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Asymmetric hydrogenation by an in situ prepared (*S*)-BINAP–Ru(II) catalytic system

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Abstract

A catalytic system obtained by in situ mixing $[RuCl_2(benzene)]_2$ and (*S*)-BINAP has been tested in the asymmetric hydrogenation of various substrates. The best results have been obtained working in methanol: excellent optical purities were achieved in the reduction of substrates such as tiglic acid (83%), geraniol (97%) and methyl 3-oxobutanoate (95%). Some investigations on the nature of the catalyst have been carried out. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Asymmetric hydrogenation; In situ catalyst; Ruthenium

1. Introduction

Ruthenium(II) complexes of atropisomeric diphosphine ligands such as 2,2′-bis(diphenylphosphino)-1,1′-binaphtyl (BINAP) have been widely used as catalysts for many homogeneous asymmetric reactions [1]. In particular, they have been used with great success in the asymmetric hydrogenation of allylic alcohols [2,3], β-ketoesters [4], α,β-unsaturated carboxylic acids [5] and α-acylaminoacrylic acids [6].

Usually, ruthenium complexes are synthesised and isolated prior to their use in asymmetric catalysis [7–12]. On the contrary, catalytic systems based on rhodium or iridium are usually prepared by in situ mixing the metal containing species and the chiral ligand without isolation [13].

Since most of the ruthenium complexes containing chelating diphosphines are very air sensitive, their in situ preparation would be very convenient. Indeed, a few efforts have been done to develop in situ prepared Ru–BINAP catalysts: for instance Taber reported the use of a mixture of $[RuCl_2(cyclooctadiene)]_n$ and BINAP in the presence of triethylamine [14] and Noyori the use of a system obtained by reacting $[RuCl_2(benzene)]_2$ with BINAP in boiling *N*, *N*-dimethylformamide [15]. These systems have been mostly used in the hydrogenation of β-ketoesters and to the best of our knowledge no detailed account on their efficiency in the reduction of other substrates has been reported.

In this paper, we wish to report the results obtained in the asymmetric hydrogenation of various substrates using the catalytic system

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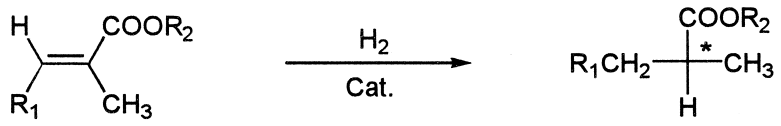


1a-c **2a-d**

a: R_1= CH_3, R_2 = H
b: R_1= CH_3, R_2 = CH_3
c: R_1 = Ph, R_2 = H

a: R_1= CH_3, R_2 = H
b: R_1= CH_3, R_2 = CH_3
c: R_1 = Ph, R_2 = H
d: R_1 = Ph, R_2 = CH_3

Scheme 1.

obtained by in situ mixing $[RuCl_2(benzene)]_2$ [16,17] and (*S*)-BINAP [18].

2. Results and discussion

The hydrogenation reactions were carried out by pressurising with hydrogen a stainless steel autoclave charged with a solution containing the prochiral substrate, $[RuCl_2(benzene)]_2$ and (*S*)-BINAP.

The catalytic activity of this system was first tested in the hydrogenation of (*E*)-2-methyl-2-butenoic acid (tiglic acid) **1a**, as representative of the important class of α,β-unsaturated carboxylic acids (Scheme 1).

The relevant results are reported in Table 1. At 80°C in CH_2Cl_2, the reduction of **1a** quantitatively affords (*S*)-2-methylbutanoic acid (*S*)-**2a** in 64% o.p. (entry 1). Attempts to improve the optical purity by lowering the reaction temperature were unsuccessful because at 50°C the catalyst proved to be inactive (entry 2).

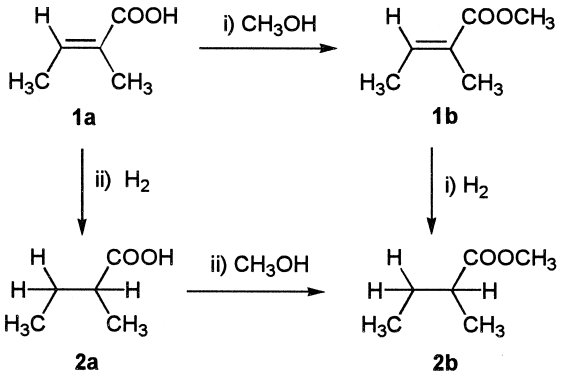
Next, we tested the effect of the hydrogen partial pressure: in general the asymmetric induction increases with increasing $P(H_2)$, however in a few cases, notably with some Ruthenium catalysts, the opposite behaviour is recognised [5]. With our system, on decreasing $P(H_2)$ both the catalytic activity and the asymmetric induction are reduced (entry 3). A substantial improvement can be obtained using *N,N*-dimethylformamide as solvent: the reaction proceeds even at 40°C (entry 4). As usual, the decrease of the reaction temperature causes an increase of the enantioselectivity and (*S*)-**2a** is obtained in 82% o.p..

