure (80°C, 30 min) in quantitative yield and 99% enantioselectivity (entry 2).

Using this approach, we also accomplished the clean conversion of **40** to **41**[21] : in the presence of 0.5% of (S)-BiphempRuBr$_2$ under 6 atm of hydrogen pressure at 80°C for 30 min, **40** was reduced to **41** (entry 3) with high enantioselectivity and with substantial concomitant formation (20%) of fully saturated ester (entry 3). Interestingly, under the same conditions and a very short reaction time (5 min), the desired alkene-containing β-

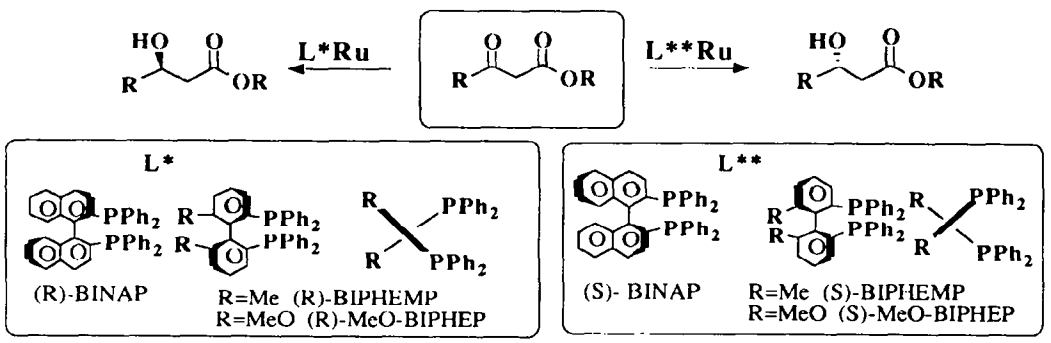
hydroxy ester **41** was obtained in quantitative yield with traces of unsaturated ester (entry 4). Using lower amounts of catalyst (0.2% of (S)-BinapRuBr$_2$) prepared *in situ* at 4 atm of hydrogen pressure, 80°C, **40** was reduced cleanly to **41** with a high reaction rate (15 min) in optically pure form (entry 5)[5]. We also investigated the reduction of 4-chloro β-ketoesters. We found that the corresponding $(\eta^3\text{-}(CH_2)_2CHCH_3)_2Ru^{II}$ complexes were efficient catalysts at 100atm of hydrogen, 80°C and displayed a high reaction rate (1h). Under these conditions, the allyl Ru^{II} containing chiraphos as a ligand afforded **43** in good yield and poor enantioselectivity (2% e.e., entry 5). The related BinapRu(allyl)$_2$ under the same conditions exhibited high selectivity **42** being reduced to **44** (up to 90% e.e., entry 7). The (S)-Binap and (S)-BiphempRuBr$_2$ respectively prepared *in situ* and preformed were active (0.06% of catalyst) : **42** was reduced to **44** in quantitative yield and acceptable selectivity (e.e. 81 and 89 %, entries 8 and 9).

As already demonstrated by Noyori[7g], this approach constituted a practical entry to carnitine. We also found that it was possible to effect direct ketone reduction of the ammonium salt **45** to (R)-**46** or (S)-**47** carnitine.

Using (S)-BiphempRuBr$_2$ (100 atm of hydrogen, 25°C, 72h), **45** was reduced to **47** in 90% yield and 80% selectivity (entry 11). Under the same conditions, we prepared (S)-carnitine **46** in 96% e.e.from **45** using a Ikariya and Saburi complex[8a] bearing (R)-Binap (entry 10).

Conclusion

The hydrogenation of β-ketoesters giving β-hydroxyesters proceeds with selectivities up to 99% under mild conditions. This reaction coupled with Fräter-Seebach alkylation[25] and highly diasteroselective electrophilic amination[26] of β-hydroxyesters is a powerful method for the synthesis of enantiomeric pure compounds. In addition, it is also shown that Me-Duphos possesses high efficiency in the reduction of olefins and ketones (e.e. up to 87%). As pointed out by Noyori, this work and other studies[13,14], a general trend in the asymmetric hydrogenation of β-ketoesters is observed.



