New *sp*^{3} diphosphine-based rhodium catalysts for the asymmetric conjugate addition of aryl boronic acids to 3-azaarylpropenones

Giorgio Facchetti,[a]* Marco Fusè,[b] Tania Pecoraro[c], Donatella Nava[a] and Isabella Rimoldi[a]

[a]Department of Pharmaceutical Sciences, Università degli Studi di Milano, Via Venezian 21, 20133 Milano, Italy

[b]Scuola Normale Superiore, Piazza dei Cavalieri 7, 56126 Pisa, Italy

[c]Department of Molecular Biochemistry and Pharmacology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, 20156, Italy

Corresponding author: giorgio.facchetti@unimi.it

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Abstract

Different chiral diphosphine ligands were successfully applied to the rhodium catalyzed asymmetric conjugate addition of differently substituted boronic acids to 3-azaarylpropenones containing both pyridinyl and imidazolyl cores. Atropoisomeric (*S*)-TetraMe-BITIANP (**L1**) and (*S*)-BITIANP (**L2**), together with ligands bearing a mixed chirality as (*S,S,S*$_{ax}$)-DIOPHEP (**L3**), (*R,R*$_{ax}$*)*-ISAPHOS C1 (**L4**) and (*S*,*R*$_{ax}$*,R*$_{ax}$*)*-ISAPHOS C2 (**L5**), and the ones containing a stereogenic sp^3 carbon ((*R*,*R*)-ZEDPHOS **L6**, (*R*,*R*)-EPHOS **L8** and their derivatives **L7** and **L9**) have been employed as source of chirality in rhodium complexes. Among this last class of diphosphines, the new phosphorus-based ligand called (*R*,*R*)-EPHOS (**L8**) has been synthesized and employed for the first time as a chiral ligand in rhodium complex for its catalytic activity. Computational studies suggested a *cis* coordination with a wide bite angle. When applied to the asymmetric conjugate addition of phenyl boronic acid to 3-azaarylpropenone **1,** the catalytic system bearing **L8** afforded the product **1a** in a remarkable 94% e.e. in THF.

Introduction

An underlying driving force yet to be fulfilled in the field of drug discovery relies on the search of practical synthetic methods able to produce safe compounds that, by specifically interacting with target elements, can arrest or ameliorate at least, a pathological condition.[1] Molecular chirality introduces an additional level of specificity in reaching this goal, starting from the assumption that mirror-image molecules behave as completely distinct compounds, and they have to be treated as well when interacting with the corresponding biological counterparts.[2] Enantioselective catalysis using metal complexes provides one of the most general and flexible methods for the synthesis of chiral compounds.[3, 4] In these regards, the proper combination of the selected metal with the correctly designed enantiopure ligand is the determining step for obtaining synthetic processes with high

efficiency. Indeed, this provides the ideal way to multiply chirality affording large amounts of chiral products of either absolute configuration exploiting only small quantity of chiral source. In such a view, ligands' properties stemming from the presence of appropriate functionalities along with substituents capable of discriminating the space in the proximity of the metal center play a pivotal role. Indeed, optically active phosphine ligands have been of fundamental importance in many transition-metal-catalyzed asymmetric reactions.[5, 6]

Asymmetric conjugate addition reaction stands out as one of the most useful methods for the preparation of chiral compounds but, although routinely employed, its application to the synthesis of chiral 3-azaarylpropenones has been scarcely investigated.[7-9] These *N*-containing heteroarenes are commonly found in a wide variety of natural products and relevant structures in many chiral biologically active molecules.[10, 11] Key contributions in their preparation include [6]asymmetric hydrogenation of alkenyl azaarenes or the nucleophilic addition to *N*-heteroaryl alkenes using Grignard reagents,[12] thiols[13] and $B_2(pin)_2$.[14-16]

Recently, an efficient Rh-catalyzed protocol for installing aryl groups on 3-azaarylpropenones in α position with high selectivity has been reported, taking advantage of the presence of a carbonyl-activating group adjacent to the commonly reactive beta position.[17] Starting from our established expertise in the synthesis of chiral phosphine ligands and in the field of asymmetric homogeneous catalysis,[18, 19] we prepared a series of novel chiral phosphorus ligands, designed and synthesized starting from the optically active 1,4-(*E*)-2-butene, taking inspiration from ZEDPHOS ligand, previously reported by our group.[20] The new diphosphine hereafter called EPHOS, features a stereogenic sp^3 carbon atom combined to the presence of a C2 axial chirality, the one typically featuring in atropoisomeric diphosphines. In this research paper, the enantiopure (*R*,*R*)-EPHOS (**L8**) and its xylyl-derivative (**L9**) along with xylyl-ZEDPHOS (**L7**) were applied to the Rh-catalyzed asymmetric conjugate addition of differently substituted organoboronic acids to 3-azaarylpropenones in comparison with a series of atropoisomeric chiral diphosphines established as being extremely efficient ligands in many different asymmetric metal-catalyzed reactions.[21]

