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ASYMMETRIC SYNTHESIS. PRACTICAL PRODUCTION OF D AND L THREONINE. DYNAMIC KINETIC RESOLUTION IN RHODIUM AND RUTHENIUM CATALYZED HYDROGENATION OF 2-ACYLAMINO-3-OXOBUTYRATES.

J.P. GENET*§, C. PINEL§, S. MALLART§, S. JUGE§, S. THORIMBERT§, J.A. LAFFITTE§§

§ Laboratoire de Synthèse Organique, Associé au C.N.R.S., Ecole Nationale Supérieure de Chimie de Paris, 11, rue Pierre et Marie Curie, 75231 Paris Cedex 05, France.
§ § Département Chimie Fine et Bioconversions, G.R.L. (Elf Aquitaine) 64170 Lacq, France.

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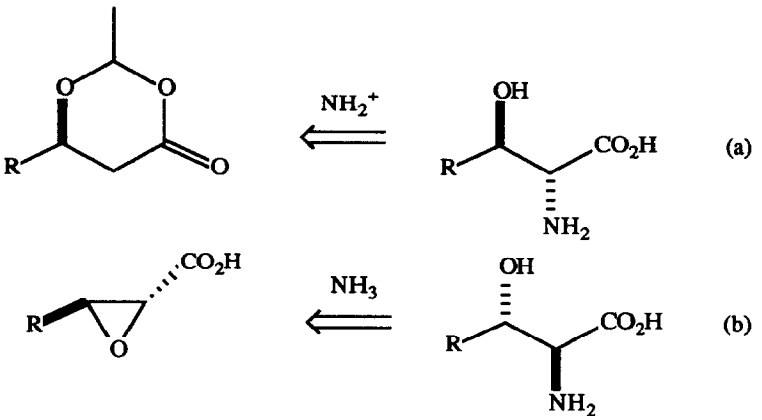
ABSTRACT : Enantioselective syntheses of D and L threonine are described. Racemic methyl and ethyl 2-acylamino-3-oxobutyrate **1** *were synthesized from the corresponding acetoacetates* **6** *and then hydrogenated stereoselectively via dynamic kinetic resolution with various chiral P * P Rh (I)* **8** *and Ru (II)* **10** *catalysts to give syn optically active alcohols which could be converted by hydrolysis and treatment with propylene oxide into threonine. The best results were obtained using (-) CHIRAPHOS Ru and (+) BINAP Ru as catalysts, in the hydrogenation step leading respectively to D threonine (ee : 99 %) and L threonine (ee : 94 %) in 26-34 % overall yields.*

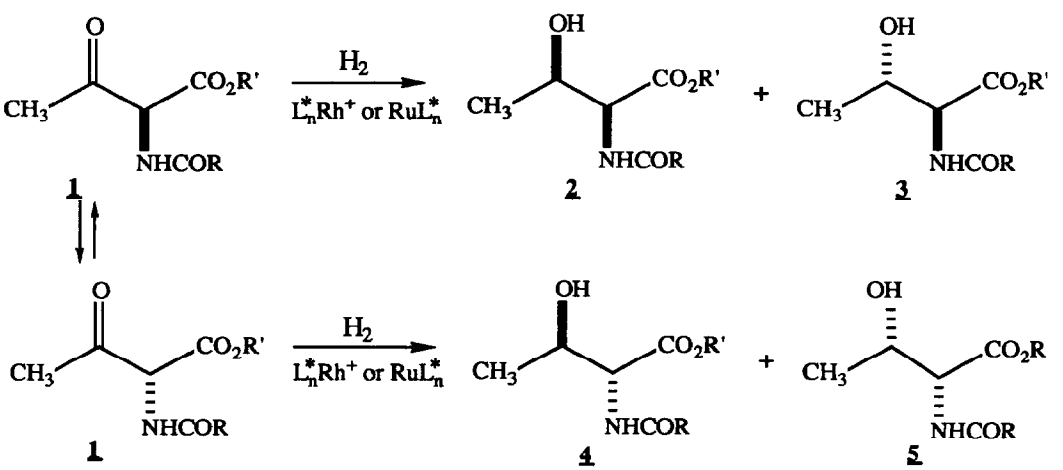
β-hydroxy-α-aminoacids are important both as natural products in human and animal nutrition (serine, threonine) and as chiral intermediates[1]. They are also components of various cyclic polypeptides[2] (e.g. vancomycin, bouvardin, cyclosporine A, teicoplanin ...etc), of peptidases[3] and of the polyxinase as enzyme inhibitors[4]. As a result of the wide interest in general of β-hydroxy amino acids[5], their economic impact is significant and has, accordingly led to the development of a variety of methods for their chemical and biochemical syntheses[6].
Recent developments in our laboratory permitted the elaboration of general methods for the synthesis of enantiomerically pure *anti* α-amino-β-hydroxy acids (Scheme I). We described a diastereoselective electrophilic amination (path a) of (R) and (S) 3-hydroxy butanoic acid under their protected dioxanone form[7] and the synthesis of D and L allothreonine by nucleophilic attack of ammonia at the C_2 of optically active epoxyacids (path b)[8].



Scheme I

However these methods and those developed recently[5] require several steps. A short and practical method for stereoselective synthesis of *syn* β-hydroxy-α-amino acids such as threonine is strongly desired. Thus, we anticipated that catalytic asymmetric hydrogenation by transition metal complexes of the readily available 2-acylamino-3-oxobutyrate **1** would be an efficient process for the synthesis of such β-hydroxy-α-amino acids.

