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Asymmetric Catalytic Reduction of Carbonyl Compounds Using C_2 Symmetric Diamines as Chiral Ligands.

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Abstract : The catalytic asymmetric reduction of prochiral ketones by hydride transfer using various C_2 symmetric chiral diamines as ligands and rhodium complexes is studied. Kinetic studies show an increase of the enantiomeric excess with the conversion.

Nitrogen containing ligands are more and more used in asymmetric catalysis[1] for reactions as different as carbonyl reduction[2,3] or allylic alkylation[4], ... They present many advantages upon their phosphorus analogs (accessibility, easy recovering,...) and in the future they could probably replace phosphines in some cases.

Optically active disymmetric alkylphenanthrolines have been shown by Gladiali[5] *et al.* to be efficient ligands in enantioselective reduction of acetophenone by hydride transfer in the presence of rhodium catalysts : up to 65% e.e. has been obtained and a mechanism has been proposed based on UV analyses and investigations on the influence of different parameters. According to the authors, a catalytic cycle for the hydrogenation of acetophenone by hydride transfer starting from compound **I**, can be drawn as reported in Figure 1.

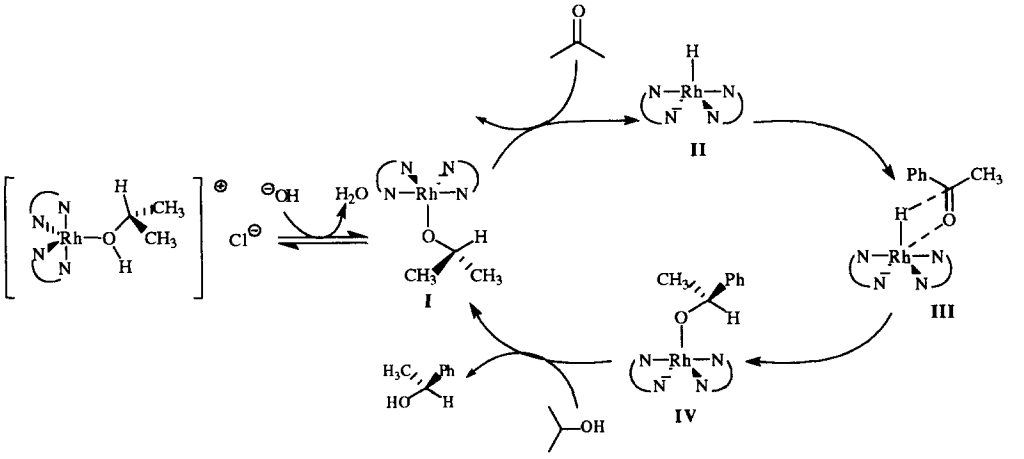


Figure 1 : Proposed mechanism for the hydride transfer reduction[5].

Hydride abstraction from the 2-propyloxy species gives the pentacoordinated Rh hydride **II** . When the (-)-(*S*)-3-(1,2,2-trimethylpropyl)-1,10-phenanthroline is used as ligand, the complex **II**, in the following stereodetermining step, should be preferentially added to the Re face of acetophenone to afford the (*S*)-alkoxy

derivative 4, the (-)-(*S*)-1-phenylethanol being the prevailing configuration. Displacement of 1-phenylethanol by 2-propanol would then restore the starting situation affording the intermediate **I** again. The hydride **II** is the key intermediate of this mechanism and the species responsible for the stereoselectivity. When a C_2 disubstituted ligand, (+)-(*S,S*)-3,8-di-*sec*.butyl-1,10-phenanthroline is used, the catalytic system exhibits a poor activity and is devoid of enantiodifferentiating ability.

More recently, we reported[3] 67% e.e. at 100% conversion for the same reaction using a C_2 symmetric diamine ligand. This encouraging result led us to test our system on other substrates for a better understanding of the catalytic process. Therefore we reduced several carbonyl substrates by hydride transfer from 2-propanol under an inert atmosphere in the presence of $[Rh(C_6H_{10})Cl]_2$ as the catalyst precursor, KOH as basic cocatalyst and chiral diamines as inductors (Figure 2).

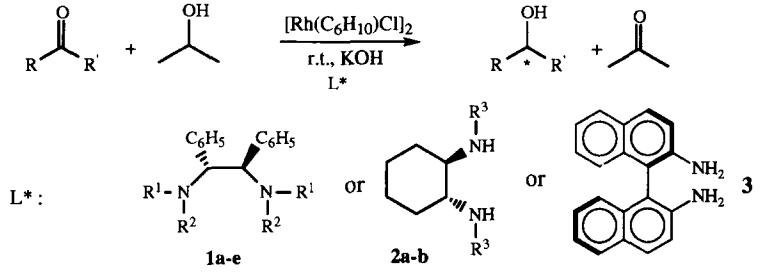


Figure 2 : Enantioselective reduction of various substrates using chiral C_2 symmetric diamines.

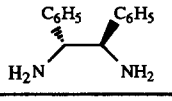
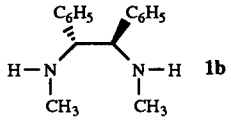
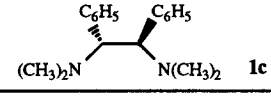
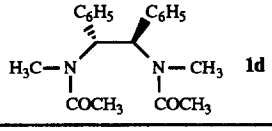
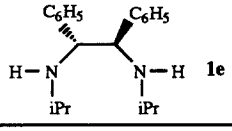
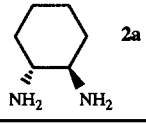
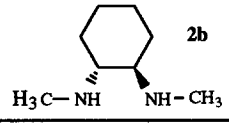
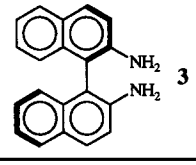
Our system appeared to be very much dependent on several of the parameters which are investigated in this work. Kinetic studies led us to draw hypotheses upon the mechanism which are also reported. Finally, a mechanism is proposed.

