# Evaluation of efficiency of chiral atropisomeric phosphorus ligands in the asymmetric catalytic processes mediated by transition metal complexes

# Part 1: Evaluation of steric effects

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**Introduction**

The development of the efficient procedures giving access to chiral, enantiomerically pure chemical compounds used in pharmaceutical, agrochemical and perfume industries, has for many years been a great challenge for synthetic chemists. Among the many approaches to a synthesis of enantiomerically pure compounds, asymmetric catalysis, where used chiral catalyst enables the transformation of a prochiral substrate into an optically active product, seems to be the most desirable strategy.

When the catalysts used are the transition metal (TM) complexs of chiral ligands, the transfer of chirality from the ligand to the prochiral substrate occurs in the coordination sphere of the metal, wherein the enantiotopic atoms, groups or faces of the prochiral molecule become sterically differentiated as the result of the proximity of the chiral ligand [1, 2].

Asymmetric catalysis is considered as an integral chemical process, in which maximum efficiency is achievable only under the circumstances of optimal selection of appropriate catalyst and proper reaction conditions. The process of efficient asymmetric catalysis should proceed with a high turnover number (TON) and high turnover frequency (TOF) and should furnish products of maximal enantiomeric excess (ee). Certain, well-designed chiral catalyst not only accelerates the chemical reaction, but also create a significant differentiation between two diastereomeric transition states usually of not less than 10 kJmol$^{-1}$, allowing to obtain the desired enantiomeric product of high optical purity.

Since the stereochemical control of reaction occurring in the coordination sphere of the metal, the key issue here is the proper choice of ligands providing stereochemical diffirintiation during the approaching the chiral catalytic centre by the prochiral substrate. The $C_2$-symmetric atropisomeric biaryl diphosphines are among of the most widely used and most efficient ligands applied in the asymmetric reactions [3, 4]. These ligands are characterized by a high racemization barrier (commonly, biaryl ligands are able to retain its absolute configuration in temperature above 400°C and pressures above $10^7$ Pa [5]); by significant conformational freedom which enables adapting the ligand geometry to coordination requirements of the transition metal, as well as by significant conformational rigidity of the formed organometallic complex, required to force the formation of only one of two possible enantiomeric products. Some of theses TM complexes used in asymmetric catalytic reactions allows to obtain products in nearly 100% enantiomeric purerity, they also found wide industrial applications [1, 2, 6, 7]. Selected examples of chiral atropisomeric diphosphine ligands are shown in Figure 1 [8].

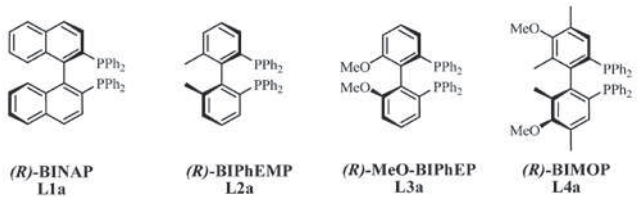



**Fig. 1. Examples of $C_2$-symmetric atropisomeric phosphine ligands**

great progress in the field of asymmetric catalysis has been noted over the last three decades. The importance of these accomplishments was highlighted in 2001 by awarding the Nobel prize in chemistry to R. Noyori [9], W. Knowles [10] and B. Sharpless [11] for asymmetric catalytic hydrogenation and oxidation reactions. However, there are many catalytic reactions and substrates, for which the efficacy of known catalysts ligands is still low. The difficulty in understanding of the influence of electron and steric effects of ligands on the sense of asymmetric catalytic reactions is reflected in the lack of versatile ligands able to ensure high level of induction in all catalytic processes. There is therefore a continuous pursuit for the novel types of ligands and for new synthetic modifications of already known ones.

Seeking of the best catalyst, providing the highest level of asymmetric induction in a given asymmetric process, still usually consists in empirical iterative and intuitive search for an optimum catalytic system (based on selection of an appropriate ligand) and optimum reaction conditions. With this approach and with consideration of growing number and structural variety of available, and usually costly ligands, selection of the proper ligand becomes highly expensive and labour-consuming [12]. The understanding of the relationship between the structure of the ligands and the catalytic efficacy of their complexes would facilitate that selection procedure.

