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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1224–1232

Asymmetric hydrogenation of aromatic ketones with new P-chirogenic monophosphine ligands

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Received 17 April 2007; accepted 23 May 2007

Abstract—Novel P-chirogenic anisylphenyl-HMOP derivatives have been synthesised from (*R*)-2,2′-bis-(trifluoromethanesulfonyloxy)1,1′-binaphthyl. Preliminary results concerning the asymmetric hydrogenation of acetophenone and 3,5-bis(trifluoromethyl)acetophenone with Ru(II)-HMOP complexes in combination with various diamines was also tackled.

1. Introduction

The catalytic enantioselective hydrogenation of C=O bonds is of a great interest for the synthesis of a large amount of enantiomerically pure compounds and considerable progress has been achieved in this area.[1–3] Typically, rhodium(I) and ruthenium(II) complexes and, most often, diphosphine-based chiral ligands, play a central role as chelating agents for transition metals in homogeneous catalysis,[4,5] because of their intrinsic electronic properties and steric variability. Among them, atropoisomeric diaryl-core diphosphanes such as BINAP are continuously attracting interest in view of their exceptional ability to induce asymmetry in transition metal-catalysed reactions.[6] Earlier in this area, P-stereogenic monophosphine ligands,[7] in which the stereogenic centre is the phosphorus atom itself, have been developed as attractive ligands. More recently, examples have proven that P-stereogenic diphosphines can be more efficient than ligands with chirality located in the ligand backbone.[8–10] Combining the chiral 1,1′-binaphthyl skeleton of the Hayashi's MeO–MOP ligand[11] with the P-stereogenic centre of the Knowles's diPAMP,[12] Gilheany very recently described[13] the synthesis of anisylphenylMOP hybrid ligands potentially relevant to the catalytic asymmetric addition of boronic acids to aldehydes. Although MOP derivatives are usually prepared from (*R*)- or (*S*)-2,2′-bis(trifluoromethanesulfonyloxy)1,1′-binaphthyl,[14,15] the authors proposed the direct coupling of the secondary phosphine with the (*R*)-2-((trifluoromethanesulfonyl)oxy)-2′-methoxy-1,1′-binaphthyl (Scheme 1) and the isolation of the enantiomerically pure P-chirogenic phosphines via their borane adducts.

Herein, we report how (*R*,*R*)-H- and (*R*,*S*)-HMOP derivatives (2-(arylphenylphosphino)-1,1′-binaphthyls) **1** can be efficiently prepared from the starting (*R*)-2,2′-bis(trifluoromethanesulfonyloxy)1,1′-binaphthyl following the same strategy that is already applied to the preparation of various substituted BINAP[16] (Fig. 1). Based on the well-known diamine/Ru/BINAP system developed by Noyori,[17–20] we also describe our preliminary results on the asymmetric hydrogenation of aromatic ketones.

2. Results and discussion

2.1. Synthesis of phosphines boranes

Chiral phosphine borane complexes were synthesised starting from the dichlorophenylphosphine following the synthetic route already described in the literature.[21,22]

Dichlorophenylphosphine reacted with the previously prepared Grignard reagent at −78 °C in THF. Treatment with $LiAlH_4$ followed by the addition of BMS in the anhydrous THF gave the desired phosphine borane (Scheme 1). Thus, *t*-butylphenylphosphine borane **2**, *o*-anisylphenylphosphine borane **3** and 2,4-dimethoxyphenylphosphine borane **4** were obtained, respectively, from the starting

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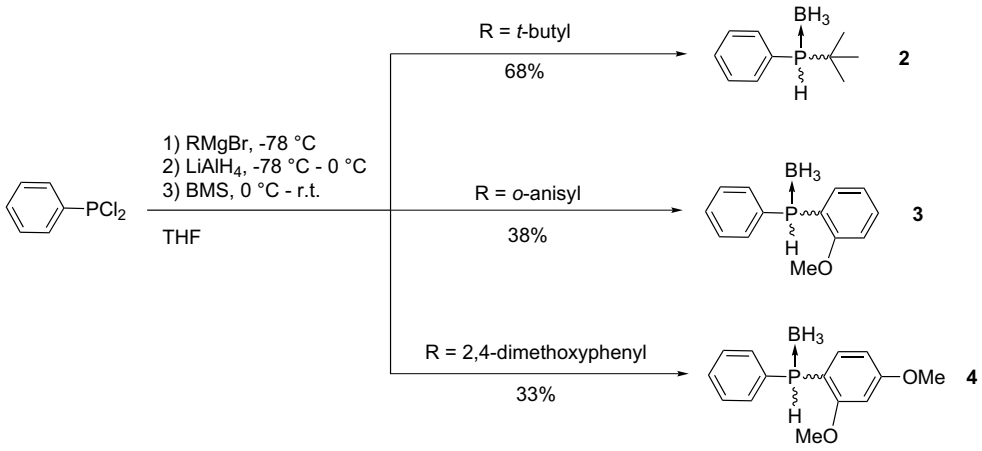
doi:10.1016/j.tetasy.2007.05.026



Scheme 1.

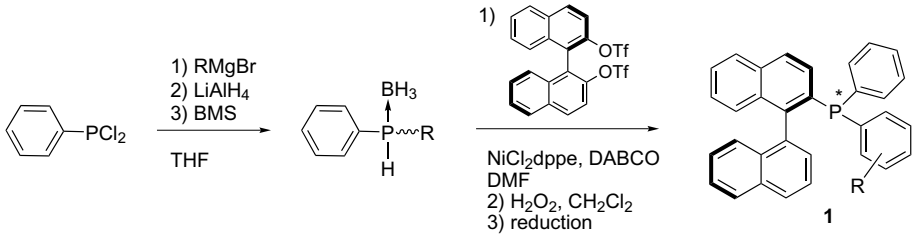


Figure 1.

t-butylmagnesium chloride, *o*-anisylmagnesium bromide and 2,4-dimethoxyphenylmagnesium bromide in 68%, 38% and 33% yields. The low isolated yields could be explained by the formation of disubstituted by-products, due to the reactivity of the chlorophenyl(aryl or alkyl)phosphine intermediates. In fact, when methyl-, isopropyl-, *p*-anisyl-, 3,4,5-trimethoxyphenyl- or cyclohexylmagnesium bromides were reacted with the dichlorophenylphosphine, only the disubstituted phenylphosphine borane complexes were obtained. As a result, we assumed that in all the cases, the monosubstituted intermediates were more reactive than the starting dichlorophenylphosphine and that only the more sterically hindered Grignard reagents (*t*-Bu, *o*-anisyl and *o*,*p*-methoxybenzene) allowed us to prepare the reactive phosphine borane complexes.