Asymmetric hydrogenation of racemic 2-acylamino-3-oxobutyrates **1** should in principle provide a mixture of the four possible stereoisomers **2**, **3**, **4**, **5** (Scheme II). However, when this study was undertaken there was at this time a serious question of whether such racemic substrate **1** possessing a chiral labile stereogenic center would undergo a dynamic stereomutation under asymmetric hydrogenation conditions and provide only one of them as outlined in Scheme II. It has been shown that the enzymatic reduction of **1a** with *saccharomyces rouxii*[9] gave *anti* and *syn* hydroxylic products **3** and **5** in a 60 : 40 ratio without significant kinetic dynamic resolution, in contrast with results reported with keto esters bearing an alkyl group at C_2[10].

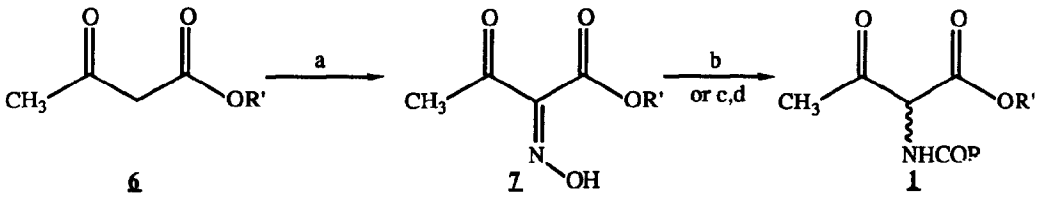


Scheme II

During our initial studies[11] on these 2-acylamino-3-oxobutyrates a very elegant work has been reported by R. Noyori et al.[12], in which BINAP-Ruthenium (II) allows efficient dynamic kinetic resolution of a variety of 2-substituted-3-oxo carboxylic esters, to lead to the corresponding alcohols with high enantiomeric and diastereo-isomeric excesses. Here we disclose examples of *syn* hydrogenation of 2-acylamino-3-oxobutyrate **1** with chiral rhodium complexes[13] **8** and a whole set of chiral mononuclear ruthenium complexes **10**[14].

RESULTS and DISCUSSION

Preparation of 2-acylamino-3-oxobutyrates **1**. The two-steps sequence shown in scheme III was employed[15]. Addition of sodium nitrite in acetic acid to the appropriate 3-oxobutyrate **6** followed by reduction of the intermediate oxime **7** with H_2-Pd/C in acetic, propionic or isobutyric anhydride provided the 2-acetamino-3-oxobutyrate **1a**, **1b**, **1c**, and **1d** (80-85 % yield).



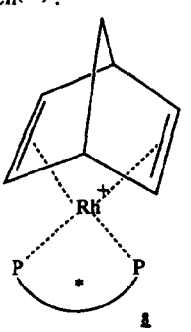
1a : R = R' = CH_3 ; **1b** : R = CH_3, R' = C_2H_5 ; **1c** : R = CH_3, R' = t.Bu ; **1d** : R = iPr, R' = CH_3

(a) Na NO_2 / AcOH ; (b) H_2 - Pd/C with $(RCO)_2O$.

Scheme III

Asymmetric hydrogenations.

(i) Rhodium catalyzed reactions. First we investigated asymmetric hydrogenation of 2-acylaminobutyrate with chiral cationic rhodium complexes **8** . Ketones or ketoesters[16,17] have been reduced with such complexes. We decided to investigate the asymmetric hydrogenation of methyl-2 acetamido **1a** using preformed catalysts prepared according to J. M. Brown's procedure[18] or more conveniently, using catalysts generated in situ as reported by B. Bosnich[19] .



8

P * P[20] = (-) BPPM, (-)DIOP, (-)CHIRAPHOS,
(+) NORPHOS, (-) BINAP, (-) DIPAMP.
$X^- = CF_3SO_3^-, ClO_4^-$

Scheme IV

The catalyst to substrate ratio was 1 : 100 and the hydrogenation time 48 hr at 20°C under 70 atm of hydrogen. The relative absolute configuration of the products has been determined by NMR (200 MHz) and the following

procedure was adopted for determination of enantiomeric excesses. After hydrogenation, the solvent was removed under reduced pressure the reaction mixture hydrolyzed with 3N HCl and the residu was taken up with propylene oxide. After removal of solvents the crude crystalline material was analyzed by HPLC on Chiralpak WH column (Daicel Industry). The results were reproductible within 2 % and given in table I.

Table I : Stereoselective hydrogenation[a] of methyl 2-acetamido-3-oxobutyrate catalyzed by cationic $(L^*RhNBD)^+X^-$ complexes[b] (8).

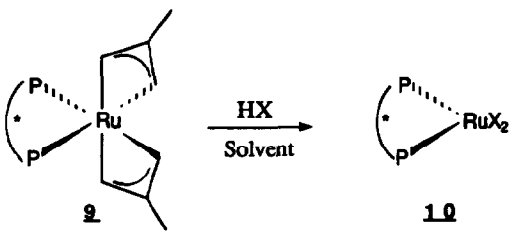
Entry	Ligand / X^-	Solvent	Yield[c] (%)	syn / anti (threo / allo)	threonine ee conf[d]	allothreonine ee conf[d]
1	(-) BPPM / $CF_3SO_3^-$	EtOH	92	70 : 30	19 (D)	6
2	(-) BPPM / $CF_3SO_3^-$	THF	95	77 : 23	25 (D)	23
3	(-) DIOP / $CF_3SO_3^-$	THF	90	71 : 29	18 (L)	25 (D)
4	(-) CHIRAPHOS $CF_3SO_3^-$	THF	85	75 : 25	23 (L)	15 (L)
5	(+) NORPHOS / ClO_4^-	THF	90	63 : 37	40 (D)	-
6	(-) BINAP / ClO_4^-	THF	49	82 : 18	40 (D)	20 (D)
7	(-) DIPAMP / $CF_3SO_3^-$	THF	50	94 : 6	39 (D)	28 (D)

a) Reactions were carried out under 70 atm of hydrogen at 20°C for 48 hr in the presence of 1 mole % of catalyst. b) Preformed catalysts or prepared in situ from bisNBD $RuCl_2$; c) Isolated yield after hydrolysis (see experimental) ; d) Diastereoisomeric and enantiomeric excesses were determined by HPLC on chiralpak WH column Daicel see text and experimental section.