The chiral (P*P)Ru(η^3-$(CH_2)_2CHCH_3)_2$ are efficient catalysts for the enantioselective hydrogenation of various prochiral α,β unsaturated acids. The halogen-containing chiral ruthenium complexes (P*P)$RuBr_2$ prepared *in situ* are very efficient. This *in situ* procedure offers new opportunities for the ruthenium-based chemistry which is of potential industrial importance. These (P*P)$RuBr_2$ catalysts can be used in crude form for highly enantioselective reductions. As we pointed out in our previous studies, our method allows screening of a wide range of chiral chelating phosphines including atropisomeric phosphines. This technic offers some advantages compared to methods described previously : mild conditions and availability of (COD)Ru(η^3-$(CH_2)_2CHCH_3)_2$[22].

Acknowledgments : We thank Elf Aquitaine for providing generous financial support and grants to S. Mallard, C. Pinel and X. Pfister. We are also grateful to CNP_q (Brazil) for a fellowship to M. C. Cano De Andrade and to the C.N.R.S. for a grant to L.Bischoff . We also thank Dr B.Heiser (Hoffman La Roche) for a generous gift of (S)-(+)-Biphemp. Dr E. Broger and Dr R. Schmid (Hoffman La Roche) for samples of (R) and (S)-MeO-Biphep. Dr C. Mercier (Rhône-Poulenc) for providing us a sample of (+) and (-)-CBD.and Dr H Frauenrath (Institut für organische chemie der technischen Hochschule) for a sample of glucose diphosphine derivative. We thank Dr F. Jung and Dr P. Siret (Zaneka Pharma, Reims) for a generous gift of acetoxy azetidinone. We thank Pr W Oppolzer (University of Geneva) and Dr J. O. Durand for a sample of (R,R)-Me-Duphos.

Experimental

General Methods. The following solvents were freshly distilled and stored under argon prior to use : hexane and toluene from calcium hydride, methanol from magnesium turnings. All experiments with organometallic elements were performed in a nitrogen-filled dry box or by using standard Schlenck techniques.
^1H and ^{13}C Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-250 or Bruker AM-200 Fourier transform spectrometer. Spectra were obtained in chloroform-*d*. Chemical shifts are reported in parts per million (ppm) with TMS as an internal reference, and coupling constants are reported in Hertz (Hz). Infrared (IR) spectra were recorded on a Perkin-Elmer 297 spectrometer. High Pressure Liquid Chromatography (HPLC) was performed with a Gilson 302 apparatus.

Preparation of the (P*P)$RuBr_2$ complexes :

- *in situ* preparation of the catalysts : (S)-Binap (8 mg, 0.013 mmol.) and Ru(COD)(η^3-$(CH_2)_2CHCH_3)_2$ (4 mg, 0.013 mmol) were placed in a 10 ml Schlenk tube and the vessel was purged with argon. 2 ml of anhydrous acetone (degassed by 3 cycles of vaccum/argon at R.T.) were added. To this suspension was added methanolic HBr (0.11 ml of a 0.29 M solution prepared by diluting 48% aq HBr in abs MeOH) and the suspension was stirred 30 min at R.T. A yellow solid precipitated. Subsequently, the solvent was thoroughly evaporated under vaccum and the (S-Binap)$RuBr_2$ thus obtained was used immediately.
- preparation *via* the **preformed** complex Ru(S)-Binap(η^3-$(CH_2)_2CHCH_3)_2$:
Ru(S)-Binap(η^3-$(CH_2)_2CHCH_3)_2$ (11 mg, 0.013 mmol) was placed in a 10 ml Schlenk tube under argon. To this complex was added degassed acetone (2 ml) and methanolic HBr (0.16 ml, 0.20 M). The reaction mixture was stirred 20 min under argon and the resulting orange suspension was thoroughly evaporated under vacuum. The complex thus obtained was ready to use for asymmetric hydrogenation.

General Procedure for hydrogenation reactions

A solution of appropriate substrate (1mmol) in degassed solvent (2ml) was placed in a 10 ml Schlenck vessel and degassed by 3 cycles of vacuum/argon. This mixture was added to the catalyst (0.25-1%) in a glass vessel and placed under argon in 250 ml stainless steel autoclave. The Argon atmosphere was replaced with hydrogen by three cycles of pressurizing. The hydrogenations were run under the reaction conditions given in preceding tables. The solvent was removed under reduced pressure. Conversion rates were determined by ^1H NMR analysis.

