# Novel Bis-1,3,2-diazaphospholidine Ligands for Asymmetric Catalysis

Inmaculada Arribas, Eleuterio Álvarez and Antonio Pizzano*

Instituto de Investigaciones Químicas (IIQ), Consejo Superior de Investigaciones Científicas and Universidad de Sevilla. Avda Américo Vespucio nº 49, Isla de la Cartuja. 41092 Sevilla, Spain.

*Corresponding author. E-mail: pizzano@iiq.csic.es
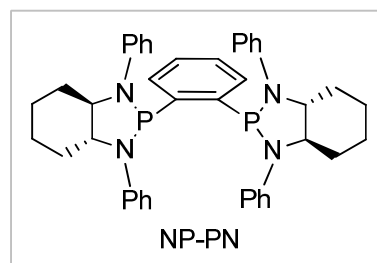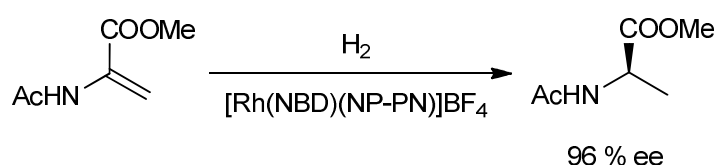
ABSTRACT: A family of modularly designed chiral bis-1,3,2-diazaphospholidines with *N*-aryl substituents (NP-PN) is reported. These compounds have been prepared in two steps from readily available (*R,R*)-1,2-diaminocyclohexane and tetrachlorodiphosphines. Examples in the set differ in the backbone and the aryl substituents aiming at their application in asymmetric catalysis. Thus, [Rh(NBD)(NP-PN)]BF$_4$ complexes lead to active catalysts in the hydrogenation

of methyl α-acetamidoacrylate, which provide enantioselectivities up to 96 % ee. In addition, NP-PN ligands also generate active catalysts in the hydroformylation of vinyl acetate, leading to high regioselectivities (*iso:n* ratio higher than 99:1) and enantioselectivities up to 65 % ee.

C_2 symmetric bis-phospholanes (Figure 1, **A**) constitute a prominent class of ligands in asymmetric catalysis.[1-2] The outstanding performance of these compounds is due to the proximity of the stereogenic centers to the metal and, as well, to the ability to finely tune the R group. However, the range of these substituents is largely limited to alkyl ones, while examples bearing aryl substituents are restricted to the 2,5-diphenylphospholane moiety,[3] due to the highly difficult synthesis of these derivatives.[4] Noteworthy, the presence of aryl substituents in positions 2 and 5 may have a profound influence on a catalytic process, as it has been observed in asymmetric hydroformylation reactions.[5]
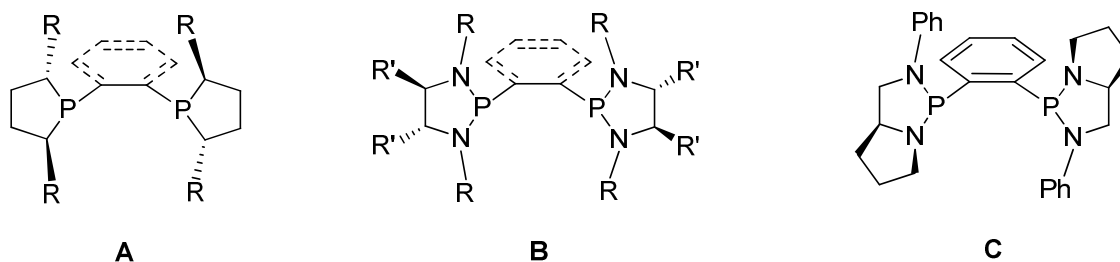

Figure 1. Generic structures of R substituted phospholanes (**A**) and 1,3,2-diazaphospholidines (**B**). ESPHOS ligand (**C**).