LIGAND STRUCTURE

Different C_2-symmetric ligands have been tested for the reduction of acetophenone : 1,2-diphenylethanediamine (Table 1, entries 1-7) or cyclohexyldiamine (Table 1, entries 8-9) derivatives and one ligand with atropoisomerism (Table 1, entry 10).

Ligands bearing NH_2 groups give poor conversion and e.e. (Table 1, entries 1, 8 and 10), whatever their overall structure. These compounds are less basic and less sterically demanding than substituted nitrogen ligands. Either one or both of these facts could explain the low activity and/or low enantioselectivity. In the case of diamine **1b**, X-ray and NMR studies have shown that, in the corresponding aminal, the nitrogen substituents arrange themselves in a *trans* configuration to the adjacent C-phenyl groups[6]. We can assume that the metal ligand complex takes the same conformation. When bound to the rhodium, the nitrogen atom becomes a stereogenic center and it is necessary to have three different substituents on the nitrogen to observe good e.e., which is not the case with diamine **1a** (Table 1, entries 1 and 3). To support this hypothesis, we have synthesized the tetramethylated diamine **1c** (Table 1, entry 4). This ligand exhibits higher activity than ligand **1b** for example, but very poor enantioselectivity. This result is consistant with the necessity of three different groups on the nitrogens and shows that the e.e. observed is not only due to the chirality of the backbone. In the case of the hindered diisopropylamine **1e** the substrate cannot approach the metal which explains the weak conversion (8% in 7 days) and the poor e.e. (28%) (Table 1, entry 6). Even if ligand **1d** induces low e.e. (Table 1, entry 6), it proves that the amide function is a potential ligand for asymmetric hydride transfer catalysis. As

Table 1 : Influence of the Ligand Structure on the Enantioselectivity.

Entry	Ligand	Time (days)	Conversion (%)	e.e. (a) (%)
1	 **1a**	8	94	17 (*R*)
2	 **1b**	3h	10	48 (*R*)
3		7	100	67 (*R*)
4	 **1c**	4	93	6 (*R*)
5	 **1d**	1	10	3 (*S*)
6		8	90	4 (*S*)
7	 **1e**	8	8	28 (*R*)
8	 **2a**	6	5.5	12 (*S*)
9	 **2b**	5	100	0
10	 **3**	3	<1	0

conditions : [Rh]/[S] = 5%; T = 25°C; [L*]/[Rh] = 2; 7 days, [S] = 1.6 10^{-2}M (initial concentration); a : absolute configuration.

for the cyclohexyldiamines **2a** and **2b**, the results are not consistent with the ones obtained for the diamine **1** series (Table 1, entries 8 and 9). This can be due to the less differenciated structure of the rhodium intermediate complexes because of the flexible cyclohexyl part of the ligand.

The ability of the ligands to form a hydrogen bond with acetophenone can also be an explanation to the differences of activity and selectivity. Ligands **1a** and **1b** are both donors and acceptors of hydrogen bonds while ligands **1c** and **1d** are only acceptors of such non covalent bonds. Moreover, ligand **1b** is linked to the acetophenone which decreases the number of possibilities for the substrate to approach the catalytic species and is favorable for a high e.e..

We have also studied the influence of the ratio of ligand to catalyst : 2, 4 and 8 equivalents of diamine per rhodium were tested and there was no difference of activity and selectivity in these 3 cases, contrary to that observed by others with tetrahydrobi(oxazole) iridium complexes[4a]. Therefore we used a ligand to catalyst ratio of 2 in the rest of our study.

EFFECTS OF THE CATALYST CONCENTRATION and TEMPERATURE

The effect of the catalyst concentration is studied in the reduction of acetophenone with ligand **1b**. The initial concentration of the substrate is kept constant in all the cases ($1.6\ 10^{-2}$M) and the catalyst concentration is thus expressed by the rhodium to substrate ratio ([Rh]/[S]) (Table 2).

Table 2 : Influence of the Catalyst Concentration on the Reaction Rate and Stereoselectivity.

Entry	T (°C)	[Rh]/[S] (%)	Time (days)	Conversion (%)	e.e. [c] (%)
1	82	0.05	7	1	49
2	82	0.1	7	2.5	53
3	82	1	5	100 (98)[a]	55[b]
4	82	5	2	100	52
5	25	5	7	100	**67**

conditions : [KOH]/[Rh] = 24; **1b**/$[Rh(C_6H_{10})Cl]_2$ = 2; [S] = $1.6\ 10^{-2}$M (initial concentration); a : isolated yield in 1-phenylethanol; b : e.e. measured by GC and polarimetry; c : e.e. measured by GC.

The activity of the catalyst depends on its concentration but its stereoselectivity is not notably affected by this parameter. This indicates that the relative concentration of the catalytic intermediate responsible for the stereoselectivity remains constant if compared to the other catalytic species. It is noteworthy that 1-phenylethanol is quantitatively obtained at 100% conversion (Table 2, entry 3).

