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New ruthenium catalysts containing chiral Schiff bases for the asymmetric hydrogenation of acetophenone

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Abstract—A series of new chiral N_4-Schiff bases, containing amine or sulfonamide functionalities has been synthesized. Coupled with ruthenium catalysts, these Schiff bases induce interesting results in the hydrogenation of acetophenone: complete conversion and 76% ee were obtained with the catalytic system $Ru(PPh_3)_3Cl_2$/(1*R*,2*R*)-*N*,*N*′-bis-(2-*p*-tosylaminobenzylidene)-1,2-diphenylethylenediamine. A very important phosphine co-ligand effect was observed on both activity and enantioselectivity of the catalysts. However, without the co-ligand, we obtained an enantioselectivity for the (*R*)-enantiomer, whereas with nonchiral co-ligand an enantioselectivity for the (*S*)-enantiomer was observed.

1. Introduction

Asymmetric hydrogenation using molecular hydrogen to reduce prochiral olefins, ketones, or imines has become one of the most efficient methods for preparing nonracemic chiral compounds. Knowles and Kagan developed in the 1970s, chiral $Rh^{(I)}$–biphosphine complexes for the enantioselective hydrogenation of ketones and olefins with ee values up to 90%. Diphosphine complexes of Rh and Ru have also been used successfully for the asymmetric hydrogenation of functionalized ketones.[1,2] In 1995, Noyori reported the diamine/Ru/BINAP catalysts for the asymmetric reduction of various simple aromatic ketones.[3] The synergetic effect of the amine was noteworthy as the addition of a chiral diamine considerably increased the activity, as well as the enantioselectivity of BINAP–Ru catalysts for asymmetric hydrogenation of ketones. *trans*-RuH(η^1-BH_4)(*S*-*xyl*BINAP)(1*S*,2*S*-DIAPEN) allowed the reduction of acetophenone to (*S*)-1-phenylethanol in 99% ee with very high TON (10^5). Without the diamine, these catalysts alone were unable to hydrogenate simple ketones.[4] Noyori et al. performed the asymmetric activation of racemic *Tol*BINAP by (1*S*,2*S*)-diphenylethylenediamine (DIPEN) with the resulting system $RuCl_2$[(±)-*Tol*BINAP]/(*S*,*S*)-DIPEN catalyzing the asymmetric hydrogenation of 2,4,4-trimethyl-2-cyclohexanone to the corresponding alcohol with 95% ee. Similar results were obtained with enantiomerically pure (*R*)-*Tol*BINAP.[5,6] The racemic catalysts could be used in various strategies of asymmetric activation or deactivation of racemic complexes.[7] The diphosphine/Ru/diamine systems were found to be the most effective method for asymmetric hydrogenation of aromatic ketones.

In our laboratory, C_2-symmetric dithioureas and diamines have been developed and complexed to rhodium, iridium, or ruthenium precursors to form efficient catalysts for the asymmetric hydrogenation of ketones. The asymmetric reduction of acetophenone catalyzed by chiral Ir^+-diamine gave 1-phenylethanol in 63% ee.[8] In other studies, we pointed out that supported diimines can be useful in the asymmetric transfer hydrogenation of acetophenone (70% ee).[9] Others diimines were tested by Vinagradov for this reaction and gave up to 55% ee in phenylethanol.[10]

Until now, there are only a few reports on the use of Schiff bases as chiral inductors for asymmetric hydrogenation of ketones. We recently reported a new and easy method for the preparation of chiral tetraaza Schiff bases containing amine or sulfonamide functionalities, which are promising ligands for a wide variety of transition metals.[11] Other research groups are also currently

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interested in the synthesis of these compounds.[12,13] Herein we report the synthesis of a new series of N_4-Schiff bases and report their first use in the asymmetric hydrogenation of acetophenone with Ir, Rh, and Ru precursors.

2. Results and discusion

2.1. Synthesis of tetradentate Schiff bases

As we have previously reported, the synthesis of chiral Schiff bases with sulfonamides functionalities is based on the preparation of diimino–diamino ligands from enantiomerically pure diamine and 2-nitrobenzaldehyde.[11] The C_2-symmetric diimino–diamino compound formed was then transformed into various sulfonamide derivatives (Fig. 1).

2.1.1. Synthesis of Schiff bases with a (1*R*,2*R*)-diaminocyclohexane core. The condensation of (1*R*,2*R*)-diaminocyclohexane and 2-nitrobenzaldehyde was easily performed in anhydrous THF to give dinitro compound **1** in good yield (91%). After selective reduction of **1** under an atmospheric pressure of hydrogen catalyzed by Pd–C, the (1*R*,2*R*)-*N*,*N*′-bis(2-aminobenzylidene)-1,2-diaminocyclohexane **2** was obtained in 65% yield.

The Schiff base **2** was then transformed into several functionalized compounds. (1*R*,2*R*)-*N*,*N*′-Bis-(2-trifluoromethylsulfonaminobenzylidene)-1,2-diaminocyclohexane (1*R*,2*R*)-H_2CyTf **3** (yield = 73%) and (1*R*,2*R*)-*N*,*N*′-bis(2-tosylamino-benzylidene)-1,2-diaminocyclohexane (1*R*,2*R*)-H_2CyTs **4** (yield = 70%) were prepared by N-sulfonation reactions of (1*R*,2*R*)-*N*,*N*′-bis(2-aminobenzylidene)-1,2-diaminocyclohexane **2** with triflic anhydride or tosyl chloride in presence of Et_3N. An anhydrous atmosphere and low temperature were needed to avoid the hydrolysis of the imine functions.[11,14]

2.1.1.1. Synthesis of (1*R*,2*R*)-H_2CyNphs 5. The reaction of (1*R*,2*R*)-*N*,*N*′-bis(2-aminobenzylidene)-1,2-diaminocyclohexane **2** with 1-naphthalenesulfonic chloride ($NphSO_2Cl$), in the presence of Et_3N at 0 °C, gave (1*R*,2*R*)-*N*,*N*′-bis(2-naphthylsulfonaminobenzylidene)-1,2-diaminocyclohexane **5** in 40% yield.

2.1.1.2. Synthesis of (1*R*,2*R*)-(−)-*N*,*N*′-bis-(2-perfluooctanoylaminobenzylidene)-1,2-diaminocyclohexane 6. Compound **2** could be transformed into either sulfonamide derivatives or compounds having amide functions. (1*R*,2*R*)-*N*,*N*′-Bis-(2-perfluorooctanoylamidobenzylidene)-1,2-diaminocyclohexane **6** containing two perfluorinated chains was obtained with a yield of 50%, via reaction of **2** with perfluorooctanoyle chloride at 0 °C, in the pres-

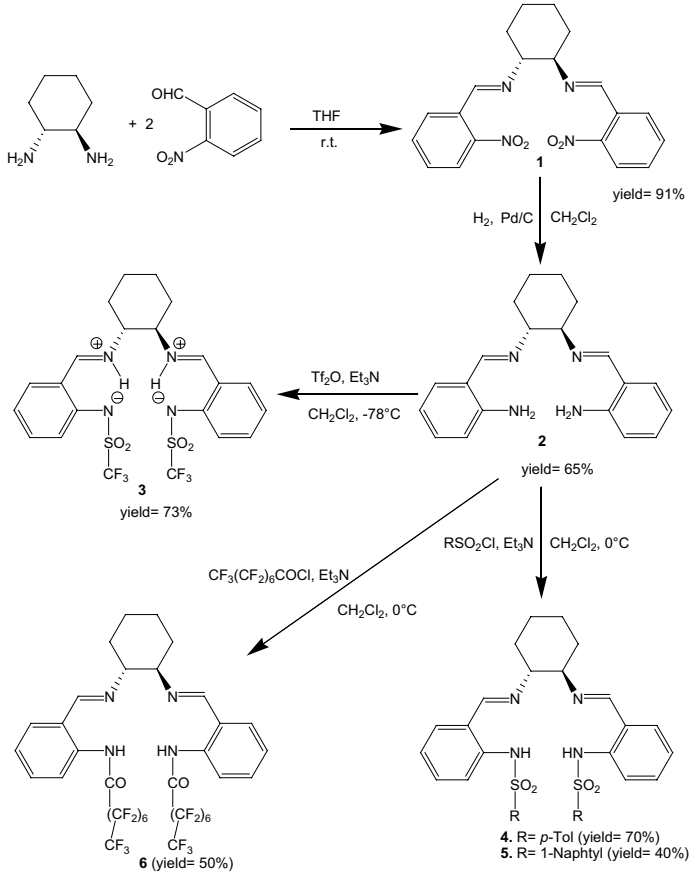


Figure 1. Synthesis of N_4-Schiff bases **1**–**6**.

