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Cyclic β-iminophosphine: New P-stereogenic ligand for the asymmetric catalysed hydrogenation of ketones

M. Lorraine Christ [a], Maria Zablocka [b], Sally Spencer [a], Rebecca J. Lavender [a], Marc Lemaire [a,*], Jean Pierre Majoral [c,*]

[a] *Laboratoire de Catalyse et Synthèse Organique, CNRS, UCBLyon 1, CPE, bât. 308, 43, bd du 11 novembre 1918, 69622 Villeurbanne, France*
[b] *Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Lodz, Poland*
[c] *Laboratoire de Chimie de Coordination, CNRS, 205 route de Narbonne, 31077 Toulouse, France*

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Abstract

A novel type of asymmetric C=O hydrogenation catalysts based on chiral β-iminophosphine rhodium and ruthenium complexes was developed. The chirality of the ligand is centered on the phosphorus atom which can induce moderate enantioselectivity. A synergetic effect on both activity and enantioselectivity is observed when amines are introduced as co-ligands. Acetophenone is thus completely hydrogenated with ee values up to 68%.
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Keywords: Asymmetric hydrogenation; P, N-chiral ligands; Chiral ligands synergy; Ruthenium catalysts

1. Introduction

Asymmetric hydrogenation of prochiral ketones is a major route to enantiopure chiral alcohols which are especially important in the synthesis of biologically active compounds [1,2]. The use of catalysts in the hydrogenation process has led to excellent conversions as well as high enantioselectivities [3]. However, the ligands employed are generally air and moisture sensitive diphosphines. Diamines or other ligands containing two nitrogen functions have the stability that the diphosphines lack but are generally less enantioselective [4]. Mixed phosphorus nitrogen compounds offer a compromise between the stability of nitrogen ligands and the activity of diphosphines. Among the development of bidentate P, N-ligands for asymmetric catalysis [5], we can point out two main types of bidentate P, N-ligands have been developed according to the hybridization of the nitrogen atom: on one hand, a large variety of aminophosphines [4–6] containing a sp^3-N atom, and on another hand, a series of iminophosphines [3,5,7] and phosphinooxazolines [3,5,8,9] bearing a sp^2-N atom. The donor properties of this sp^2 nitrogen atoms allow the formation of very efficient P, N-ligands containing catalysts for enantioselective transformations such as C=C bond hydrogenation, ketone hydrosilylation, allylic substitution and Diels–Alder reactions [3–5,7–9].

Some of us developed a series of new P, N compounds and reported the synthesis of bi- and tricyclic β-iminophosphines [10] as well as the use of their palladium complexes in catalytic Stille coupling reactions [11]. Enantiopure derivatives were prepared in the case of the tricyclic β-iminophosphine **1**. This compound presents therefore chirality at the framework and at the phosphorus atom itself. In the (R_P) enantiomer depicted in Scheme 1, the C8 and C11 atoms have an *S* configuration while the P atom has an *R* configuration [12].

We are now investigating the asymmetric properties of the P-stereogenic ligand **1** in metal catalysed reactions such as the Pd-mediated allylic substitution [12] in which encouraging results are already observed. The use of several P-chirogenic diphosphine ligands in catalytic asymmetric hydrogenation of β-keto esters proved to be successful [13] and prompted us to consider ligand **1** as a potential chiral inductor for C=O reductions. For this purpose, we first checked the ligand stability under hydrogenation conditions: no imine reduction was observed. Herein, we report the use of chiral tricyclic β-iminophosphine rhodium and ruthenium complexes as new catalysts for the asymmetric hydrogenation of aryl ketones. In a second time, we describe the synergetic effects observed in presence of amine co-ligands.

* Corresponding authors.

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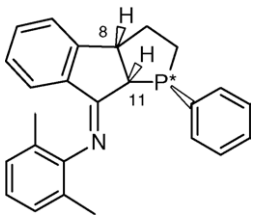
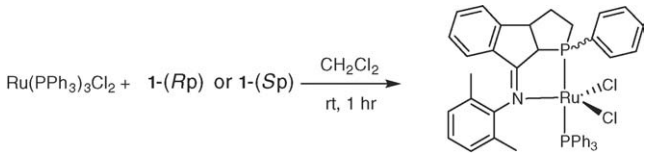


Scheme 1. Chiral tricyclic β-iminophosphine enantiomer **1**-(R_P).