An increase of the temperature leads to a decrease of the difference between the diastereoisomeric transition states. Thus, working at low temperature permits generally an increase in the enantioselectivity of the catalytic system. Nevertheless, Gladiali[5] *et al.* have not noticed any beneficial effect on the stereoselectivity with their system by lowering the reaction temperature from 83°C (2-propanol reflux) to 60°C. In our case, the e.e. goes from 52% at 83°C (Table 2, entry 4) to 67% at 25°C (Table 2, entry 5) but it takes 7 days to reach 100% conversion instead of 2 days. Therefore no experiment was carried out below 25°C and this temperature was chosen for the rest of our work.

KOH CONCENTRATION

The concentration of KOH is an important factor as the deprotonation of the alcohol (either before or after its coordination to the rhodium) leads to the first intermediate complex of the catalytic cycle (Figure 1, complex 1). We have thus tested the influence of KOH concentration ([KOH]) on the reaction (Table 3).

The catalytic system is inactive without a basic cocatalyst (Table 3, entry 1). The conversion increases with the KOH concentration but there is an optimum in enantioselectivity for a [KOH] to [Rh] ratio between 6 and 10 ([Rh] = constant).

Table 3 : Influence of the Co-catalyst Concentration.

Entry	[KOH]/[Rh]	Conversion (%)	e.e.* (%)
1	0	0	0
2	1	5	47
3	6	64	66
4	10	100	61
5	24	100	60
6[a]	100	100	52

conditions : [Rh]/[S] = 5%; T = 25°C; **1b**/[Rh] = 2; 7 days, [S] = 1.6 10^{-2}M (initial concentration); a) : 2 days. *measured by gas chromatography on the crude product.

It remains unclear whether the deprotonation of iPrOH occurs before[5] or after its coordination to the rhodium. Nevertheless, when a large excess of KOH is used, we can assume that $iPrO^-$ is formed in the reaction medium and the alcoholate and OH^- can compete with the diamine ligands which could thus explain the drop of e.e. (Table 3, entry 6). This phenomenon was not observed in the case of phenanthrolines[5] probably because they are soft ligands whereas our diamines, OH^- and $iPrO^-$ are more basic but harder ligands and thus are in competition one with the others for coordination with the metal.

A [KOH]/[Rh] ratio of 6 has been used in the rest of our work (Table 3, entry 3).

SUBSTRATE

Different substrates have been reduced to test the efficiency of our catalytic system using diamine **1b** as ligand. Some of them have electron withdrawing and hydrogen-bond acceptor group on the aromatic ring (Table 4, entries 2-4) or at the α position of the carbonyl function (Table 4, entries 5, 7 and 8). The others are hydrogen-bond donors (Table 4, entries 1 and 6). The best result is obtained with the methylphenylglyoxylate (Table 4, entry 7) and the methylpyruvate gives the lowest e.e. (Table 4, entry 8). This last result could probably be explained by the weak steric differenciation between the methyl and the methylester group. It is also noticeable that the reaction rate is the highest for the substrate which leads to the best e.e.. The cyclohexylketone (Table 4, entry 6) is less reactive than the other substrates (only 78% conversion in 9 days). Nevertheless, this result remains interesting, the aliphatic ketones being always difficult to reduce enantioselectively.

The acetophenones, substituted or not on the aromatic ring (Table 4, entries 1 to 4) are totally converted into their corresponding alcohols in around 7 days with e.e. from 21% for the 4-trifluoromethylacetophenone (Table 4, entry 3) to 73% for the 4-cyanoacetophenone (Table 4, entry 2). In all the cases, the major enantiomer is the *R* form (the hydride addition occures by the Si face of the ketones). These apparent similar approaches of the substrate is only due to the application of the Cahn-Ingold-Prelog rules (Figure 3).

Table 4 : Efficiency of the Catalytic System on Different Substrates.

Entry	Substrate R	Substrate R'	Time (days)	Conversion (%)	e.e.* (a) (%)
1	Ph[b]	CH_3	7	100	67(*R*)
2	4 CN-Ph	CH_3	8	100	73 (*R*)
3	4 CF_3-Ph	CH_3	6	96	21 (*R*)
4	2 CF_3-Ph	CH_3	8	100	68 (*R*)
5	Ph	CF_3	2	100	33 (*R*)
6	C_6H_{13}	CH_3	9	78	40 (*R*)
7	Ph	COOMe	1h	99	>99 (*R*)
8	CH_3	COOMe	5	100	5 (*R*)

conditions : [Rh]/[S] = 5%; T = 25°C; **1b**/[Rh] = 2; [KOH]/[Rh] = 6; [S] = 1.6 10^{-2}M (initial concentration). *measured by gas chromatography on the crude product; a : absolute configuration determined by comparison with literature values (see experimental part); b : Ph = Phenyl group.

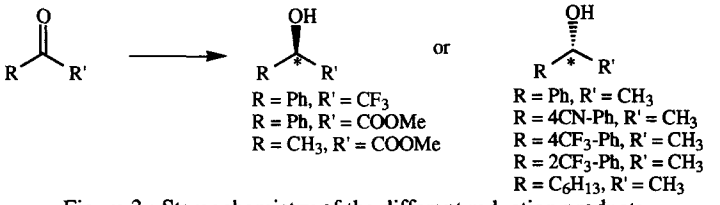


Figure 3 : Stereochemistry of the different reduction products

Depending on the nature of the R' group, the substrates approach the active catalytic species responsible for the enantioselectivity in a different way. When R' is an hydrogenbond acceptor (Table 4, entries 5, 7 and 8), we assume that the substrate is linked both by coordination to the metal and to the ligand by the hydrogen of the amine, the interaction between the substrate and the catalytic species becomes thus stronger and this could explain why in these cases, the reaction rate is generally higher. When the hydrogen-bond acceptor group (Table 4, entries 2-4) is on the aromatic ring, no supplementary bonding could be obtained with the catalyst complex. The reaction rate is ruled by steric factors and becomes thus lower. In the other cases (Table 4, entries 1 and 6), the interaction substrate-metal-ligand complex is weaker and probably, the reaction rate is also ruled by steric factors.