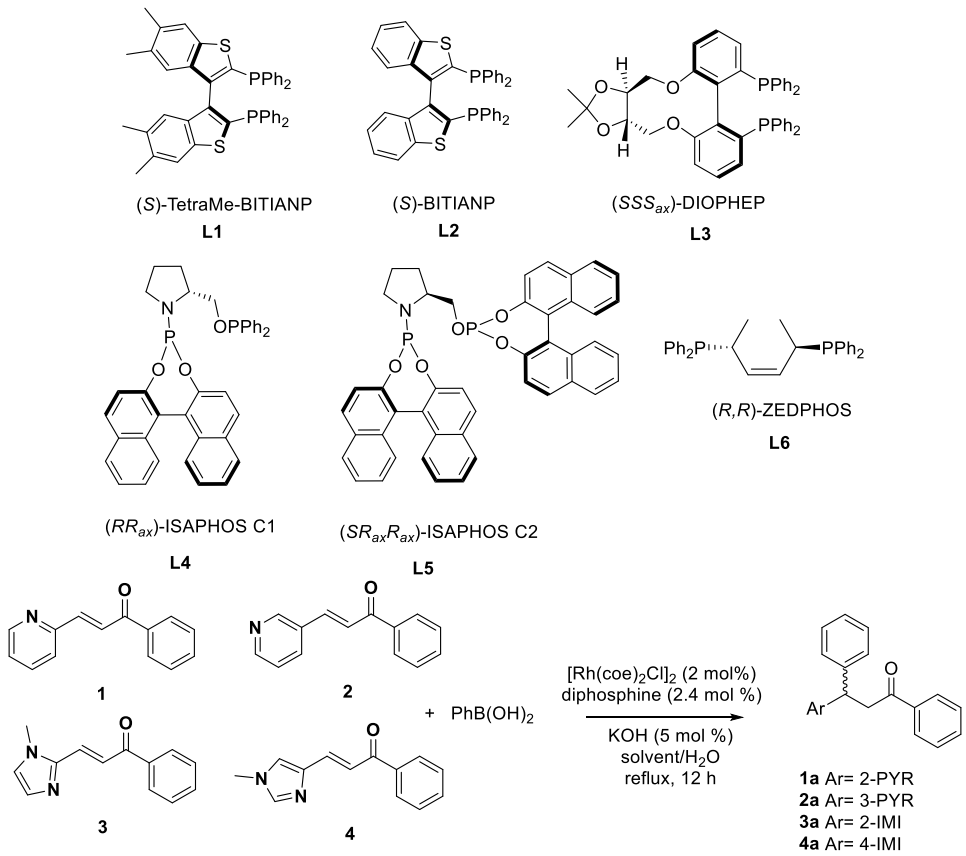
Results and Discussion

As reported by Dou and co-workers arylboronic acids can be effectively added to carbonyl-activated alkenyl azaarenes through an asymmetric metal catalyzed reaction by employing atropoisomeric diphosphines as source of chirality.[22] The performance of other types of chiral phosphines either featuring a sp^3 carbon atom or bearing a mixed chirality resulted significant only when chalcones were used as substrates. In the last decades in our laboratory different types of chiral diphosphines have been synthesized having different sources of chirality and the corresponding metal complexes have been successfully applied to many enantioselective organic transformations.[23-25] In this paper, we reported the use of these phosphorus based chiral scaffolds in coordination with a rhodium center in the asymmetric catalyzed 1,4 conjugate addition of different substituted arylboronic acids to 3-azaarylpropenones. A preliminary screening with atropoisomeric ligands on (*E*)-chalcone had

already stated the importance of the 3-aza core for affecting both the reactivity and the enantioselectivity of the rhodium system in this type of reaction. When **L1** and commercially available (*S*)-BIPHEP as reference ligand were employed on (*E*)-chalcone in the asymmetric conjugate addition of phenylboronic acid, the reaction afforded the products only in traces (data not reported).