A seemingly related structure to bis-phospholanes **A** is provided by bis-1,3,2-diazaphospholidines (**B**). The latter compounds are attractive ligands for synthetic reasons due to the easy formation of P-N bonds from appropriate amines and phosphorus chlorides. Some alkyl examples (R = Me, CH$_2$-t-Bu, CH$_2$Ph) have already been described in the literature, although the efficiency of compounds **B** as ligands for asymmetric catalysis has not been substantiated yet.[6]

At this respect, a problem arises from the poorly defined position of R substituents in **B**, due to the expectedly easy nitrogen inversion. This aspect has successfully been circumvented by the use of bridgehead N atoms in ESPHOS (**C**)[7] and related diaminophosphite ligands.[8] In contrast, an arrested N inversion in **B** could rely on an steric interaction between appropriate R and R' groups. Some precedents suggest the feasibility of this approach. For instance, the group of Tsuji has described an efficient Pd catalyst based on secondary aryl diamines with chiral backbones.[9] On the other hand, Pfaltz and coworkers have described highly enantioselective Ir phosphine-oxazoline catalysts containing *N*-aryl diazaphospholidine fragments.[10] In this contribution we describe the synthesis of the first bis-1,3,2-diazaphospholidine ligands bearing *N*-aryl substituents, along with preliminary catalytic results which include a highly enantioselective hydrogenation reaction.

As the starting diamine scaffold, *trans*-1,2-cyclohexanediamine was chosen because it is readily available in both enantiomers and can easily be arylated to provide a wide variety of chiral secondary amines.[9-11] Among the latter phenyl (**1a**) and *p*-tolyl (**1b**) diamines, were selected as representative examples and reacted with commercially available tetrachlorodiphosphines, in the presence of an excess of NEt$_3$ (Scheme 1). These reactions provide a family of bis-1,3,2-diazaphospholidines **2**-**4**, which differ in the nature of the backbone. In contrast with the reaction between secondary aliphatic amines with 1,2-bis(dichlorophosphino)ethane,[6b] the generation of the present bis-diazaphospholidines is slow at room temperature and a prolonged heating is needed to reach a good conversion. For instance, reaction between **1a** and 1,2-bis(dichlorophosphino)benzene shows at room temperature the formation of the intermediate mono diazaphospholidine compound (P-P', Figure 2), characterized by two doublets centered at 104 and 154 ppm with a J_{PP} coupling constant of 151

Hz, along with some starting material at 150 ppm. These signals disappeared upon heating and the singlet of desired compound **3a** started to grow as the very predominant product. Interestingly, this reaction is rather clean and shows a high conversion. However, in order to guarantee the elimination of reactive phosphorus chloride impurities, the resulting mixture was purified through neutral alumina with some decrease in the yield of isolated **3a**.
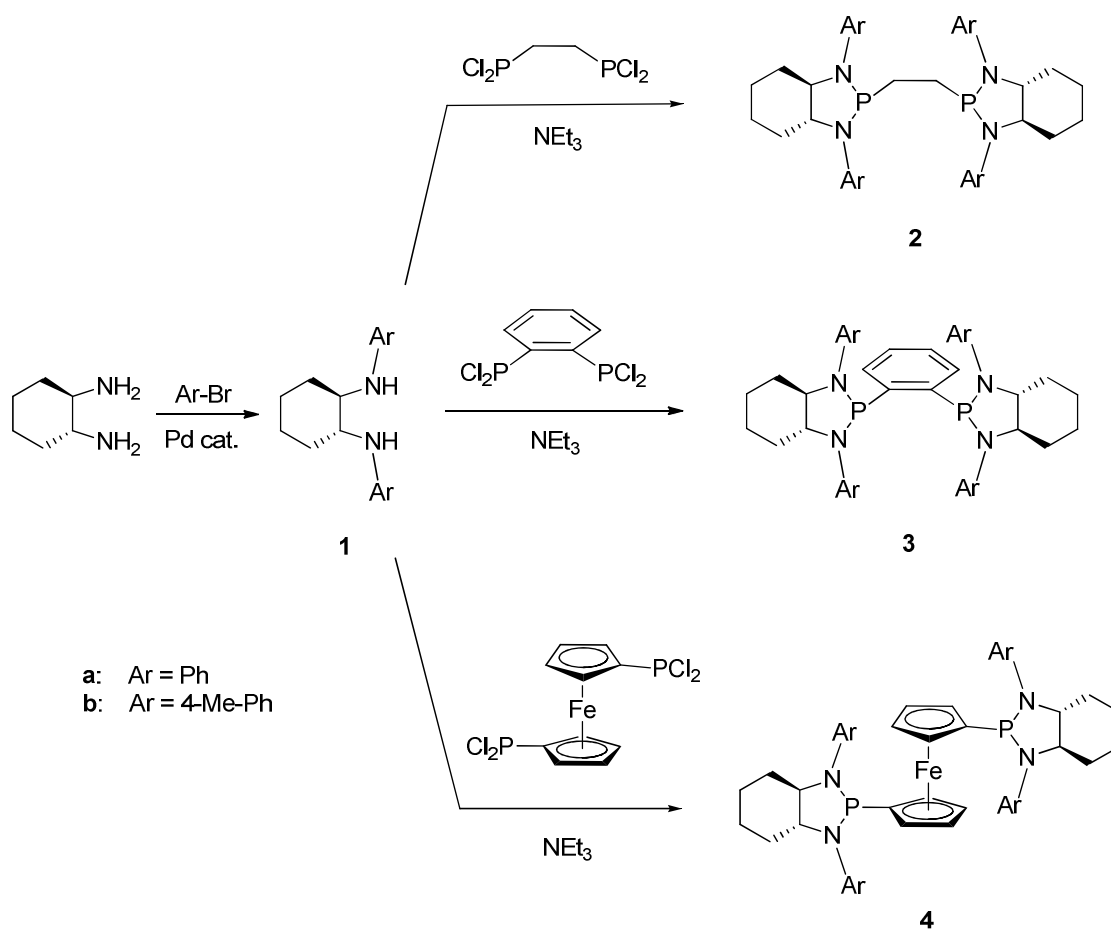
Scheme 1. Preparation of bis(diazaphospholidines) **2**-**4**.