2.2. Coupling of the phosphine borane complexes

The coupling reaction of the (*R*)-2,2′-bis(trifluoromethanesulfonyloxy)1,1′-binaphthyl (*R*)-**5** with the phosphine borane complexes **2**–**4** was carried out according to the method of Cai[23] in the presence of $NiCl_2$/dppe and DABCO in DMF at 125 °C.[24,25]

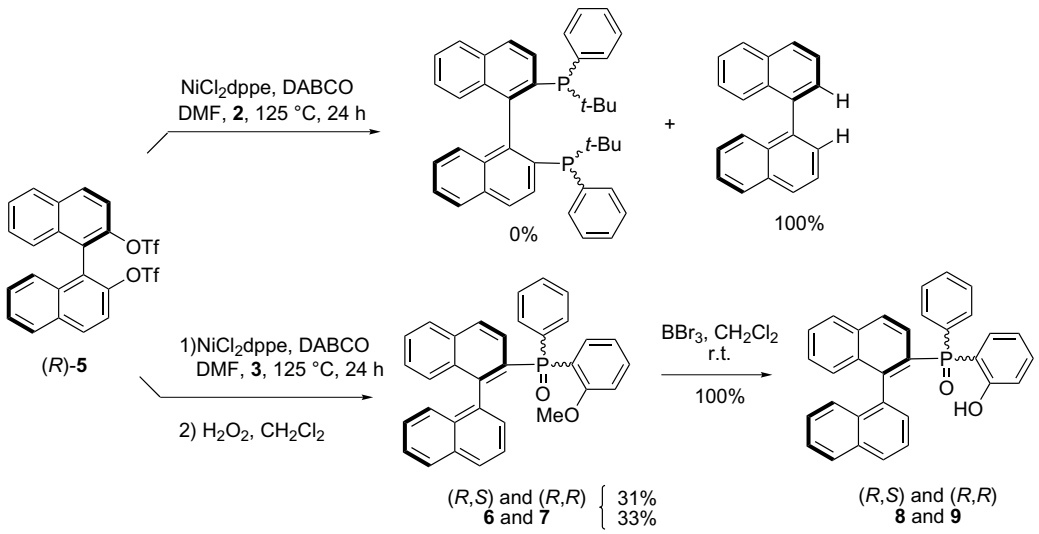
The first aim of our work was focused on the direct synthesis of P-chirogenic diphosphines type BINAP (Scheme 2). Surprisingly, the coupling reaction of *tert*-butylphenylphosphine borane **2** with (*R*)-**5** failed and only the reduction product 1,1′-binaphthyl was recovered.

On the other hand, when *o*-anisylphenylphosphine borane **3** was engaged in the coupling reaction, a diastereoisomeric mixture of two monophosphines was isolated in 70% yield, which were unfortunately inseparable. ^{31}P NMR confirmed the presence of two diastereoisomeric monophosphines with two phosphorus resonance signals located at −22.6 ppm and −23.0 ppm, whereas four resonance signals were kept if the diphosphine structures had been obtained, giving three diastereoisomers. With no resonance signal, ^{19}F NMR confirmed that the second triflate group was cleaved during the reaction. Oxidation of the mixture was then achieved with H_2O_2 in dichloromethane affording pure monophosphine oxides **6** and **7**, which were isolated by column chromatography in 31% and 33% yields, respectively. Subsequent cleavage of the methyl group with BBr_3 in CH_2Cl_2 at 0 °C led to hydroxyl derivatives **8** and **9** in quantitative yield.

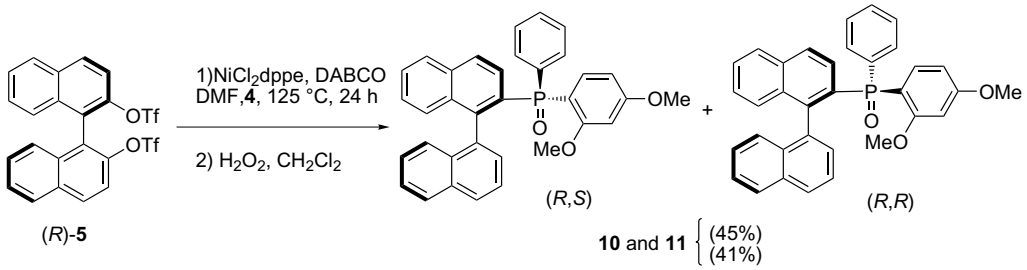
The coupling reaction of the 2,4-dimethoxyphenylphosphine borane complex **4** with (*R*)-**5** followed by the oxidation of the corresponding monophosphines intermediates afforded a mixture of monophosphine oxides **10** and **11** in 45% and 41% yields, respectively, after purification on column chromatography (Scheme 3).

2.3. Determination of the enantiomeric excess of the monophosphines oxides 6 and 7

In order to determine the enantiomeric excess of the isolated monophosphine oxides **6** and **7**, a mixture of diastereo-



Scheme 2.



Scheme 3.

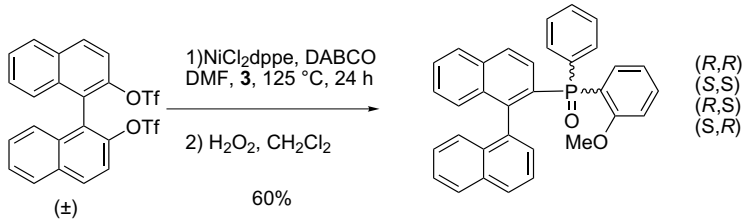
isomers (*R*,*R*), (*R*,*S*), (*R*,*R*) and (*S*,*R*) were synthesised in 60% yield, starting from the racemic 2,2′-bis(trifluoromethanesulfonyloxy)1,1′-binaphthyl (Scheme 4). Purification by column chromatography afforded two mixtures of enantiomers which were analysed and compared with diastereoisomers **6** and **7** by chiral HPLC (DAICEL Chiral pack AD column). Analysis of the obtained chromatograms ensured that the enantiomeric excess of **6** and **7** was close to 99%.

In order to assign their configuration, we focused our efforts on the structure elucidation of **6** and **7** by X-ray crystallographic study. However recrystallisation of both pure compounds failed.