- typical procedure for saturated ß-hydroxyesters :

Methyl 3-oxo-pentanoate (5 g, 38 mmol) was degassed by a 3 times cycle of vaccum/argon at R.T. and diluted in 5 ml of abs MeOH (degassed by the same procedure). This solution was canulated into a 25 ml Schlenk tube containing the (S-Binap)$RuBr_2$ complex (0.1 mol %). This suspension was immediately placed in an autoclave which was purged 3 times with hydrogen and pressurised under 20 atm. (290 psi). The autoclave was heated at 50°C and stirring was maintained overnight. After cooling, the reaction mixture was concentrated under reduced pressure and the residue was distilled under vaccum (85°C, 0.8 mm Hg) to afford 5.1 g (100%) of Methyl 3-(S)-3-hydroxypentanoate. $[\alpha]_D$ = + 37.6 (1, $CHCl_3$). The enantiomeric excess was determined by gas chromatography (lipodex A, Macherey Nagel) : 25.6 min. for the (S)-enantiomer and 26.2 min. for the (R)-enantiomer ; only traces of the (R)-enantiomer were observed.(e.e. >99%)

- typical procedure for unsaturated ß-hydroxyesters :

3 g (17.4 mmol) of methyl 3-oxo-5-(E)-octen-5-oate (prepared by the Wemple procedure[23]. were degassed as described above and diluted in degassed methanol (3 ml). This solution was canulated into a 10 ml Schlenk tube containing the (S)-BiphempRuBr2 complex (0.3 mol %). The reaction mixture was immediately placed in an autoclave which was purged 3 times with hydrogen and pressurised under 6 bars (87 psi). The autoclave was heated to 80°C and magnetic stirring was started as soon as the required temperature was reached. Stirring was stopped after 30 min and the autoclave was cooled to R.T. The brownish solution obtained was concentrated under reduced pressure and the residue was distilled under vacuum (135°C, 2 mm Hg) to afford 3 g (100 %) of methyl 3-(S)-3-hydroxy-5-(E)-octen-5-oate which was pure by ^1H NMR.$[\alpha]_D$ = +18 (1, $CHCl_3$).

The absolute configuration was confirmed by total hydrogenation and comparison with the $[\alpha]$ given in the literature [24] (+22.4 measured vs 22.2 given for the (R) enantiomer). The enantiomeric excess was determined by ^1H NMR in the presence of (+)$Eu(tfc)_3$. (the CH_3O group was shifted to 3.78ppm ; comparison with the racemate and integration values gave an e.e.>99%). Note : chiral G.C. could not be applied to long-chain (> 6 C) molecules because of an unsatisfactory separation.

References and notes

1) For several excellent reviews see : a) *Comprehensive Organometallic Chemistry* Kagan, H. B.; Vol. 8, 453 Ed. G. Wilkinson, Pergamon Press **1982** Oxford; b) Morrisson, J.D.; Ed, *Asymmetric Synthesis*, Vol. 5 Academic Press **1985**, New York; c) Bosnich, B.; *Asymmetric Catalysis* NATO AST Series E 103, Martinus Nijhoft Publishers Dordrecht **1986**; d) Apsimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157; e) Consiglio, G.; Waymouth, R.M. *Chem. Rev.* **1989**, *89*, 257; f) Brunner, H.; Topic in Stereochemistry Ed. Vol. **1989**, *129*; g) Blysrone,S.I. *Chem. Rev.* **1989**, *89*, 1664; h) Ojima, J.; Clos, N.; Bastos, C.

Tetrahedron **1989**, *45*, 6901; i) Gao, Y.; Hanson, R.M.; Klunder, J.M.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; j) Sharpless, K. B. *Janssen Chimica Acta*, **1988**, *1*, 3; k) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768 and references cited therein.

2) Reviews : For a synthesis of chiral ligands see a) Kagan, H. B. *Asymmetric Synthesis*, J.D. Morrison, Ed. Academic Press, New York, **1985**, *1*, Vol 5; b) see also Topics in stereochemistry H. Brunner (ref.1f) for an informative presentation of optically active ligands with their generally accepted acronyms.