The best results are obtained in methanol (entry 5); in this solvent at 40°C the hydrogenation of **1a** is much faster than in DMF giving (*S*)-**2a** in 83% o.p. In methanol a little amount of the saturated methyl ester (*S*)-**2b** is also formed (yield 7%, o.p. 70%). Two pathways (Scheme 2) can account for the formation of **2b**: path (i) involves the esterification of the unsaturated carboxylic acid **1a** followed by its hydrogenation, vice versa path (ii) implies the hydro-

Table 1
Asymmetric hydrogenation of tiglic acid **1a** using an in situ prepared ruthenium catalyst

Run	Solvent	*T* (°C)	*t* (h)	Conversion (%)	Products	Yield (%)	o.p.[a] (%)
1	CH_2Cl_2	80	30	100	(*S*)-**2a**	100	64
2	CH_2Cl_2	50	136	0	–	–	–
3[b]	CH_2Cl_2	80	80	94	(*S*)-**2a**	94	51
4	DMF[c]	40	24	34	(*S*)-**2a**	34	82
5	CH_3OH	40	9	63	(*S*)-**2a**	56	83
					(*S*)-**2b**	7	70
6	CH_3OH	0	72	22	**2a**	12	n.d.
					2b	8	n.d.
					2c	2	n.d.

Reaction conditions: $[RuCl_2(benzene)]_2$ /(*S*)-BINAP = 1/2 (mol/mol); Solvent = 10 ml; Substrate = 51.5 mmol; Substrate/Ru = 1000 (mol/mol); $P(H_2)$ = 100 atm.
[a] Maximum rotatory powers are reported in Section 4.
[b] $P(H_2)$ = 50 atm.
[c] DMF = *N,N*-dimethylformamide.



Scheme 2.

genation of **1a** to give the saturated acid **2a** followed by its esterification.

The formation of (*S*)-**2b** proceeds via pathway (ii) as demonstrated by an independent experiment. In fact, under the same reaction conditions the hydrogenation of methyl 2-methyl-2-butenoate (methyl tiglate) **1b** affords **2b** of prevailing (*R*) configuration in 5% o.p. (entry 1 of Table 2). This change in stereochemistry is noteworthy, even if it is not unusual to find large differences between the asymmetric induction obtained in the hydrogenation of a carboxylic acid and its ester [19–21] owing to the higher coordinating ability of the carboxylic group.

A decrease of the reaction temperature to 0°C (entry 6 of Table 1) does not afford any improvement since the hydrogenation reaction becomes exceedingly slow, meanwhile an enhanced formation of esters is observed indicating that the catalyst takes on an acid behaviour.

The hydrogenation of α-methylcinnamic acid **1c** (Scheme 1) proceeds at high temperatures. As a matter of fact even using high catalyst/substrate ratios and prolonged reaction times, neither at 40°C in methanol nor at 80°C in dichloromethane any reaction is observed. At 80°C in methanol, the substrate is quantitatively converted affording a mixture of (*S*)-**2c** (80% yield, 34% o.p.) and of its methyl ester **2d** (20% yield) (entry 2 of Table 2).

At 40°C in methanol, α-acetamidocinnamic acid **3** is quantitatively hydrogenated to give (*R*)-*N*-acetyl-3-phenylalanine (*R*)-**4** (Scheme 3) in 50% o.p. The difference in reactivity between **1c** and **3** is not surprising and has been also recognised with Rhodium based catalysts [22,23].

At 30°C and $P(H_2) = 100$ atm in methanol, the hydrogenation of geraniol **5** (entry 1 of Table 3) affords a mixture of (*R*)-**6a** (yield 54%, 80% o.p.) and dihydrocitronellol **6b** (yield 46%) (Scheme 4); no products due to double bond migration or (*E*)–(*Z*) isomerization are observed.