Conversely, the addition of phenylboronic acid was evaluated for four different 3-azaarylpropenones as substrates, hereafter called **1** ((*E*)-1-phenyl-3-(pyridin-2-yl)prop-2-en-1-one), **2** ((*E*)-1-phenyl-3-(pyridin-3-yl)prop-2-en-1-one), **3** ((*E*)-3-(1-methyl-1H-imidazol-2-yl)-1-phenylprop-2-en-1-one) and **4** ((*E*)-3-(1-methyl-1H-imidazol-4-yl)-1-phenylprop-2-en-1-one) respectively.[26] In order to get a prognostic insight into the reactivity of different rhodium based catalytic systems in this type of reaction, we employed diphophine ligands characterized by varied types of chirality: phosphorus based ligands bearing only an atropoisomeric chirality as in (*S*)-TetraMe-BITIANP (**L1**) and (*S*)-BITIANP (**L2**),[23, 27]; diphosphines endowed with a mixed chirality (both sp^3 and atropoisomeric) as in (*S,S,S*$_{ax}$)-DIOPHEP (**L3**)[28] and (*R,R*$_{ax}$)-ISAPHOS C1 (**L4**) and (*S*,*R*$_{ax}$,*R*$_{ax}$)-ISAPHOS C2 (**L5**) [29, 30]; or only a sp^3 chirality as in the case of (*R*,*R*)-ZEDPHOS (**L6**).[20]

Table 1. Asymmetric conjugate addition of phenylboronic acid to 3-azaarylpropenones **1**, **2**, **3** and **4**.



Entry	Ligand	Substrate	Solvent	Conversion(%)	e.e.(%)
1	**L1**	**1**	THF	98	88
2		**2**	IPA	73	53

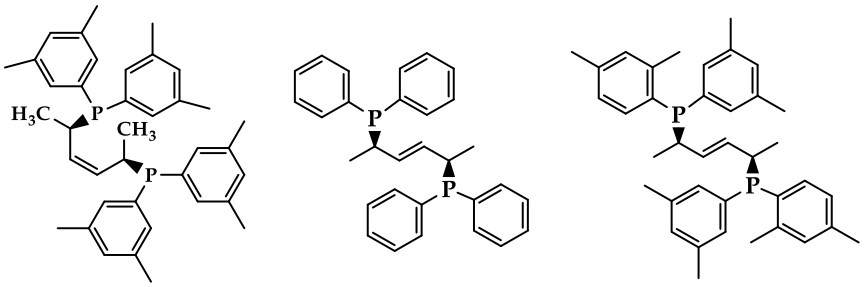
3		**3**	IPA	55	72
4	**L2**	**1**	IPA	95	67
5		**2**	IPA	82	54
6		**3**	THF	70	65
7	**L3**	**1**	THF	96	80
8		**2**	IPA	54	87
9		**3**	IPA	50	65
10	**L4**	**1**	THF	62	72
11		**2**	THF	55	57
12		**3**	THF	45	74
13	**L5**	**1**	THF	47	60
14		**2**	THF	27	40
15		**3**	THF	25	65
16	**L6**	**1**	THF	44	49
17		**2**	IPA	55	26
18		**3**	IPA	-	-

Reaction conditions: 0.1 mmol substrate, final concentration 0.1 M; 0.15 mmol $PhB(OH)_2$; Rh catalyst 1% mol; KOH 5% w/w in water: 50 µL/1 mL of solvent; reflux temperature, 12 h. Enantiomeric excess was determined using HPLC.

The addition of phenylboronic acid to substrate **4**, the 1-methyl-1H-imidazol-4-yl azarene, did not work with all types of diphosphine ligands and under the different reaction conditions (isopropanol (IPA) or tetrahydrofuran (THF) and KOH as base). Unfortunately, any attempt to obtain the product by changing both the solvent (*i.e.* dioxane) and the base (*i.e*. K_2CO_3) failed when applied to substrate **4**. The data reported in Table 1 underlined that for all the other substrates the best results, both in terms of enantioselectivity and conversion, were obtained when an atropoisomeric chirality was present in the used ligand. In particular, **L1** gave 88% e.e. and almost complete conversion for substrate **1** (Table 1, entry 1); when **2** was used as substrate ligand **L3** afforded the product in a significant 87% e.e., (Table 1, entry 8) even if the conversion resulted lower than in the case of substrate **1** using the same ligand. Regarding the reaction involving substrate **3**, even if the conversion remained lower than using the pyridinyl substrates, **L4** allowed to reach a good enantioselectivity (74% e.e., Table 1, entry 12). Different reaction conditions as solvent, base and pre-catalyst were evaluated confirming that THF was the best choice as solvent for the reaction involving substrate **1,** whereas an increase in conversion was evinced using isopropanol (IPA) for