Scheme 2. Synthesis of both enantiomers of complex **2**.

2. Results and discussion

Catalytic tests were carried out with in situ and ex situ formed complexes. The in situ species were obtained by mixing the chiral tricyclic β-iminophosphine ligand **1** with a metallic precursor in the reaction solvent before adding the substrates. Both enantiomers of the 16 electron complex **2** were prepared and isolated ex situ. The [**1**-(R_P)]Ru(PPh_3)Cl_2 and [**1**-(S_P)]Ru(PPh_3)Cl_2 were easily synthesized from Ru(PPh_3)$_3Cl_2$ and the corresponding β-iminophosphine enantiomers (Scheme 2) [11].

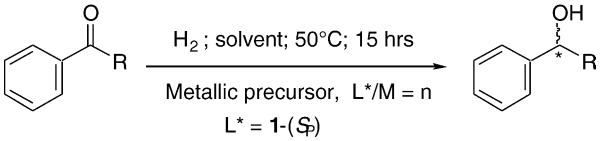
2.1. Asymmetric ketone reduction induced by cyclic β-iminophosphine ligand

Initial work was carried out using a hydrogen transfer reaction (HTR), according to a successful method using an achiral iminophosphine ruthenium (II) complex [14]. We used similar conditions for acetophenone reduction by isopropanol at 70 °C with 0.5 mol% of NaOH and 0.2 mol% of the catalyst. We evaluated the catalytic properties of the pre-formed complex [**1**-(R_P)]Ru(PPh_3)Cl_2 and of the in situ species prepared from **1**-(R_P) ligand and [Ru(*p*-cymene)Cl_2]$_2$. No reduction was observed overnight but slow acetophenone reduction occurs after 2 days (15% conversion) without any enantioselection, using the in situ formed catalyst.

2.1.1. Reduction without base

In previous work using chiral diamine complexes [15], we noticed that hydrogen pressure could lead to better ketone reduction yields than HTR conditions. We thus tested the cyclic β-iminophosphine ligand **1** as chiral inductor in presence of various Ru, Rh and Ir metallic precursors. The active species were formed in solution by stirring the starting complex with the iminophosphine compound in a defined molar ratio (n = ligand molecules/metal atom) for at least 30 min. To these in situ formed catalyst solutions were added the corresponding amount of ketone before transfer of the resulting mixture to an autoclave which was then purged with argon and pressurized with dihydrogen and the solutions stirred overnight. Conversions, yields and enantiomeric excess values were determined by chiral gas chromatography (see Section 4). Results are summarized in Table 1. The discrepancy in some cases between conversion and yield is due to over-reduction producing a second alcohol (characterized by coupled CPG/mass spectrum) formed by the simultaneous hydrogenation of the ketone and of the aromatic ring. In all those cases we noticed a slight formation of grey Rh or Ir particles, which indicates that the β-iminophosphine complex is not enough stable under these particular reduction conditions. It is to notice that the metallic precursors employed in this study are

Table 1
Ketone hydrogenation catalysed with in situ prepared β-iminophosphine complexes



Entry	R	Metallic precursor (%mol vs. ketone)	L*/M n	Solvent	H_2 (bar)	% Conversion (% yield)[a]	% ee (R)
1	CH_3	[RhCODCl]$_2$ (2.5)	2.5	MeOH	50	99	0
2	CO_2CH_3	[RhCODCl]$_2$ (2.5)	2.5	MeOH	50	81	11
3		(1)	3			56	33
4		(0.5)	3			50	30
5		(0.1)	3			29	29
6	CO_2CH_3	[RhCODCl]$_2$ (0.5)	2	MeOH	50	58 (52)[a]	0
7		(0.5)	2.5			18	23
8		(0.5)	5			36	29
9	CO_2CH_3	[RhCODCl]$_2$ (0.5)	3	MeOH	20	35	19
10		(0.5)			10	16	10
11	CO_2CH_3	[RhCODCl]$_2$ (0.5)	3	THF	50	3	2
12		(0.5)		CH_2Cl_2		46 (28)[a]	7
13	CO_2CH_3	[IrCODCl]$_2$ (0.5)	3	MeOH	50	93 (56)[a]	0
14		[RuCODCl$_2$]$_n$ (0.5)		MeOH		12	0
15	CH_3	[RhCOD$_2$]SO_3CF_3 (2.5)	2.5	MeOH	0	0	0
16	CO_2CH_3	[RhCOD$_2$]SO_3CF_3 (2.5)	2.5	MeOH	50	39	0

[a] Formation of 1-cyclohexyl-ethanol as by-product.

able to catalyse the ketone hydrogenation leading to the racemic alcohol when used without ligand **1**.