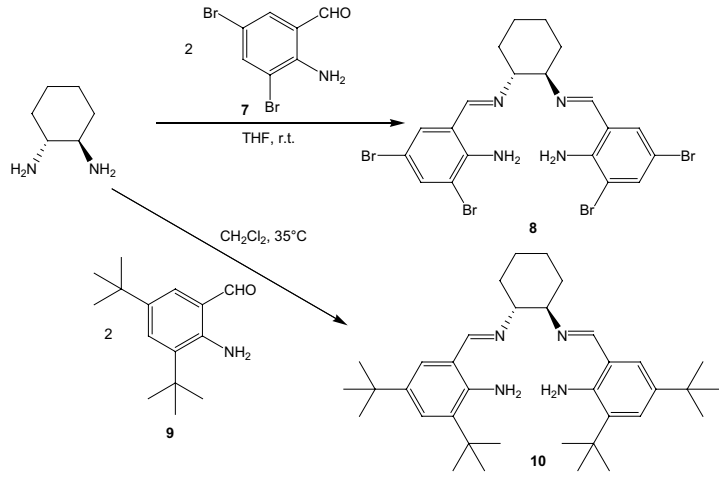


Figure 2. Synthesis of Schiff bases **8** and **10**.

ence of Et_3N (Fig. 1). This synthetic path enabled us to prepare other perfluorinated chiral Schiff bases.

2.1.1.3. Synthesis of Schiff bases 8 and 10. Schiff bases, with substituents on the aromatic rings were prepared from (1*R*,2*R*)-diaminocyclohexane and aminocarboxaldehyde compounds **7** or **9**, which are stable. Schiff base (1*R*,2*R*)-*N*,*N*′-bis-(3,5-dibromo-2-aminobenzylidene)-1,2-diaminocyclo hexane **8**, which contains bromine atoms on both aromatic rings, was synthesized by condensation of 2-amino-3,5-dibromobenzaldehyde **7** and (1*R*,2*R*)-diaminocyclohexane in good yield (73%) (Fig. 2).

In order to prepare a Schiff base with *tert*-butyl substituents on the aromatic rings, we first used the method described above (Section 2.1.1, Fig. 1) by preparing the diimine–dinitro compound to be reduced further under hydrogen pressure (1 bar). The 3,5-di-*tert*-butyl-2-nitrobenzaldehyde **12**, was prepared by the nitration of 3,5-di-*tert*-butylbenzaldehyde **11** (77% yield). This aldehyde was obtained in two steps: Bromination of 3,5-di-*tert*-butyltoluene with NBS in CCl_4, followed by an

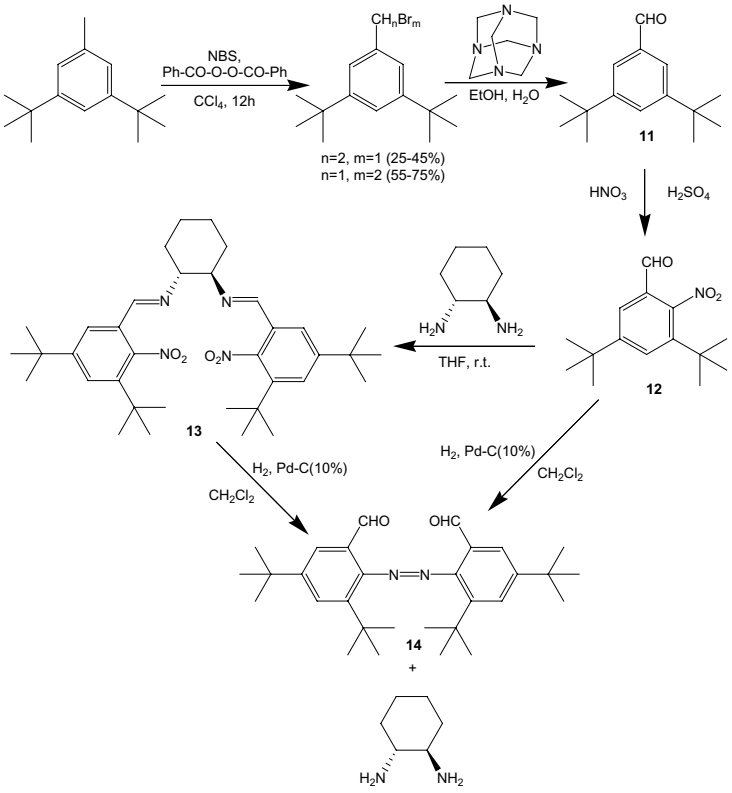


Figure 3. Synthesis of 3,5-di-*tert*-butyl-2-nitrobenzaldehyde **12** and Schiff base **13**.

oxidation/hydrolysis with hexamethylenetetraamine in methanol/water (50/50) gave 95% yield of 3,5-di-*tert*-butylbenzaldhyde **11** (Fig. 3).

The Schiff base **13**, (1*R*,2*R*)-*N*,*N*′-bis-(3,5-di-*tert*-butyl-2-nitrobenzylidene)-1,2-diaminocyclohexane, was obtained in an excellent yield (95%) via reaction of the 3,5-di-*tert*-butyl-2-nitrobenzaldehyde **12** with (1*R*,2*R*)-diaminocyclohexane in THF.

The reduction of the dinitro compound **13** under 1 bar of hydrogen, did not allow the formation of diimine-diamine derivative **10**. Instead we observed the formation of diazo compound **14**, which is a derivative of 3,5-di-*tert*-butyl-2-nitrobenzaldehyde. The same secondary product was obtained by reduction of 3,5-di-*tert*-butyl-2-nitrobenzaldehyde under 1 bar of hydrogen (Fig. 3). The use of hydride reageants such as $NaBH_4$ or $LiAlH_4$ gave a reduction of the imine groups, while the nitro functions remained intact. Preparation of diaza compounds from the nitrated products has already been reported by Kitaura and Mastuura,[15] Gowda and coworkers,[16] and Khan et al.[17] Thus, the diaza compound **14** could result from the reaction between **12** and the amino-aldehyde **9**. In order to avoid this reaction and favor the formation of 3,5-di-*tert*-butyl-2-aminobenzaldehyde **9**, we carried out the reduction of **12** under an hydrogen pressure of 20 bar, at 50 °C for 2 days: **9** was the only product obtained in 95% yield (Fig. 4).

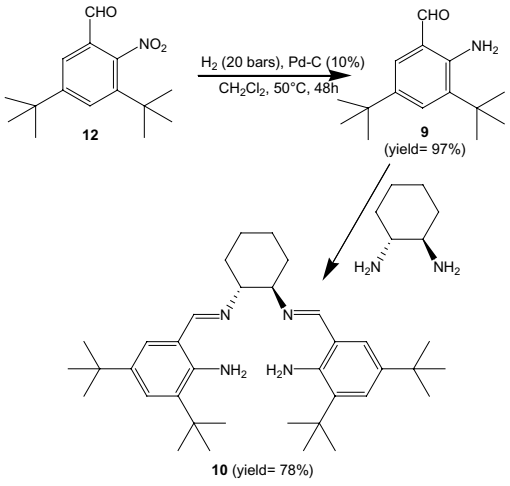


Figure 4. Preparation of Schiff base **8**.

The (1*R*,2*R*)-bis-(3,5-di-*tert*-butylamino-2-aminobenzylidene)-1,2-diaminocyclohexane **10** was then prepared by coupling 3,5-di-*tert*-butyl-2-aminobenzaldehyde **9** and (1*R*,2*R*)-diaminocyclohexane and purified by precipitation in methanol: 78% of pure product was obtained (Fig. 4).

2.1.2. Synthesis of Schiff bases with a (1*R*,2*R*)-diphenylethylenediamine core. For the synthesis of (1*R*,2*R*)-*N*,*N*′-bis-(2-amino-benzylidene)-1,2-diphenylethylenediamine, we used the method described in Figure 1, based on the coupling of the corresponding chiral diamine with 2-nitrobenzaldehyde. The reaction between (1*R*,2*R*)-diphenylethylenediamine and 2-nitrobenzaldehyde in THF, CH_2Cl_2, or methanol with molecular sieves, did not allow the formation of compound **15** (Fig. 5). This compound seemed unstable as when it appeared, it degraded rapidly.

We next considered the synthesis of compound **16**, directly from 2-nitrobenzaldehyde in a one step reaction. The (1*R*,2*R*)-diphenylethylenediamine and 2-nitrobenzaldehyde were dissolved in CH_2Cl_2 and mixed with molecular sieves under 1 bar of hydrogen and catalytic amounts of Pd–C (10%) at 0 °C. The (1*R*,2*R*)-*N*,*N*′-bis-(2-aminobenzylidene)-1,2-diphenylethylenediamine **16** crystallized in methanol and was obtained in 60% yield (Fig. 5).