SOLVENT

The influence of the nature of the solvent has been studied by addition of a cosolvent to the iso-propanol (1/1 in volume) which cannot be suppressed as it acts as hydride donor. The chosen substrate was the α,α,α-trifluoroacetophenone (Table 5).

When a polar and aprotic solvent is added (Table 5, entry 3) the activity of the catalytic system increases (100% conversion in 1 day instead of 5 days) but the e.e. decreases. In this case, THF, which has high donor properties (normalized donor number for THF : $DN^N = 0.52$, for acetonitrile $DN^N = 0.36$[7]) can thus compete with the diamines which can explain both the low e.e. and the high activity of the new rhodium complexes formed with the THF, less sterically demanding than the diamine ligands. The addition of water (Table 5, entry

Table 5 : Influence of the Co-solvent on the e.e. for the Reduction of α,α,α-trifluoroacetophenone.

Entry	co-solvent	Time (days)	Conversion (%)	e.e.* (%)
1	-	5	89	33
2	heptane	5	100	13
3	THF	1	100	15
4[a]	Water	8	95	41

conditions : [Rh]/[S] = 5%; T = 25°C; **1b**/[Rh] = 2; [KOH]/[Rh] = 6; [S] = 1.6 10^{-2}M (initial concentration). *measured by gas chromatography on the crude product; a :[KOH]/[Rh] = 12.

4) decreases the reaction rate but increases the e.e.. Thus low activity can be due to the decrease of [iPrOK] versus [OH^-].

KINETIC STUDIES

Kinetic studies have shown that the e.e. increases with the conversion until reaching a maximum without further decrease (Figure 4).

This fact is noticeable as generally the e.e. remains constant or decreases with the conversion, due to the low stability of the active complex. We have examined several hypotheses to explain this result and they are discussed in the following part of this article.

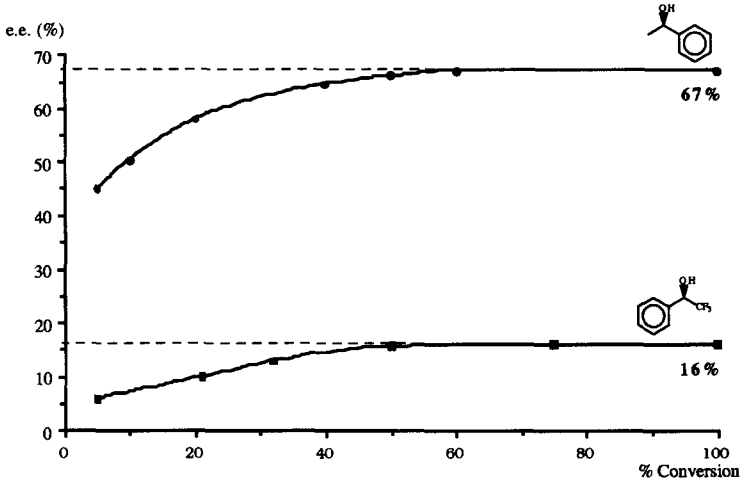


Figure 4 : Evolution of the enantiomeric excesses with the conversion.

conditions : [Rh]/[S] = 5%; T = 25°C; **1b**/[Rh] = 2; [KOH]/[Rh] = 6; [S] = 1.6 10^{-2}M (initial concentration).

OXIDATION OF THE 1-PHENYLETHANOL

The reaction product, 1-phenylethanol, could be a better hydride donor than isopropanol. Thus, the reverse reaction, the oxidation of 1-phenylethanol into acetophenone could occur, and if one of the enantiomeric forms, the *S* for example, is oxidized faster than the *R* form, this could explain the e.e. increase. Therefore, we

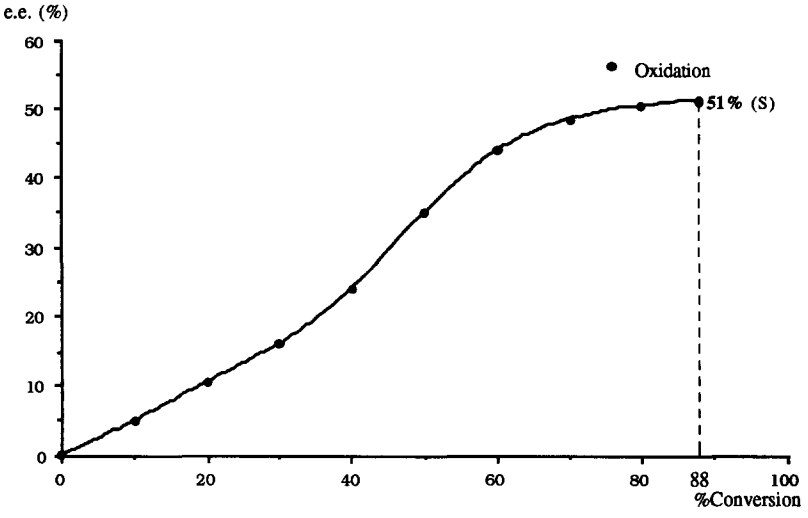


Figure 5 : kinetic resolution

Conditions : 1-phenylethanol=5mmol; acetone=1mmol; $[Rh(C_6H_{10})Cl]_2$=0.05mmol; diamine **1b**=0.1mmol; [KOH]/[Rh]=6