We used acetophenone as substrate but as no enantioselection was observed despite complete conversion, we focussed our efforts on a more reactive ketone, such as phenylglyoxylate methyl ester. As the few tests we carried out with cationic rhodium precursors lead to very low hydrogenation yields (entries 15–16), we will focus on the results obtained with neutral species.

First of all, we fixed the metal amount by varying the molar ratio of the metallic precursor from 2.5% to 0.1% (entries 2–5): as activity decreases, enantioselectivity rises up to 30%, therefore further studies were ran with 0.5% of $[RhCODCl]_2$. One can notice that a β-iminophosphine ligand to metal ratio equal to 2 does not allow the in situ formation of stable catalysts and racemic alcohol is formed (entry 6). A molar ratio of 3 gave better results and there is no need to increase it to 5 which leads to similar ee and lower conversion (entries 4 and 8). We can thus assume that during the formation of the in situ catalysts, an equilibrium between various species occurs and that the enantioselective catalyst is formed when a certain ligand to metal ratio is reached.

Comparison of entries 4, 9 and 10 shows that the catalytic system needs significant hydrogen pressure (50 bar) to avoid a decrease on both activity and enantioselectivity. The catalytic species are sensitive to the solvent used and can be stabilized by THF which is a coordinating solvent (almost avoiding the hydrogenation, see entry 11). On another hand, a chlorinated solvent can lead to partial decomposition of the catalyst thus forming rhodium particles which increases the conversion with no significant ee (entry 12). Other alcohols were tested as solvent giving similar results than MeOH.

Using the optimised reaction conditions, we tested similar iridium and ruthenium precursors. In this later case, low conversion and the lack of metal particles precipitation, reflects the formation of stable Ru-**1** species under these reaction conditions. This is opposite to the iridium precursor which does not complex ligand **1** and decomposition occurs (entries 13 and 14). Ruthenium species are therefore more encouraging than iridium ones.

2.1.2. Reductions in basic media

Asymmetric ketone reduction can also be achieved in basic alcohol media under dihydrogen pressure. We tested both substrates, acetophenone and phenylglyoxylate methyl ester in isopropanol solutions with a KOH/metal = 4/1. Better results were obtained for acetophenone hydrogenation catalysed with β-iminophosphine ruthenium complexes (Table 2).

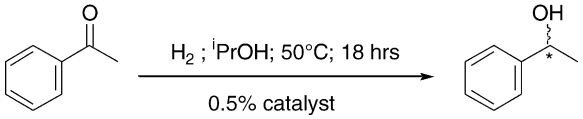
We first noticed that slight amounts of base are needed to obtain 1-phenylethanol without hydrogenation of the aromatic ring. The configuration of the main enantiomer formed (*R*) or (*S*) strongly depends on the metallic ruthenium precursor: no enantioselectivity occurs with an η^6 aromatic ligand, while the presence of the two η^2 bonds with cyclooctadiene led to an (*S*) enriched alcohol mixture. In contrast (*R*) alcohol is favoured when at least one extra triphenylphosphine is coordinated to the ruthenium centre.

The use of the ex situ prepared complex [**1**-(R_P)]$Ru(PPh_3)Cl_2$ improved the catalytic activity of the corresponding in situ formed species (entries 4 versus 5) but a higher H_2 pressure is needed to avoid its decomposition (entries 4–6), although enatioselectivity remains disappointing (17% ee). NaOH was chosen instead of KOH due to the higher solubility of the former under the reaction conditions; both bases lead to similar ee values.