The conformational freedom of free phosphorus ligands is usually high. So the geometry of the ligand, even in its most stable conformation, does not correspond to geometry of the ligand included in an active catalyst. In the case of bidentate ligands, however, complexation with a metal significantly enhance the conformational stability and molecular rigidity. Thus the geometry of such complexes can by predicted and characterized by such parameters as bite angle, dihedral angle, P-Met bond length (Fig. 2) and electron density at the phosphorus and metal atoms. On the other hand, the geometry of complexes, even those derived from the same ligand, will differ depending on the type of transition metal, counterion, other molecules coordinated to metal and on such factors as solvent, temperature, etc. Taking in consideration all mantioned above it seems reasonable to make the evaluation of

the efficacy of ligands by comparisons only between the complexes of the same metal with similar ligands applied in the same catalytic processes and run under identical conditions.

**Modification of the structure of $C_2$-symmetric atropisomeric diphosphine ligands –seeking for a good catalytic system**

All undertaken so far attempts to improve the efficiency of the catalysts by modification made in the structure of atropisomeric ligands [13] were based on two complementary approaches aimed to control the conformation of the ligands in the catalytic complex (which is the topic of this review) or to control the electron density at phosphine centres of the ligand (this approaches will be described in Part 2**: Evaluation of electronic effects**).

**Steric control**

There are a number of derivatives of known ligands of the **L1**-**L4** type, where the change of catalytic properties of their complexes was caused mainly by structural modifications that implicated change of conformations of the ligands, and subsequently change of conformations of their complexe. This approach may be considered as an attempt to control asymmetric induction by steric control of the ligand.

**Concept of using of "minor and major grooves" of binaphthyl core**

Among the earliest structural modifications of **L1** type ligands were those within the binaphthyl skeleton which led to the change of the P-Met-P angles (bite angles $\alpha$) (Fig.2). Such modification of ligand **BINAP** (**L1a**) leads to increasing of the bite angle ($\alpha$). It is represented by the **NAPHOS** (**L5**) ligand [14] (Fig. 2), wherein phosphine groups are connected with the atropisomeric binaphthyl core via $CH_2$ bridges.

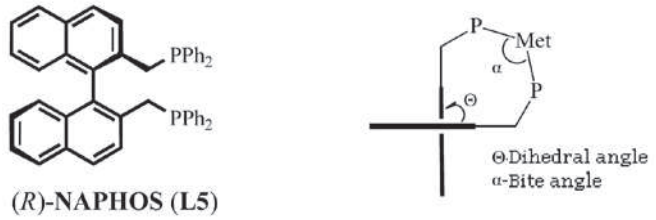



**Fig. 2. *(R)*-NAPHOS ligand (L5) and definitions of angles Θ and α**

According to X-ray structural data, the bite angle of Rh-**BINAP** complex ([Rh(nbd)binap]$^+$) is 91.8° [15] and it is almost equal to the computed value of 91.6° of this angle[16]. In the same time the computed bite angle of corresponding **NAPHOS** complex [Rh(nbd) naphos]$^+$ was significantly larger - 102.4° (Fig. 2), unfortunately there is lack of X-Ray structure of this compound published.

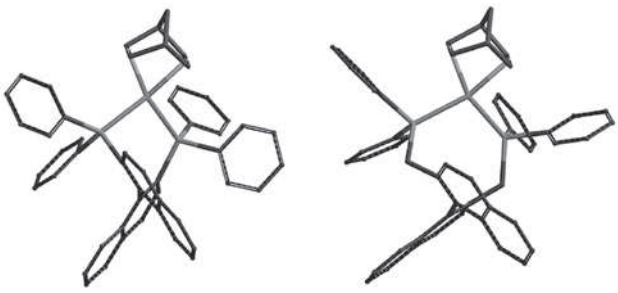
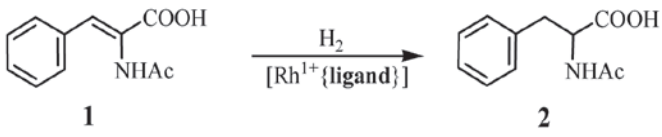