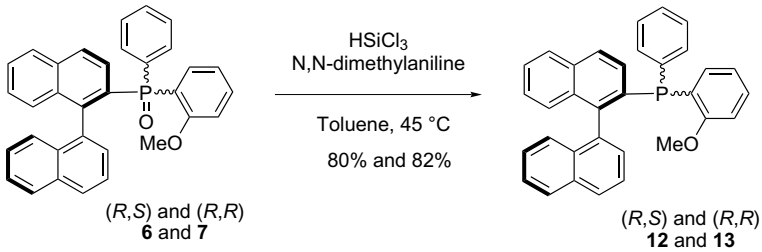
2.4. Reduction of the phosphine oxides

Reduction of the phosphine oxides was ineffective with traditional reducing agents, such as $HSiCl_3$,[26] $LiAlH_4$[27] and $PhSiH_3$.[28] Full reduction to the phosphine occurred but significant epimerisation was observed, from ^{31}P NMR spectra of the reduction products, which varied depending on the experimental conditions.

When **6** and **7** were treated with trichlorosilane and *N*,*N*-dimethylaniline in toluene at 45 °C, the corresponding pure HMOP **12** and **13** were obtained in 80% and 82% yields with a retention of the optical integrity of the compounds (Scheme 5).



Scheme 4.

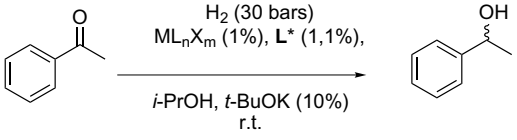


Scheme 5.

Nevertheless when the reaction was carried out on enantiomerically pure diastereoisomers **10** and **11**, epimerisation occurred (15%). Epimerisation was also observed for the reduction of diastereoisomers **8** and **9** (30%). Reduction of **8**–**11** was then performed according to the method developed by Imamoto[29] ($LiAlH_4$, MeOTf), which allowed the reduction of several chiral phosphine oxides with an inversion of their configuration. With total conversions and expected inversion of configuration, the level of epimerisation nevertheless varied from 10% to 20%, which limited the use of these ligands in the continuation of our work in asymmetric catalysis.

2.5. Hydrogenation of aromatic ketones

The asymmetric hydrogenation of acetophenone was firstly carried out under hydrogen pressure (30 bars) at room temperature in the presence of the chiral catalyst prepared in situ. 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 (Scheme 6).



Scheme 6.

Monophosphine (*R*)-2((*R* or *S*)-*o*-anisylphenylphosphino)-1,1′-binaphthyl **13** was evaluated in the asymmetric hydrogenation of acetophenone with several ruthenium precursors (Table 1). Hydrogenation reaction with the ruthenium species was carried out under experimental conditions already described by Noyori et al. (*t*-BuOK, *i*-PrOH). When the reaction mixture was stirred for 24 h without H_2, no reaction occurred.

When $[Ru(COD)Cl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ were used with **13** under H_2 (30 bars), conversions were not quantitative and enantiomeric excesses were low (entries 1 and 2). Only $[Ru(C_6H_6)Cl_2]_2$/**13** catalytic system in isopropanol gave a quantitative conversion of acetophenone (Table 1, entries 4 and 5) but low enantioselectivities were also observed. A small improvement in enantioselectivity was obtained when the catalyst was prepared in the isopropanol starting from $[Ru(C_6H_6)Cl_2]_2$ and **13** for 7–16 h at room temperature (Table 1, entries 2 and 4). It should be noted that complex $[Ru(C_6H_6)Cl_2]_2$/**13** in methanol led to a low activity and did not allow any enantioselectivity. Therefore, the $[Ru(C_6H_6)Cl_2]_2$ dimer gave the best result with monophosphine **13** and has been used as catalytic precursor in the continuation of our study.

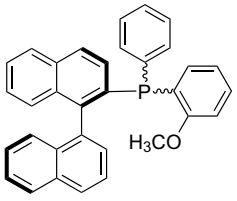
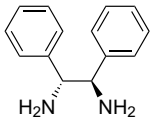
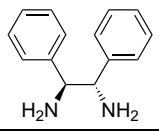
Table 1. Asymmetric hydrogenation of acetophenone with catalysts containing **13**

Entry	Metallic precursors	Solvent	Base	Conv. (%)	ee (%)
1[b]	$[Ru(COD)Cl_2]_x$	*i*-PrOH	*t*-BuOK	60	3 (*S*)
2[b]	$[Ru(p\text{-cymene})Cl_2]_2$	*i*-PrOH	*t*-BuOK	76	9 (*S*)
3[a]	$[Ru(C_6H_6)Cl_2]_2$	MeOH	*t*-BuOK	23	0
4[b]	$[Ru(C_6H_6)Cl_2]_2$	*i*-PrOH	*t*-BuOK	100	13 (*S*)
5[c]	$[Ru(C_6H_6)Cl_2]_2$	*i*-PrOH	*t*-BuOK	100	9 (*S*)

[S] = 0.3 M and S/M/*t*-BuOK/L* = 100/1/10/1; 30 bar of H_2; 50 °C; 18 h.
[a] [M]+**13**+MeOH, 1 h at 50 °C, then addition of acetophenone.
[b] [M]+**13**+*i*-PrOH, 7–16 h at rt, then addition of *t*-BuOK and acetophenone.
[c] [M]+**13**+Toluene, 1 h at rt, then evaporation of toluene and addition of *i*-PrOH and *t*-BuOK and acetophenone.

Since the role of a co-ligand, such as a diamine, was crucial in these experimental conditions of hydrogenation,[17–20] (1*R*,2*R*)-DPEN (DPEN: 1,2-diphenylethylenediamine) was first combined with $[Ru(C_6H_6)Cl_2]_2$/**13** catalytic system. The complex $[Ru(C_6H_6)Cl_2]_2$ (1% M), the chiral monophosphine **13** (1% M) and diamine (1% M) were mixed in *i*-PrOH. After 16 h of stirring, *t*-BuOK (5–10% M) and acetophenone were added successively before being set under a hydrogen pressure. An increase of the ee to 33% was then obtained with a quantitative conversion (Table 2)

Table 2. Monophosphines **12** and **13** in asymmetric hydrogenation of acetophenone with $[Ru(C_6H_6)Cl_2]_2$ and co-ligand

General structure	L*	Diamine	Conv. (%)	ee (%)
	**12**		90	0
	13		100	33 (*S*)
	12		95	4 (*S*)
	13		100	11 (*R*)

[S] = 0.3 M and S/M/*t*-BuOK/L*/diamine = 100/1/10/1.1/1; *i*-PrOH, 16 h at rt then addition of *t*-BuOK and acetophenone; 30 bar of H_2.

in favour of the (*S*)-phenylethanol. With (1*S*,2*S*)-DIAPEN, the ee was lower (11%) in favour of the (*R*)-phenylethanol. Thus, the asymmetric induction seemed to be predominantly governed by the nature of the DPEN. Moreover, whatever the configuration of the DPEN, the reduction was not quantitative with diastereoisomer **12** and no enantioselectivity was observed.