2.2. Synergetic effect of amines and cyclic β-iminophosphine ligands

As seen in Section 2.1, the use of β-iminophosphine **1** as chiral ligand in presence of metallic precursors containing Cl and cyclooctadiene could not induce good conversions for the hydrogenation of aryl ketones. Moreover, the presence of a phosphine ligand in the metallic precursor afforded complete acetophenone hydrogenation but with low enantioselectivity (Table 2; entries 6–7). This trend suggest the use of co-ligands to stabilize the catalytic species. Co-ligands can have a key role in catalytic behaviour and the most impressive example is the extremely active catalysts developed by Noyori combining BINAP ligands with diamine co-ligands [16]. A series of diamines as well as various monoamines were first chosen. We also focussed

Table 2
Acetophenone hydrogenation catalysed with β-iminophosphine-ruthenium complexes



Entry	Catalyst	KOH eq. vs. Ru	H_2 (bar)	Conversion (%) (yield%)[a]	ee (%)
1	$[RuCODCl_2]_n$ + 3 eq. **1**-(R_P)	0	20	18	2 (*S*)
2		2	20	29 (25) [a]	10 (*S*)
3		4	20	72	17 (*S*)
4	$Ru(PPh_3)_3Cl_2$ + 3 eq. **1**-(R_P)	4	20	50	4 (*R*)
5	[**1**-(R_P)]$Ru(PPh_3)Cl_2$ [b]	4	20	89 (76) [a]	17 (*R*)
6	[**1**-(R_P)]$Ru(PPh_3)Cl_2$ [b]	4	50	100	15 (*R*)

[a] Formation of 1-cyclohexyl-ethanol as by product.
[b] 0.2 mol% vs. acetophenone.

on the effect of the chirality of the co-ligands (chiral or non-chiral amines) for the ruthenium/β-iminophosphine catalysed acetophenone hydrogenation.

2.2.1. Monoamines as co-ligands

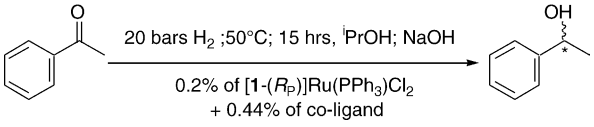
Non-chiral or chiral monoamines can be used as co-ligands for the ruthenium/β-iminophosphine catalytic system: the co-ligand is added to the catalytic precursor solution just before the substrate to be reduced. A preliminary study on ruthenium catalysed acetophenone hydrogenation pointed out the need of 2.2 equivalents of amine per molecule of complex [**1**-(R_P)]Ru(PPh_3)Cl_2. The structure of the employed amines and the corresponding results are reported in Table 3. For chiral amines both enantiomers were tested as co-ligands in separate tests.

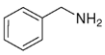
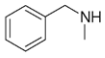
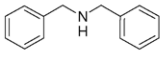
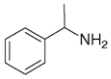
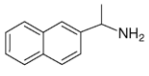
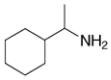
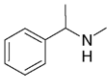
Primary amines afforded good conversions for acetophenone hydrogenation whilst secondary amines induced a lower activity (entries 1 versus 2 and 7 versus 8). Some tests were carried with tertiary amines as co-ligands leading to less than 20% of acetophenone hydrogenation with low ee values (<12).

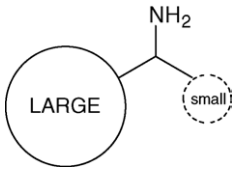
Except for dibenzylamine (Table 3; entry 3), all ee values are higher (38–67% ee) than those obtained without an amine co-ligand: 15–17% ee (*R*) (Table 2; entries 5–6), also favouring the formation of the (*R*) alcohol.

When using chiral monoamines as co-ligands, we observe that the enantioselection mainly depends on the chirality of the β-iminophosphine ligand present in the starting complex [**1**-(R_P)]Ru(PPh_3)Cl_2: (*R*) and (*S*) monoamines led to the major formation of the same 1-phenylethanol enantiomer. Conversion and ee values for both chiral amines are only reported in the case of the α-methylbenzylamine (entries 4–5) and in the other cases (entries 6–8) one set of values is listed, which is very close to the results obtained with the opposite amine enantiomer.

Table 3
Acetophenone hydrogenation catalysed with β-iminophosphine ruthenium complexes and monoamines as co-ligands



Entry	Co-ligand		Conv. (%)	ee (%)
1			90	38 (*R*)
2			75	52 (*R*)
3			33	16 (*R*)
4		(*R*)	96	61 (*R*)
5		(*S*)	100	68 (*R*)
6		(*S*)	86	62 (*R*)
7		(*R*)	100	67 (*R*)
8		(*R*)	47	40 (*R*)



Scheme 3.

Steric hindrance seems to be an essential factor for the amine co-ligand: interesting ee values (62–68%) are obtained for α-methyl-benzylamine, 1-(2-naphthyl)-ethylamine and 1-cyclohexyl-ethylamine in which a "large/small" geometry is observed for the alkyl or aromatic substituents (Scheme 3).