**Fig. 3. Rhodium complexes of BINAP (L1a) and NAPHOS (L5). [16]**

Catalytic properties of rhodium complexes of **NAPHOS** and **BINAP** were compared in the catalytic hydrogenation of *N*-acetaminocinnamic acid (Scheme 1). The utilisation of **NAPHOS** complex resulted in an asymmetric induction of 54% ee, while the use of **BINAP** complex furnished a product of ca. 15% ee only [13a]. Apparently, the large bite angle enhanced asymmetric induction in the presented reaction.




**Scheme 1. Hydrogenation of *N*-acetaminocinnamic acid mediated by rhodium complexes of NAPHOS (L5) and BINAP (L1a)**

Another structural modification of **BINAP** was realised by introducing of phosphine groups into the positions 7,7' (instead of positions usual 2,2') of the binaphthyl core. The sense of this modification consisted in utilizing the more open "side" of the binaphthyl (larger groove) (Fig.4) which offered much larger bite angles as compared to those observed in ligands possesind phosphine groups at 2,2' positions.

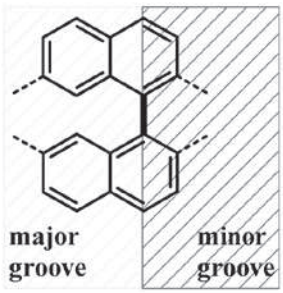



**Fig. 4. Minor and major groove of 1,1'-binaphthyl core**

This concept was applied in the synthesis of ligands **L6** and **L7** (Figs. 5, 6) [17, 18]. As evidenced by calculations made for π-allyl-palladium complexes [Pd(**L6**)allyl]$^+$ and [Pd(**L7**)allyl]$^+$, the corresponding bite angles were equal to 106.7° and 110.2°, respectively [16]. In the case of allyl-Pd complexes the *cis*- configuration of the ligands was forced by the bidentate allyl ligand, whereas in the case of [Pd(**L6**)$Cl_2$] and [Pd(**L7**)$Cl_2$] complexes the calculated difference of energies for *cis*- and *trans*- complexes was marginal. In addition, the utilization of a larger groove of the binaphthyl core increases the conformational freedom of the palladium complexes of **L6** and **L7** enabling the formation of complexes with a completely different geometry. Thus according to computer simulations [16] in *cis*- complexes ([Pd(**L6**)$Cl_2$]) and [Pd(**L7**)$Cl_2$] the bisectors of the P-Pd-P angles (in contrast to the usually perpendicular one) situate at an angle of ca. 45° and ca. 10° respectively to the axis connecting two naphthyl moieties (Fig. 6).