This study revealed as shown in table I that the steric course of hydrogenation of **1a** catalyzed by rhodium complexes proceeds with a *syn* preference. The diastereoselectivity is influenced by the solvent and the catalyst. In ethanol containing the (-) BPPM-Rh complex the racemic compound **1a** was hydrogenated with 70 / 30 : *syn/anti* diastereoselectivity (entry 1) to give after hydrolysis D threonine (19 % ee). In THF the selectivity was better *syn/anti* : 77 / 23 (25 % ee for D threonine) (entry 2). Using related catalysts containing (-) DIOP, (-) CHIRAPHOS and (+) NORPHOS as ligand and THF as solvent *syn* preference ranging from 63% to 70% was obtained. The enantiomeric excesses were up to 40% (entries 3,4 and 5). The best results were observed with (-) BINAP-Rh (entry 6) and (-) DIPAMP-Rh (entry 7) for which the *syn/anti* ratio were 80:20 and 94:6 and the enantomeric excesses 39% and 40% respectively for D threonine. Noteworthy, the racemisation of the stereogenic center C_2 is faster than hydrogenation and useful kinetic resolution is achieved here with rhodium catalysts bearing chiral ligands such as DIPAMP, NORPHOS and BINAP.

(ii) Ruthenium catalyzed reactions : Then we turned our efforts towards chiral ruthenium catalysts which may have higher facial recognition as reported by Ikariya and Saburi[21], Noyori and Takaya[22]in the case of BINAP complexes. In contrast with rhodium there are relatively few known chiral ruthenium complexes[23].

However we found recently an efficient and reliable general synthesis[14] of hexacoordinate mononuclear ruthenium complexes P * P Ru(II) (2-methylallyl)$_2$, **2** (Scheme V). These catalysts are not efficient for the hydrogenation of keto derivatives **1** even under high pressure (100 atm, 48 hr see table II entry 13) but they are readily converted into the corresponding halogeno and trifluoroaceto with the formula P * P RuX_2 by reaction with HX (CF_3CO_2H, HCl, HBr) or $(CH_3)_3SiI$[24]. These catalysts are used in situ and their activity is strongly dependent on the solvent in the protonation reaction. For example (+)DIOP RuX_2 preformed in acetonitrile from (+)DIOP Ru(Metallyl)$_2$ is inactive whereas the same catalyst prepared in acetone or toluene has high catalytic activity (compare entries 1 and 2). The hexacoordinate bistrifluoroacetate showed some catalytic activity (25% of conversion entry 12) in contrast with BINAP Ru bisacetate[24].



2 **10**

P * P = (+) ou (-) DIOP, (-)NORPHOS
(-) CHIRAPHOS, (-)BPPM, (-) BINAP, (-) CBD

X = Cl, Br, CF_3CO_2

Scheme V

We have chosen to investigate the asymmetric hydrogenation of 2-acetamido-3-oxobutyrates **1**. The catalyst to substrate ratio was usually 1-1.5 : 100, a 10 : 100 ratio was used in one instance. The hydrogenation time for the present substrates spanned 48-72 hr at 20°C under 92-100 atm of hydrogen. After hydrogenation the same work up as in the case of rhodium catalyzed reactions was adopted for isolation and determination of enantiomeric excesses of threonine and allothreonine.

This study provided us with the opportunity to evaluate the influence of whole set of chiral ruthenium catalysts with methyl 2-acetamido 3-oxobutyrate. Inspection of the data on the stereoselective reduction of ruthenium catalysts bearing six different chiral ligands reveals that under standard conditions (MeOH, 90 atm. of H_2, 1% of catalyst) an acceptable *syn* selection (70-76%) is seen with DIOP and BINAP (entries 2 and 9 respectively) but the highest degree of *syn* selection was obtained with CBD (87% entry 5) and CHIRAPHOS Ru catalyst (93% entry 15). However the enantioface discrimination is dramatically affected by the nature of the catalyst. The CBD Ru catalyst is the least effective (13% ee)(D threonine entry 6) : (-) BPPM (19% ee)(L threonine), (+) DIOP (20% ee)(D threonine), (+) NORPHOS (28% ee)(D threonine) (entries 4,3 and 7 respectively). A very high enantioface discrimination is observed with (-) CHIRAPHOS (85% ee)(D threonine entry 14) and (+) BINAP (95% ee)(L threonine entry 9).

A series of substrates **1** was examined to test the scope and limitations of catalyst directivity with the most efficient chiral ruthenium catalysts (e.g CHIRAPHOS and BINAP). The results of this study revealed a number of significant observations. First the hydrogenation with a series of carboxylic esters **1** (R = Me **1a**, Et **1b**, tBu **1c**) as well as substrates with two different substituents at the stereogenic center (NHCOR) was investigated (entries 9-11 and 15-18).

Table II : Hydrogenation of 2-acylamino-3-oxobutyrates catalyzed by (chiral biphosphine RuX_2) complexes.