In order to improve the enantioselectivity of the hydrogenation with **13**, several chiral diamines were also tested as co-ligands (Table 3). Nevertheless, none of them caused an increase in the ee which did not exceed 33% (Table 3, entries 1 and 5) with the (1*R*,2*R*)-diphenylethylenediamine and the (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2,diphenyl-1,2-ethanediamine. In all cases, the (*S*)-enantiomer of the phenylethanol was mainly obtained when (*R*,*R*)- or (*R*)-diamines were engaged in the reaction (Table 3, entries 1, 3, 5 and 7). Contrary, (1*R*)-phenylethanol was obtained with (*S*,*S*)- or (*S*)-diamines (Tables 3, entries 2, 4, 6 and 8).

Table 3. Asymmetric hydrogenation of acetophenone with $[Ru(C_6H_6)Cl_2]_2$/**13** and diamine as co-ligands

Entry	Co-ligand	Conv. (%)	ee (%)
1	(1*R*,2*R*)-Diphenylethylenediamine	100	33 (*S*)
2	(1*S*,2*S*)-Diphenylethylenediamine	100	11 (*R*)
3	(1*R*,2*R*)-Diaminocyclohexane	100	6 (*S*)
4	(1*S*,2*S*)-Diaminocyclohexane	100	2 (*R*)
5	(1*R*,2*R*)-*N*,*N*′-Dimethyl-1,2,diphenyl-1,2-ethanediamine	100	33 (*S*)
6	(1*S*,2*S*)-*N*,*N*′-Dimethyl-1,2,diphenyl-1,2-ethanediamine	100	20 (*R*)
7	(*R*)-1,1′Binaphthyl-2,2′-diamine	100	13 (*S*)
8	(*S*)-1,1′Binaphthyl-2,2′-diamine	100	2 (*R*)

[S] = 0.3 M and S/M/*t*-BuOK/L*/diamine = 100/1/10/1.1/1; *i*-PrOH, agitation 12 h at rt then addition of *t*-BuOK and acetophenone; 30 bar of H_2.

In order to evaluate the real contribution of the P-chirogenic ligand towards the asymmetric induction of the hydrogenation of acetophenone, achiral diamines were also studied as a co-ligand (Table 4).

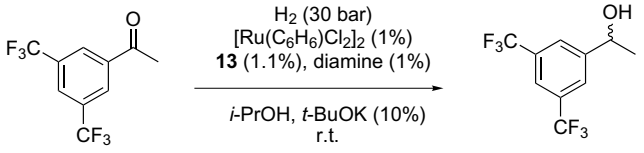
Quantitative conversions were reached and ee's proportionally increased with an increase in the number of carbon atoms between the two nitrogen atoms (Table 4, entries 1–3). The ee reached its maximum (61%) in the presence of 1,4-diaminobutane (Table 4, entry 3). With longer alkyl chains (Table 4, entries 4 and 5), the ee's, as well as the conversions rate, decreased. We have also studied the effect of the Ru/**13**/diamine ratio and no changes concerning the enantioselectivity were noticed when more than 1 equiv of diamine was introduced in the reaction mixture. We assumed that the active catalyst was a 1/1/1 metal/ligand/diamine system.

Table 4. Asymmetric hydrogenation of acetophenone with $[Ru(C_6H_6)Cl_2]_2$/**13** and diamine as co-ligands

Entry	Co-ligand	Conv. (%)	ee (%)
1	1,2-Diaminoethane	100	10 (*S*)
2	1,3-Diaminopropane	100	46 (*S*)
3	1,4-Diaminobutane	100	61 (*S*)
4	1,5-Diaminopentane	63	6 (*S*)
5	1,6-Diaminohexane	53	0
6	*N*,*N*′-Dimethylethylenediamine	100	0

[S] = 0.3 M and S/M/*t*-BuOK/L*/diamine = 100/1/10/1.1/1; *i*-PrOH, 12 h at rt then addition of *t*-BuOK and acetophenone; 30 bar of H_2.

In order to evaluate the reliability of the catalytic system with other aromatic ketones, the asymmetric hydrogenation of 3,5-bis(trifluoromethyl)acetophenone was carried out under optimised conditions applied to the reduction of acetophenone (Scheme 7).



Scheme 7.

Since the (*R*)-1-[3,5-bis-(trifluoromethyl)phenyl]ethanol was used as a key intermediate in the synthesis of the tachykinin NK1 receptor antagonist L-754030, a potent antidepressant,[30,31] several options for the asymmetric reduction of the 3,5-bis(trifluoromethyl)acetophenone were considered. To the best of our knowledge, the Noyori's diamine/Ru/BINAP combination has not been evaluated for the particular hydrogenation of this aromatic ketone. On the other hand, the enantioselective hydrogenation of the 3,5-bis(trifluoromethyl)acetophenone with Ru(II) complexes composed of achiral monophosphine ligands in combination with the enantiopure DPEN was studied in *n*-PrOH with *t*-BuOK and gave an ee of 90%.[32]

The hydrogenation of the 3,5-bis(trifluoromethyl)acetophenone was carried out by using the BINAP or monophosphine **13** and $[Ru(C_6H_6)Cl_2]_2$ with various diamines (Table 5).

Table 5. Asymmetric hydrogenation of *m*-bisfluoromethylacetophenone with $[Ru(C_6H_6)Cl_2]_2$/(**13** or BINAP) and diamine as co-ligands

Entry	Ligand	Co-ligand	Conv. (%)	ee (%)
1	(*R*)-BINAP	(1*R*,2*R*)-DIAPEN	4	0
2	(*R*)-BINAP	1,3-Diaminopropane	8	0
3	**13**	1,3-Diaminopropane	91	53 (*S*)
4	**13**	1,4-Diaminobutane	100	63 (*S*)

[S] = 0.3 M and S/M/*t*-BuOK/L*/diamine = 100/1/10/1.1/1; *i*-PrOH, 18 h at rt then addition of *t*-BuOK and acetophenones; 30 bar of H_2.

Reduction of 3,5-bis(trifluoromethyl)acetophenone in the presence of the BINAP proved inefficient with DPEN and 1,3-diaminopropane (entries 1 and 2). On the other hand, with monophosphine **13**, good conversion rates were obtained. Moreover, enantioselectivity reached 53% in the presence of 1,3-diaminopropane as a co-ligand and 63% in the presence of the 1,4-diaminobutane.