have reduced in our conditions acetone into isopropanol, the hydride source being a racemic mixture of 1-phenylethanol. We have followed the evolution of the e.e. in 1-phenylethanol with the reduction of acetone (Figure 5). At 88% conversion, 51% e.e. are measured, the major isomer being the *S* form. The oxidation of the *R* isomer into the corresponding ketone is thus faster and, as it is the (*R*)-1-phenylethanol which is obtained preferentially with our catalytic system, this hypothesis of selective re-oxidation cannot be kept. Nevertheless, in order to define the extent of reversibility of the oxidation of 1-phenylethanol into acetophenone, we performed labelling experiments. Acetophenone was reduced in deuteriated isopropanol and after 20 days, 100% of labelled 1-phenylethanol was obtained. The reaction rate is 5 to 10 times higher in the case of hydride transfer than in the case of deuterium transfer which indicates that the hydride interferes in the rate determining step. The deuteriated 1-phenylethanol and acetone were put under reaction in isopropanol and in 7 days only 7.5% of non-labelled 1-phenylethanol and 15% acetophenone were detected, which confirms that the reoxidation of 1-phenylethanol is only a minor side reaction.

EVOLUTION OF THE CATALYTIC SPECIES

In this catalytic process, different species could coexist in solution. The system is efficient if the complex responsible for the enantioselectivity is preferentially formed and/or reacts faster than the others (Figure 1). We have thought that the initial equilibrium between the different catalytic species could change during the reaction and that the formation of the complex which induces the stereoselectivity is favoured after a certain period of time. We therefore left the catalyst, the diamine ligand, iPrOH and KOH together in solution for 48 h before adding the substrate, 48 h being the point where the maximum e.e. was reached. We have registred the e.e. evolution with the conversion of acetophenone into 1-phenylethanol (Figure 6).

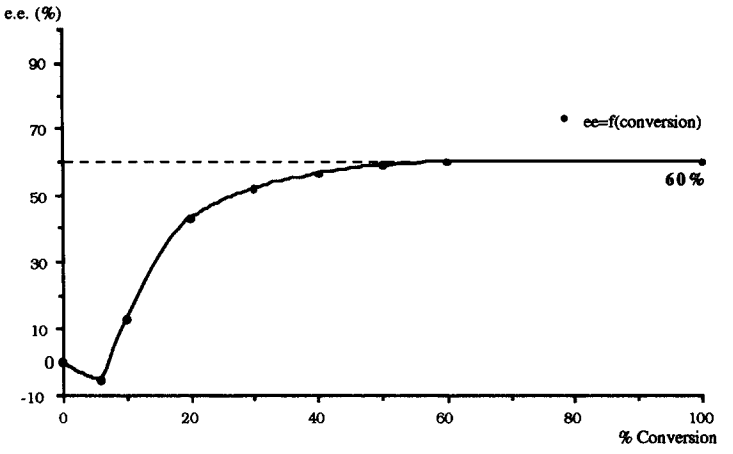


Figure 6 : Influence of the evolution of the catalytic species on the e.e..

Conditions : [Rh]/[S] = 5%; T = 25°C; **1b**/[Rh] = 2; [KOH]/[Rh] = 6; [S] = 1.6 10^{-2}M (initial concentration).

At the beginning of the reaction (conversion <7%), the *S* isomer is preferentially formed instead of the *R* form usually obtained. At 10% conversion, 13% e.e. of the *R* form are measured, for 50% e.e. in the standard conditions and at the end of the reaction, only 60% e.e. (instead of 67%) are registred. The hypothesis of the evolution of the equilibrium between different diastereoisomeric complexes cannot thus be excluded but it is not the predominant phenomenon. Nevertheless, this result shows once again that the catalytic cycle is complex and that many different mechanisms should interfere.

PARTICIPATION OF THE REACTION PRODUCT : AUTOINDUCTION

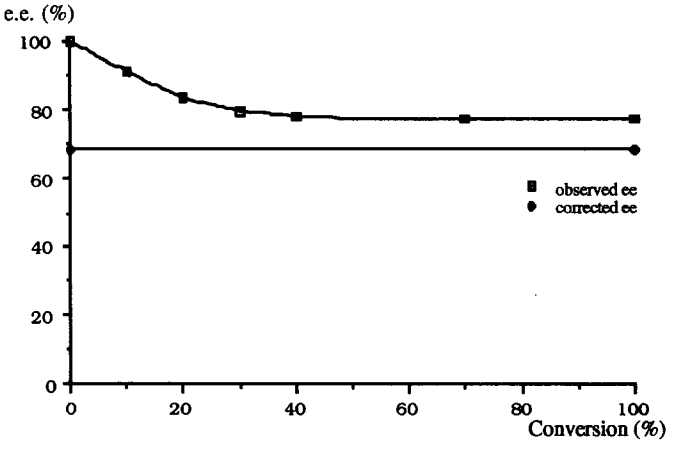


Figure 7 Influence of the addition of (*R*)-1-phenylethanol on the e.e..