substrates **2** and **3**. Regarding metal pre-catalysts, different rhodium complexes were screened, *i.e*. $Rh(acac)(CO)_2$, $Rh(COD)_2ClO_4$, $[Rh(COD)Cl]_2$, with a general decrease of enantioselectivity in all cases in comparison to $[Rh(coe)_2Cl]_2$ used in this preliminary study (data not reported). When **L4** and **L5** were chosen as chiral ligands in rhodium complexes, IPA was not employed as reaction solvent because these diphosphines were proved unstable in alcohols, thus impairing the performance of the catalyst. Whilst in the case of substrate **1** the conversion could be considered satisfying with all the diphosphine ligands in 12 h, substrates **2** and **3** resulted less reactive probably due to a less operative activating effect exerted by the carbonyl group when the nitrogen of the azaarene is not proximal to the alpha position where the addition took place. By comparison with data reported in literature[17] using (*R*)-BIPHEP, we assigned the absolute configuration of **1a** to (*R*) and consequently to all the other products as demonstrated by HPLC spectra affording the same predominant enantiomer for all the ligands employed. For the same reason the enantioface selection could be assigned to a predominant α*si*-face coordination of rhodium to the double bond of the enones.

From our point of view, despite lower values in terms of enantioselectivity and reaction rate, the results with **L6**, a diphosphine with only the sp^3 chirality, should deserve to be deeply investigated taking into consideration its less time-consuming synthesis and optical purification if compared to the atropoisomeric counterparts. With this aim, we decided to synthetize a series of new chiral diphosphines: the xylyl derivative of **L6**, called (*R*,*R*)-Xylyl-ZEDPHOS (**L7)** together with the corresponding isomeric analogues in *trans* configuration, (*R*,*R*)-EPHOS (**L8**) and the corresponding xylyl analogue, (*R*,*R*)-Xylyl-EPHOS (**L9**) (Figure 1).



(*R*,*R*)-Xylyl-ZEDPHOS **L7** (*R*,*R*)-EPHOS **L8** (*R*,*R*)-Xylyl-EPHOS **L9**

Figure 1. ZEDPHOS derivatives

Surprisingly, for substrate **1** the results obtained using **L8** as ligand were better in terms of enantioselectivity in comparison with those obtained with (*R*,*R*)-ZEDPHOS, (*R*,*R*)-Xylyl-ZEDPHOS and (*R*,*R*)-Xylyl-EPHOS as reported in Table 2 (entry 5 versus entries 1, 3 and 8), leading to product **1a** in a remarkable 94% e.e. in THF and 84% e.e in IPA. Moreover, (*R*,*R*)-Xylyl-ZEDPHOS outstood its precursor **L6**, affording the product in 64% e.e. in THF (entry 3 versus entry 1). Conversely, the asymmetric conjugation addition reaction on substrates bearing imidazole moiety, **3** and **4**, were not operative. These data were collected using the highly active achiral Xantphos as reference, taking

into consideration its wide bite angle in transition metal complexes, that made it comparable to our sp^3 diphospines.[31]

Table 2. Asymmetric conjugate addition of phenylboronic acid using **L6-L9** as ligands.

Entry	Ligand	Substrate	Solvente	Conversion (%)	e.e. (%)
1	**L6**	**1**	THF	44	49
2		**2**	IPA	55	26
3	**L7**	**1**	THF	54	64
4		**2**	IPA	31	18
5	**L8**	**1**	THF	58	94
6		**1**	IPA	65	84
7		**2**	IPA	38	24
8	**L9**	**1**	THF	45	46
9		**2**	IPA	27	20
10	**Xantphos**	**1**	THF	13	-

Reaction conditions: 0.1 mmol substrate, final concentration 0.1M; 0.15 mmol $PhB(OH)_2$; Rh catalyst 1% mol; KOH 5% w/w in water: 50 µL/1 mL of solvent; reflux temperature, 12 h. Enantiomeric excess was determined using HPLC.

Ligand (*R*,*R*)-ZEDPHOS is indeed known to have a wide bite angle with a reported value of 103.9° in the [((*R*,*R*)-ZEDPHOS)$PtCl_2$] complex.[20] This value was expected to increase in the *trans* isomer, leading to values even more comparable to the ones of the achiral Xantphos.[32]

The different species formed after reaction with $[Rh(coe)_2Cl]_2$ in THF-d_8 at room temperature for 30 minutes, mimicking the reaction conditions employed for *in situ* preparation of the catalyst, were evaluated by ^{31}P-NMR spectroscopy. (Figure 2)