3. Conclusion

In conclusion, despite the growing interest in chiral monophosphine ligands, only a few examples of atropoisomeric

chiral monophosphine have been reported in the literature. We have devised a new approach for the synthesis of new P-chirogenic atropoisomeric monophosphines combining nickel-catalysed coupling reactions of easily available binaphthyl building-blocks with various complexes of phosphine borane.

To the best of our knowledge, this study is the first report on the use of monophosphine chiral inductors for aromatic ketones hydrogenation. In the case of ruthenium species, we have developed a new catalytic and enantioselective system for the asymmetric hydrogenation of acetophenone: the best result (100% conversion, 61% ee) was obtained with (*R*)-2((*R* or *S*)-*o*-anisylphenylphosphino)-1,1′-binaphthyl **13** and 1,4-diaminobutane coordinated to $[Ru(C_6H_6)Cl_2]_2$. On the other hand for the asymmetric hydrogenation of 3,5-bis(trifluoromethyl)acetophenone: the best result (100% conversion, 63% ee) was obtained with (*R*)-2((*R* or *S*)-*o*-anisylphenylphosphino)-1,1′-binaphthyl **13** and 1,4-diaminobutane. This is the first result obtained for the asymmetric hydrogenation of aromatic ketones with a P-chirogenic monophosphorus ruthenium catalyst. We have noticed a synergetic co-ligand effect between the monophosphine and some achiral diamines, increasing both the activity and enantioselectivity of the ruthenium catalysts.

4. Experimental

4.1. General

All the organic and organometallic reagents used were of pure commercial products. The solvents from Carlo Erba, anhydrous THF were prepared in the laboratory. Enantiomerically pure BINOL was obtained from ACROS, dichlorophenylphosphine from Aldrich. All manipulations of organometallic compounds were carried out under an argon atmosphere. The metallic precursors were purchased from STREM.

Melting points (mp), were determined with a Köfler Bench type WME (HeIZBANK) and are uncorrected. Elemental analyses (C, H, P) were obtained from the Service Central d'Analyse of the CNRS (Solaize). High resolution mass spectra: HR LSIMS (Liquid Secondary Ionisation 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. $[\alpha]_D^{25}$ was determined with a Perkin–Elmer 241 polarimeter ($l = 1$ dm; 25 °C; concentration c in g/mL). ^{1}H, ^{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) or AC-300 FT (300.13 MHz for ^{1}H, 75.46 MHz for ^{13}C, 81 MHz for ^{31}P) spectrometer; δ values are given in ppm and J in hertz. The ee values and conversion were determined by chiral GC (Cyclodex b column, 30 m).

4.2. Synthesis

4.2.1. Phosphine borane complexes

4.2.1.1. *t*-Butylphenylphosphine-borane 2. To a stirred mixture of dichlorophenylphosphine (2.25 mL, 16.5 mmol) in 20 mL of dry THF at −78 °C was added a 1.30 M solution of *t*-butylmagnesium chloride in THF (12.75 mL, 16.5 mmol) for 1 h under Ar. $LiAlH_4$ (0.63 g, 16.5 mmol) was then added portionwise at −78 °C and stirring was continued at room temperature for 1 h. The mixture was then cooled at 0 °C and borane-methyl sulphide complex (2 M in THF, 8.25 mL, 20 mmol) added. After stirring for an additional 1 h, the reaction mixture was carefully poured into a 1 M aqueous solution of HCl (50 mL), water (50 mL) and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×20 mL). The combined extracts were washed with brine (3×20 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 95/5) affording **2** (2 g, 68%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (d, $J = 14.0$ Hz, 9H, $3 \times CH_3$), 5.05 (dq, $^1J_{H-P} = 360$ Hz, $^3J_{H-H} = 7$ Hz, 1H, HP), 7.40–7.55 (m, 3ArH); 7.60–7.70 (m, 2ArH); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 31.5$ (m); Elemental Anal. Calcd for $C_{10}H_{18}BP$ (180.12): C, 66.71; H, 10.08. Found: C, 66.83; H, 10.08.

4.2.1.2. *o*-Anisylphenylphosphine-borane 3. This was obtained by the same procedure from *o*-anisylmagnesium bromide and purified by flash chromatography (SiO_2, heptane/dichloromethane 7/3) as a white solid (38%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.65$–1.3 (m, 3H, BH_3), 3.84 (s, 3H, OCH_3), 6.52 (dq, $^1J_{H-P} = 395.2$ Hz, $^3J_{H-H} = 6.85$ Hz, 1H, HP), 6.92 (dd, $J = 8.28$, 3.39 Hz, 1ArH), 7.06 (td, $J = 7.41$, 1.11 Hz, 1ArH), 7.35–7.51 (m, 4ArH), 7.61–7.72 (m, 2ArH), 7.77 (td, $J = 6.30$, 1.89 Hz, 1ArH); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = -15.2$ (m); Elemental Anal. Calcd for $C_{13}H_{16}BOP$ (230.10): C, 67.87; H, 7.01. Found: C, 67.93; H, 7.00.

4.2.1.3. 2,4-Dimethoxyphenylphenylphosphine-borane 4. This was obtained by the same procedure from 2,4-methoxyphenylmagnesium bromide and purified by flash chromatography (SiO_2, heptane/dichloromethane 7.5/2.5) as a white solid (814 mg, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.63$–1.35 (m, 3H, BH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.45 (dq, $^1J_{H-P} = 394.68$ Hz, $^3J_{H-H} = 6.78$ Hz, 1H, HP), 6.48 (t, $J = 5.25$ Hz, 1ArH), 6.62 (d, $J = 8.49$ Hz, 1ArH), 7.37–7.43 (m, 3ArH), 7.61–7.69 (m, 1ArH), 7.72 (d, $J = 8.49$, 1ArH), 7.78 (d, $J = 8.67$, 1ArH); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = -16.8$ (m); Elemental Anal. Calcd for $C_{14}H_{18}BO_2P$ (260.11): C, 64.65; H, 6.98. Found: C, 64.97; H, 7.05.