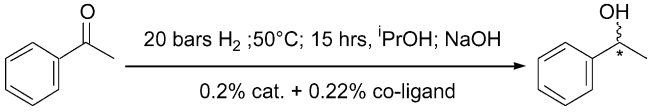
2.2.2. Diamines as co-ligands

Use of diamines in a slight excess towards the complex **2** (1.1–1 molar ratio) was then undertaken as co-ligand in non-chiral and chiral series. The obtained results for acetophenone hydrogenation are listed in Tables 4 and 5.

As seen for the monoamines, good conversions of the acetophenone hydrogenation are attained if the co-ligand has at least one primary amine group. When adding C_2-symmetric diamines derived from ethylenediamine, asymmetric induction is almost lost (entries 1–4). Using the complex [**1**-(R_P)]Ru(PPh_3)Cl_2 without co-ligand induces low enantioselectivities (Table 2; entries 5–6) that are enhanced in presence of *N*,*N*-dimethyl-ethylenediamine or 1-(2-aminoethyl)-pyrrolidine, affording up to 43% ee (*R*). It is to notice that this effect favours the same 1-phenylethanol enantiomer, that was the major product formed without the co-ligand.

With no co-ligand, the [$RuCODCl_2$]$_n$/β-iminophosphine ligand **1**-(R_P) catalyst (Table 2, entry 3) gave 72% of 1-phenyl ethanol and 17% ee (*S*). The opposite enantiomer is the major

Table 4
Acetophenone hydrogenation catalysed with β-iminophosphine ruthenium complexes and racemic diamines as co-ligands



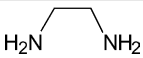
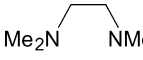
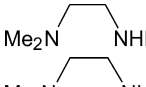
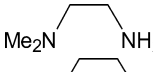
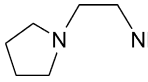
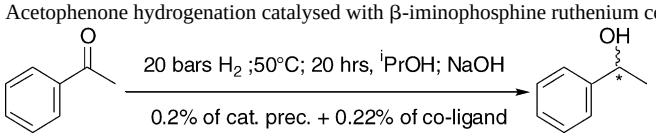
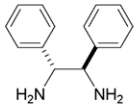
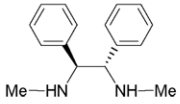
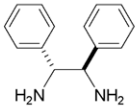
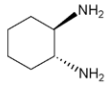
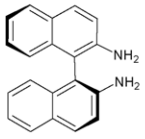
Entry	Catalyst	Co-ligand	Conversion (%)	ee (%)
1	[**1**-(R_P)]Ru(PPh_3)Cl_2		100	11 (*S*)
2	[**1**-(S_P)]Ru(PPh_3)Cl_2		29	5 (*S*)
3	[**1**-(S_P)]Ru(PPh_3)Cl_2		9	11 (*S*)
4	[**1**-(R_P)]Ru(PPh_3)Cl_2		88	43 (*R*)
5	[**1**-(R_P)]Ru(PPh_3)Cl_2		71	37 (*R*)

Table 5
Acetophenone hydrogenation catalysed with β-iminophosphine ruthenium complexes and chiral diamines as co-ligands



Entry	Catalytic precursor	Co-ligand structure	Co-ligand configuration	Conv. (%)	ee (%)
1	$[RuCODCl_2]_n$ [a]		(1*R*,2*R*)	22	42 (*R*)
2			(1*R*,2*R*)	100	45 (*S*)
3	$[RuCODCl_2]_n$ + 1.1 eq. **1**-(R_P)		(1*S*,2*S*)	100	14 (*R*)
4			racemic	100	34 (*S*)
5	$[RuCODCl_2]_n$ + 1.1 eq. **1**-(S_P)		(1*R*,2*R*)	100	5 (*S*)
6			(1*S*,2*S*)	100	53 (*R*)
7			racemic	99	34 (*R*)
8	$[RuCODCl_2]_n$ + 1.1 eq. **1**-(R_P)		(1*R*,2*R*)	80	14 (*R*)
9	$[RuCODCl_2]_n$ + 1.1 eq. **1**-(S_P)			44	32 (*S*)
10	[**1**-(*Rp*)]$Ru(PPh_3)Cl_2$		(1*R*,2*R*)	100	64 (*S*)
11			(1*S*,2*S*)	100	56 (*R*)
12	[**1**-(*Rp*)]$Ru(PPh_3)Cl_2$		(1*R*,2*R*)	100	57 (*S*)
13	[**1**-(*Sp*)]$Ru(PPh_3)Cl_2$		(*S*)	9	3 (*S*)