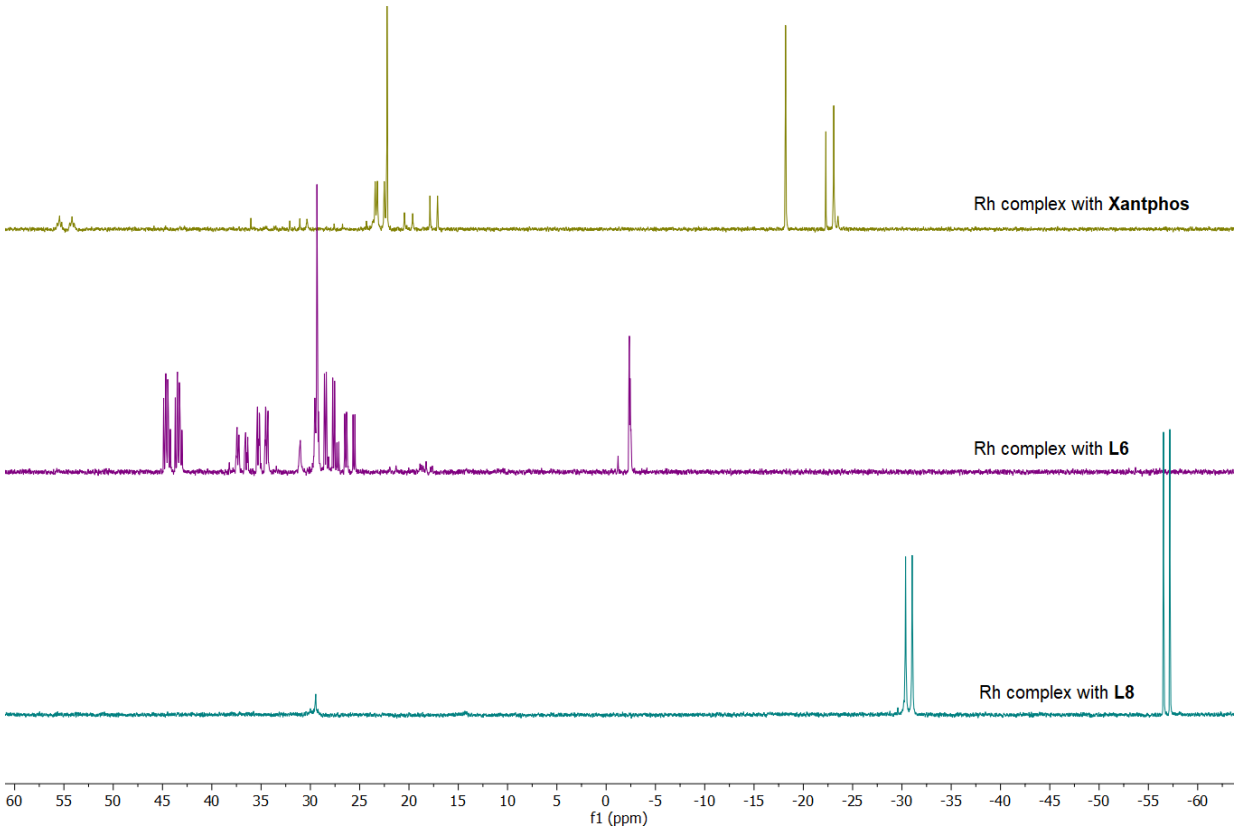


Figure 2. ^{31}P-NMR of rhodium(I) complexes for ligands **L6** and **L8** in comparison with Xantphos.

As reflected by the reported spectra the species present are very different for the three ligands and the real complexes structures are difficult to assign.[33, 34] In particular when **L8** was employed, the two species are characterized by ^{31}P-NMR chemical shifts at high field in comparison to the signals present in the spectra of the other two disphosphines.[35] Considering the absence of crystals suitable for X-ray analysis of rhodium-EPHOS complex, able to clarify how it is structured, and in order to distinguish between the *cis*/*trans* coordination mode in square planar complexes, the Pt(II) complexes of the (*R*,*R*)-ZEDPHOS (**L6**), (*R*,*R*)-EPHOS (**L8**) and Xantphos were synthesized and their ^{31}P-NMR spectra were recorded. The spectra are reported in Figure 3 and the chemical shift (δ) for *cis*-[(Xantphos)$PtCl_2$] resulted in agreement with the reported values.[36] Starting from this premise, a computational study was thus performed. Models were generated from the X-ray crystal structures reported in literature that were then optimized by employing the tight-binding GFN2-xTB method[37] including the implicit solvation model (GBSA). The structures were then further optimized at the B3LYP-D3(BJ) level of theory and the ^{31}P chemical shifts were evaluated taking PH_3 as reference (values collected in the Supporting information). Despite the small size of the basis set employed, the chemical shifts of (*R*,*R*)-ZEDPHOS (**L6**) and Xantphos complexes are in excellent agreement with the experimental values and allowed to assess the formation of *cis* complexes. The same behavior is observed in the case of (*R*,*R*)-EPHOS (**L8**), where both the relative stability (the *cis* isomer is ~ 48 kJ/mol more stable than the *trans* one) and the ^{31}P δ suggested the formation of the *cis* isomer.