4.2.2. Phosphine oxides 6, 7, 10 and 11

4.2.2.1. (*R*)-2(*R* or *S*)[(-*o*-Anisylphenyl)phosphinyl]-1,1′-binaphthyl 6 and 7. To a solution of [1,2-bis(diphenylphosphino)-ethane]dichloronickel (291 mg, 0.55 mmol) in dry DMF (28 mL), (*R*)-2,2′-bis(trifluoromethanesulfonyloxy)-1,1′binaphthyl (*R*)-**5** (3 g, 5.50 mmol), 1,4-diazabicyclo[2,2,2]octane (3.70 g, 33.10 mmol) and (*o*-anisylphenylphosphine) borane-complex **3** (2.39 g, 11.0 mmol) were added at room temperature under Ar. The mixture was stirred at room temperature for 30 min and then at 125 °C for 24 h. DMF was evaporated under reduced pressure, then dichloromethane (50 mL) and

H_2O_2 10% (7 mL) were added at 0 °C. The mixture was stirred at room temperature for 8 h, then poured into water (10 mL). The organic layer was washed with a saturated solution of sodium bisulfite (1 mL) and extracted with dichloromethane (3 × 20 mL). Solvents were evaporated under reduced pressure and the dark yellow residue was purified by flash chromatography on silica gel (SiO_2, cyclohexane/ethyl acetate 6/4) to afford pure **6** as a yellow solid and **7** as a yellow solid (0.85 g and 0.89 g, 31% and 33%, respectively) with a global yield of 65%.

Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.41$ (s, 3H, OCH_3), 6.05 (dd, $J = 8.31$, 5.88 Hz, 1ArH), 6.50 (td, $J = 7.53$, 1.14 Hz, 1ArH), 6.83–6.93 (m, 2ArH), 7.05 (td, $J = 8.28$, 1.32 Hz, 1ArH), 7.20 (td, $J = 3.21$, 1.89 Hz, 1ArH), 7.23–7.28 (m, 4ArH), 7.33–7.39 (m, 4ArH), 7.42 (t, $J = 6.78$ Hz, 2ArH), 7.47–7.54 (m, 2ArH), 7.88–7.92 (m, 4ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 54.4$ (OCH_3); 109,2; 109.3; 119.1; 120.4; 120.5; 125.1; 125.2; 125.3; 126.8; 127.0; 127.6; 127.8; 128.1; 128.1; 128.2; 128.4; 128.5; 129.0; 131.4; 131.4; 132.3; 132.4; 132.6; 132.8; 132.9; 133.1; 133.4; 133.5; 133.6; 133.8; 134.6; 134.7; 134.8; 143.6; 158.7; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 27.1$ (s); MS (ESI): m/z: 485.2 $[M+H]^+$; Elemental Anal. Calcd for $C_{33}H_{24}O_2P$ (484.16): C, 81.80; H, 5.2; P, 6.39. Found: C, 82.40; H, 5.65; P, 6.5; mp 190 °C; $R_f = 0.45$ (cyclohexane/ethyl acetate 5/5); $[\alpha]_D^{25} = -33.3$ (c 0.75, CH_2Cl_2).

Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.63$ (s, 3H, OCH_3), 6.76 (dd, $J = 8.07$, 5.46 Hz, 1ArH), 6.84 (td, $J = 7.71$, 3 Hz, 2ArH), 6.94 (td, $J = 7.53$, 1.14 Hz, 1ArH), 7.00 (td, $J = 7.14$, 1.32 Hz, 1ArH), 7.09 (d, $J = 8.1$, 1ArH), 7.22–7.41 (m, 8ArH), 7.51–7.70 (m, 2ArH), 7.71–7.79 (m, 2ArH), 7.91–7.96 (m, 4ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.33$ (OCH_3); 111.0; 121.2; 121.3; 125.0; 125.5; 125.8; 126.9; 127.0; 127.2; 127.4; 127.6; 127.8; 127.9; 128.1; 128.2; 128.7; 128.9; 128.9; 130.3; 130.4; 130.6; 131.6; 131.2; 133.1; 133.3; 133.6; 133.7; 133.8; 134.7; 134.8; 134.9, 135; 135.1; 143.4; 143.5; 160.1; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 28.1$ (s); MS (ESI): m/z: 485.2 $[M+H]^+$; Elemental Anal. Calcd for $C_{33}H_{24}O_2P$ (484.16): C, 81.80; H, 5.2; P, 6.39. Found: C, 79.70; H, 6.51; P, 5.86; mp 103–105 °C; $R_f = 0.46$ (cyclohexane/ethyl acetate 5/5); $[\alpha]_D^{25} = -63.1$ (c 0.75, CH_2Cl_2).

4.2.2.2. (*R*)-2(*R* or *S*)[(-2,4-dimethoxyphenyl)phenylphosphinyl]-1,1′-binaphthyl 10 and 11. These were obtained by the same procedure from **4** (1.28 g, 5.20 mmol) and purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 5/5) affording **10** (0.6 g, 45%) and **11** (0.54 g, 41%) as yellow solids with a global yield of 86%. Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.30$ (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 5.52 (dd, $J = 4.89$, 2.07 Hz, 1ArH), 5.91 (td, $J = 8.67$, 1.86 Hz, 1ArH), 6.79 (d, $J = 8.28$ Hz, 1ArH), 6.97 (td, $J = 6.96$, 1.32 Hz, 1ArH), 7.02 (d, $J = 4.71$ Hz, 1ArH), 7.03–7.05 (m, 1ArH), 7.11 (dd, $J = 7.71$, 1.11 Hz, 1ArH), 7.12–7.21 (m, 2ArH), 7.24 (dd, $J = 6.96$, 3.0 Hz, 1ArH), 7.28 (dd, $J = 8.10$, 5.28 Hz, 1ArH), 7.35–7.43 (m, 1ArH), 7.53 (td $J = 8.1$, 6.0 Hz, 2ArH), 7.57–7.67 (m, 2ArH), 7.78–7.82 (m, 4ArH), 7.93 (s, 1ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 54.4$ (OCH_3), 55.5 (OCH_3), 97.2, 105.4, 125.1, 125.2, 125.3, 126.7, 127.1, 127.5, 127.6, 127.7, 128.0, 128.0, 128.1, 128.2, 128.5, 128.7, 128.9, 131.2, 131.3, 132.5, 132.7, 132.9, 133.1, 133.2, 133.7, 133.8, 134.4, 134.5, 134.6, 134.7, 134.8, 134.9, 143.4, 143.5, 160.2, 162.8, 163.6; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = +27.0$ (s); MS (ESI): m/z: 515.2 $[M+H]^+$; Elemental Anal. Calcd for $C_{34}H_{27}O_3P$ (515.2): C, 79.36; H, 5.29; P, 6.02. Found: C, 79.00; H, 6.17; P, 5.37; mp 199 °C; $R_f = 0.52$ (cyclohexane/ethyl acetate 4/6); $[\alpha]_D^{25} = -30.25$ (c 0.79, CH_2Cl_2).

Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.60$ (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.26 (dd, $J = 4.71$, 2.07 Hz, 1ArH), 5.42 (td, $J = 8.46$, 1.68 Hz, 1ArH), 6.84 (td, $J = 7.74$, 3.03 Hz, 2ArH), 6.99 (td, $J = 6.03$, 3.21 Hz, 1ArH), 7.03 (d, $J = 7.71$ Hz, 1ArH), 7.15 (td, $J = 6.78$, 3 Hz, 2ArH), 7.23 (td, $J = 6.6$, 1.14 Hz, 1ArH), 7.33 (td, $J = 8.07$, 1.14 Hz, 2ArH), 7.39 (dd, $J = 12.46$, 1.32 Hz, 1ArH), 7.42 (d, $J = 12.6$ Hz, 1ArH), 7.51 (d, $J = 6.6$ Hz, 2ArH), 7.53–7.68 (m, 3ArH), 7.77–7.84 (m, 1ArH), 7.92–7.97 (m, 2ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.3$ (OCH_3), 55.7 (OCH_3), 98.6, 98.7, 105.4, 105.5, 125.0, 125.5, 125.7, 126.8, 127.0, 127.2, 127.4, 127.6, 127.7, 127.8, 128.1, 128.2, 128.8, 128.9, 129.0, 130.2, 130.3, 130.4, 131.1, 131.2, 133.1, 133.2, 133.6, 133.8, 134.8, 134.8, 135.0, 135.1, 136.2, 136.3, 143.4, 161.6; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = +28.0$ (s); MS (ESI): m/z: 515.2 $[M+H]^+$; Elemental Anal. Calcd for $C_{34}H_{27}O_3P$ (515.2): C, 79.36; H, 5.29; P, 6.02. Found: C, 79.85; H, 5.99; P, 6.02; mp 171 °C; $R_f = 0.16$ (cyclohexane/ethyl acetate, 4/6); $[\alpha]_D^{25} = -38.0$ (c 0.79, CH_2Cl_2).

4.2.3. Phosphine oxides 8 and 9

4.2.3.1. (*R*)-2(*R* or *S*)[(-2-Hydroxyphenyl)phenylphosphinyl]-1,1′-binaphthyl 8. A solution of **6** (200 mg, 0.41 mmol) in dry dichloromethane (4 mL) was cooled at 0 °C. A 1 M solution of BBr_3 in dichloromethane (1.2 mL, 1.2 mmol) was added and the reaction mixture stirred at 0 °C for 1 h, then at room temperature for 24 h. The solution was cooled to 5 °C and methanol (3 mL) was carefully added. After removal of the organic solvents, the residue was dissolved in dichloromethane (1 mL) and the solution was passed through a short column of silica gel. The filtrate was concentrated to give **8** (195 mg, 100%) as a grey solid.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.10$ (td, $J = 7.14$, 2.07 Hz, 1ArH), 6.40 (dd, $J = 7.92$, 4.89 Hz, 1ArH), 6.78–6.83 (m, 2ArH), 7.01–7.09 (m, 2ArH), 7.24 (t, $J = 7.14$ Hz, 1ArH), 7.32–7.36 (m, 2ArH), 7.38–7.52 (m, 6ArH), 7.68–7.81 (m, 3ArH), 7.85–7.93 (m, 4ArH), 7.42 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 110,4$; 111.8; 117.7; 117.8; 118.8; 119.0; 125.4; 125.9; 126.0; 127.2; 127.5; 128.2; 128.3; 128.4; 128.5; 128.7; 128.8; 128.9; 129.0; 129.1; 129.2; 130.4; 130.5; 132.1; 132.2; 132.3; 132.4; 132.8; 132.9; 132.9; 133.3; 133.6; 133.8; 134.0; 134.6; 134.7; 135.2; 135.3; 146.0; 146.1; 162.4; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = +39.9$ (s); MS (ESI): m/z: 471.2 $[M+H]^+$; Elemental Anal. Calcd for $C_{32}H_{23}O_2P$ (471.2): C, 81.69; H, 4.93; P, 6.58. Found: C, 81.65; H, 5.12; P, 6.48; mp 197 °C; $[\alpha]_D^{25} = -19.6$ (c 0.72, CH_2Cl_2).

4.2.3.2. (*R*)-2(*R* or *S*)[(-2-Hydroxyphenyl)phenylphosphinyl]-1,1′-binaphthyl 9. This was obtained by the same procedure from **7** (200 mg, 0.41 mmol) as a grey solid (193 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.64$ (td, $J = 7.74$, 4 Hz, 1H, Harom.), 6.78–6.84 (m, 3ArH), 6.91–6.95 (m, 3ArH), 7.04 (d, $J = 7.71$ Hz, 1ArH), 7.09 (d, $J = 6.39$ Hz, 1ArH), 7.22–7.32 (m, 5ArH), 7.46 (t, $J = 7.14$ Hz, 1ArH), 7.53–7.59 (m, 2ArH), 7.63 (d, $J = 9.06$ Hz, 1ArH), 7.87 (td, $J = 8.49$, 2.25 Hz, 2ArH), 11.12 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 111.7$; 118.9; 119.0; 119.1; 119.2; 125.0; 125.8; 126.1; 127.2; 127.4; 127.7; 127.9; 128.2; 128.3; 128.7; 128.9; 129.1; 129.3; 130.3; 130.5; 130.5; 130.6; 130.9; 131.0; 131.7; 131.9; 132.0; 133.1; 133.8; 133.9; 134.1; 134.2; 134.5; 134.6; 135.2; 135.3; 145.6; 164.4; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = +40.2$ (s); MS (ESI): *m*/*z*: 471.2 $[M+H]^+$; Elemental Anal. Calcd for $C_{32}H_{23}O_2P$ (471.2): C, 81.69; H, 4.93; P, 6.58. Found: C, 80.76; H, 6.06; P, 6.24; mp 144–145 °C; $[\alpha]_D^{25} = -35.5$ (*c* 0.49, CH_2Cl_2).