Entry	Substrate	Catalyst %	Solvent	Yield	syn : anti	Threo ee (conf)	Allo ee (conf)
1	1a	(+)DIOP $RuBr_2$[a] (1.5)	MeOH	0			
2	1a	(+)DIOP $RuBr_2$[b] (1)	MeOH	75	70 : 30	7 (D)	37 (D)
3	1a	(+)DIOP $RuBr_2$[b]	CH_2Cl_2	70	95 : 5	20 (D)	
4	1a	(-) BPPM $RuBr_2$[b] (1.5)	MeOH	80	88 : 12	19 (L)	20 (L)
5	1a	CBD $RuBr_2$[b] (1)	MeOH	60	87 : 13	3 (D)	20 (D)
6	1a	CBD $RuBr_2$[b] (1)	CH_2Cl_2	45	96 : 4	13 (D)	
7	1a	(+)NORPHOS $RuBr_2$[b] (1.5)	MeOH	54	80 : 20	28 (D)	32 (L)
8	1a	(+) BINAP $RuCl_2$, NEt_3[c] (1)	AcOH	90	62 : 38	42 (L)	38 (D)
9	1a	(+) BINAP $RuCl_2$[b] (1)	MeOH	90	76 : 24	95 (L)	
10	1c	(+) BINAP $RuBr_2$[b] (1)	MeOH	75	77 : 23	85 (L)	95 (D)
11	1d	(+) BINAP $RuBr_2$[b] (1)	MeOH	90	77 : 23	92 (L)	90 (D)
12	1a	(+) BINAP $Ru(CF_3CO_2)_2$[b] (1)	CH_2Cl_2	21	95 : 5	51 (L)	
13	1a	(-) CHIRAPHOS $Ru(Met)_2$ (1)	MeOH	0			
14	1a	(-) CHIRAPHOS $RuBr_2$[b] (10)	MeOH	90	85 : 15	33 (D)	
15	1a	(-) CHIRAPHOS $RuBr_2$[b] (1)	MeOH	85	93 : 7	75 (D)	
16	1b	(-) CHIRAPHOS $RuBr_2$[b] (1)	MeOH	90	91 : 9	63 (D)	
17	1c	(-) CHIRAPHOS $RuBr_2$[b] (1)	MeOH	90	87 : 13	36 (D)	
18	1d	(-) CHIRAPHOS $RuBr_2$[b] (1)	MeOH	80	85 : 15	70 (D)	95 (D)
19	1a	(-) CHIRAPHOS RuI_2[b] (1)	MeOH	60	90 : 10	76 (D)	70 (D)
20	1a	(-) CHIRAPHOS $RuBr_2$[b] (1)	CH_2Cl_2	40	97 : 3	85 (D)	99 (D)

Protonation reaction a) in acetonitrile ; b) in acetone or toluene ; c) According to Ikaria procedure.

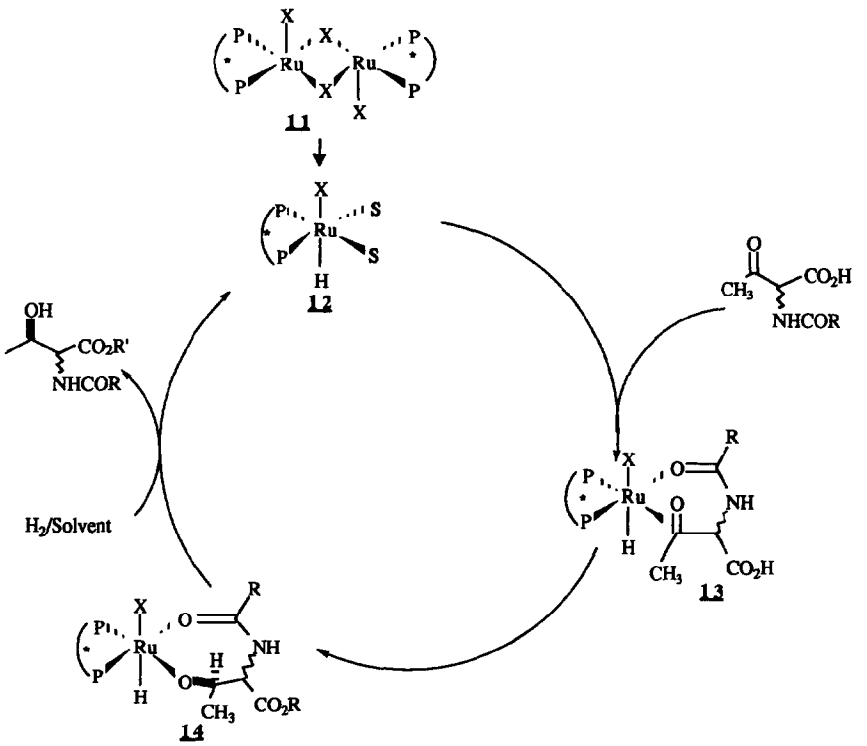
BINAP Ru catalyzed this hydrogenation with two different acylamino groups at C_2 on the substrate (**1a** and **1d**) and afforded similar levels of diastereoselection 77 : 23 (*syn:anti*) and enantioselection (92-95% entries 9, 11). 10% loss of enantioselectivity is observed when the bulk of carboxylic group is increased (Me vs tBu, entries 9, 10).When CHIRAPHOS $RuBr_2$ is used as the catalyst, the nature of the alkoxide moiety has noticeable effect on both the diastereoselection (93 : 7 with R'=Me **1a** vs 87:13 with R' =tBu **1c**) and the chiral recognition (75 vs 36% ee, entries 15, 17), whereas the size of acylamino group has little effect on the enantioselectivity (75 ee for R= Me **1a** vs 70% for R= iPr **1d**) (entries 15 and 18).

Second, factors such as substrate / catalyst ratio and solvent have important effects on the diastereo and enantioselection in the hydrogenation process. The hydrogenation of **1a** with P * P Ru was beneficially affected by decreasing the substrate / catalyst ratio. The *syn : anti* preference is lower (85 : 15) using 10% of catalyst than in the presence of only 1% in methanol as solvent (93:7) (compare entries 14 and 15). This observation supported the fact that hydrogenation needs to be slower than racemisation of the α-center in order to achieve high selectivities.

The influence of solvent was also particularly interesting. When hydrogenation of **1a** was run in acetic acid a poor diastereoselectivity was observed (*syn:anti* 62 : 38) with a moderate enantioselectivity 42% (entry 8). Switching from methanol (entry 9) a substantial increasing of *syn* preference is seen (*syn:anti* 77 : 23). In dichloromethane very high *syn* selection is observed with CBD (96 vs 87%), DIOP (95 vs 70%), CHIRAPHOS (97 to 93%). This interesting solvent effect has been observed by Noyori with BINAP Ru catalyst (95 vs 80%)[12a]. Noteworthy the CHIRAPHOS Ru complex seems less dependent on reaction solvent than the other catalysts.