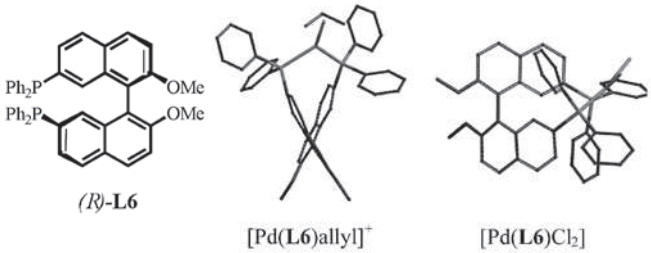



**Fig. 5. Ligand L6 and its palladium complexes [16]**

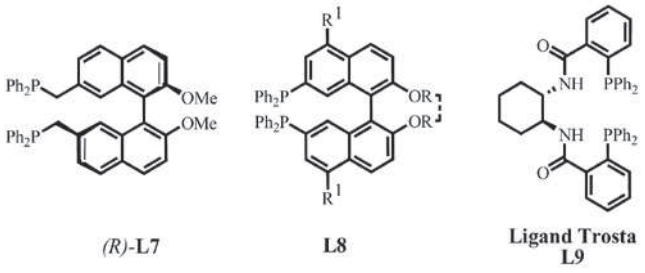
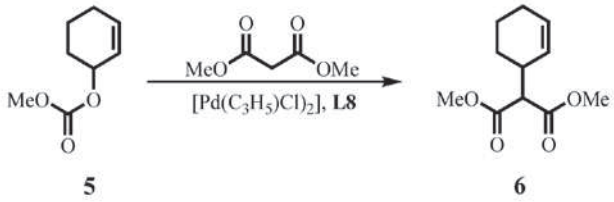



**Fig. 6. Ligands L7, L8 and L9**

The series of ligands of the **L8** type were also synthesized [19] (Fig.6). In those ligands the substituents $R^1$ were introduced in the *meta-* in relation to phosphorus atom position of binaphthyl rings, and wherein the groups R were (or not) bridged.

Complexes of these ligands were used in model asymmetric allylic substitution reaction (Scheme 2). Depending on the nature of R and $R^1$ substituents, the observed asymmetric induction ranged from 5 to 99% ee. Best results were obtained in the reaction of 2-cyclohexen-1-ol carbonate and dimethyl malonate in presence of 0.45%-mol of $[Pd(C_3H_5)Cl)_2]$ and ligand **L8** where R = $-(CH_2-)_4$, $R^1$ = H. The highest reported enantioselectivity of this particular reaction (98% ee) was obtained by using of 5%-mole of Trost's ligand complex (**L9**) (ligand of large bite angle capable for forming *cis-* complexes) (Fig. 6) [20].




**Scheme 2. Model asymmetric allylic substitution reaction**

Ligands (**L5**–**L8**) have never been used in the same model reaction, this prevents the direct comparison of the effects of structural modifications on ligands efficacy . On the other hand, it would also be difficult to compare ligands of such dissimilar steric properties.

### The control of ligands conformation

The relationship between the properties of catalytic complexes and spatial structures of the ligands can be clearly demonstrated on example of biphenyl-based ligands. A single and well defined conformation of the atropisomeric ligand **BIPhEMP** (**L2**) was ensured by linking of two methyl groups by an oxygen bridge. (Fig. 7, **L10**) [21].

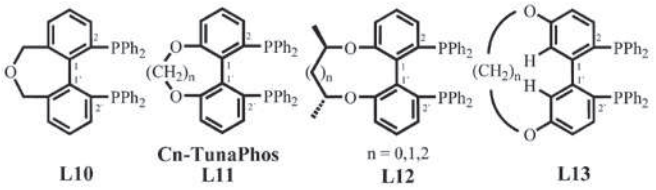
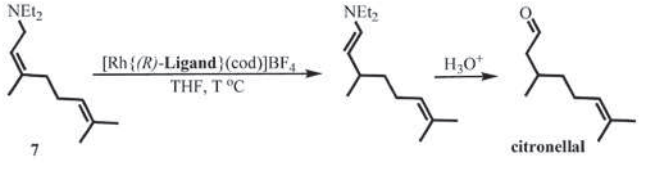



**Fig. 7. Ligand L10, $C_n$-TunaPhos (L11), L12, and L13**

Thus stiffened ligand, in contrast to **BIPhEMP**, has a lower conformational freedom, what reduces an ability of it complexes to change the geometry. The X-ray structural analysis data indicate that the dihedral angle $C_2C_1$-$C_{1'}C_{2'}$ ($\Theta$) in the rhodium complex **L10** was 56.7°, while in the free ligand **L2** this angle was sililar and amointed to 64.9° [21].

Catalytic activity of complexes of ligands **L10** and **BIPhEMP** has been compared in the asymmetric isomerization of N,N-diethylnerylamine (**7**) catalyzed by Rh-**BIPhEMP** and Rh-**L10** rhodium complexes (Scheme 3). These complexes provided similarly high yields in synthesis of citronellal (95% and 89%, respectively) and similar asymmetric induction of 98% ee for Rh-**BIPhEMP** and 98.5% ee for Rh-**L10**. This suggests that this particular reaction is rather insensitive to changes of the bite angle in the catalytic complex [21].