Compound **17** was prepared from (1*R*,2*R*)-*N*,*N*′-bis-(2-aminobenzylidene)-1,2-diphenylethylenediamine **16**, by

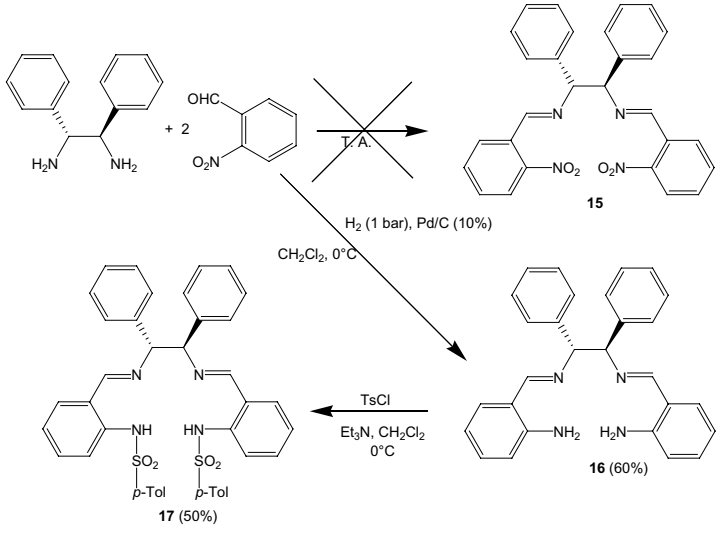


Figure 5. Synthesis of Schiff bases **16** and **17**.

N-tosylation with tosyl chloride in anhydrous CH_2Cl_2, in presence of Et_3N at 0 °C. After purification in methanol, (1*R*,2*R*)-*N*,*N*′-bis-(2*p*-tosyl-aminobenzylidene)-1,2-diphenylethlenediamine **17** was obtained in 50% yield (Fig. 5).

2.2. Asymmetric hydrogenation of acetophenone

The asymmetric hydrogenation reaction was carried out under hydrogen pressure (30 bar) at room temperature in the presence of the chiral catalyst prepared in situ. The catalysts were prepared by the addition of the chiral ligand to the metal precursor in an appropriate solvent. The base was added to the reaction mixture just before the addition of acetophenone (Fig. 6).

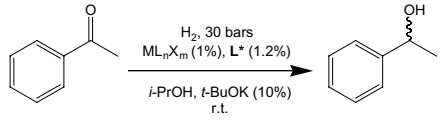


Figure 6. Asymmetric hydrogenation of acetophenone.

2.2.1. Catalysts formed with Schiff base 16. The Schiff base (1*R*,2*R*)-*N*,*N*′-bis-(2-aminobenzylidene)-1,2-diphenylethylenediamine **16** was used in the asymmetric hydrogenation of acetophenone with several metallic precursors of rhodium, iridium, and ruthenium. The reaction conditions along with the main results are listed in Table 1. When coupled with Schiff base **16**, the cationic rhodium species did not allow any enantioselectivity. In the case of iridium, the cationic precursor gave moderate activity and enantioselectivity, whereas the neutral one used in presence of base, led to almost complete conversion but with disappointing ee. The ruthenium complexes allowed complete acetophenone hydrogenation. $[Ru(COD)Cl_2]_x$ and $[Ru(C_6H_6)Cl_2]_2$ gave 41% and 20% ee, respectively and, in both cases, the (*R*)-enantiomer was the major product. It is noteworthy that the use of the phosphorus ruthenium precursor $[Ru(PPh_3)_3Cl_2]$ gave 54% ee of the opposite enantiomer, (1*S*)-phenylethanol. This result was the best obtained with Schiff base **16**.

The hydrogenation reaction with the ruthenium species was carried under conditions close to those of the hydrogen transfer reaction (*t*-BuOK, *i*-PrOH). When the reaction mixture was stirred for 24 h without H_2, no reaction was observed. Only 5 equiv of *t*-BuOK are enough for a complete conversion and a good enantioselectivity.

2.2.2. Catalysts formed with $[Ru(PPh_3)_3Cl_2]$ and various Schiff bases. The $[Ru(PPh_3)_3Cl_2]$ precursor was used with various Schiff bases in the asymmetric hydrogenation of acetophenone (Table 2). Results and reaction conditions are summarized in Table 2.

In the presence of $Ru(PPh_3)_3Cl_2$, all the N_4-Schiff bases tested form active catalysts and only in two cases was conversion not completed (ligands **3** and **7**). Concerning the enantioselection, (1*R*,2*R*)-*N*,*N*′-bis(2-aminobenzylidene)-1,2-diaminocyclohexane **2** and its derivatives **3**–**6** and **10** led to moderate ee values (49–58%). The replacement of NH_2 by $NHSO_2R$ or $NHCO(CF_2)_6CF_3$ in the Schiff bases with a diaminocyclohexane core did not affect their activity nor their enantioselectivity, except in the case of **3**, which has $NHSO_2CF_3$ groups. Two factors that could be responsible for the decreasing activity: (i) the sulfonamide functions have particularly acidic protons, which are easily removed with the resulting R_2N^- groups coordinating to the metal as X^- ligands, thus blocking active sites on the catalyst, or (ii) the conformation change, as shown by ORTEP views[14] of **3** could affect the catalytic hydrogenation results. The bromide substituents at the *ortho*- and *para*-positions on the aromatic groups (ligand **8**) strongly decrease the enantioselectivity, whereas the *tert*-butyl groups (ligand **10**) do not affect the activity or enantioselectivity of the catalysts. In both cases, the catalyst appears to be soluble. The Schiff base **16** with a (1*R*,2*R*)-diphenylethylenediamine core also gave complete conversion and 54% ee. The (1*R*,2*R*)-*N*,*N*′-bis-(2-*p*-tosylaminobenzylidene)-1,2-diphenylethylnediamine **17** with NHTs groups led to 72% ee with complete conversion (Table 2). The best enantiomeric excess (76% ee) was obtained by preparing the catalyst directly in isopropanol from $Ru(PPh_3)_3Cl_2$ and **17**.

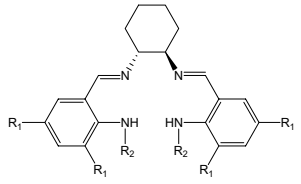
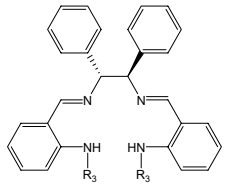
2.2.3. Role of the amine and sulfonamide functionalities. All the tetradentate Schiff bases used herein, present an amine or a sulfonamide group at the *ortho*-position of

Table 1. Asymmetric hydrogenation of acetophenone with catalysts containing **16**

Metallic precursor	Solvent	Base	Conversion (%)	Ee (%)
$[Rh(COD)_2]OTf$[a]	MeOH	—	74	0
$[Ir(COD)_2]BF_4$[a]	MeOH	—	56	43 (*S*)
$[Ir(COD)Cl]_2$[b]	*i*-PrOH	*t*-BuOK	99	20 (*S*)
$[Ru(COD)Cl_2]_x$[c]	*i*-PrOH	*t*-BuOK	100	41 (*R*)
$[Ru(C_6H_6)Cl_2]_2$[c]	*i*-PrOH	*t*-BuOK	100	20 (*R*)
$[Ru(PPh_3)_3Cl_2]$[c]	*i*-PrOH	*t*-BuOK	100	54 (*S*)

[S] = 0.3 M and S/*k*-BuOK/L*/M = 100/10/1/1; 30 bar of H_2; 50 °C; 16 h.
[a] [M]+**16**+MeOH, 1 h at 50 °C, then addition of acetophenone.
[b] [M]+**16**+*i*-PrOH, 1 h at 50 °C, then addition of *t*-BuOK and acetophenone.
[c] [M]+**16**+toluene, 1 h at rt, then evaporation of toluene and addition of *i*-PrOH and *t*-BuOK and acetophenone.

Table 2. Various Schiff bases in asymmetric hydrogenation of acetophenone

General structure	Ligand L*	Conversion (%)	Ee (%)
	2. $R_1 = R_2 = H$	100	55 (*S*)
			58[a] (*S*)
	3. $R_1 = H$, $R_2 = Tf$	60	49 (*S*)
	4. $R_1 = H$, $R_2 = Ts$	100	57 (*S*)
	5. $R_1 = H$, $R_2 = C_{10}H_7SO_2$	100	56 (*S*)
	6. $R_1 = H$, $R_2 = CF_3\ (CF_2)_6CO$	100	50 (*S*)
	8. $R_1 = Br$, $R_2 = H$	75	7 (*R*)
	10. $R_1 = t$-Butyl, $R_2 = H$	100	50 (*S*)
	16. $R_3 = H$	100	54 (*S*)
	17. $R_3 = Ts$	100	72 (*S*)
			76[a] (*S*)

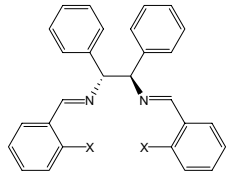
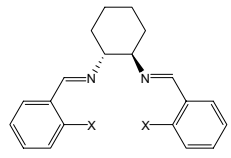
[S] = 0.3 M; L/M = 1.2; S/metal = 100; *t*-BuOK/metal = 10; 30 bar of H2; t.a.; 16 h.
[M]+L*+toluene, 1 h at rt, then evaporation of toluene+*i*-PrOH+*t*-BuOK+acetophenone.
[a] [M]+**2** or **17**+*i*-PrOH, then agitation 6–16 h at rt, then addition of *t*-BuOK+acetophenone.