(iii) Comparison of hydrogenation of 1 with P * P Rh and P * P Ru catalyst systems and mechanism.

Interestingly a very high syn prefence > 94 % for hydrogenation of 2-acylamino-3-oxobutyrate is seen with both P * P rhodium and P * P ruthenium catalysts. For example with DIPAMP-Rh in THF (*syn:anti* 94:6) as well as CHIRAPHOS-Ru (*syn:anti* 97:3) or CBD (*syn:anti* 96:4). Noteworthy comparison of tables reveals that BPPM-Rh and NORPHOS-Rh catalysts gave better optical purities than the corresponding Ru catalysts (compare table I entries 2, 5 and table II entries 4, 7)



S = Solvent ; X = H, Cl, Br, I ; P * P = CHIRAPHOS, DIOP, BPPM, BINAP ...

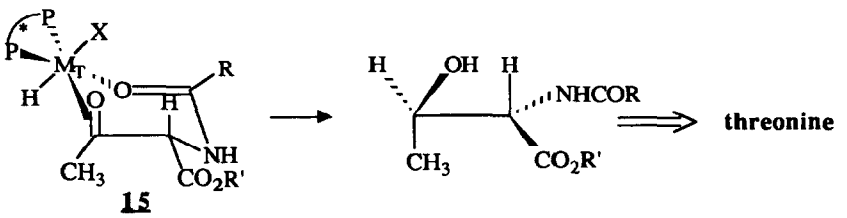
Plausible mechanism for asymmetric hydrogenation of 3-keto acylaminobutyrates with P * P Ru catalysts.

Scheme VI

In this study we have established that asymmetric hydrogenation of 2-acylamino-3-oxobutyrate with dynamic kinetic resolution produce the same dominant isomer with Rh and Ru catalysts bearing DIOP, NORPHOS and BINAP (compare table I and II). However the direction of asymmetric induction effected by (-) BPPMRu catalyst affording the L threonine (88 : 12) is the reverse of that with (-) BPPM Rh described above (see table I and II entries 1 and 4 respectively). The same effect is observed with (-) CHIRAPHOS (compare entry 4 table I and 15 table II)

The mechanism of hydrogenation catalyzed by Ru(II) species has not yet been completely clarified. For activated olefins James has postulated the formation of unsaturated monohydride species[25]. Saburi has proposed a tentative sketch for the catalytic cycle of asymmetric hydrogenation of N-acyldehydroaminoacids by ruthenium complexes[26]. More recently Takaya, Noyori and Halpern have examined the stereochemical course of hydrogenation of unsaturated carboxylic acids by BINAP $Ru(OAc)_2$[27]. These reactions are characterized by the operation of monohydride mechanism. A tentative catalytic cycle of asymmetric hydrogenation of 2-acetamido-3-oxobutyrates **1** is given in scheme VI. One plausible structure for the catalytically active species **12** could be a coordinatively unsaturated or saturated complex with solvent such as toluene or acetone generated presumably from binuclear species **11** prepared by protonation in an appropriate solvent of chiral mononuclear hexacoordinate ruthenium complexes **9**. The catalyst precursor undergoes ligand exchange with 2-acetamido-3-oxobutyrate forming a Ru(II) center with prefered hexahedral coordination. This step is inhibited with a good coordinating solvent such as acetonitrile for protonation (table II entry 1). Presumably ketoester is not able to displace acetonitrile. We supposed the formation of a chelate ruthenium amide complex **13** in which the amide carbonyl group are bounded to the metal[28]. This is supported by the observations that both rhodium and ruthenium complexes afforded a high syn preference and it is well established with rhodium in the asymmetric hydrogenation of dehydroamino acids the key factor is the formation of a chelate rhodium amide complex[29].The carbonyl insertion leads to Ru-alkoxy derivative **14** which is cleaved either by protic solvent or dihydrogen to give the hydroxylic compound with regeneration of ruthenium monohydride **12**.

(i) **Si face coordination of the keto group**



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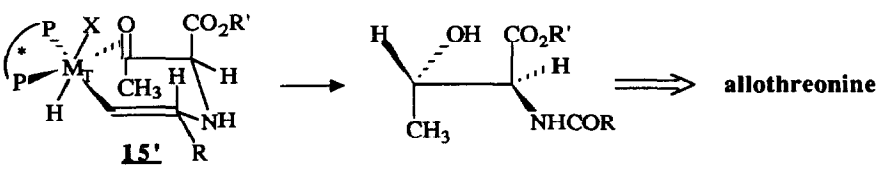
(ii) **Re face coordination of the keto group**



15'

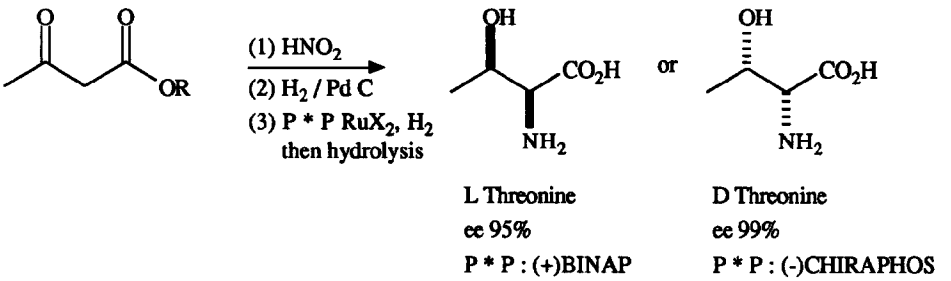
M_T = Rh ; X = H ; M_T = Ru ; X = Cl, Br or Solvent

Scheme VII

Considering the mechanism in the bidentate coordination of substrate to rhodium and ruthenium complexes formation of the chelate between the amide carbonyl group and methyl ketone can give rise to formation of two chair transition states by coordination of the *Si* and the *Re* faces of the keto group (Scheme VII). The chair transition state, *Si* coordination **15** was assumed to be predominant (CO_2R equatorial) rather than *Re* coordination **15'** of the methyl ketone (CO_2R axial) resulting in the preferential formation of threonine.