**Scheme 3. Asymmetric rhodium catalysed isomerisation of *N,N*-diethylnerylamine**

More systematic comparative investigations of steric control of ligand conformation and action were performed on the case of **MeO-BIPHEP** (**L3a**) [13d-f, 21, 22]. This ligand was converted into a series of new rigid ligands with tenable dihedral angles generaly named **$C_n$-TunaPhos** (**L11**) (Fig.7). The two oxygen atoms at positions 6, 6' of biaryl core were linked by $-(CH_2-)_n$ bridges of variable lengths (n = 1-6) to restrict the conformational freedom of the ligands. It was observed that in a line with the growing of linkers length the dihedral angle of the ligands were also increased what induced preference for complexation at higher angles (Fig.8). [23]

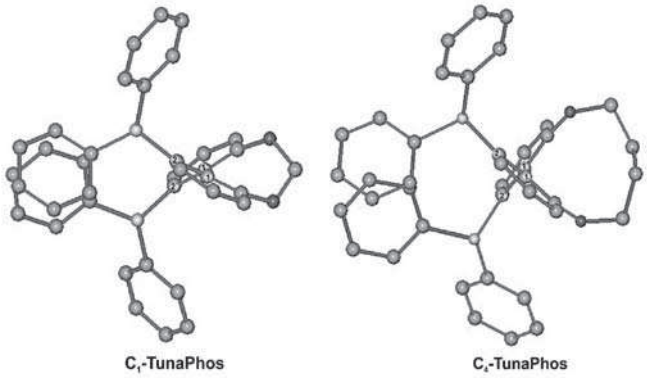



**Fig. 8. The demonstration of changing of $C_2C_1$-$C_{1'}C_{2'}$ angles in $C_{1\text{-}4}$-TunaPhos**

The studies on **$C_n$-TunaPhos** complexes catalytic activity have clearly indicate that it is possible to gently control asymmetric induction by precise tuning of biphenyl core conformation to ensure optimal bite angle for the given substrate and reaction.

**Table 1**

**Relationship between asymmetric induction, bridge length (n) and dihedral angle $\Theta$ of $C_n$-TunaPhos (L11) in the hydrogenation reactions of 8, 9, 10 and 11**

| Substrate | n | 1 | 2 | 3 | 4 | 5 | 6 | L3a | BINAP |
|---|---|---|---|---|---|---|---|---|---|
| | Dihedral angle $\Theta$ | 60° | 74° | 77° | 88° | 94° | 106° | 87° | 87° |
| 8 | Ee, %[a] | 90.0 | 93.9 | 99.0 | 99.2 | 96.8 | 95.9 | 98.5 | 97.6 |
| 9 | Ee, %[b] | 95.9 | 95.9 | 92.1 | 88.9 | 91.9 | 92.3 | - | - |
| 10 | Ee, %[c] | 91.3 | 90.3 | 98.5 | 95.1 | 95.3 | 90.7 | 94.3 | 96.1 |
| 11 | Ee, %[d] | 98 | 99 | 99 | 99 | 99 | 97 | 99 | 99 |

[a] ($H_2$, 750 psi, 1,2%-mol [RuCl{$C_n$-TunaPhos}($C_6H_6$)]Cl)
[b] ($H_2$, 3 atm, 1%-mol $[NH_2Me_2][\{RuCl((S)\text{-}C_n\text{-TunaPhos})\}_2(\mu\text{-}Cl)_3]$)
[c] ($H_2$, 1500 psi, 80 °C, 2%-mol $[NH_2Me_2][\{RuCl((S)\text{-}C_n\text{-TunaPhos})\}_2(\mu\text{-}Cl)_3]$)
[d] ($H_2$, 50 atm, 5%-mol Rh(metallil)$_2$ $C_n$-TunaPhos + $HBF_4$)

The observed asymmetric induction in hydrogenation of β-ketoester **8** (Tab.1) initially increased from 90% ee (n = 1), to 99.2% ee (n = 4), and after that is decreased again to 95.9% ee (n = 6). The best results were obtained in the case od use of **$C_4$-TunaPhos** characterised by the dihedral angle of 88°, close to that angle found in **MeO-BIPhEP** (**L3a**) and **BINAP** (**L1a**), which also provided excellent asymmetric induction in this reaction.