A few experiments at lower hydrogen pressures or lower temperatures have been carried out in order to optimise the yield and the o.p. of (*R*)-**6a**. At 30°C and $P(H_2) = 50$ atm (entry 2), the **6a**/**6b** ratio increases up to 4/1, however the o.p. of (*R*)-**6a** decreases to 69%. The best results were achieved at 0°C and $P(H_2) =$

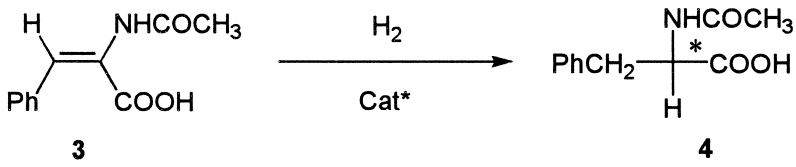
Table 2
Asymmetric hydrogenation of α,β-unsaturated carboxylic acids and esters using an in situ prepared ruthenium catalyst

Run	Substrate	*T* (°C)	*t* (h)	Conversion (%)	Products	Yield (%)	o.p.[a] (%)
1	**1b**	40	72	95	(*R*)-**2b**	95	5
2	**1c**	80	20	100	(*S*)-**2c**	80	34
					2d	20	n.d.
3[b]	**3**	40	113	100	(*R*)-**4**	100	50

Reaction conditions: $[RuCl_2(benzene)]_2$/(*S*)-BINAP = 1/2 (mol/mol); CH_3OH = 10 ml; Substrate = 51.5 mmol; Substrate/Ru = 1000 (mol/mol); $P(H_2) = 100$ atm.

[a] Maximum rotatory powers are reported in Section 4.

[b] Substrate/Ru = 500 (mol/mol).



3 4

Scheme 3.

100 atm (entry 3): in these conditions (*R*)-**6a** is obtained almost chemoselectively in 97% o.p.

At 80°C in methanol, acetophenone **7** gives (*S*)-1-phenylethanol (*S*)-**8** (Scheme 5) very slowly and with very poor o.p. (4%) (entry 4 of Table 3). On the other hand it is known that the presence of additional functional groups is necessary to achieve high asymmetric inductions in the reduction of ketones [24].

At 30°C in methanol, methyl 3-oxobutanoate **9** is quantitatively hydrogenated to (*S*)-methyl 3-hydroxybutanoate (*S*)-**10** (Scheme 6) in 95% o.p. (entry 5).

The hydrogenation of **9** slowly proceeds also in dichloromethane giving (*S*)-**10** in 94% o.p. (entry 6). When the hydrogenation of **9** is carried out in methanol at 0°C only a very little amount of the hydrogenated product **10** is formed; the main reaction product is methyl 3,3-dimethoxybutanoate **11** which formally arises from the addition of methanol to the substrate. Thus, at low temperature the catalytic system once more acts as an acid catalyst promoting the formation of ketals [25]. By comparing the results obtained at 0°C with tiglic acid, geraniol and methyl 3-oxobutanoate it appears that the nature of the substrate plays an important role in determining the temperature below which the acid behaviour of the catalyst occurs.

Finally, it should be noted that the best asymmetric induction has been obtained using a BINAP to Ru ratio = 1 and that the use of higher ligand to metal ratios leads to a large decrease of enantioselectivity even if accompanied by higher reaction rates.

Some studies were carried out to get a better insight on the nature of the catalytic species by monitoring via NMR spectroscopy the species

Table 3
Asymmetric hydrogenation of various substrates using an in situ prepared ruthenium catalyst

Run	Substrate	*T* (°C)	*t* (h)	Conversion (%)	Products	Yield (%)	o.p.[a] (%)
1[b]	**5**	30	18	100	(*R*)-**6a**	54	80
					6b	46	
2[b,c]	**5**	30	26	97	(*R*)-**6a**	80	69
					6b	20	
3	**5**	0	26	82	(*R*)-**6a**	81	97
					6b	1	
4	**7**	80	261	99	(*S*)-**8**	98[d]	4
5	**9**	30	14	100	(*S*)-**10**	100	95
6[e]	**9**	30	140	100	(*S*)-**10**	100	94

Reaction conditions: $[RuCl_2(benzene)]_2$/(*S*)-BINAP = 1/2 (mol/mol); CH_3OH = 10 ml; Substrate = 51.5 mmol; Substrate/Ru = 1000 (mol/mol); $P(H_2)$ = 100 atm.