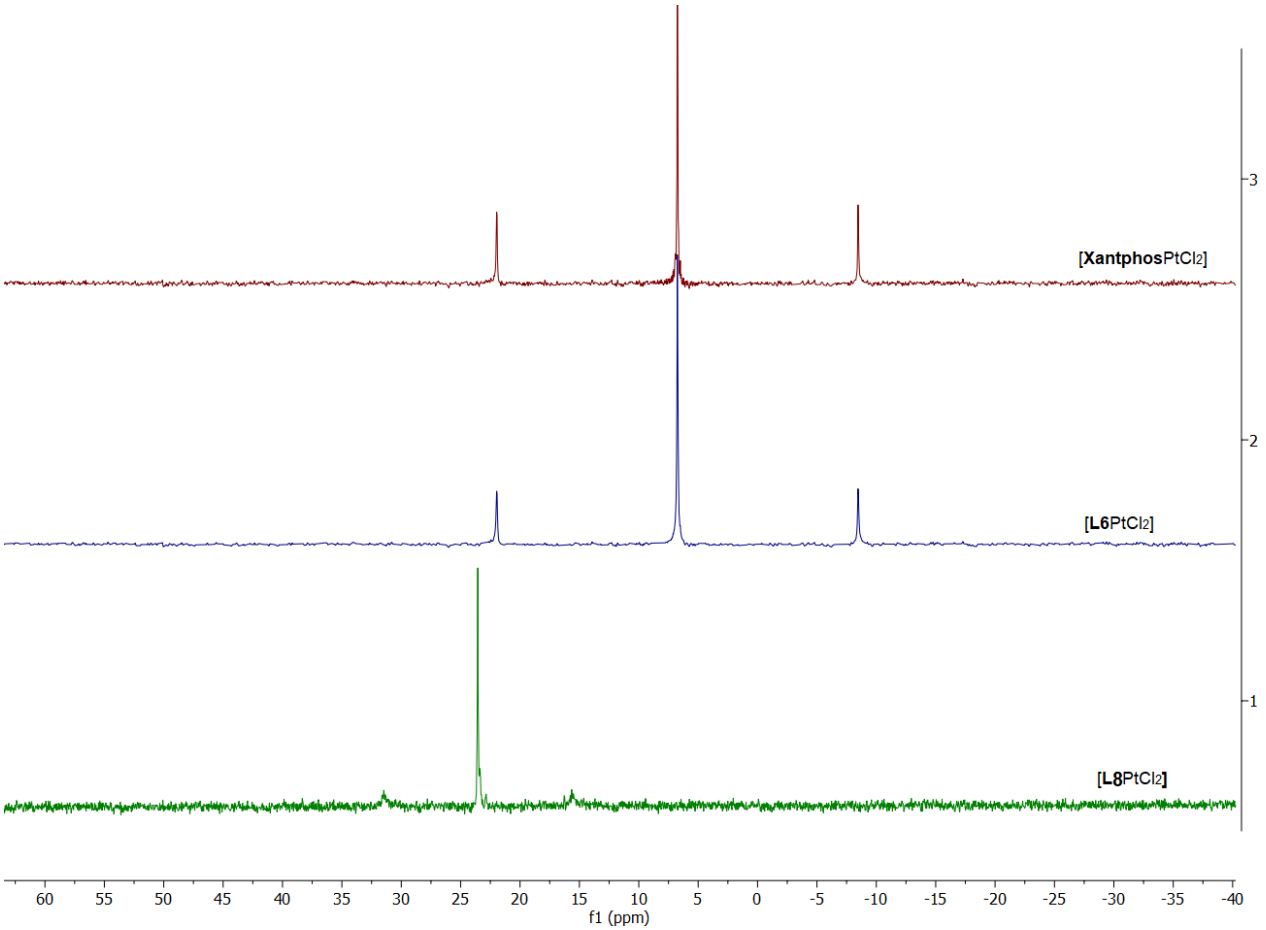


Figure 3. ^{31}P-NMR of platinum(II) complexes for ligand **L6** and **L8** in comparison with Xantphos.

Turning the attention on the conformation of the coordinated ligands, as observed from the X-Ray structure of the Pd(II) complex,[20] the optimized structure of [((*R*,*R*)-ZEDPHOS)$PtCl_2$] revealed a symmetrical arrangement of the four phenyl rings that are above and below the molecular plane. On the other hand, the asymmetric disposition of the aryl groups can direct the chiral recognition of the substrate enantiofaces (Figure 4).

a) b) c)