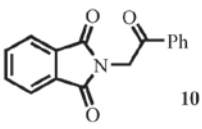
Another example of similar effect was observed in asymmetric reduction of 1-(2-naphthyl)vinyl acetate (**9**) using ruthenium **$C_n$-TunaPhos** complexes [24], occurring with greater than 99% conversion (Tab.1). Ligands with the shortest bridges (n = 1 and 2) were the best chiral inductors in the case of this reaction.. In the hydrogenation of *N*-phenacylphthalimide (**10**) the highest enantioselectivity was afforded when the **$C_3$-TunaPhos** ligand ($\Theta$ = 77°) was utilised. Complexes of **$C_n$-TunaPhos** (n = 2-5) also proved to be effective catalysts in asymmetric hydrogenation of cyclic β-dehydroaminoester **11** (Tab.1) [25].

A similar modification of **MeO-BIPhEP** (**L3a**) is represented by a series of ligands in which two 6,6' oxygen atoms were connected by two to four carbon atoms linkers, containing two additional stereogenic centres **L12** (Fig.7). The presence of additional substituents in the bridge enable aven more precise tuning of complex conformations than that posible for **$C_n$-TunaPhos**. **L12** ligands were used to study the influence of bridge length and in consequence of values of dihedral angles on the asymmetric induction in asymmetric hydrogenation of C=C, C=O and C=N bonds [26]. In the asymmetric hydrogenation of 2-(6-metoxy-2-naphthyl)acrylic acid and methyl acetylacetate carried out in the presence of (*R*, *S*, *S*)-**L12** ligand (n = 0) the high levels of asymmetric induction were acheaved (97% ee and 99.8% ee, respectively), while in the cases of hydrogenation of *N*-heteroaromatic compounds better inductions approaching 93% ee were observed when (*S, R, R*)-**L12** ligand (n = 1) was used.

Recently, a series of unusual chiral ligands **L13** was presented (Fig.7). The conformational freedom of the ligands **L13** was restricted by $-(CH_2-)_n$ bridge (n = 7-10 and 12) connecting the positions 5,5' of the biphenyl core. Notable that the ligands **L13** were not substituted at positions 6, 6'. Palladium complexes of these ligands were successfully applied in the hydrogenation of *N*-phenacylphthalimide (**10**). The effect of the bridge length on asymmetric induction is presented in Table 2 [27].

**Table 2**

**Relationship between asymmetric induction and length (n) of the bridges in ligand L13 observed in the hydrogenation of substrate 10**

| Substrate | n | 7 | 8 | 9 | 10 | 12 |
|---|---|---|---|---|---|---|
| | Dihedral angle Θ | (no data) | 59.7° | 64.1° | 72.4° | 65.0° |
|  10 | Ee, %[a] | 93 | 96 | 97 | 98 | 90 |

[a] ($H_2$, 100 atm, 80 °C ,2%-mol $Pd(CF_3CO_2)_2$

### Effect of substituents in PAr2 groups at positions 3 and 5

Study concentrated on introduction of substituents in diphenylphosphine function (-$PPh_2$) at position 3 or positions 3,5 of phenyl groups has appointed another significant steric effect. It was observed that in catalytic reactions mediated by complexes of both biphenyl ligands, as well as binaphthyl ligands, substituted at positions 3 (or 3,5) of the diphenylphosphine moiety observed enantioselectivities were significantly increased [28÷30].