Conditions : [Rh]/[S] = 5%; T = 25°C; **1b**/[Rh] = 2; [KOH]/[Rh] = 6; [S] = 1.6 10^{-2}M (initial concentration); [(*R*)-1-phenylethanol] = 1.6 10^{-3}M (initial concentration).

The (*R*)-1-phenylethanol could essentially induce its own formation during the reaction which could explain the e.e. increase with the conversion. Therefore, we have added 10% of (*R*)-1-phenylethanol to the reaction mixture and followed the e.e. with the conversion of acetophenone into 1-phenylethanol (Figure 7).

Figure 7 shows the influence of the addition of (*R*)-1-phenylethanol on the e.e.. After correction, 67% e.e. are measured. As the same e.e. are obtained with or without addition of 10% (*R*)-1-phenylethanol, it is not an autoinduction phenomenon.

PARTICIPATION OF THE SUBSTRATE : COMPETITION BETWEEN KETONE AND ISOPROPANOLATE

In the catalytic cycle, 1-phenylethanol can be liberated in the reaction medium after substitution by the isopropanolate or it can act as an hydride donor after coordination of a second molecule of acetophenone to the rhodium complex. We have thus tested the influence of the dilution on the e.e.. With a concentration in acetophenone of 1.6 10^{-2}M, 67% e.e. were obtained against 53% at 10^{-1}M. The same experiments realised with the α,α,α-trifluoroactophenone allow us to increase the e.e. from 33% to 45% by decreasing the concentration to a factor 4, whereas an increasing of concentration from 0.016M to 1M leads to 18% e.e. instead of 45% (Figure 8).

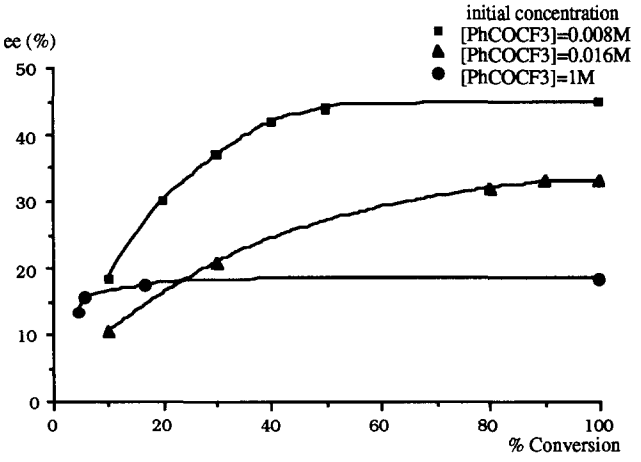


Figure 8 : reduction of the α,α,α-trifluoroacetophenone : influence of the substrate concentration on the e.e..

Conditions : [Rh]/[S] = 5%; T = 25°C; **1b**/[Rh] = 2; [KOH]/[Rh] = 6.

These results show that the e.e. decreases when the substrate concentration increases, which is in favour of the presence of a second molecule of ketone in the catalytic cycle. When the ketone concentration decreases, the probability of the coordination of a second molecule of ketone is lower and thus the e.e. increases. This last hypothesis agrees with the augmentation of the e.e. due to the conversion into 1-phenylethanol. Nevertheless, during these three experiments, the ratio catalyst/substrate remains constant (5%) and thus the overall rhodium concentration increases with the substrate concentration too. Gladiali *et al.*[5] have shown that the catalyst activity and stereoselectivity are dependant of the catalyst concentration, due probably to a competitive formation of inactive dimer species. But, a decrease of the rhodium concentration could not explain the increase of the e.e. with the conversion. In addition, we have tested the reaction at lower concentration in metal (0.05 10^{-2} to 5 10^{-2}M) at constant initial substrate concentration (1.6 10^{-2}M) without observing any variation in enantioselectivity.

The involvement of a second molecule of acetophenone should, if the concentration is high enough, lead to the (*S*)-alcohol. We have thus made the same experiment with acetophenone at a weak concentration (0.016M) and at a high one (2M, Figure 9).

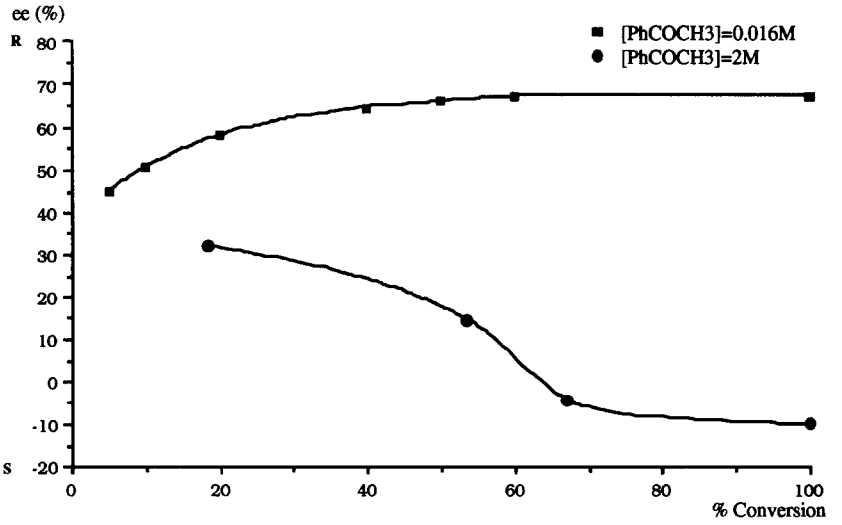


Figure 9 : Reduction of the acetophenone : influence of the substrate concentration on the e.e..