Compounds **2**-**4** have been characterized by NMR and the data collected are in accord with the structure proposed for them. Thus, they show relatively simple ^{1}H and ^{13}C{^{1}H} NMR spectra due to the C_2-symmetry of these compounds. In addition, the two ^{31}P nuclei are equivalent and

appear as a singlet in the ^{31}P{^{1}H} NMR spectra. The latter signals appear at ca. 110 ppm for ligands **2** and **4**, and at ca. 130 ppm for compounds **3**.
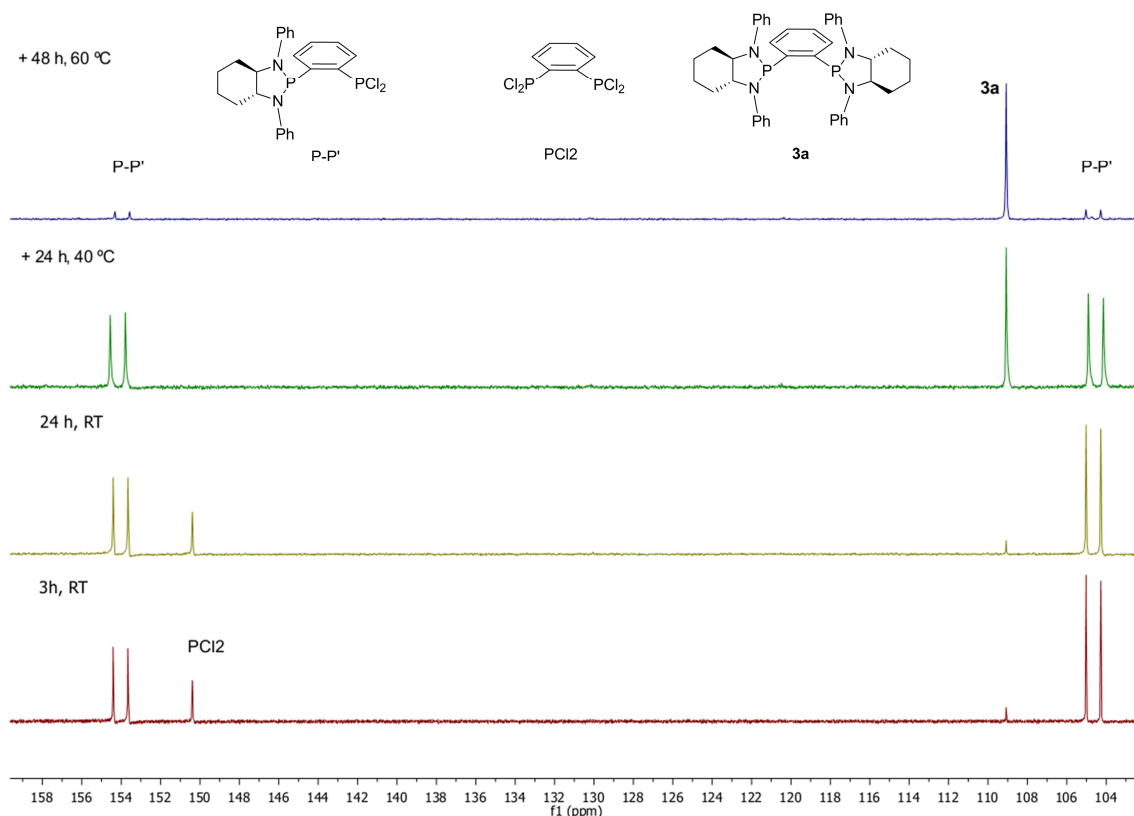