3) a) Klabunovski, E. I. *Russ. Chem. Rev.*, **1982**,*51*, 7; b) Knowles, W.S. *Acc. Chem. Res.* **1983**, *16*, 106 c) Coplar, V.; Comisso G.; Sunjic, V.*Synthesis* **1981**, 85.d) Brown, J. M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 190. For a recent review on homogeneous catalysis, see Dunina V. V.; Beletskaya, I. P. *Zhurnal Organicheskoi Khimii.* **1992**, *28*, 1929.

4) For mechanistic aspects of the rhodium catalysed enantioselective hydrogenation of double bonds, with dihydrogen and hydrogen transfer see : a) Landis, C.R.; Halpern, X. *J. Am. Chem. Soc.* **1987**, *109*, 1746; b) Leitner, W.; Brown, J.M.; Brunner, H. *J. Am. Chem. Soc.* **1993**, *115*, 152.

5) Kagan, H.B. *Bull. Soc. Chim. Fr.* **1988**, *27*, 566.

6) For reviews see : a) Noyori, R.; Kitamura M. in *Modern Synthetic Methods* Ed. Scheffold, R. *Spinger Verlag*, **1989**, *128*; b) Noyori, R.; *Chem. Soc. Rev.* **1989**, *18*, 209; c) Noyori, R.; Takaya H.*Acc. Chem. Res.* **1990**, *23*,345; d) Noyori, R.; *Science* **1990**, *248*, 1194; e) *Organic Synthesis in Japan Past, Present, and Future*, Noyori, R. Ed Tokyo Kagaku Dozin, **1992**,301.

7) For references see : a) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596.; b) Noyori, R.; Okhuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856; c) Ohta, T.; Takaya, H.; Kitamura, M.; Noyori, R. *J.Org.Chem.* **1987**, *52*, 3176; d) Kitamura, M.; Okhuma, T.; Takaya, H.; Noyori, R.*Tetrahedron Lett*, **1988**, *29* (13) 1555 ; e) Kitamura, M.; Okhuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R.; *J. Am. Chem. Soc.* **1988**, *110*, 629; f) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708; g) Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Takemoti, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134; h) Kitamura, M.; Nagai, K.; Hsiao, Y.; Noyori, R *Tetrahedron Lett*, **1990**, *31* (4) 549; i) Kitamura, M.; Okhuma, T ; Tokunaga, M.; Noyori, R *Tetrahedron : Asymmetry*, **1990**, *1* (1) 1; j) Kitamura, M.; Tokunaga, M.; Okhuma, T.; Noyori, R *Tetrahedron Lett*, **1991**, *32* (33) 4163; k) Mashima, K.; Matsumara, Y.; Kusano, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H.*J. Chem. Soc. Chem. Commun.* **1991**, 609; l) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1992**, *33*,(5), 635; m) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144.

8) a) Ikariya, T.; Ischii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc. Chem. Commun.* **1985**, 922.; b) Kawano, H.; Ishii, Y.; Ikariya, T.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H.*Tetrahedron Lett.*, **1987**, *28*, 1905; c) Kawano, H.; Ischii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc. Chem. Commun.* **1988**; 87 d) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida Y.; Kumobayashi, H. *J. Chem. Soc. Perkin Trans I*, **1989**, 1571; e) Muramatsu, H.; Kawano, H. ; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc. Chem. Commun.* **1989**, 769; f) Saburi, M.; Shao, L.; Sakurai, T.; Uchida, Y.*Tetrahedron Lett*, **1992**, *33* , 7877; g) Saburi, M.; Takeuchi, H.; Ogasawara, M.; Tsukahara, T.; Ishi, Y.; Ikariya, T.; Takahashi, T.; Uchida, Y. *J. Organomet. Chem.* **1992**, *428*, 155.

9) For mechanistic studies of Ru-based catalyzed asymmetric hydrogenations of olefins:a) Ashby, M. T.; Khan, M. A.; Halpern, J. *Organometallics*,**1991**,*10*, 2011; b) Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc*, **1991**, *113*, 589; c) Ohta, T.; Takaya, H.; Noyori, R.*Tetrahedron lett*, **1990**, *31*, 7189.