Conditions : [Rh]/[S] = 5%; T = 25°C; **1b**/[Rh] = 2; [KOH]/[Rh] = 6.

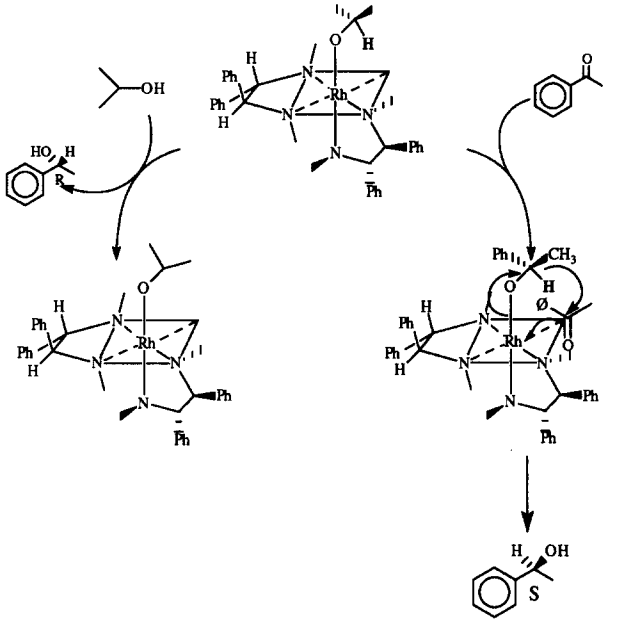


Figure 10 : proposed competitive mechanism.

At 2M, we see a decrease of the e.e. which shows that at the beginning of the reaction the (*R*) isomer is formed but rapidly the (*S*) alcohol is produced in high yield. Nevertheless, this is not against our hypothesis of the involvement of a second molecule of ketone in the catalytic cycle, as at such a high concentration (2M, 6.5mol of isopropanol per mol of ketone) other interactions like the ketone-ketone ones may interfere. We have thus proposed the following competitive mechanism (Figure 10).

Conclusion

This work shows that chiral diamines are good ligands for the asymmetric catalytic reduction of carbonyls by hydride transfer as e.e.s up to 99% have been measured. It is noteworthy that, in our case, ligands with sp^3 nitrogen atoms containing N-H and N-CH_3 bonds give the best results, whereas this type of ligands is generally not suitable for most organometallic reactions[1]. We have shown that it is necessary to have two different substituents on the nitrogen which thus becomes a stereogenic center, to obtain good e.e.. As for the substrate, the approach to the metal complex is ruled by either steric factors or by its ability to accept hydrogen bond. Kinetic studies have shown that the e.e. increases with the conversion and an explanation for this phenomenon is the participation of a second molecule of substrate to a competitive catalytic cycle. Thus, working at high dilution allows to increase the e.e. and this could be performed in a continuous flow reactor[8]. Moreover, we have also noticed that our system can be used for kinetic resolution and that the equilibrium between the different species which leads either to the *R* enantiomeric form or to the *S* form evolves throughout the reaction. Nevertheless, even though all these results show that our system is very complex, it remains efficient.

Experimental

All the solvents are commercial (analytical grade, Aldrich) and used without any purification.
^1H and ^{13}C Nuclear Magnetic Resonance (NMR) : spectra were recorded on a Bruker AM-200 Fourier transform spectrometer and 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 spectra were recorded on a Perkin-Elmer 1720-X spectrometer. The enantiomeric excesses were measured by capillary gas chromatography using a chiral column Macherey-Nagel-Düren, Lipodex E (25m x 0.25mm Ø). Optical rotations were measured with a Perkin-Elmer 241 polarimeter after purification (SiO_2).

Ligands **1a**, **2a** and **2b** are commercial.

(S, S)-(+)-N,N'-dimethyl-1,2-diphenyl-1,2-ethanediamine **1b**. This diamine has been synthesized according to the procedure already described by Mangeney *et al.*[9].

(S, S)-(+)-N,N,N',N'-tetramethyl-1,2-diphenyl-1,2-ethanediamine **1c**. This diamine has been synthesized according to the procedure already described by *Horner et al.*[10] starting from diamine **1a**. $[\alpha]^{20}_D = +10$ (c=1, Et_2O); ^1H NMR : δ_H : 2.2 (s, 12H, NCH_3),4.15 (s, 2H, NCH), 7.1 (m, 10H, aromatic ring); ^{13}C NMR δ : 40.9 (CH N), 67.9 (CH–N), 126.6 (CH, para), 127.3 (CH, ortho), 130.0 (CH, meta), 133.9 (CH-CH).

(S, S)-(+)-N,N'-dimethyl-diacetyl-1,2-diphenyl-1,2-ethanediamine **1d.** The diamine **1b** was acylated according to the method of Steglich and Hofle[11] : diamine **1b** (741mg, 3.1mmol) and 4-dimethylaminopyridine (0.155mmol, 19mg) are heated at 100°C for 2 days in acetic anhydride (2.16mg, 21.3mmol). Then, 100mL of methylene chloride were added and the organic phase was washed 3 times with water. After evaporation of the solvent, the desired product **1d** is obtained quantitatively. mp : 150°C; $[\alpha]^{20}_D$ =+560 (c=5, EtOH); IR ν_{max} (KBr disc) cm^{-1} : 1645 (C=O), 1120 (C-N); ^1H NMR : δ_H : 2.09 (6H, s, *CH*$_3$-CO), 2.73 (6H, s, *CH*$_3$-N), 6.72 (2H, s, CH), 7.15-7.30 (10H, m, Carom-H); ^{13}C NMR δ : 22.4 (*CH*$_3$-CO), 31.4 (*CH*$_3$-N), 53.1 (CH-N), 127.6 (CH, para), 128.4 (CH, ortho), 129.2 (CH, meta), 136.9 (CH-CH), 171.0 (C=O); elemental analysis : calculated C : 74.05, H : 7.46, N : 8.63, O : 9.86; found C : 73.57, H : 7.51, N : 8.76, O : 10.28.