Figure 2. ^{31}P{^{1}H} NMR (162 MHz, toluene) monitoring of the formation of **3a**.

In order to estimate the donor properties of this family of ligands, the reaction between **3a** and Se has been performed. This reaction produces the corresponding diselenophosphine **5a** which appears as a singlet at 73.1 ppm in the ^{31}P{^{1}H} NMR spectrum. Measurement of the $^1J_{SeP}$ coupling constant in the satellites corresponding to the ^{77}Se isotopomer indicates a coupling of 868 Hz. This value shows, as expected, an intermediate donor ability between phosphines and phosphites.[12] However, the *N*-aryl fragments in **3a** reduce the σ-donor ability of **2a**, compared

with *N*-alkyl 1,3,2-diazaphospholidines,[13] and make it comparable with that provided by structurally related diaminophosphites.[14]
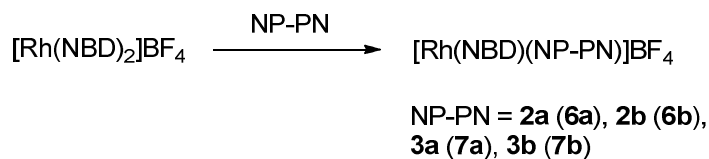
To provide information about the structural features of the diazaphospholidine fragment in compounds **2**-**4**, a representative example (**4b**) has been characterized by X-ray crystallography (Figure 4). The structure of this compound clearly shows the presence of the two phosphorus heterocycles, each fused with a cyclohexane ring in a *chair* conformation. Most interesting aspect regards the *anti* position of the *N*-aryl substituents, defined by C(7) and C(14), relative to the cyclohexane carbons C(6) and C(3), respectively. On the other hand, the sum of the bond angles involving the nitrogen atoms amount 342.1° [ΣN(1)] and 350.9° [ΣN(2)], indicative of an intermediate geometry between tetrahedral and trigonal planar for these atoms. The important influence of the chiral cyclohexane fragment on nitrogen geometry in **4b** is evident upon comparison with the structure of 2-phenyl-1,3-di(-*p*-tolyl)-1,3,2-diazaphospholidine,[15] which shows two planar nitrogens with a ΣN value of 359.1°. It should finally be mentioned that the N-C(aryl) distances in **4b** (1.416 and 1.425 Å), are significantly shorter than the exocyclic N-C bond lengths observed in related *N*-alkyl derivatives (1.72-1.75 Å).[6b]