Conclusion : In this study the optimum conditions for hydrogenation of 2- acetamido-3-oxobutyrate with an ideal dynamic kinetic resolution has been realized not only with BINAP Ru complexes as reported by R. Noyori and H. Takaya[12a] but with CHIRAPHOS Ru catalysts[11, 13]. A practical synthesis of syn β-hydroxy α-aminoacid such as L and D threonine (94-99 % ee) is described in three steps from methyl or ethyl acetoacetate in 34% and 26% overall yield respectively after cristallization in ethanol.

We also provided in this synthetic reaction a general method for preparing complexes of known chiral bidentate phosphines complexes. The development for the first time of such ruthenium catalysts offers new opportunities in homogeneous catalysis and such studies are in progress.



Schema VIII

Acknowledgments: We thank Dr. Mercier (Rhône-Poulenc) for a gift of (+) and (-) CBD, Professor P. Dixneuf (Université de Rennes) for a gift of $RuCl_3,3H_2O$ and Professor H. Takaya (Kyoto University, Japan) for providing us a sample of (+) and (-) BINAP.

Experimental Section

General Methods. The following solvents were freshly distilled and stored under nitrogen 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 part per million (ppm) with TMS as an internal reference, and coupling are reported in hertz (Hz). Infrared (IR) spectra were recorded on a Perkin-Elmer 297 spectrometer. High Pressure Liquid Chromatography (HPLC) were recorded on Gilson 302 with Daicel Chiralpak W.H. column.

Ethyl oximino acetoacetate 7b : In one liter-three necked flask, fitted with a thermometer and reflux condenser, were placed 146 mL (1.16 mol) of ethyl acetoacetate and 168 mL of glacial acetic acid. The flask was cooled with an ice-salt bath, and a solution of 90 g sodium nitrite in 200 mL water was added slowly in order that the temperature stay below 30°C. The mixture was then stirred for a half an hour at 25°C, 600 mL of water added, and stirring continued for two hours. The mixture was extracted with 3 x 200 mL of ether, and the etheral extracts were washed with 100 mL of water, 4 x 100 mL of $NaHCO_3$ saturated, and once more with water. The ether was dried (Na_2SO_4), filtered, and the solvents were removed in vacuo. The oil crystalized to give 120 g of product (Yield : 65%). ^1H NMR δ 1.32 (t, 3H) ; 2.45 (s, 3H) ; 4.45 (q, 2H) ; 9.4 (sl, 1H) ; ^{13}C NMR δ 13.7 ; 25 ; 62.5 ; 150.8 ; 162.1 ; 195. mp = 47-48 °C.

Methyl oximino acetoacetate 7a : In an analogous procedure to that used for **7b**, 117 g of oil were obtained (Yield : 70%) ^1H NMR δ 2.45 (s, 3H) ; 3.95 (s, 3H) ; 9.7 (sl, 1H) ; ^{13}C NMR δ 25 ; 52.6 ; 150.7 ; 162.5 ; 194.7.

tButyl oximino acetoacetate 7c : In an analogous procedure to that used for **7b**, 13 g of white solid were obtained from 10 g of tButyl acetoacetate (Yield : 95%).^1H NMR δ 1.6 (s, 9H) ; 2.4 (s, 3H) ; 7 (sl, 1H). mp = 68°C.

Methyl-2-acetamido-3-oxobutanoate 1a : In a Schlenck apparatus, 25 g of oxime **7a**, 80 g of acetic anhydride and 800 mg of 10% Pd/C were introduced. The argon atmospher was replaced with hydrogen. After completion of reaction the suspension was filtered, and solvent removed under vacuo. The solid was recrystalized from ethyl acetate and hexane. 25 g of white needles were obtained (Yield : 90%). ^1H NMR δ 2.08 (s, 3H) ; 2.4 (s, 3H) ; 3.82 (s, 3H) ; 5.28 (d, J = 6.6, 1H) ; 6.81 (dl, 1H) ; ^{13}C NMR δ 22.3 ; 27.8 ; 53.1 ; 62.8 ; 166.6 ; 170 ; 198.6. Anal. Calcd. for $C_7H_{11}O_4$: C, 48.5 ; H, 6.3 ; N, 8.1. Found C, 48.7 ; H, 6.4 ; N, 8.0. mp = 88°C.

Methyl-2-propionamido-3-oxobutanoate 1b : In an analogous procedure to that used for **1a**, 2.4 g of product were obtained (Yield : 66%). ^1H NMR δ 1.05 (t, 3H) ; 2.3 (q, J = 7 Hz, 2H) ; 2.35 (s,3H) ; 3.9 (s, 3H) ; 5.3 (d, J = 7 Hz, 1H) ; 6.9 (dl, 1H) ; ^{13}C NMR δ 19.1 ; 27.9 ; 34.8 ; 53.1 ; 62.6 ; 166.6 ; 176.6 ; 198.6. Anal. Calcd. for $C_8H_{13}NO_4$: C, 51.34 ; H, 6.95 ; N, 7.49. Found C, 50.7 ; H, 7.0 ; N, 7.3.