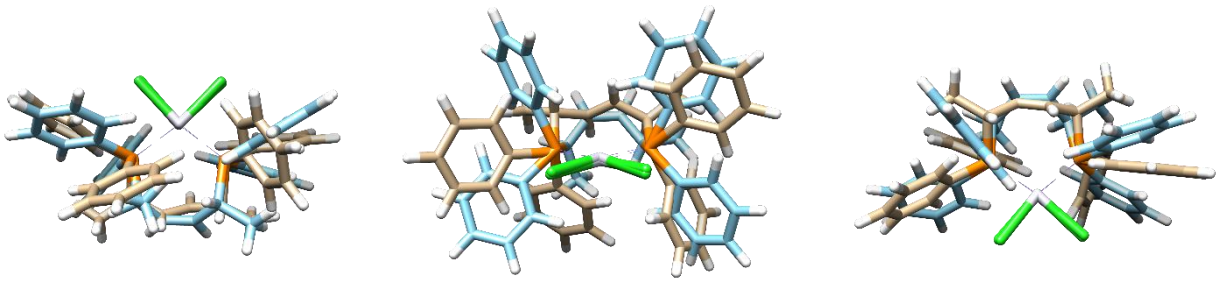
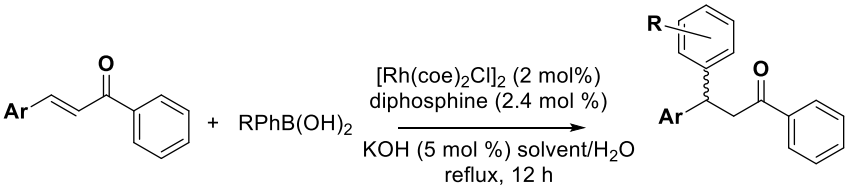
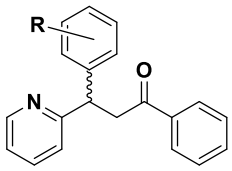


Figure 4. Superposed molecular geometries of the a) ZEDPHOS (**L6**) and c) EPHOS (**L8**) Pt(II) complexes. The central panel b) highlighted the different disposition of the phenyl rings with respect to the molecular plane.

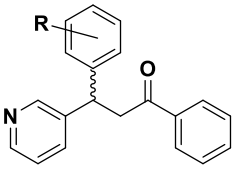
Indeed, the disposition of the phenyl groups around the metal center could explain the different behavior evinced in catalysis for the two ligands **L6** and **L8** (Table 2 entry 1 vs entry 5). Under the same optimized reaction conditions employed for the asymmetric conjugation addition of phenylboronic acid, the scope was extended to differently substituted arylboronic acids using all types of ligands (L1-L9) (Table 3).

Table 3. Asymmetric conjugate addition of differently substituted phenylboronic acids to 3-azaarylpropenones **1**, **2**, **3** and **4**.

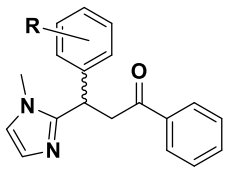




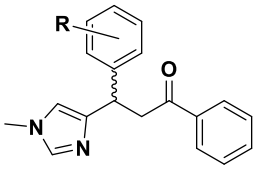
1a R= H
1b R= 3-OMe
1c R= 4-OMe
1d R= 3-Br
1e R= 4-Br
1f R= 3-Me
1g R= 4-Me
1h R= 3,5-Me
1i R= 3-NO_2
1l R= 4-NO_2



2a R= H
2b R= 3-OMe
2c R= 4-OMe
2d R= 3-Br
2e R= 4-Br
2f R= 3-Me
2g R= 4-Me
2h R= 3,5-Me
2i R= 3-NO_2
2l R= 4-NO_2



3a R= H
3b R= 3-OMe
3c R= 4-OMe
3d R= 3-Me



4c R= 4-OMe

Entry	Substrate	Ligand	Solvent	Conversion (%)	e.e.%
1	**1b**	**L8**	THF	78	91
2	**1c**	**L1**	THF	96	95
3	**1d**	**L1**	THF	67	85
4	**1e**	**L1**	THF	93	90
5	**1f**	**L1**	THF	77	75
6	**1g**	**L1**	THF	93	87

7	**1h**	**L1**	THF	68	84
8	**1i**	**L1**	THF	60	80
9	**1l**	**L1**	IPA	83	46
10	**2b**	**L3**	IPA	85	62
11	**2c**	**L3**	IPA	92	85
12	**2d**	**L3**	IPA	90	64
13	**2e**	**L3**	IPA	99	85
14	**2f**	**L3**	IPA	83	66
15	**2g**	**L3**	IPA	90	73
16	**2h**	**L4**	THF	94	88
17	**2i**	**L3**	IPA	62	80
18	**2l**	**L3**	IPA	65	55
19	**3b**	**L4**	THF	65	80
20	**3c**	**L4**	THF	78	83
21	**3d**	**L4**	THF	61	77
22	**4c**	**L4**	THF	56	71