In view of the tendency to ***privileged*** orientation of the aryl groups in P-$Ar_2$ substituents of transition metals complexes at almost right angle (edge-to-face arrangement), it is assumed that in the presence of substituents at positions 3 and 3, 5 this tendency is substantially strengthened due to increasing of spatial hindrance of aryl groups in an edge arrangement (Fig.9). Consequently, this increases a sterical diversity of the directions toward which the reagents are approaching the catalytic centre. The similar phenomenon was originally described by Knowles [31].

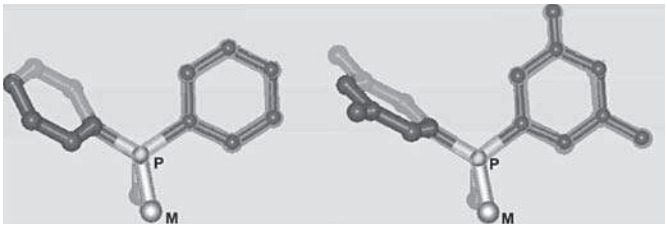
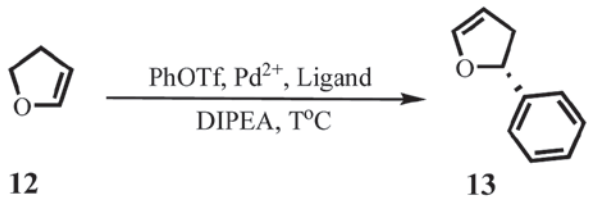



**Fig. 9. Effect of substituents at positions 3, 5 of the phenyl groups**

Also this effect have been confirmed in a number of asymmetric processes, such as reduction of >C=C< bonds catalyzed by ruthenium complexes [32], asymmetric allylic substitution catalyzed by palladium complexes [28], reduction of - and -ketoesters on ruthenium catalysts [29, 33] as well as asymmetric Heck reaction [34].

In the Heck arylation of dihydrofuran catalyzed by palladium complex of unmodified **MeO-BIPhEP** (**L3a**) the product of 84% ee enantiomeric purity was obtained, whereas the same reaction catalyzed by palladium complex of **MeO-BIPhEP** derivative (**L3b**) (Scheme 4, Fig. 10) with *tert*-butyl groups at positions 3 and 5 in P-aryl function gave product of greatly improved enantiomeric purity up to 99% ee.




**Scheme 4. Asymmetric Heck reaction**

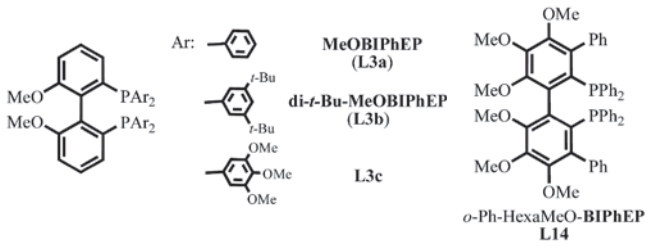


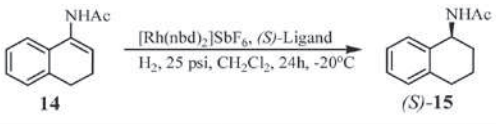

**Fig. 10. Ligands of the series L3 and L14**

### Effect of substituents at positions 3, 3' in the biaryl core

An interesting example of the steric effect of *ortho*- to phosphorus atoms substituents in biaryl core has for the first time been presented on the case of ligand ***o*-Ph-HexaMeO-BIPhEP** (**L14**) (Fig.10) [35]. The affectivity of this ligand was verified in the Rh-catalysed hydrogenation reactions of cyclic enamides (Tab. 3).