benzylidene groups. In order to evaluate the role of these functionalities, we tested phenyl diimines, which we prepared according to reported procedures from benzaldehyde and the corresponding chiral diamines and then evaluated their chiral inductor properties in acetophenone hydrogenation. The results of the catalytic tests are summarized in Table 3. Contrary to ligands **16** and **17**, the (1*R*,2*R*)-*N*,*N*′-bis-(benzylidene)-1,2-diphenylethylenediamine **19** combined with $Ru(PPh_3)_3Cl_2$ did not allow any chiral induction. In this particular case, the cisoid conformation of **19** is less stable than the transoid thanks to steric hindrance. In the case of ligand **16**, the amine–amine and amine–imine interactions allow a rigidity of the Schiff base structure. In the case of ligand **17**, we can assume an increasing rigidity due to the face to face π-stacking interaction between the two tosyl groups. A π-stacking interaction of that type has been noted in ligand **4** in our previous study and also been reported by Bermejo and co-workers.[13]

The (1*R*,2*R*)-*N*,*N*′-bis-(benzylidene)-1,2-diaminocyclohexane **18** and (1*R*,2*R*)-*N*,*N*′-bis-(2-aminobenzylidene)-1,2-diaminocyclohexane **2** tested with $Ru(PPh_3)_3Cl_2$ gave identical results. The cyclohexyl skeleton can induce a relative rigidity to ligand **18**. Therefore, if we used the $[Ru(COD)Cl_2]_x$ without any phosphine, the Schiff base **2** containing NH_2 functions gave a better result than ligand **18**. The ligands with amine and sulfonamide groups contributed to the formation of the rigid catalysts and constitute the N-donor ligands easily replaced by phosphines.

2.2.4. Phosphines as co-ligands. The metallic precursor $Ru(PPh_3)_3Cl_2$ has three triphenylphosphine ligands, which can have a synergetic effect with diimine ligand. In order to avoid this influence, we used $[Ru(C_6H_6)Cl_2]$ with ligand **17** (Table 4): 44% conversion and 12% ee (*S*) were then observed. The addition of 1, 2, and 3 equiv of PPh_3 to the $[Ru(C_6H_6)Cl_2]_2$/**11** system, allowed

Table 3. Schiff base de **2**, **16**, **17**, **18**, and **19** in asymmetric hydrogenation of acetophenone

L*	X	Metallic precursor	Conversion (%)	Ee (%)
	H (19)	$Ru(PPh_3)_3Cl_2$	100	0
	NH_2 (16)	$Ru(PPh_3)_3Cl_2$	100	54 (*S*)
	NH-tosyle (17)	$Ru(PPh_3)_3Cl_2$	100	76 (*S*)
	H (18)	$Ru(PPh_3)_3Cl_2$	100	56 (*S*)
	H (18)	$[Ru(COD)Cl_2]_x$	37	0
	NH_2 (2)	$[Ru(COD)Cl_2]_x$	100	37 (*R*)
	NH_2 (2)	$Ru(PPh_3)_3Cl_2$	100	55 (*S*)

[S] = 0.3 M and S/*t*-BuOK/L*/M = 100/10/1.2/1; 30 bar H_2; rt; 16 h.

Table 4. Co-ligand phosphines used in asymmetric hydrogenation of acetophenone par **17**/[$Ru(C_6H_6)Cl_2$]

Co-ligand	Conversion (%)	Ee (%)
None	44	12 (S)
PPh_3	100	73 (*S*)
$P(Cy)_3$	100	7 (*S*)
$P(p\text{-Tol})_3$	100	67 (*S*)
$P(o\text{-Tol})_3$	96	10 (*S*)
$P(TMOPh)_3$	100	5 (*S*)
$P(bTFMP)_3$	90	15 (*S*)
DPPE	100	33 (*S*)
DPPP	100	48 (*S*)
DPPB	100	54 (*S*)

[S] = 0.3 M; S/metal = 100; *t*-BuOK/Ru = 10; L*/M = 1.2; phosphine/Ru = 1; 30 bar H_2; rt; 16 h.

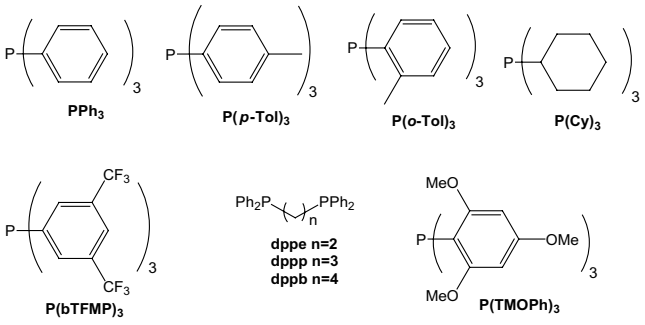


Figure 7. Phosphines used as co-ligands for acetophenone hydrogenation with Ru catalyst.

72–73% ee with complete conversion. This result was identical to the one obtained for [$Ru(PPh_3)_3Cl_2$]/**17** (Table 2).

Several phosphines (Fig. 7) have also been used in order to form a co-ligand with diimine (Table 4). Low enantioselectivities (15%) were observed with $P(Cy)_3$, $P(o\text{-Tol})_3$, $P(TMOPh)_3$, and $P(bTFMP)_3$, which are bulky phosphines. $P(p\text{-Tol})_3$ was the only phosphine able to give results close to those obtained with PPh_3. The use of diphosphine co-ligands such as DPPE, DPPP, and DPPB also decreased the enantioselectivity. This effect was noticeable when the number of carbons between the two phosphorus atoms decreased. This could be explained by the low possibility of DPPB acting as a mono phosphine due to the chelating effect.

2.2.5. Mechanism. Morris and co-workers[18] have proposed a mechanism for hydrogenation of simple ketones catalyzed by BINAP–Ru–diamine system, in which the dihydride complex reacts with a ketone to produce the alcohol and novel amino–amido complex in the unconventional second coordination sphere transfer of dihydrogen. This transfer of dihydrogen as first proposed by Noyori et al., was studied later by other groups[19] and our laboratory.[20] Before the discovery of Noyori catalysts, simple aromatic ketones such as the acetophenone, were not hydrogenated by ruthenium catalysts. Whereas Komiya and Yamamoto proposed in 1979, a mechanism for hydrogenation of olefins (C=C) with ruthenium dihydride.[21,22] This mechanism carries four steps. In the various mechanisms proposed for the asymmetric hydrogenation reaction with ruthenium (monohydride or dihydride), the presence of a base proved essential for the exchange of the chloride ligand by the hydride in the active species.[23–25]

Although the metal precursors [$Ru(COD)Cl_2]_2$ and $Ru(PPh_3)_3Cl_2$ are both ruthenium complexes, the first with ligand **16** supported the majority formation of (1*R*)-phenylethanol (41% ee), whereas the second supported the majority formation of (1*S*)-phenylethanol (52% ee). This difference was also observed in the case of ligand **2** (Table 5).

The complex formed from [$Ru(COD)Cl_2]_x$ and chiral ligand L* is undoubtedly different to that formed from $Ru(PPh_3)_3Cl_2$ and the same ligand L*. We can thus consider that two different mechanisms occur during acetophenone hydrogenation. In the case of [$Ru(COD)Cl_2]_x$, the catalyst formed is probably of $Ru(L^*)H_2$ **21** type where the chiral ligand is coordinated to the metal center by the four nitrogen atoms. A clear difference in activity and enantioselectivity was observed with [$Ru(COD)Cl_2]_x$ when coordinated to ligand **2** ($c = 100\%$, ee = 37%) or ligand **18** ($c = 37\%$, ee = 0%). This indicates the effective participation of amine groups in the formation of catalysts. The dihydride complex $Ru(L^*)H_2$ **21** should be formed from the dichloride complex $Ru(L^*)Cl_2$ **20** in basic media (Fig. 8).

We suggest the mechanism (α) for the reduction carried out with $Ru(L^*)H_2$ **21** similar to that proposed by Morris (Fig. 9). In this mechanism, the nitrogen atom takes part not only in the coordination to metal, but also to the hydrogen donation.

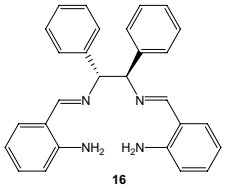
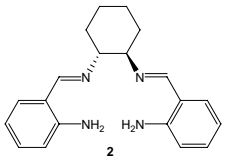
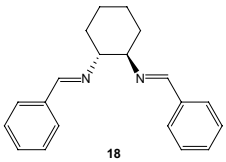
The same results were obtained with ligand **2** or ligand **18** in the presence of $Ru(PPh_3)_3Cl_2$ (55–56% ee); the formation of two similar complexes can be assumed. The presence of one or three triphenylphosphines co-ligands gave identical results (Tables 1 and 5); the active species should be dihydrides of a general formula $Ru(L^*)(PPh_3)H_2$ **26**, and should be formed from the corresponding dichlorides $Ru(L^*)(PPh_3)Cl_2$ **25** in basic media (Fig. 10).