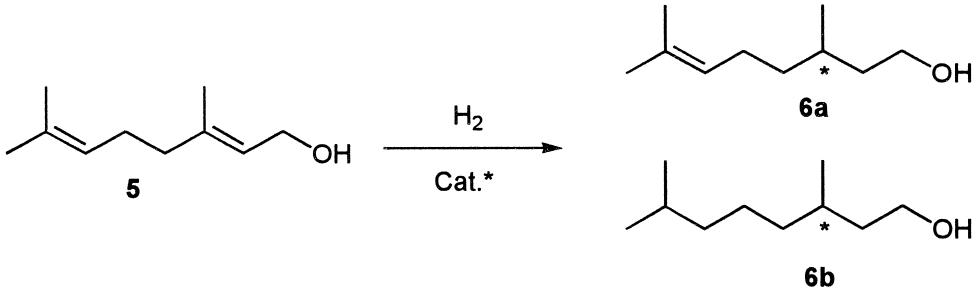
[a] Maximum rotatory powers are reported in Section 4.

[b] The optical purity of **6a** was calculated according to a widely used procedure based on the measurement of the optical rotation of a sample of pure **6b** obtained upon hydrogenation of the **6a**/**6b** mixture in the presence of Pd/C.

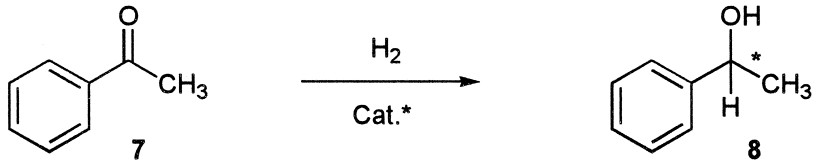
[c] $P(H_2)$ = 50 atm.

[d] Methyl(1-phenylethyl)ether is also formed (1%).

[e] Dichloromethane as solvent.



Scheme 4.

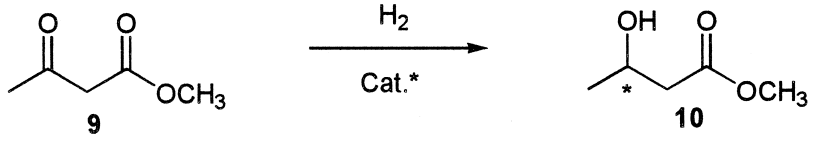


Scheme 5.

present in solution just before the pressurisation with hydrogen and in the crudes after the reaction.

Treatment of $[RuCl_2(benzene)]_2$ with an equivalent of BINAP in dichloromethane under nitrogen atmosphere produces a brown suspension which upon addition of small amounts of methanol affords a clear orange solution. The ^{31}P and ^{1}H NMR spectra show that under these conditions the known complex [RuCl(benzene)(BINAP)]Cl **12** is formed [8]. The presence of methanol is not necessary to form **12**: as a matter of fact this species is also formed when a polar substrate like tiglic acid is added to the $[RuCl_2(benzene)]_2$/BINAP mixture. These findings demonstrate that complex **12** is the metal containing species present in the reactor before pressurisation with hydrogen. During the reaction this species must undergo further rearrangements because experiments of catalyst recovering demonstrate that the signals stemming from **12** are no more recognisable in the NMR spectra after the reaction.

We were unable to get conclusive evidences on the nature of the true catalytic species since three sets of resonances are present in the ^{31}P NMR spectra of the crudes recovered after the reaction: an AB spin system ($\delta_a = 76.1$ ppm, $\delta_a = 72.3$ ppm, $J(P-P) = 49$ Hz) and two broad singlets centred at $\delta = 56.0$ and $\delta = 50.9$ ppm, respectively. The chemical shifts of these resonances do not change on changing the substrate. The relevant ^{1}H NMR spectra are not much revealing since they display only complex patterns in the aromatic region of the spectrum which can be attributed to the BINAP ligand.



Scheme 6.

Table 4
Maximum rotatory powers and sign-configuration relations adopted as reference in this work

	$[\alpha]^{T}_{D\ max}$	T (°C)	Medium	D^{T} (g/ml)	Sign-configuration	Ref.
2-Methylbutanoic acid	19.2	25	Neat	0.931	(+)-(*S*)	[27]
Methyl 2-methylbutanoate	26.0	21	c 2.0, MeOH	–	(+)-(*S*)	[27]
3-Phenyl-2-methylpropanoic acid	17.87	21	c 5.0, EtOH	–	(+)-(*S*)	[28]
2-Acetyl-3-phenylalanine	47.6	25	c 4.0, EtOH	–	(+)-(*R*)	[29]
Methyl 3-hydroxybutanoate	23.5	22	Neat	1.05	(+)-(*S*)	[30]
3,7-Dimethyloctanol	4.20	25	c 5.0, $CHCl_3$	–	(+)-(*R*)	[31,32]
3,7-Dimethyloct-6-en-1-ol	5.37	20	Neat	0.857	(+)-(*R*)	[31,32]
1-Phenylethanol	43.6	25	Neat	0.979	(+)-(*R*)	[33]