4.2.4. HMOP 12 and 13

4.2.4.1. (*R*)-2(*R* or *S*)[(-*o*-Anisyl)phenylphosphino]-1,1′-binaphthyl 12. A mixture of phosphine oxide **6** (290 mg, 0.60 mmol), *N*,*N*-dimethylaniline (0.76 mL, 6 mmol) and trichlorosilane (0.61 mL, 6 mmol) in dry toluene (7 mL) was warmed at 45 °C for 24 h under vigorous stirring. The mixture was cooled at 5 °C, and a 1 M degassed aqueous solution of NaOH (3 mL) was added carefully. The mixture was stirred at 40 °C until the organic and aqueous layers became clear. Ethyl acetate (10 mL) was then added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by short flash chromatography (SiO_2, cyclohexane/ethyl acetate 95/5) affording **12** (217 mg, 80%) as a grey solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.51$ (s, 3H, OCH_3), 6.68 (m, 2ArH), 6.77 (td, $J = 7.53$, 0.75 Hz, 1ArH), 6.9 (dd, $J = 8.49$, 1.11 Hz, 1ArH), 7.11–7.32 (m, 12ArH), 7.4 (td, $J = 6.96$, 1.32 Hz, 2ArH), 7.79 (d, $J = 8.49$ Hz, 1ArH), 7.87 (td, $J = 8.07$, 2.82 Hz, 3ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.6$ (OCH_3), 110.4, 125.2, 126.0, 126.1, 126.6, 126.7, 127.1, 127.3, 127.4, 127.5, 128.0, 128.2, 128.4, 128.6, 128.6, 128.7, 128.8, 129.3, 129.4, 129.8, 129.9, 130.1, 133.3, 133.7, 133.8, 133.9, 134.7, 135.0, 135.4, 137.2, 137.6, 137.7, 137.8, 144.5, 144.9, 161.3; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = -22.9$ (s); MS (ESI): *m*/*z*: 468.16 $[M+H]^+$; Elemental Anal. Calcd for $C_{33}H_{25}OP$ (468.16): C, 84.60; H, 5.38; P, 6.61. Found: C, 85.04; H, 5.93; P, 6.29; mp 186 °C; $[\alpha]_D^{25} = +152$ (*c* 0.5, CH_2Cl_2).

4.2.4.2. (*R*)-2(*R* or *S*)[(-*o*-anisyl)phenylphosphino]-1,1′-binaphthyl 13. This was obtained by the same procedure from **7** (390 mg, 0.80 mmol) affording **13** (300 mg, 80%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.50$ (s, 3H, OCH_3), 6.62–6.69 (m, 2ArH), 6.72–6.79 (m, 2ArH), 6.95–7.12 (m, 12ArH), 7.35 (dd, $J = 14.49$, 0.93 Hz, 1ArH), 7.37 (d, $J = 15.24$ Hz, 1ArH), 7.71–7.79 (m, 4ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.9$ (OCH_3); 110,5; 121.3; 125.5; 125.8; 126.1; 126.6; 126.8; 126.9; 127.0; 127.6; 127.6; 128.1; 128.2; 128.3; 128.4; 128.5; 128.9; 129.0; 130.3; 130.8; 133.3; 133.4; 133.6; 133.7; 133.8; 133.9; 134.2; 135.4; 137.5; 137.7; 137.8; 161.4; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = -22.6$ (s); MS (ESI): *m*/*z*: 468 $[M+H]^+$; Elemental Anal. Calcd for $C_{33}H_{25}OP$ (468.16): C, 84.60; H, 5.38; P, 6.61. Found: C, 83.61; H, 5.95; P, 5.61; mp 100–102 °C; $[\alpha]_D^{25} = +96.3$ (*c* 0.54, CH_2Cl_2).

4.3. General procedures for catalytic hydrogenation

4.3.1. General procedure for hydrogenation of acetophenone with the $[Ru(C_6H_6)Cl_2]_2$/L* catalysts. Method 1: In a Schlenk tube, $[Ru(C_6H_6)Cl_2]_2$ (2 mg, 8 μmol) and the selected ligand (8.80 μmol) were mixed in 1 mL of toluene under Ar at room temperature. After 1 h of stirring, the solvent was evaporated and 1 mL of isopropanol was added. Then, *t*-BuOK (9 mg, 80 μmol) and acetophenone (93 μL, 0.8 mmol) were introduced and the resulting solution stirred under hydrogen pressure (30 bars) in a stainless-steel reactor (previously degased three times with argon and twice with hydrogen) for 7–16 h at room temperature.

Method 2: In a Schlenk tube, $[Ru(C_6H_6)Cl_2]_2$ (2 mg, 8 μmol) and the desired ligand (8.80 μmol) were mixed in 1 mL of isopropanol under argon atmosphere at room temperature. After 7–12 h of stirring, *t*-BuOK (9 mg, 80 μmol) and acetophenone (93 μL, 0.8 mmol) were introduced and the resulting solution stirred under hydrogen pressure (30 bars) in a stainless-steel reactor (previously degassed three times with argon and twice with hydrogen) for 7–16 h at room temperature.

4.3.2. General procedure for hydrogenation of acetophenone with the $[Ru(C_6H_6)Cl_2]_2$/L*/diamine system. In a Schlenk tube, $[Ru(C_6H_6)Cl_2]_2$ (2 mg, 8 μmol), the desired ligand (8.80 μmol) and the desired amine (8 μmol) were mixed in 1 mL of isopropanol under Ar at room temperature. After 7–12 h under stirring, *t*-BuOK (9 mg, 80 μmol) and acetophenone (93 μL, 0.8 mmol) were introduced and the resulting solution was stirred under a hydrogen pressure (30 bars) in a stainless-steel reactor (previously degased three times with argon and twice with hydrogen) for 7–16 h, at room temperature.

4.3.3. Procedure for hydrogenation of *m*-bisfluoromethylacetophenone with the system $[Ru(C_6H_6)Cl_2]_2$/L*/diamine. In a Schlenk tube, $[Ru(C_6H_6)Cl_2]_2$ (2 mg, 8 μmol), the desired ligand (8.80 μmol) and the desired amine (8.80 μmol) were mixed in 1 mL of isopropanol. After 7–12 h stirring under Ar at room temperature, *t*-BuOK (9 mg, 80 μmol) and *m*-bisfluoromethylacetophenone (144 μL, 0.8 mmol) were introduced and the resulting solution stirred under a hydrogen pressure (30 bars) in a stainless-steel reactor (previously degased three times with argon and twice with hydrogen) for 7–16 h, at room temperature.

4.4. GC conditions

Substrate	Conditions	Retention time
Acetophenone	Cyclodex β 60 °C (5 min)–1 °C/min–150 °C (1 min)	Starting material: 22.99 min Enantiomers: 30.52; 33.42 min
m-Bisfluoromethyl acetophenone	Cyclodex β 60 °C (1 min)–5 °C/min–150 °C (1 min)	Starting material: 8.82 min Enantiomers: 31.03; 31.86 min

4.5. HPLC conditions for the phosphine oxide separation

Chiral pack® AD DAICEL column, heptane/isopropanol (75/25), wavelength: 254 nm.
Phosphine oxide: **6**, retention time = 18.5 min (99%).
Phosphine oxide: **7**, retention time = 19.5 min (99%).
Phosphine oxide: (*R*,*R*) and (*R*,*S*), retention time = 18.5 min and 27.5 min.
Phosphine oxide: (*R*,*S*) and (*S*,*R*), retention time = 19.5 min and 28.8 min.

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