We propose the mechanism (β), which is possible during hydrogenation with the catalyst **26** and can be carried out in four principal steps (Fig. 11): 1)—coordination of substrate, 2)—migration 1–2 of the substrate, 3)—reductive elimination and formation of Ru^0 species, and 4)—oxidative addition and regeneration of catalyst.

The amine or sulfonamides functionalities do not seem to participate in coordination to the metal center during the reaction. These functions can play a part in the hindrance and stabilization of catalysts. With ligands **16** and **17**, we observed better results than with **19** (Table 3).

The addition of 0.5 equiv of PPh_3 to the catalytic system [$Ru(COD)_2Cl_2]_x$/**2** allowed the formation of the two

Table 5. Selection results obtained with different catalytic system of ruthenium

Ligand (L*)	Metallic precursor (1%)	Co-ligand	Conversion (%)	Ee (%)
 **16**	$[Ru(COD)Cl_2]_x$	—	92	41 (*R*)
	$Ru(PPh_3)_3Cl_2$	—	100	52 (*S*)
 **2**	$[Ru(COD)Cl_2]_x$	—	100	37 (*R*)
	$[Ru(COD)Cl_2]_x$	PPh_3 (1.2%)	100	54 (*S*)
	$[Ru(COD)Cl_2]_x$	PPh_3 (0.5%)	100	57 (*S*)
	$Ru(PPh_3)_3Cl_2$	—	100	55 (*S*)
 **18**	$[Ru(COD)Cl_2]_x$	—	37	0
	$Ru(PPh_3)_3Cl_2$	—	100	56 (*S*)

[S] = 0.3 M; and S/*t*-BuOK/L*/M = 100/10/1.2/1; 30 bar H_2; rt; 18 h.

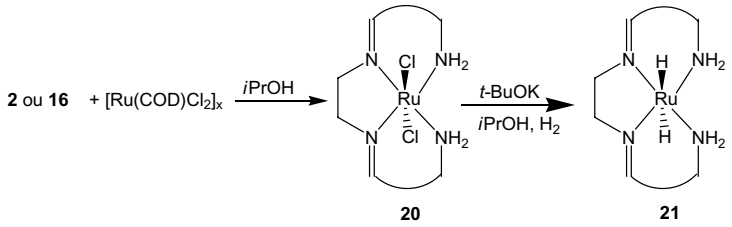


Figure 8. Preparation of catalyst from chiral Schiff base L* and $Ru(PPh_3)_3Cl_2$.

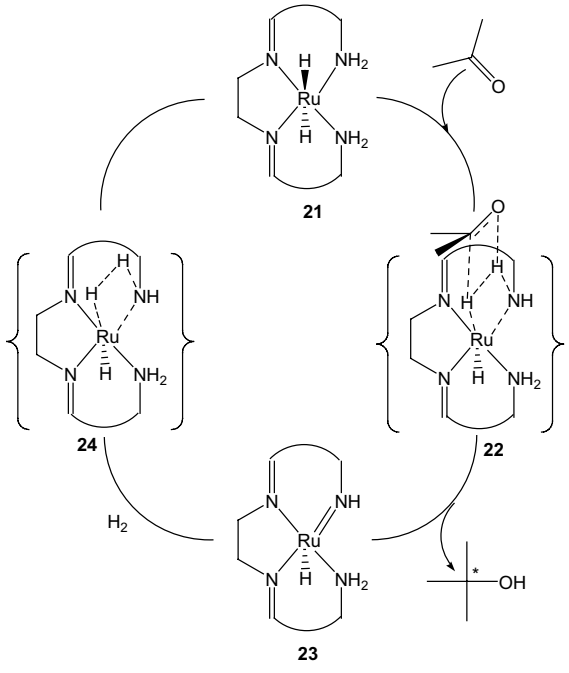


Figure 9. Mechanism (α) proposed with catalyst $Ru(L^*)H_2$ **21**.

catalysts **21** and **26** in reaction mixture. As the results obtained with 0.5 or 1 equiv of PPh_3 are identical, we assume that the rate of the reduction carried with **26** is much larger than that of the reduction carried with **21**.

3. Conclusion

This study is to the best of our knowledge the first report on the use of Schiff bases as chiral inductors for acetophenone hydrogenation. In the case of ruthenium species, we have developed a new catalytic and enantioselective system: the best result (100% conversion, 76% ee) was obtained with (1*R*,2*R*)-*N*,*N*′-bis-(2-*p*-tosylaminobenzylidene)-1,2-diphenylethylenediamine **17** coordinated to $[Ru(PPh_3)_3Cl_2]$. $[Ru(COD)Cl_2]$/(1*R*,2*R*)-*N*,*N*′-bis-(2-aminobenzylidene)-1,2-diphenylethylenediamine **16** led to an encouraging enantiomeric excess (41%) with complete conversion. This is one of the best results obtained for asymmetric hydrogenation of acetophenone with a nonphosphorus ruthenium catalyst. We have noticed a synergetic co-ligand effect between some Schiff bases and triphenylphosphine, increasing both the activity and

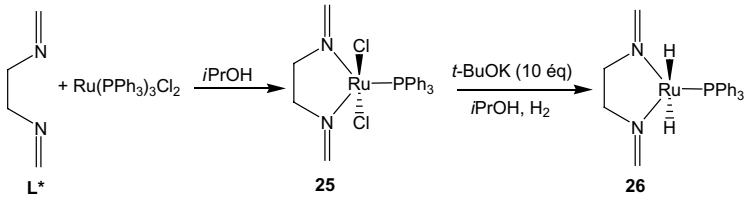


Figure 10. Preparation of catalyst from chiral Schiff base L* and $[Ru(COD)Cl_2]_x$.

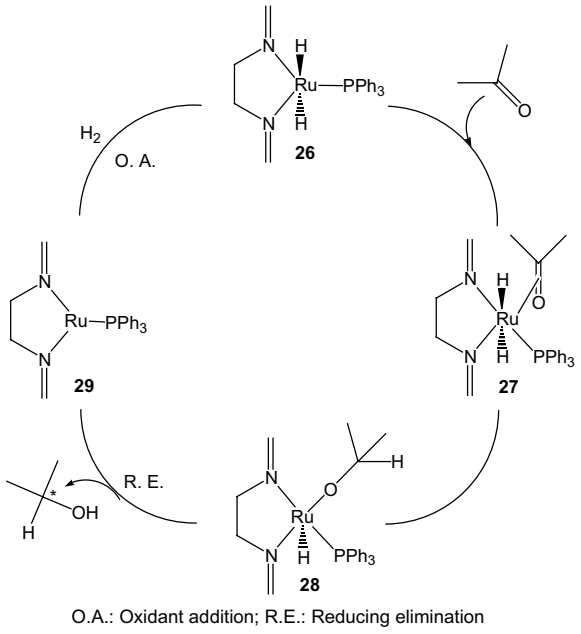


Figure 11. Mechanism (β) proposed with catalyst $Ru(L^*)PPh_3H_2$ **26**.

enantioselectivity of the ruthenium catalysts. In the case of diimine–diamine ligands, the presence of phosphine supported the majoritary formation of the opposite (*S*)-enantiomer than the one formed without phosphine (*R*)-1-phenylethanol. This difference suggests that two different mechanisms of acetophenone hydrogenation can occur with ruthenium complexes. The diimine/Ru/phosphine system can be alternative catalysts to those developed by Noyori. We are now focusing on the development of these catalysts and on the study of the complexes and the different effects, which can improve better enantioselectivity.

4. Experimental section

4.1. General remarks

All the organic and organometallic reagents used were pure commercial products. The solvents from Carlo Erba, anhydrous THF from Aldrich, dry CH_2Cl_2 were prepared in the laboratory. Enantiomerically pure diamines (1*R*,2*R*)-cyclohexanediamine and (1*R*,2*R*)-diphenylethylenediamine were obtained from Fluka, 2-nitrobenzaldehyde from Avocado. All manipulations of organometallic compounds were carried out under an argon atmosphere. The metallic precursors were purchased from STREM.

Melting points (mp), uncorrected, were determined with a Köffler Bench type WME (HεIZBANK). Elemental analyses (C, H, N, S, O, F) were obtained from the Service Central d'Analyse of the CNRS (Solaize). High resolution mass spectra: HR LSIMS (Liquid Secondary Ionization Mass Spectrometry: Thioglycerol), HR CIMS (Isobutan), and HR EIMS were carried out on a Finnegan MAT 95xL by the UCBL Centre de Spectroscopie de Masse. IR spectra (KBr plates) were recorded on a FT Nicolet impact spectrometer 410: I.R.F.T. or on a FT Perkin–Elmer spectrometer. $[\alpha]_D^{20}$ was determined with a Perkin–Elmer 241 polarimeter ($l = 1$ dm; 25 °C; concentration c in g/mL). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for ^1H, 50.32 MHz for ^{13}C, 188.29 MHz for ^{19}F) or AC-300 FT (300.13 MHz for ^1H, 75.46769 MHz for ^{13}C, 282.4481 MHz for ^{19}F) spectrometer; δ values are given in ppm and J in hertz. The ee values and conversion were determined by chiral GC (Cyclodex β colum, 30 m).