[a] 0.5 mol% of catalyst.

product of acetophenone hydrogenation in 42% ee (*R*), when (1*R*, 2*R*)-*N*,*N*′-1,2-diphenyl-ethylenediamine is used as chiral ligand (Table 5, entry 1). When these two ligands are used simultaneously, a noticeable synergetic effect on activity and enantioselectivity is observed in favour of the (*S*) alcohol: complete hydrogenation with 45% ee is observed (Table 5, entry 2). The same trend is noticed with the opposite couple of ligands: **1**-(S_P) combined to (1*S*, 2*S*) diamine, improving both conversion and ee towards the (*R*) enantiomer of the alcohol (Table 5, entry 6). For these catalysts, the chiral induction is thus determined by the chirality of both, ligand and co-ligand. A mismatch [16] effect is observed for the couple of ligands **1**-(R_P) and (1*R*, 2*R*) diamine, which led to poor enantioselectivities (as well as the couple **1**-(S_P) and (1*S*, 2*S*) diamine) (Table 5; entries 3 and 6). The results obtained with racemic diamines are indeed an average of the enantioselectivities attained by each of the co-ligand enantiomers (entries 4 and 7).

In previous work [15] we have demonstrated the interest of using a secondary diamine such as (1*R*, 2*R*)-*N*,*N*′-dimethyl-1,2-diphenyl-ethylenediamine for the asymmetric hydrogenation of ketones. In the present study, adding this diamine as co-ligand gave the opposite enantiomer in lower excess: 14% ee (*R*) compared to the 17% ee (*S*) obtained without the diamine (Table 2, entry 3).

As above described for the Ru/COD/**1**-(R_P) catalytic system, a synergetic effect is also evidenced for the Ru/PPh_3/**1**-(R_P) species. Using complex [**1**-(R_P)]$Ru(PPh_3)Cl_2$ alone (Table 2; entries 6–7) or combined to the *N*,*N*′-dimethyl-1,2-diphenyl-ethylenediamine we observe an enhanced chiral induction towards the opposite enantiomer: 64% ee (*S*) (Table 5, entry 10) in presence of the diamine co-ligand instead of 17% ee (*R*) without diamine.

As the results obtained with the ex situ prepared Ru/β-iminophosphine complexes [**1**-(R_P)]$Ru(PPh_3)Cl_2$ and [**1**-(S_P)]$Ru(PPh_3)Cl_2$ are better than those obtained with the in situ

species (by comparing entries 10 and 1, Table 5 versus entries 2 and 3, Table 5), we directly used complex **2** in order to evaluate other diamine co-ligands. (1*R*, 2*R*)-cyclohexanediamine has a co-ligand effect close to the one of (1*R*, 2*R*)-*N*,*N*′-dimethyl-1,2-diphenyl-ethylenediamine, favouring the formation of the (*R*) alcohol in 57% ee. Besides, the (*S*)-1,1′-binaphthyl-2,2′-diamine caused dramatic loss of both, activity and enantioselectivity: very stable ruthenium species seem to be formed, thus avoiding the ketone hydrogenation.