Methyl-2-dimethylacetamido-3-oxobutanoate 1d : In an analogous procedure to that used for **1a**, 5.6 g of product were obtained (Yield : 65%). ^1H NMR δ 1.1 (d, J = 6 Hz, 6H) ; 2.3 (s, 3H) ; 2.45 (hept, J = 6 Hz, 1H) ; 3.68 (s, 3H) ; 5.15 (d, J = 7 Hz, 1H) ; 6.7 (dl, J = 7 Hz, 1H) ; ^{13}C NMR δ 19.1 ; 28 ; 34.9 ; 53.1 ; 62.7 ; 166.6 ; 176.6 ; 198.6

t-Butyl-2-acetamido-3-oxobutanoate 1e : In an analogous procedure to that used for **1a**, 4 g of product were obtained (Yield : 98%) ^1H NMR δ 1.45 (s, 9H) ; 2 (s, 3H) ; 2.2 (s, 3H) ; 5.15 (d, J = 6.4 Hz, 1H) ; 6.7 (dl, J = 6.4 Hz, 1H); ^{13}C NMR δ 22.2 ; 27.5 ; 27.9 ; 63.5 ; 83.5 ; 164.9 ; 169.9 ; 199.2.

Ethyl-2-acetamido-3-oxobutanoate : In an analogous procedure to that used for , 3.1 g of product were obtained (Yield : 82%). ^1H NMR δ 1.1 (t, J = 6.7 Hz, 3H) ; 2.1 (s, 3H) ; 2.4 (s, 3H) ; 4.35 (q,J = 6.7 Hz, 3H) ; 5.32 (d, J = 7.4 Hz, 1H) ; 6.75 (dl, 1H). ^{13}C NMR δ 13.8 ; 22.5 ; 27.9 ; 62.4 ; 63 ; 167.4 ; 169.9 ; 198.7.

Preparation of catalysts : The NORPHOS, DIOP, CHIRAPHOS, BPPM, BINAP ligands are commercially available from Aldrich, Merck, Janssen or Fluka. DIPAMP was synthetized on a multigram scale with the procedure developed recently in our laboratory[31].

Rhodium catalyst :

Bis(norbornadiene) rhodium perchlorate. In a Schlenck vessel, 69 mg of chloronorbornadiene rhodium (0.15 mmol), 27.6 mg of norbornadiene, and 3 mL of degassed dichloromethane were introduced. 62 mg of silver perchlorate (0.3 mmol) were added. The mixture was stirred without light for 1 hour and filtered under argon. The solid was washed three times with dried THF. The solvents were removed, and crystals washed twice with THF (Yield : 80%). 1H NMR d 1.15 (m, 4H) ; 4.12 (m, 4H) ; 5.2 (m, 8H).

Diphosphine norbornadiene rhodium perchlorate 8. In Schlenck vessel, 58 mg of bis(norbornadiene rhodium perchlorate (0.15 mmol) and diphosphine (1 equiv.) were diluted in 1 mL of degassed dichloromethane/THF (1/1). The mixture was vigorously stirred for 2 hours and poured in 50 mL degassed hexane. The precipitate was filtered and washed with hexane.

Ruthenium catalyst : The complex $CodRuMet_2$ was prepared by the literature method from $RuCl_3$, $3H_2O$[30].

Diphosphine ruthenium bis methylallyl complexes 9. General method : They were prepared as we described previously. $CodRuMet_2$ (0.5 mmol) and chiral diphosphine (1 equiv.) were placed under argon in Schlenck vessel. 2 mL of degassed hexane were added and the mixture was heated to 50°C during 5 hours. Solid was filtered under argon and washed with 2 mL degassed hexane. Complexes were stored under argon. $BINAPRu(bismethylallyl)_2$: hexane was replaced by hexane/toluene (3/7).

(-) DIOP Ru(Met)$_2$: ^1H NMR (250 MHz, C_6D_6) : 1.0 (m, 2H) ; 1.3 (s, 6H) ; 1.32 (q, J = 14.5 Hz, 4H) ; 2.04 (s, 6H) ; 2.55 (m, 2H) ; 2.79 (dd, J_1 = 8.5 Hz, J_2 = 13 Hz, 6H) ; 3.25 (t, J = 13 Hz, 6H) ; 4.15 (m, 2H) ; 6.8-8.0 (m, 20H, aromatics). ^{13}C NMR (62 MHz, C_6D_6) : 25.77 ; 27.2 ; 31.5 (m) ; 42.5 ; 48.31 (m) ; 78.8 ; 95.7 ; 107.9 ; 127-140 (aromatics). ^{31}P NMR (100 MHz, C_6D_6) : 36 (ref : H_3PO_4 85%). IR (Nujol) : 1595, 1240 cm^{-1}. $[\alpha]_D^{25}$ = +202 (c = 0.43, toluene). m. p. = 204°C (decomposition).

(-) CHIRAPHOS Ru(Met)$_2$: ^1H NMR (250 MHz, C_6D_6) : 1.06 (d, J = 6.5 Hz, 2H) ; 1.12 (d, J = 6.5 Hz, 2H) ; 1.24 (q, J = 2.5 Hz, 6H) ; 1.61 (d, J = 2.5 Hz, 2H) ; 1.74 (d, J = 2.5 Hz, 2H) ; 2.15 (s, 6H) ; 6.8-8.0 (m, 20H, aromatics). ^{13}C NMR (62 MHz, C_6D_6) : 18.4 ; 26.1 ; 40.3 (m) ; 44.3 (d, J = 28 Hz) ; 44.7 (d, J = 28 Hz) ; 45.9 ; 97.1 ; 127-133 (aromatics). ^{31}P NMR (100 MHz, C_6D_6) : 87.6 (ref : H_3PO_4 85%). IR (Nujol) : 1580, 1085, 1015, 760, 720 cm^{-1}. $[\alpha]_D^{25}$ = +60 (c = 0.2, toluene). m. p. = 183°C (decomposition).