4.2. Synthesis of ligands and organic compounds

4.2.1. (1*R*,2*R*)-*N*,*N*′-Bis-(2-naphthalene-sulfonaminobenzylidene)-1,2-diaminocyclohexane, 5. (1*R*,2*R*)-*N*,*N*′-Bis-(2-aminobenzylidene)-1,2-diaminocyclohexane (0.54 g, 1.68 mmol) was dissolved in dry dichloromethane (10 mL), Et_3N (490 μL, 3.53 mmol) then added and the resulting solution cooled to −10 °C under an argon atmosphere. At this temperature, 1-naphthalenesulfonyl chloride (0.8 mg, 3.53 mmol) was added and the resulting solution stirred overnight (the temperature was allowed to rise at room temperature). The solvent was then removed and ligand **5** (0.3 g) was obtained after a flash chromatography as a yellow solid (silica, dichloromethane/ethyl acetate, 99.5/0.5). Isolated yield = 40%. MW = 700.87; $[\alpha]_D^{20} = -207$ (c 11.35×10^{-3} g/mL; CH_2Cl_2). Mp 140 °C. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C), δ (ppm) = 13.73 (s, 2H, $NHSO_2$), 8.74 (m, 2H, Ar–H), 8.30 (s, 2H, Ar–H), 8.27 (m, 2H, Ar–H), 7.98 (m, 2H, Ar–H), 7.88 (m, 2H, Ar–H), 7.57 (m, 4H, Ar–H), 7.41 (m, 4H, Ar–H), 7.14 (m, 4H, Ar–H), 6.82 (m, 2H, Ar–H), 3.49 (m, 2H, HC–N), 2–1.5 (m,8H, $-CH_2-$). ^{13}C NMR ($CDCl_3$, 300 MHz, 25 °C): δ (ppm) = 164.9 (C_4=N), 139.7 (C_q–Ar), 135.4 (C_q–Ar), 134.7 (C–Ar), 134.6 (C_q–Ar), 134.0 (C–Ar), 131.7 (C–Ar), 130.0 (C–Ar), 129.4 (C–Ar), 128.6 (C_q–Ar), 128.48 (C–Ar), 127.1

(C–Ar), 124.9 (C–Ar), 124.5 (C–Ar), 122.2 (C–Ar), 119.9 (C_q–Ar), 116.3 (C–Ar), 73.6 (CH–N), 33.5 (CH_2), 24.7 (CH_2). IR (KBr), ν (cm^{-1}) = 2857–2928 (NH), 1629 (C=N), 1134–1160 (SO_2). HR LSIMS calcd for $C_{40}H_{36}N_4O_4S_2 \cdot H^+ = 701.2178$; found = 701.2247.

4.2.2. (1*R*,2*R*)-*N*,*N*′-Bis-(2-perfluooctanoylsulfonaminobenzylidene)-1,2-diaminocyclohexane 6. The (1*R*,2*R*)-*N*,*N*′-bis-(2-aminobenzylidene)-1,2-diaminocyclohexane (0.26 g, 0.8 mmol) was dissolved in dry CH_2Cl_2 (10 mL), before addition of Et_3N (0.27 mL, 1.9 mmol). The resulting solution was cooled to −10 °C, and $CF_3(CF_2)_6Cl$ (750 mg, 1.9 mmol) was then added dropwise. The solution was stirred overnight (the temperature was allowed to rise at room temperature) and washed with 4 × 10 mL of a saturated solution of NaCl. After separation, the organic layer was dried over Na_2SO_4, and the solvent evaporated. Ligand **6** was obtained as a yellow oil and dried under vacuum (P = 0.1 mmHg). Isolated yield = 50%. FW = 1169.46; $[\alpha]_D^{20} = -283$ (c 0.01 g/mL, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ (ppm) = 14.2 (s large, 2H, NH), 8.63 (m, 2H, Ar–H), 8.23 (s, 2H, HC=N), 7.4 (m, 2H, Ar–H), 7.26 (m, 2H, Ar–H), 7.18 (m, 2H, Ar–H), 3.37 (m, 2H, CH–N), 1.9 (m, 4H, –CH_2–), 1.7 (m, 2H, –CH_2–), 1.5 (m, 2H, –CH_2–). ^{13}C NMR ($CDCl_3$, 300 MHz, 25 °C): δ (ppm) = 164 (C=N), 156 (C=O), 138 (Cq–Ar), 133.6 (C–Ar), 132 (C–Ar), 125 (C–Ar), 121.7 (Cq–Ar), 120.5 (C–Ar), 74.8 (C–N), 33.5 (–CH_2), 24.56 (–CH_2–). ^{19}F NMR ($CDCl_3$, 300 MHz, 25 °C): δ (ppm) = −81.2 (m, 6F, CF_3), −119.4 (m, 4F, –CF_2–), −121.8 (m, 4F, –CF_2–), −122.3 (m, 4F, –CF_2–), −122.6 (m, 4F, –CF_2–), −123.1 (m, 4F, –CF_2–), −126.5 (m, 4F, –CF_2–CO). IR (NaCl) ν (cm^{-1}) = 1150–1330 (CF_2, CF_3), 1636 (C=N), 1724 (CHO). HR LSIMS calcd for $C_{36}H_{22}F_{30}N_4O_2 \cdot H^+$ = 1113.1340; found = 1113.13378.

4.2.3. (1*R*,2*R*)-(−)-*N*,*N*′-Bis-(2-amino-3,5-dibromobenzylidene)-1,2-diaminocylohexane 8. To a solution of (1*R*,2*R*)-(−)-diaminocyclohexane (0.564 g, 4.94 mmol) in anhydrous THF (10 mL), 2-amino-3,5 dibromobenzaldehyde (2.755 g, 9.88 mmol) and molecular sieves 4 Å were added. After stirring for 17 h under an argon atmosphere at room temperature, the mixture was filtered through silica (CH_2Cl_2). The solvents were evaporated to give 2.28 g of ligand **7** as a yellow solid. Isolated yield = 73%. FW = 632.4; Mp = 174 °C. $[\alpha]_D^{20} = -244$ (c 0.01 g/mL, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 8.27 (s, 2H, CH=N), 7.5 (d, 2H, $^4J_{H,H}$ = 2.15 Hz, Ar–H), 7.16 (d, 2H, $^4J_{H,H}$ = 2.16 Hz, Ar–H), 7 (br s, 4H, NH_2), 3.26 (m, 2H, CH–N), 1.5–2 (m, 8H, –CH_2–). ^{13}C NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 161.6 (C=N), 145 (Cq–Ar), 135.8 (C–Ar), 135.1 (C–Ar), 119.7 (Cq–Ar), 110.3 (Cq–Ar), 106.5 (Cq–Ar), 74.8 (CH–N), 33.6 (–CH_2–), 24.7 (–CH_2–). IR (KBr), ν (cm^{-1}) = 3231–3464 (NH_2), 1627 (C=N). HR LSIMS calcd for $C_{20}H_{20}N_4$-$Br_4 \cdot H^+$ = 632.8500; found = 632.84993. Anal. Calcd (%) for $C_{20}H_{20}N_4Br_4$ (632.4 g mol^{-1}): C, 37.985; H, 3.187; N, 8.86. Found: C, 37.85; H, 3.00; N, 8.08.

4.2.4. 3,5-Di-*tert*-butyl-2-amino-benzaldehyde 9. 3,5-Di-*tert*-butyl-2-nitrobenzaldehyde (1 g, 0.0038 mmol) was dissolved in 75 mL of CH_2Cl_2. To this solution 1 g of Pd–C (10%) was added and the resulting mixture stirred under hydrogen pressure (20 bar) at 50 °C. After 48 h the mixture was filtered on Celite, the solvent removed by evaporation to give 0.859 g of 3,5-di-*tert*-butyl-2-aminobenzaldehyde **9** as a yellow solid. Isolated yield = 97%. FW = 233.35; Mp = 95 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 9.9 (s, 1H, CHO), 7.5 (d, $^4J_{H,H}$ = 2.08 Hz, 1H, Ar–H), 7.33 (d, $^4J_{H,H}$ = 2.08 Hz, 1H, Ar–H), 6.6 (br s, 2H, Ar–NH_2), 1.45 (s, 9H, *tert*-butyl), 1.3 (9H, s, *tert*-butyl). ^{13}C NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 194.9 (C=O), 146.9 (Cq–Ar), 138.2 (Cq–Ar), 133.4 (Cq–Ar), 130.5 (C–Ar), 118.8 (Cq–Ar), 34.5 (Cq, $C(CH_3)_3$), 34 (Cq, $C(CH_3)_3$), 31.3 (CH_3, *t*-Bu), 29.6 (CH_3, *t*-Bu). IR (KBr) ν (cm^{-1}) = 1662 (CHO), 3319 (NH_2). HR EIMS calcd for $C_{15}H_{23}NO$ = 233.177964; found = 233.17768.