We have next examined the coordination of ligands **2** and **3** in cationic rhodium complexes. Thus, these bis-(diazaphospholidines) cleanly react with [Rh(NBD)$_2$]BF$_4$ to give the corresponding complexes [Rh(NBD)(NP-PN)]BF$_4$ (**6**, **7**, Scheme 2). These compounds appear in the ^{31}P{^{1}H} NMR spectra as a doublet centered between 120 and 140 ppm, with $^1J_{RhP}$ coupling constants between 208 and 215 Hz. In addition, the ^{1}H and ^{13}C{^{1}H} NMR spectra show the equivalence between groups according to the presence of a C_2 symmetry axis.
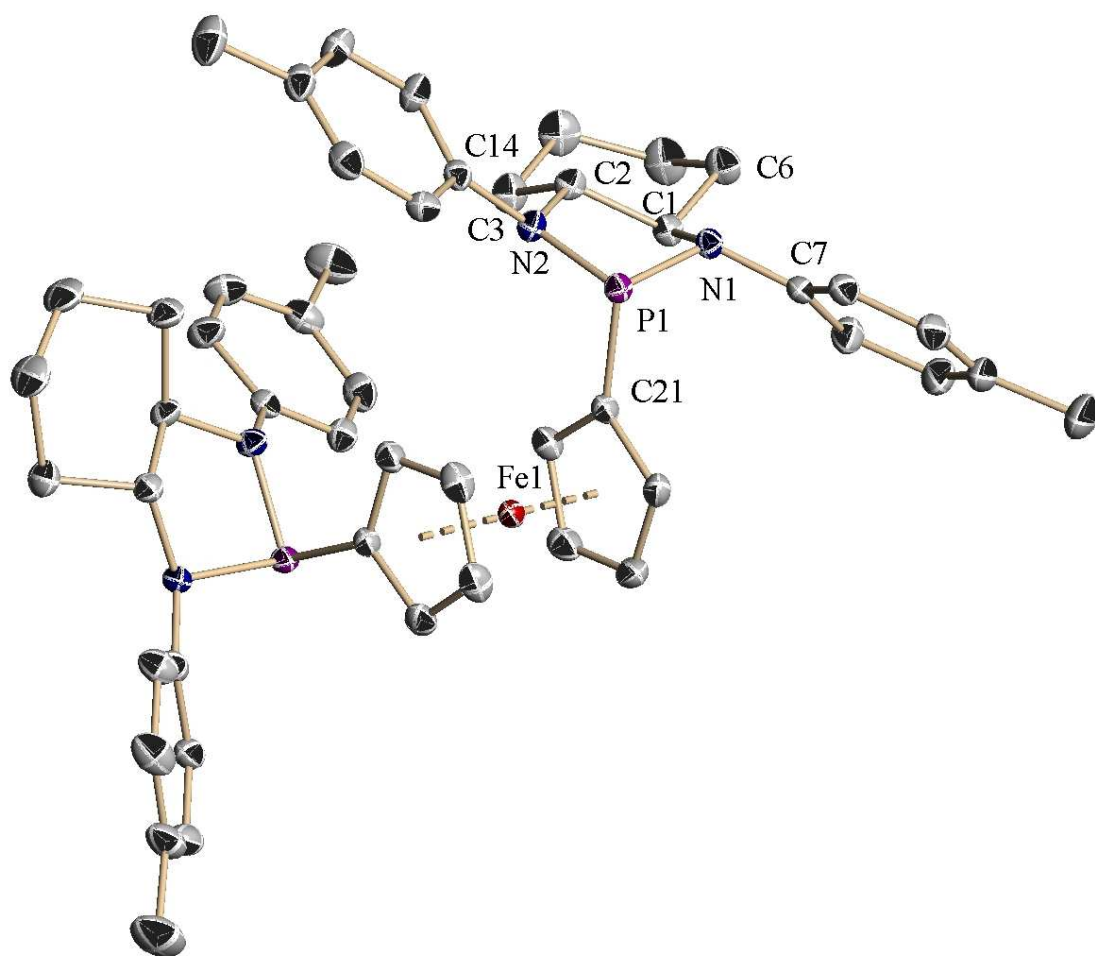
**Figure 4.** ORTEP view of complex **4b** at the 50 % probability level (H atoms have been omitted for clarity). Selected bond lengths [Å] and angles [deg]: P(1)-C(21) = 1.8191(13); P(1)-N(1) = 1.7474(10); P(1)-N(2) = 1.7225(11); N(1)-C(7) = 1.4250(16); N(2)-P(1)-N(1) = 91.40(5); C(7)-N(1)-P(1) = 114.96(8); C(14)-N(2)-P(1) = 120.88(9); C(14)-N(2)-C(2)-C(3) = 76.63(15); C(7)-N(1)-C(1)-C(6) = 64.09(15).

$$[\text{Rh(NBD)}_2]\text{BF}_4 \xrightarrow{\text{NP-PN}} [\text{Rh(NBD)(NP-PN)}]\text{BF}_4$$

NP-PN = **2a** (**6a**), **2b** (**6b**),
3a (**7a**), **3b** (**7b**)

Scheme 2. Preparation of Rh complexes **6**-**7**.