(S, S)-(-)-N,N'-diisopropyl-1,2-diphenyl-1,2-ethanediamine **1e.** The diamine **1a** was N-alkylated according to the Eschweiler-Clarke procedure[12] : diamine **1a** (1g, 4.71mmol), Pd/C 10% (1g, 0.94mmol) and acetone (547mg, 9.42mmol) were stirred in 14mL ethanol under 50bar H_2 at room temperature for 15h. After evaporation of the solvent and recrystallization (C_5H_{12}/Et_2O : 1/1) 80% (1.11g, 3.75mmol) of the desired pure product **1e** are obtained. mp = 30°C; $[\alpha]^{20}_D$ = -5 (c = 4.8, $CHCl_3$); IR : ν_{max} (KBr disc) cm^{-1} : 3430 (NH), 1200 (C-N); ^1H NMR : δ_H : 0.95 (6H, d, *J*=6.4Hz, *CH*$_3$-CH), 1.00 (6H, d, *J*=6.2Hz, *CH*$_3$-CH), 2.58 (2H, q, *J*=6.3Hz, *CH*-(CH_3)$_2$), 2.92 (2H, s, NH), 3.75 (2H, s, *CH*-N), 7.00-7.32 (10H, m, Carom-H); ^{13}C NMR : 23.1 (CH_3-CH), 47.5 (CH-(CH_3)$_2$), 52.9 (CH-N), 127.7 (CH, para), 127.9 (CH,ortho), 128.3 (CH, meta), 135.1 (CH-CH); elemental analysis : calculated C : 81.03, H : 9.52, N : 9.45; found C : 81.68, H : 8.98, N : 9.34.

Typical procedure for the reduction of ketones : diamine (0.125mmol), the catalyst precursor $[Rh(C_6H_{10})Cl]_2$ (13.8mg, 0.062mmol) and potassium hydroxide in pellets (20.9mg, 0.372mmol) were dissolved in 2-propanol (39mL) under an inert atmosphere and stirred for 1h. Then, ketone (1.25mmol) was added and the mixture was stirred at room temperature under nitrogen. The reaction was monitored by capillary gas chromatography.

Typical procedure for the oxidation of 1-phenylethanol : diamine **1b** (24mg, 0.1mmol), the catalyst precursor $[Rh(C_6H_{10})Cl]_2$ (11mg, 0.05mmol) were dissolved in acetone (581mg, 10mmol) under an inert atmosphere and stirred for 1h. Then, racemic 1-phenylethanol (611mg, 5mmol) was added and the mixture was stirred at room temperature under nitrogen. The reaction was monitored by capillary gas chromatography.

Labelling experiments : diamine **1b** (6.12mg, 0.025mmol), the catalyst precursor $[Rh(C_6H_{10})Cl]_2$ (3.1mg, 0.0127mmol) and potassium hydroxyde in pellets (4.3mg, 0.077mmol) were dissolved in deuteriated 2-propanol ($(CD_3)_2OD$, 2ml) under an inert atmosphere and stirred for 1h. Then, acetophenone (30.5mg, 0.25mmol) was added and the mixture was stirred at 82°C under nitrogen. The reaction was monitored by capillary gas chromatography. 100% of deutariated 1-phenylethanol (C_6H_5-C_2H_3D-OD) were obtained in 20 days (e.e. = 48%). ^1H NMR : δ_H : 1.15 (3H, t, CH_3-D), 7-7.5 (5H, m, Carom-H). After evaporation of the solvant, the labelled 1-phenylethanol thus obtained, acetone (14.2mg, 0.25mmol) were refluxed under an inert atmosphere in 2-propanol (2ml). After 7 days, 7.5 % of non-labelled 1-phenylethanol and 15% of acetophenone were measured by ^1H NMR. ^1H NMR : δ_H : 1.15 (3H, t, CH_3-D) attributed to deuteriated 1-phenylethanol. 2.25 (3H, s, CH_3) attributed to acetophenone; 3.41 (1H, q, *J* = 7.1Hz, CH_3-H) attributed to 1-phenylethanol; 7-7.5 (5H, m, Carom-H)

All the reduction products were identified by comparison with literature data or with authentic commercial products.

- (*R*)-(+)-sec-Phenethyl alcohol [1517-69-7] and (*R*)-(1)-methylmandelate [20698-91-3], Aldrich
- (*R*)-(-)-1-phenyl-2,2,2-trifluoroethanol [10531-50-7] and (*R*)-(-)-methyl L-lactate [27871-49-4], Fluka
- (*R*)-4-cyano-phenethyl alcohol[13], (*R*)-4-trifluoromethyl-phenethyl alcohol[14], (*R*)-2-trifluoromethyl-phenethyl alcohol[15], (*R*)-cyclohexylethyl alcohol[16].

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