4.2.5. (1*R*,2*R*)-(−)-*N*,*N*′-Bis-(3,5-di-*tert*-butyl-2-aminobenzylidene)-1,2-diaminocyclohexane 10. To a solution of 3,5-di-*tert*-butyl-2-aminobenzaldehyde (0.437 g, 18.7 × 10^{-4} mmol) in 10 mL of dichloromethane, 0.107 g (9.35 × 10^{-4} mmol) of (1*R*,2*R*)-diaminocyclohexane and 4 Å molecular sieves were added. The resulting mixture was stirred overnight at 35 °C. After the mixture was filtered through Celite and the solvent removed by evaporation, the residue was washed with methanol and filtered through a Millipore filter (vv type, pore size 0.10 μm). Finally, it was dried under vacuum to give 0.4 g of ligand **10** as a white solid. Isolated yield = 78%. FW = 544.86. Mp = 194 °C. $[\alpha]_D^{20} = -313$ (c 0.001 g/mL, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 8.3 (s, 2H, HC=N), 7.26 (d, $^4J_{H,H}$ = 2.16 Hz, 2H, Ar–H), 7.0 (d, $^4J_{H,H}$ = 2.16 Hz, 2H, Ar–H), 6.76 (br s, 4H, Ar–NH_2), 3.22 (m, 2H, CH–N), 1.9–1.5 (m, 8H, –CH_2–), 1.35 (s, 18H, $C(CH_3)_3$), 1.22 (s, 18H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 200 MHz, 25 °C) δ (ppm) = 164.6 (C=N), 145 (Cq–Ar), 137.2 (Cq–Ar), 132.5 (Cq–Ar), 128.5 (C–Ar), 125.5 (C–Ar), 117.8 (Cq–Ar), 74.4 (CH–N), 34.5 (Cq–$C(CH_3)_3$), 33.8 (Cq–$C(CH_3)_3$), 33.6 (–CH_2), 31.5 (CH_3–$C(CH_3)_3$), 29.7 (CH_3–$C(CH_3)_3$), 24.6 (–CH_2). IR (KBr) ν (cm^{-1}) = 1633.49 (C=N), 3139–3515 (NH_2). Anal. Calcd (%) for $C_{36}H_{56}N_4$: C, 79.36; H, 10.36; N, 10.28. Found (%): C, 79.15; H, 10.32; N, 10.11. HR LSIMS calcd for $C_{36}H_{56}N_4 \cdot H^+ = 545.4584$; found = 545.4590.

4.2.6. 3,5-Di-*tert*-butylbenzaldehyde 11. A solution of 3,5-di-*tert*-butyltoluene (5 g, 24.46 mmol) of *N*-bromosuccinimide (9 g, 50.56 mmol) and 40 mg of benzoyl peroxide in 80 mL of CCl_4 was heated at reflux for 15 h. When the reaction was finished (CG control) the reaction mixture was filtered through Celite and the CCl_4 was removed on a rotary evaporator to give an oily mixture of 3,5-di-*tert*-butylbenzylbromide (38%) and 3,5-di-*tert*-butylbenzyldibromide (62%). ^{1}H NMR for 3,5-di-*tert*-butylbenzylbromide ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 7.4–7.25 (m, 3H, Ar–H), 4.53 (s, 2H, CH_2Br), 1.37 (s, 18H, $C(CH_3)_3$). For 3,5-di-*tert*-butyl-

benzyldibromide δ (ppm) = 7.4–7.25 (m, 3H, Ar–H), 6.7 (s, 1H, $CHBr_2$), 1.37 (s, 18H, $C(CH_3)_3$). The mixture of 3,5-di-*tert*-butylbenzylbromide and 3,5-di-*tert*-butylbenzyldibromide was added to a solution of 9.45 g of hexamethylenetetramine in 7 mL of water and 7 mL of ethanol. This solution was refluxed for 4 h. After liquid–liquid extraction with a mixture of Et_2O/toluene (50/50), the organic layer was washed with 3 × 20 mL of brine, and dried with Na_2SO_4. The solvents were evaporated to give 4 g of **11** as a white solid. Isolated yield = 75%. FW = 218.33. Mp = 86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 10.02 (s, 1H, CHO), 7.73 (m, 3H, Ar–H), 1.37 (s, 18, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 200 MHz, 25 °C) δ (ppm) = 193.24 (CHO), 151.9 (Cq–Ar), 136.3 (Cq–Ar), 129.9 (C–Ar), 124.2 (C–Ar), 35 (Cq, $C(CH_3)_3$), 31.4 ($3CH_3$, $C(CH_3)_3$). IR (KBr) ν (cm^{-1}) = 1693 (CHO). HR EIMS calcd for $C_{15}H_{22}O$ = 218.1671; found = 218.16749.

4.2.7. Compound 12: 3,5-di-*tert*-butyl-2-nitro-benzaldehyde. The 3,5-di-*tert*-butylbenzaldehyde (4 g, 18.32 mmol) was dissolved in 12 mL of concentrated solution of H_2SO_4. After the mixture was cooled at 0 °C, 0.9 mL of concentrated solution of HNO_3 was added drop by drop. The mixture was stirred for 30 min at 0 °C and then poured into 50 mL of water containing chopped ice. The organic product was separated by extraction with 3 × 50 mL of CH_2Cl_2, the organic layer was washed with water, dried with Na_2SO_4, and evaporated on a rotary evaporator to give 4.1 g of **12** as a yellow solid. Isolated yield = 85%. FW = 263.33. Mp = 90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 9.82 (s, 1H, CHO), 7.83 (d, $^4J_{H,H}$ = 2.07 Hz, 1H, Ar–H), 7.82 (d, $^4J_{H,H}$ = 2.07 Hz, 1H, Ar–H), 1.45 (s, 9H, $C(CH_3)_3$), 1.34 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 200 MHz, 25 °C) δ (ppm) = 187.5 (CHO), 153.56 (Cq–Ar), 140.8 (Cq–Ar), 135 (Cq–Ar), 127.35 (Cq–Ar), 125.63 (C–Ar), 36.3 (Cq, $C(CH_3)_3$), 35.35 (Cq, $C(CH_3)_3$, 31.08 ($3CH_3$, $C(CH_3)_3$), 30.85 ($3CH_3$, $C(CH_3)_3$). IR (KBr) ν (cm^{-1}) = 1701 (CHO), 1541 (NO_2). HR EIMS calcd for $C_{15}H_{21}NO_2{\cdot}H^+$ = 263.1521; found = 263.1599.

4.2.8. (1*R*,2*R*)-(−)-*N*,*N*′-Bis-(3,5-di-*tert*-butyl-2-nitrobenzylidene)-1,2-diaminocyclohexane 13. To a solution of 1 g of (1*R*,2*R*)-1,2-diaminocyclohexane (8.75 mmol) in 15 mL of anhydrous THF, 4.612 g of 3,5-di-*tert*-butyl-2-nitrobenzaldehyde (17.514 mmol) and 4 Å molecular sieves were added. The mixture was stirred overnight at room temperature under an argon atmosphere. Dichloromethane (15 mL) were added and the resulting mixture filtered through silica (CH_2Cl_2), the solvents evaporated and the residual oil dried under vacuum to give 3.44 g of product **13** as a yellow solid. Isolated yield = 65%. FW = 604.82. Mp = 98 °C. $[\alpha]_D^{20} = -58$ (*c* 0.001 g/mL, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 8 (s, 2H, HC=N), 7.68 (d, $^4J_{H,H}$ = 2.2 Hz, 2H, Ar–H), 7.5 (d, $^4J_{H,H}$ = 2.2 Hz, 2H, Ar–H), 3.4 (m, 2H, CH–N), 1.8–1.4 (m, 8H, $-CH_2-$), 1.37 (s, 18H, $C(CH_3)_3$), 1.26 (s, 18H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 200 MHz, 25 °C) δ (ppm) = 155.27 (CHO), 162.65 (Cq–Ar), 148.5 (Cq–Ar), 139.6 (Cq–Ar), 127.9 (Cq–Ar), 127.2 (C–Ar), 123.3 (C–Ar), 74.33 (CH–N), 36 (Cq, $C(CH_3)_3$), 35.11 (Cq, $C(CH_3)_3$), 32.5 ($-CH_2-$), 31.05 ($3CH_3$, $C(CH_3)_3$), 30.9 ($3CH_3$, $C(CH_3)_3$), 24.3 ($-CH_2-$). IR (KBr) ν (cm^{-1}) = 1530 (NO_2), 1644 (C=N). HR LSIMS calcd for $C_{36}H_{52}N_4O_4{\cdot}H^+$ = 605.4068; found = 605.40775.