It is important to note that upon coordination of ligands **2**-**4**, different structures for complexes **6** and **7** are possible due to nitrogen inversion (a-c, Figure 3). Interestingly, these structures differ on the steric interaction between the Ar substituents and the cyclohexane fragment and in the proximity of the aryl rings to the NBD olefinic protons. At this respect, an inspection of the ^{1}H NMR spectra of complexes **6** and **7**, indicates that one of the olefin signals appear between 5.62 and 5.97 ppm, in the range found for other NBD complexes with diphosphine ligands.[16] In contrast, the second olefinic signal for **6** and **7** appears significantly shifted upfield, between 4.36 and 5.10 ppm. The shift of the latter signal can be attributed to the shielding caused by a close aryl ring (d). As a confirmation, an analysis of complex **7b** by a 2D NOESY experiment has allowed us to assign signals corresponding to tolyl groups pointing to the NBD ligand. Notably, the *ortho* hydrogens of the latter aryl rings exhibits a NOE signal with the high field olefin protons. Moreover, an examination of the NOE signals observed between these aromatic protons and the protons of the closer CHN and CH$_2$ fragments of the cyclohexane ring do not show evidence of inversion of N configuration in solution (see supplementary material), in accord with a preferred C_2 symmetric *anti-anti* structure in solution for this complex.
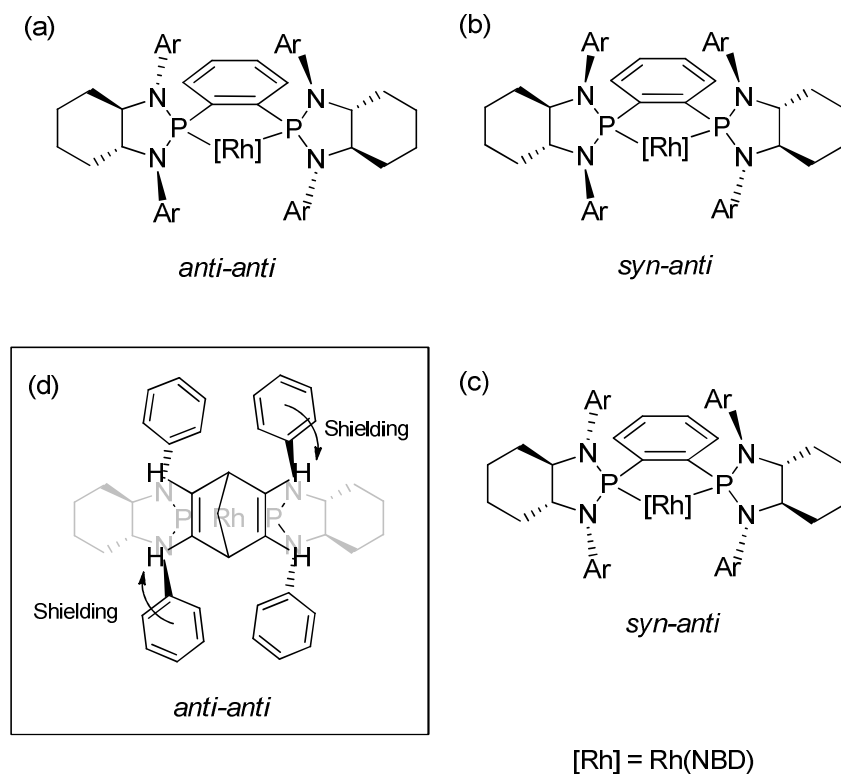
Figure 3. (a-c): Conformers resulting from N epimerization (for clarity, only structures corresponding to one N inversion from the *anti-anti* structure have been drawn). (d) Schematic drawing rationalizing the shielding effect on the NBD olefin protons.