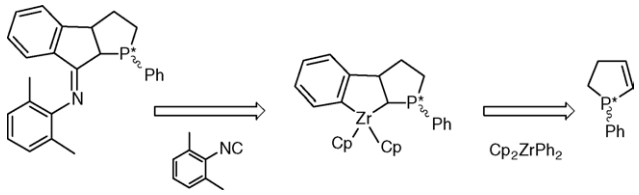
3. Conclusion

In this study we have shown that enantiopure tricyclic β-iminophosphine compounds are interesting P, N-ligands for ruthenium catalysed asymmetric hydrogenation of aryl ketones: slightly basic conditions are requested probably to form the dihydride catalytic species from the dichloride precursors [17]. The low chiral induction afforded by the β-iminophosphine ligand (∼17% ee) can be significantly improved by using N co-ligands as monoamines (61–68% ee) or diamines (45–64% ee). Even if the best ligand synergy is observed for (*S*)-methylbenzylamine, it is noticeable that some non-chiral amines clearly led to an asymmetric activation (37–52% ee). Those synergetic effects strongly depend on the involved mechanism which is also related to the nature of all the ligands surrounding the ruthenium center. In other ruthenium hydrogenation catalysts [18], we already noticed that COD and PPh_3 often lead to the formation of opposite alcohol enantiomers, except when chiral diamines are added as co-ligands. In those cases, diamines act as bidentate ligands and ruthenium coordination sphere is completed by P, N-ligand **1** and hydrides. From these results, we can infer chiral β-iminophosphine-amine compounds as promising N, P, N-ligands for asymmetric catalysis. Synthetic efforts to develop such molecules are on course. As the enantioselective hydrogenation of imines can be achieved with a diverse library of ruthenium diphosphine/diamine precatalysts [19] it should be interesting to evaluate the synergetic effect of ruthenium/**1**/diamine systems for this reaction.

4. Experimental section

4.1. General

All the inorganic and organic reagents, organometallic complexes and enantiomerically pure diamines were used as pure commercial products. The solvents were degassed or distilled under nitrogen atmosphere before use. All manipulations were carried out under an argon atmosphere with standard Schlenk tube techniques. [α] 20; *D* was determined with a Perkin-Elmer 241 polarimeter (l = 1 dm; 25 °C; concentration c in g dm^{-3}). ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for ^1H, 50.32 MHz for ^{13}C, 81.1 MHz for ^{31}P). ee values and yields were determined by analytical GLC with a chiral Lipodex A (25 m) column on Shimadzu GC-14A chromatograph using a flame-ionization detector and Shimadzu C-R6A integrator.



Scheme 4. Retrosynthesis of enantiopure β-iminophosphines **1**-(R_P) and **1**-(S_P)

4.2. Ligand synthesis

Chiral tricyclic β-iminophosphines **1**-(R_P) and **1**-(S_P) were obtained via a reductive elimination reaction of the corresponding chiral α-phosphino zirconocene–iminoacyl complexes [10]. These Zr derivatives were prepared from the separated (*R*) and (*S*) phospholene enantiomers (Scheme 4). NMR data [11] and [α] 20; *D* values measured for ligands **1**-(R_P) and **1**-(S_P) are analogous to those reported [20,21].

4.3. Catalysts

4.3.1. Ex situ catalysts

Both enantiomers of complex **2** were prepared according to the method previously described for the corresponding racemic species. A degassed solution of the enantiopure tricyclic β-iminophosphine ligand **1**-(R_P) or **1**-(S_P) (0.17 g, 0.46 mmol in 10 mL of CH_2Cl_2) was added to a $Ru(PPh_3)_3Cl_2$ (0.44 g, 0.46 mmol in 10 mL of CH_2Cl_2) solution under argon atmosphere. The reaction mixture was stirred 1 h at room temperature, then evaporated to ca. 5 mL of a deep brown solution. Ten milliliters of pentane were slowly added to precipitate the desired complex as a brown microcrystalline powder. The solid was washed with 5 mL of pentane and dried under vacuo. NMR data are analogous to those obtained for the racemic species [11]. Complex [**1**-(R_P)]$Ru(PPh_3)Cl_2$: 57% yield (0.212 g). Complex [**1**-(S_P)]$Ru(PPh_3)Cl_2$: 42% yield (0.156 g).

Preparation of the ex situ catalytic solutions: starting complex **2** was dissolved in 2 mL of the chosen solvent under argon atmosphere and stirred at room temperature for 15 min before adding the ketone.

4.3.2. In situ catalysts

For the catalytic solutions of in situ prepared catalysts, the metallic precursor and the ligand were dissolved in 2 mL of the chosen solvent under argon atmosphere and stirred at room temperature for 1 h before adding a corresponding co-ligand (when needed). Stirring was then pursued over 30 min before adding the ketone.

4.4. Ketone hydrogenation

In a typical hydrogenation procedure, the ketone (1.55 mmol in) was added to the solution containing the catalytic species. When needed, a KOH or NaOH solution (total solvent volume ca. 4 mL) was added and the reaction mixture was immediately transferred to an argon purged stainless steel reactor. The autoclave was then purged and pressurized with dihydrogen (up

to 50 bar), heated (50 °C) and stirred overnight. The reactor was then cooled and degassed and the reaction mixture filtered through Celite® before CPV analyses.

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