4.2.9. 3,5-Di-*tert*-butyl-2-azobenzaldehyde 14. A brown oil was obtained by reduction of 3,5-di-*tert*-butyl-2-aminobenzaldehyde, in dichloromethane under one atmosphere of hydrogen at 50 °C. Compound **14** was also obtained as a secondary product, if the reduction of 3,5-di-*tert*-butyl-2-nitrobenzaldehyde did not go to completion. In this case **14** and **9** were separated by flash chromatography on silica (eluent: CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 9.03 (s, 2H, CHO), 7.26 (d, $^4J_{H,H}$ = 1.5 Hz, 2H, Ar–H), 7.22 (d, $^4J_{H,H}$ = 1.5 Hz, 2H, Ar–H), 1.56 (s, 18H, $C(CH_3)_3$), 1.35 (s, 18H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm) = 154.57 (Cq–Ar), 153.3 (C=O), 146.9 (Cq–Ar), 138.1 (Cq–Ar), 125.3 (C–Ar), 119.8 (Cq–Ar), 110.5 (Cq–Ar), 35.8 (Cq–$C(CH_3)_3$), 35 (Cq–$C(CH_3)_3$), 30.5 ($3CH_3$, $C(CH_3)_3$), 29.8 ($3CH_3$, $C(CH_3)_3$). IR (NaCl) ν (cm^{-1}) = 1636 (CHO), 1532–1557 (N=N).

4.2.10. (1*R*,2*R*)-*N*,*N*′-Bis-(2-aminobenzylidene)-1,2-diphenylethlenediamine 16. To a solution of (1*R*,2*R*)-1,2-diphenylethlenediamine (0.4 g, 1.088 mmol) in anhydrous dichloromethane (8 mL), 2-nitrobenzaldehyde (0.56 g, 3.74 mmol), 0.1 g of Pd–C (10%) and molecular sieves (4 Å) were added and the resulting mixture stirred under one atmosphere of hydrogen at 0 °C. After consumption of the required volume of H_2 (275 mL), the mixture was filtered on Celite and the solvent removed. The resulting residue was washed with methanol, filtered through a Millipore filter and dried under vacuum (P = 0.1 mmHg) to give ligand **16** (0.47 g) as a grey solid. Isolated yield: 60%. FW = 418.54; Mp = 200 °C. $[\alpha]_D^{20} = -37$ (*c* 10^{-3} g/mL, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ (ppm) = 8.27 (s, 2H, HC=N), 7.20 (m, 10H, Ar–H), 7.09 (m, 4H, Ar–H), 6.63 (m, 4H, Ar–H), 6.47 (s large, 4H, NH_2), 4.67 (s, 2H, CH–N). ^{13}C NMR ($CDCl_3$, 300 MHz, 25 °C): δ (ppm) = 165.0 (C_6=N), 148.9 (C_q–Ar), 141.6 (C_q–Ar), 134.0 (C–Ar), 131.3 (C–Ar), 128.7 (C–Ar), 128.3 (C–Ar), 127.4 (C–Ar), 118.1 (C_q–Ar), 116.3 (C–Ar), 115.9 (C–Ar), 82.5 (C_5–N). IR (KBr) ν (cm^{-1}) = 3256–3460 (Ar–NH_2) 1626 (C=N). HR CIMS calcd for $C_{28}H_{26}N_4H^+$ = 419.22364; found = 419.2240. $C_{28}H_{26}N_4$ (418.54 g mol^{-1}): Anal. Calcd: C, 79.04; H, 6.53; N, 13.17. Found: C, 78.99; H, 6.22; N, 13.29.

4.2.11. (1*R*,2*R*)-*N*,*N*′-Bis-(2*p*-tosylaminobenzylidene)-1,2-diphenylethlenediamine 17. (1*R*,2*R*)-*N*,*N*′-Bis-(2-aminobenzylidene)-1,2-diphenylethlenediamine (0.36 g, 0.86 mmol) was dissolved in 4 mL of dry CH_2Cl_2, Et_3N (250 μL, 1.8 mmol) was added and the solution cooled at −10 °C under an argon atmosphere. At this temperature, *p*-toluenesulfonyle chloride (0.34 g, 1.8 mmol) was added and the resulting mixture stirred overnight (the

temperature was allowed to rise at room temperature). The solvent was removed and methanol (5 mL) was added to the yellow residual oil. A yellow precipitate was formed, collected by filtration through a Millipore filter, and dried under vacuum ($P = 0.1$ mmHg) to give ligand **17** (0.32 g) as a yellow solid. Isolated yield: 50%. FW = 726.91; Mp 205 °C. $[\alpha]_D^{20} = -67$ (c 16.75×10^{-3} g/mL; CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ (ppm) = 13.17 (s, 2H, $NHSO_2$), 8.43 (s, 2H, HC=N), 7.45 (m, 6H, Ar–H), 7.26 (m,14H, Ar–H), 6.88 (m, 2H, Ar–H), 6.73 (m, 4H, Ar–H), 4.88 (s, 2H, HC–N), 2.1 (s, 3H, Ar–CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz, 25 °C): δ (ppm) = 166 (C_6=N), 143.7 (C_q–Ar), 140.2 (C_q–Ar), 139.7 (C_q–Ar), 136.9 (C_q–Ar), 134.5 (C–Ar), 132 (C–Ar), 129.8 (C–Ar), 128.9 (C–Ar), 128.5 (C–Ar), 128 (C–Ar), 127.5 (C–Ar), 122.7 (C–Ar), 120.5 (C–Ar), 117.2 (C–Ar), 81.4 (CH–N), 21.7 (CH_3). IR (KBr) ν (cm^{-1}) = 2870–3100 (NH), 1634 (C=N), 1167 (SO_2). HR LSIMS calcd for $C_{42}H_{38}N_4O_4S_2H^+ = 727.24135$; found = 727.24123. Elementary analysis for $C_{42}H_{38}N_4O_4S_2$ (726.91 g mol^{-1}): Anal. Calcd: C, 69.4; H, 5.27; N, 7.71; O, 8.8; S, 8.82. Found: C, 69.27; H, 5.54; N, 7.93; O, 8.5; S, 8.6.

4.3. Typical procedures for catalytic hydrogenation tests

All hydrogenation tests were carried out in stainless-steel reactors, previously degassed three times with argon and twice with hydrogen. It was then pressurized to 30 bar at room temperature and stirred for the reaction time (7–16 h). At the end of the reaction time, the reactor was degassed and the reaction mixture filtered throught Celite before chiral GC analysis (Cyclodextrin β column, 30 m).

4.3.1. Hydrogenation of acetophenone with the system $Ru(PPh_3)_3Cl_2$/chiral ligand. *Method 1:* In a Schlenk tube, 3.2 mg (3.3 μmol) of $[Ru(PPh_3)Cl_2]$ and 4 μmol of the desired ligand were mixed in 1 mL of toluene. After 1 h stirring under an argon atmosphere at room temperature, the solvent was removed and 1 mL of isopropanol added. Then, 3.7 mg (33 μmol) of *t*-BuOK and 40 mg (0.33 mol) of acetophenone were introduced and the resulting solution stirred under hydrogen pressure (30 bar) in a stainless-steel reactor.

Method 2: In a Schlenk tube, 3.2 mg (3.33 μmol) of $Ru(PPh_3)_3Cl_2$ and 4 μmol of the desired ligand were mixed in 1 mL of isopropanol. After 7–12 h stirring under an argon atmosphere at room temperature, 3.7 mg (33 μmol) of *t*-BuOK and 40 mg (0.33 mol) of acetophenone were added. The resulting solution was stirred under hydrogen pressure (30 bar) in a stainless-steel reactor.

4.3.2. Hydrogenation of acetophenone with chiral ligand, phosphines and $[Ru(COD)Cl_2]_x$ or $[Ru(C_6H_6)Cl_2]_2$. In a Schlenk tube, (3.33) μmol of $[Ru(COD)Cl_2]_x$ (or $[Ru(C_6H_6)Cl_2]_2$), 4 μmol of desired chiral ligand and x μmol ($x = 4$, 8, or 12 μmol) of phosphine were mixed in 1 mL of isopropanol. After stirring 7–12 h under an argon atmosphere at room temperature, 3.7 mg (33 μmol) of *t*-BuOK and 40 mg (0.33 mol) of acetophenone were added. The resulting solution was stirred under hydrogen pressure (30 bar) in a stainless-steel reactor.

4.3.3. Hydrogenation of acetophenone with chiral ligand and $[Ru(COD)Cl_2]_x$ or $[Ru(C_6H_6)Cl_2]_2$. In a Schlenk tube, 3.33 μmol of $[Ru(COD)Cl_2]_x$ (or $[Ru(C_6H_6)Cl_2]_2$), and 4 μmol of desired chiral ligand were mixed in 1 mL of isopropanol. After stirring for 7–12 h under an argon atmosphere at room temperature, 33 μmol of *t*-BuOK and 40 mg (0.33 mol) of acetophenone were added. The resulting solution was stirred under hydrogen pressure (30 bar) in a stainless-steel reactor.

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