To investigate the ability of the present bis-diazaphospholidine ligands in inducing enantioselectivity in a catalytic process, their performance in representative asymmetric hydrogenation and hydroformylation reactions has been examined. First, compounds **6** and **7** have been tested in the hydrogenation of methyl acetamido acrylate (Eq 1, Table 1). Under mild conditions, 4 bar of hydrogen and room temperature, these compounds lead to active catalysts able to complete reactions at S/C = 100 in 24 h. A comparison between catalysts indicates that those bearing a benzene backbone afforded better enantioselectivities. Of them the Ph substituted complex **7a** gave a good value of 96 % ee (entry 3).

$$\text{(1)}$$
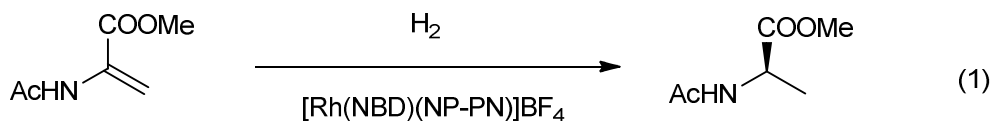
Table 1. Hydrogenation of MAA using complexes **6-7**[a]

Entry	Cat. Precursor	% conv	% ee (conf)
1	**6a**	100	75 (*R*)
2	**6b**	100	39 (*R*)
3	**7a**	100	96 (*R*)
4	**7b**	100	88 (*R*)

[a]Reactions were carried under an initial hydrogen pressure of 4 bar at a S/C = 100 in CH_2Cl_2 at room temperature. Reaction time 24 h. Conversion was determined by ^1H NMR and enantiomeric excess (ee) by chiral GC. Absolute configuration drawn in parentheses.

On the other hand, a preliminar study of the utility of ligands **2**-**3** in the asymmetric hydroformylation of vinyl acetate as a representative reaction has also been performed (Eq 2, Table 2). Reactions were performed at Rh/L = 1 at 50 ºC and 10 atm of H_2/CO (1:1) mixture. These reactions showed high conversions with the exception of catalyst based on **3a**, which provided a moderate conversion (73 % conv, entry 3). Catalysts showed a high regioselectivity, with branched to linear ratio higher than 98:2. In contrast, enantioselectivities were only moderate and among the catalysts tested, that based on ligand **2a** provided the best value (65 % ee, entry 1).

$$\text{(2)}$$
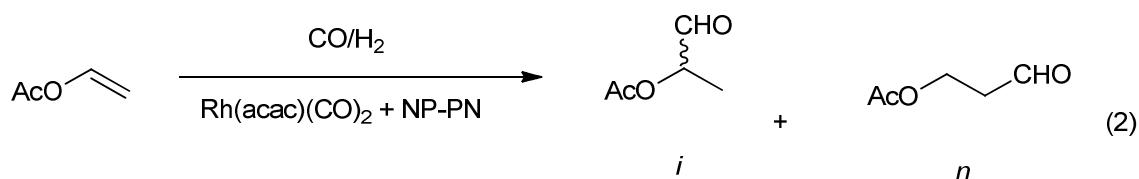
Table 2. Vinyl acetate hydroformylation using ligands **2-3**[a]

Entry	Ligand	Rh/L	*i:n*	% conv	% ee (conf)
1	**2a**	1	99:1	99	65 (*R*)
2	**2b**	1	99:1	99	63 (*R*)
3	**3a**	1	98:2	73	47 (*R*)
4	**3b**	1	99:1	99	60 (*R*)

[a]Reactions were carried under an initial H_2/CO (1:1) pressure of 10 bar at a S/C = 500 in toluene at 50 ºC. Reaction time 24 h. Conversion was determined by ^1H NMR and enantiomeric excess (ee) by chiral GC. Absolute configuration drawn in parentheses.

In summary, a convenient synthesis of modularly designed C_2 symmetric bis-(1,3-diaryl-1,3,2-diazaphospholidines), based on *trans*-1,2-diaminocyclohexane has been reported. The preliminary results indicate promising results in hydrogenation and hydroformylation reactions. Research on the extension of this class of ligands, as well as their application in asymmetric catalysis, is currently under progress.

Supporting Information. Representative experimental procedures, characterization data and crystallographic information for **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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