On the other hand, they show that the benzene molecule is no more coordinated to the metal as inferred by the disappearance of the relevant resonance at 5.76 ppm. [1]

All these findings support the hypothesis that complex **12** in the hydrogenation reaction must be regarded only as a catalyst precursor. This idea is strengthened by the observation that complex **12** is the sole species present in the crudes recovered after the experiments carried out using **9** at 0°C. As reported above, under these conditions very little hydrogenation of the substrate is observed and the system behaves as an acid catalyst: in keeping it may be concluded that the acid behaviour is due to complex **12**.

3. Concluding remarks

The in situ system here reported allows to obtain catalytic activities and stereoselectivities close to those obtained using corresponding air sensitive preformed catalysts. Since this in situ system requires a minimum handling of the catalyst precursor and both BINAP and $[RuCl_2(benzene)]_2$ are commercially available (e.g., by Aldrich) we believe that it is particularly well suited for preliminary investigations.

[1] ^{1}H NMR of [RuCl(benzene)(BINAP)]Cl ($CDCl_3$): δ (ppm) 8.0–6.6 (m, H_{arom}), 6.48 (d, H_{arom}, $J = 8.5$ Hz), 5.96 (d, H_{arom}, $J = 8.6$ Hz), 5.76 (s, C_6H_6). In Ref. [8], no detailed ^{1}H NMR data are reported for complex [RuCl(benzene)(BINAP)]Cl.

4. Experimental

(*S*)-(−)-BINAP [18] and $[RuCl_2(benzene)]_2$ [16,17] were synthesised as described in literature. Methyl tiglate was prepared by esterification of commercial tiglic acid (Aldrich). All the other substrates were commercial (Aldrich) and used as received. Analytical grade solvents (C. Erba) were purified according to standard methods [26]. Optical rotations were measured on a Perkin Elmer 241 polarimeter assuming as maximum values those reported in Table 4.

GLC analyses were carried out on a Hewlett-Packard 5890 gas chromatograph. GC-MS analyses were carried out on Hewlett-Packard 5890 gas chromatograph interfaced to a Hewlett-Packard 5971 mass detector. All manipulations were carried out under Argon in Schlenk-type glassware. The hydrogenation apparatus consists of a magnetically stirred 150 ml stainless steel autoclave equipped with valves and manometer.

4.1. General procedure for hydrogenation reactions

In a typical experiment (run 6 of Table 3), 6.0 g (51.5 mmol) of methyl 3-oxobutanoate were introduced in a Schlenk tube together with 10 ml of CH_3OH. The system was evacuated and then filled with argon. Under argon, 13 mg (26×10^{-3} mmol) of $[RuCl_2(benzene)]_2$ and 32 mg (52×10^{-3} mmol) of (*S*)-(−)-BINAP were added to the solution and kept under stirring until an orange solution was obtained. The reac-

tion mixture was transferred via cannula into the autoclave. The autoclave was pressurised with 100 atm of H_2 and heated with a thermostatic bath (± 0.1°C) to 30°C. After 14 h, the autoclave was cooled to room temperature, the residual gas vented off, the reaction mixture analysed by GLC and GC-MS and the product was recovered by distillation at reduced pressure.

4.2. Characterisation of the catalytic system

A total of 10 mg (20×10^{-3} mmol) of [$RuCl_2$(benzene)]$_2$ were added under argon to an oxygen free solution of (*S*)-(−)-BINAP (25 mg, 40×10^{-3} mmol) in $CDCl_3$ (3 ml). The resulting brown suspension was treated with 200 μl of degassed CH_3OH and kept under stirring until a clear orange solution was obtained. This latter was transferred via cannula into a NMR tube for the spectroscopic investigations.

4.3. Recovery of the catalyst

In a typical experiment (run 6 of Table 3), at the end of the reaction the crude was transferred via cannula into a distillation apparatus. The volatile components were distilled off under high vacuum using minimum heating. The red solid obtained was dissolved in degassed $CDCl_3$ (1 ml). The resulting red solution was transferred via cannula into an NMR tube for the spectroscopic investigations.

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