Reaction conditions: 0.1 mmol substrate, final concentration 0.1M; 0.15 mmol $PhB(OH)_2$; Rh catalyst 1% mol; KOH 5% w/w in water: 50 µL/1 mL of solvent; reflux temperature, 12 h

Table 3 reported the best results obtained with the different disphosphines. Generally, in the addition of the diverse substituted arylboronic acids on substrate **1**, **L1** resulted the ligand of choice displaying the best performances both in terms of enantioselectivity and conversion (Table 3, entries 2-9). However, it's worth noting that in the addition of (3-methoxyphenyl)boronic acid, (*R*,*R*)-EPHOS (**L8**) outstood other diphosphine ligands affording the product **1b** in an appreciable 91% e.e. (Table 3, entry 1). In the case of substrate **2**, the best matching in the rhodium catalyzed conjugate addition reaction of the substituted aryl boronic acids was realized by **L3**-catalytic system in all cases. In this case the atropoisomeric ligands always outperformed the sp^3 chiral ligands. In fact for the addition of both (4-methoxyphenyl)boronic acid **(2c**) and (4-bromophenyl)boronic acid (**2e**) (Table 3, entries 10-15) a good 85% e.e was achieved, unless in the case of product **2h**, obtained with 88% e.e. using Isaphos C1 (**L4**) (Table 3, entry 17). The same diphosphine **L4** has demonstrated significantly performing also in the case of substrate **3,** although a general decrease in reactivity was evinced, that is indeed in accordance with the trend already outlined in the preliminary screening (Table 3, entries 19-21). In particular, with this class of ligands the reaction cannot be performed in IPA already resulted detrimental for the ISAPHOSs (**L4** and **L5**) stability. In this case, product **3c** was isolated in a good 83% e.e., that is however extremely striking considering that this is the first time that, to the best of our knowledge, the asymmetric phenylboronic acid conjugation addition reaction had been extended to the imidazolyl azarenes. Surprisingly, although the addition of phenylboronic acid on

substrate **4** did not work as observed from the preliminary screening, in the case in which there is an activating group as the methoxy substituent in *para* position, the reaction proceeded smoothly leading to the reaction product in a notable 71% e.e. (Table 3, entry 22). All the obtained data underlined, as a general trend, a marked decrease of reactivity for the 3-imidazolyl-arylpropenones in comparison with the pyridinyl counterparts, probably due to the electronic depletion in α position to the carbonyl-activating group in the imidazolyl 3-imidazolyl-arylpropenones, due to the well-known tautomerism operating in the imidazole ring. Regarding the diphosphine ligands, interesting results were obtained using Isaphos C1 (**L4**) and the newly synthesized EPHOS (**L8**), containing a mixed and a sp^3 chirality respectively. Moreover, both the diphosphines **L4** and **L8** afforded rhodium complexes endowed with better enantiodiscriminating ability if compared to their corresponding analogues Isaphos C2 (**L5)** and (*R*,*R*)-ZEDPHOS **(L6**), that probably resulted more sterically hindered and thus leading to less favorable transition states when interacting with the substrates.

Conclusion

In conclusion, nine diphosphines (**L1**-**L9**), characterized by different source of chirality, were evaluated for their performance in the catalytic addition of substituted arylboronic acids to 3-azaarylpropenones. The effect of the solvent and the reactivity of different azaarenes were highlighted, with the pyridinyl substrates proving more reactive than the imidazolyl ones, with the only exception in the case of an activated arylboronic acid (**4c, Table 3, line 22**). The behavior of the newly synthesized sp^3 chiral diphosphine **L8,** here reported for the first time with **L7** and **L9**, was compared to its *cis* analogue **L6** in terms of their catalytic performance and their different enantiodiscriminating ability was indeed rationalized by computational studies shedding light on the importance of the different arrangement of the phenyl rings around the metal center. As expected, the *cis* or *trans* configuration of the alkyl chain present in this series of ligands, considerably affected the conformation of the corresponding metal complexes and the consequent outcomes in the addition reaction here investigated. Surprisingly, when **L8** was employed as ligand, the corresponding rhodium catalyst afforded product **1a** in an excellent 94% e.e. and **1b** in 91% e.e. with good to moderate yields. The corresponding xylyl derivatives **L7** and **L9**, conversely, did not improve the selectivity and reactivity of the reaction on the other substrates. As a general trend, the atropoisomeric diphosphine **L1** along with **L3** and **L4,** both featuring a mixed chirality, resulted the most versatile ligands in this type of asymmetric conjugate addition reaction allowing to obtain very good enantiomeric excesses (up to 95% e.e. for **1c** with **L1**, 85% e.e. for **2e** with **L3** and 88% e.e. for **2h** with **L4**) and reaction conversions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

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Supporting Information Available

The Supporting Information is available free of charge at **……**

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