Dihalogenodiphosphine ruthenium complexes 10. General method : Diphosphine ruthenium bis methyl allyl complex was dissolved in 1 mL degassed solvent (dichloromethane, toluene or acetone). 2 equivalents of 2-3N HX in methanol (X = Cl, Br) were slowly added. After the resulting dark red solution was stirred for 1 hour, the solvent was removed under reduced pressure to give dihalogeno complexes which were used directly as hydrogenation catalyst.

Hydrogenation procedure : A solution of requisite substrate (1 mmole) in degassed solvant (2 mL) was placed in 10 mL Schlenck vessel and degassed by 3 freeze-thaw cycles. This mixture was added to the catalyst (0.25-1%) in glass vessel and placed under argon in 250 mL stainless steel autoclave. Argon atmospher was replaced with hydrogen. Hydrogen was pressurized to 70-100 atm, and the solution was stirred for 48-72 h. The solvent was removed under reduced pressure. Conversion rate were determined with ^1H NMR analysis.

(2S, 3R) Methyl-2-acetamido-3-hydroxybutanoate : ^1H NMR δ 1.22 (d, J = 6.2 Hz, 3H) ; 2.07 (s, 3H) ; 3.6 (sl, 1H) ; 3.76 (s, 3H) ; 4.34 (dq, J_1 = 6.2 Hz, J_2 = 2.4 Hz, 1H) ; 4.6 (dd, J_1= 10 Hz, J_2 = 2.4 Hz, 1H) ; 6.82 (dl, J = 10 Hz, 1H) ; ^{13}C NMR δ 19.9 ; 22.6 ; 52.2 ; 57.7 ; 67.5 ; 171.1 ; 171.5. Anal. calcd. for $C_7H_{13}NO_4$: C, 48.0 ; H, 7.43 ; N, 8.0. Found C, 48.2 ; H, 7.5 ; N, 8.1.mp = 92-94°C.

(2S, 3S) Methyl-2-acetamido-3-hydroxybutanoate : ^1H NMR δ 1.19 (d, J = 6.6 Hz, 3H) ; 2.10 (s, 3H) ; 3.6 (sl, 1H) ; 3.78 (s, 3H) ; 4.17 (dq, J_1 = 6.6 Hz, J_2 = 3.4 Hz, 1H) ; 4.69 (dd, J_1= 7.2 Hz, J_2 = 3.4 Hz, 1H) ; 6.82 (dl, J = 7.2 Hz, 1H) ; ^{13}C NMR δ 19.0 ; 22.7 ; 52.2 ; 58.2 ; 68.5 ; 170.7 ; 171.2.

(2S, 3R) Ethyl-2-acetamido-3-hydroxybutanoate : ^1H NMR δ 1.17 (m, 6H) ; 2.10 (s, 3H) ; 3.4 (sl, 1H) ; 4.28 (q, J = 7 Hz, 2H) ; 4.17 (m, 1H) ; 4.56 (dd, J_1= 8.9 Hz, J_2 = 2.6 Hz, 1H) ; 6.74(dl, 1H) ; ^{13}C NMR δ 14.1 ; 20.0 ; 22.9 ; 57.7 ; 61.5 ; 67.8 ; 170.3 ; 171.2.

(2S, 3S) Ethyl-2-acetamido-3-hydroxybutanoate : ^1H NMR δ 1.17 (m, 6H) ; 2.07 (s, 3H) ; 3.4 (sl, 1H) ; 4.28 (q, J = 7 Hz, 2H) ; 4.3 (m, 1H) ; 4.65 (dd, J_1= 4.7 Hz, J_2 = 3.3 Hz, 1H) ; 6.74 (dl, 1H) ; ^{13}C NMR δ 14.1 ; 18.8 ; 22.8 ; 58.3 ; 61.7 ; 68.7 ; 170.3 ; 171.2.

(2S, 3R) t-Butyl-2-acetamido-3-hydroxybutanoate : ^1H NMR δ 1.25 (d, J = 6.25 Hz, 3H) ; 1.44 (s, 9H) ; 2.04 (s, 3H) ; 3.13 (sl, 1H) ; 4.25 (qd, J_1 = 2.75 Hz, J_2 = 6.25 Hz, 1H) ; 4.44 (dd, J_1= 8.5 Hz, J_2 = 2.75 Hz, 1H) ; 6.59 (dl, J = 8.5 Hz, 1H) ; ^{13}C NMR δ 19.9 ; 22.6 ; 27.7 ; 58.0 ; 67.7 ; 81.6 ; 170.0 ; 171.0. Anal. calcd. for $C_{10}H_{19}NO_4$: C, 55.3 ; H, 8.7 ; N, 6.4. Found C, 53.5 ; H, 8.5 ; N, 6.2.

(2S, 3S) t-Butyl-2-acetamido-3-hydroxybutanoate : ^1H NMR δ 1.14 (d, J = 6.25 Hz, 3H) ; 1.45 (s, 9H) ; 2.04 (s, 3H) ; 3.13 (sl, 1H) ; 4.15 (dq, J_1 = 3 Hz, J_2 = 6.25 Hz, 1H) ; 4.56 (dd, J_1= 7 Hz, J_2 = 3 Hz, 1H) ; 6.59 (dl, 1H) ; ^{13}C NMR δ 18.3 ; 22.6 ; 27.7 ; 58.5 ; 66.5 ; 82.5 ; 169.0 ; 171.0.

Obtention of threonine : α-amido β-hydroxybutanoate ester were hydrolyzed (3N HCl, reflux, 3 hours). The mixture was filtered and solvents were removed under vacuo. The crude product was diluted in 3 mL dry ethanol, 3 mL of propylene oxide were added and the mixture refluxed for 15 mn. The white solid was filtered, enantiomeric excesses were determined by HPLC (Eluent : $CuSO_4$ (0.25 mM), Flow rate : 1mL/mn T = 50°C). Retention Time : D-Allothreonine (16.97) ; D-Threonine (19.37) ; L-Threonine (25.88) ; L-Allothreonine (31.34).

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