10) a) Genêt, J.P.; Mallart, S.; Pinel, C.; Jugé, S. *Tetrahedron : Asymmetry* **1991**, 2, 43; b) Genêt, J.P.; Ratovelomanana-Vidal, V., Pinel, C. *Synlett*, **1993**, 478.

11) Genêt, J.P.; Pinel, C.; Mallart, S.; Caihlol, N.; Laffitte, J.A. *Tetrahedron Lett.*,**1992**, *33* , 5343.

12) a) Genêt, J.P.; Mallart, S.; Jugé, S. Brevet Français n° 8911159 (August 1989) b) Genêt, J.P.; Pinel, C.; Mallart, S.; Jugé, S.; Thorimbert, S.; Laffitte, J.A.*Tetrahedron : Asymmetry* **1991**, *2*, 555.

13) Heiser, B.; Broger, E. A.; Crameri, Y. *Tetrahedron : Asymmetry* **1991**, *2* (1), 51.For the preparation of (+) and (-) Biphemp and (+) and (-) MeO-Biphep see respectively Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.J. *Helv. Chim. Acta* **1988**, *71*, 897 Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.

14) Cesarotti, E. ; Antognazza, P.; Mauri, A. *Helv. Chim. Acta* **1992**,*75*, 2563.

15) a) Alcock, N. W.; Brown, J. M.; Rose, M.; Wienand, A. *Tetrahedron : Asymmetry* 2, 47, **1991**.b) Taber, D.F.; Silverbert, L. J. *Tetrahedron Lett.* **1991**, *34*, 4227; c) Stahly, P. G.; Manimaran, T.; Wu, T. C.; Klobucar, W. D.; Kolich, C. H.; Franczek, F. R.; Watkins, S. E. *Organometallics* **1993**, *12*, 1467; d) Hoke, J. B.; Hollis, L. S.; Stern, E. W. *J. Organomet. Chem.* **1993**, *455*, 193; e) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J Org. Chem* **1992**, *57*, 6689; f) Mezzetti, A.; Consiglio, G. *J. Chem. Soc. Chem Commun.* **1991**, 1675.

16) Taken in part from the doctoral Thesis of C. Pinel. (Université P&M Curie 1992).

17) For the preparation and use of this new class of ligand in Rh-catalyzed hydrogenations see : a) Burk, J., Feaster, J.E.; Nagent, W.A.; Harlow, R.L. *J Am. Chem. Soc.* **1993**, *115*, 10125; b) Burk, M.J.; Feaster, J.E.; Harlow, R. L. *Organometallics*, **1990**, *113*, 8518.

18) This excellent diastereoselectivity was in agreement with results described by Noyori using (R) $BinapRu(OAc)_2$.

19) A new synthesis of this key material from the (3S,4R)-3-[(R)-1-(t-butydimethylsilyl)oxy]ethyl]-4acetoxy-2-azetidinone has been devised in our laboratory. Taken in part from the doctoral Thesis of J. O. Durand. (Université P&M Curie, 1993). Results will be reported in due course.

20) An excellent enantioselectivity has been reported recently using chiral rhodium catalysts, see Roucoux, A.; Agbossou, F.; Mortreux, A.; Petit, F. *Tetrahedron : Asymmetry* **1993**, 2279 and references cited therein.

21) This chemoselective reduction of the β-ketoester has been reported using Ikariya and Saburi complex[15b].

22) This material will be available from Janssen Chimica.

23) Clay, R.J.; Collom, T.A.; Karrick G.L.; Wemple, J. *Synthesis* **1992**, *290*.

24) Schreiber, S.L.; Kelly, S.E.; Porco, J.A.; Sammakia, J.T.; Suh, E.M. *J. Am. Chem. Soc.* **1988**,*110*, 6210

25)a) G. Fräter, *Helv. Chim. Acta* **1979**, *62*, 2825. b) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448. c) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T. *J. Am. Chem. Soc.* **1988**, *110*, 4763.

26) Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Piveteau, E.; Genêt, J. P. *Synlett* **1993**, 475.

(*Received in UK* 31 *January* 1994; *accepted* 8 *March* 1994)