**Table 3**

**Reduction of enamide 14: comparison of catalyst efficacy**




| Ligand | Yield, % | Ee, % |
|---|---|---|
| **o-Ph-HexaMeO-BIPhEP** (**L14**) | 100 | 98 |
| **HexaMeO-BIPhEP** (**L3c**) | 100 | 65 |
| **MeO-BIPhEP** (**L3a**) | 100 | 67 |
| **BINAP** (**L1a**) | 100 | 55 |

In fact the use of complexes of electron-rich ligands enhanced the observed asymmetric induction (Tab.3), but it seems that this the decisive impact on the enantioselectivity of the reaction had been made because of presence of the phenyl substituents at positions 3, 3' (*ortho* in relation to phosphorus groups) of the biphenyl core in ligand **L14**. The analysis of the computation data suggests, that the excellent asymmetric induction in the case of the **L14** ligand resulted from the significant increasing of the dihedral angle $C_1C_2$-$PC_3$ (Fig.10) (from 70° in **HexaMeO-BIPhEP** (**L3c**) to 90° in ***o*-Ph-HexaMeO-BIPhEP** (**L14**)). In addition, in the rhodium complex of ligand **L14** the rotation of phenyl groups of $PPh_2$ moiety is rather impossible because of the presence of phenyl substituents at positions 3, 3' which stiffen the conformation of the complexes (Fig.11).

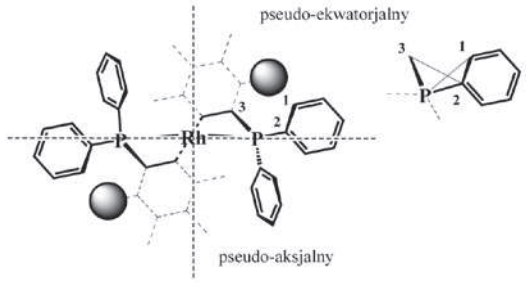



**Fig. 11. Schematic structure of *o*-Ph-HexaMeO-BIPhEP Rh-complex**

The observation of the positive influence of substituents at positions 3, 3' of biaryl core on asymmetric induction has contributed to growing interest to this type of modifications, and as a consequence to preparation of a series of new binaphthyl and biphenyl ligands shown in Figure 12 [36].

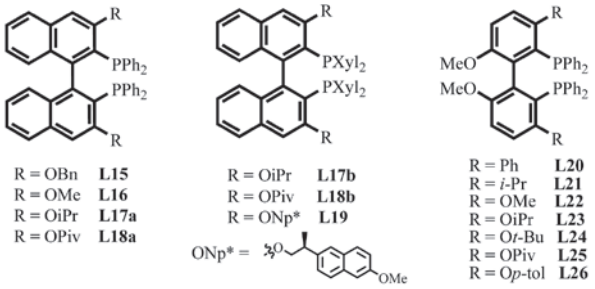
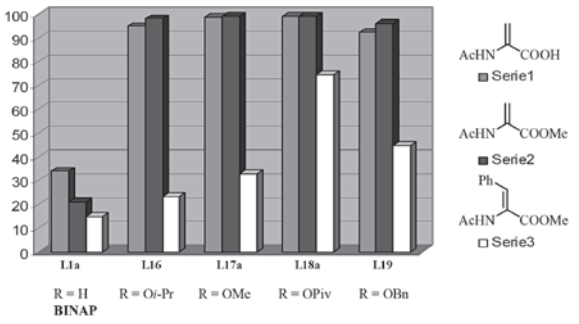



**Fig. 12. 3,3'-disubstituted atropisomeric ligands**

The efficacy of the series of Rh-catalysed of ligands **L16-19** in asymmetric hydrogenation of α-acetaminocinnamic acid, α-acetamidoacrylic acid and its methyl ester has been comprehensively studied (Graph 1).




**Graph 1. Relationship between asymmetric induction and the nature of substituents at positions 3, 3' in the model hydrogenations of enamides**

Data shown in Graph 1 clearly indicate the substantially higher efficacy of complexes of *ortho*- substituted BIPHEP or BINAP ligands compared to corresponding complexes of ligand **L1a** bearing no *ortho*- to phosphorus groups substituents.

## Conclusions

Despite the extensive number of ligands obtained up to date, not many of them have structures enabling the direct comparison of "pure" steric (or electronic) effects made on enantioselectivity of asymmetric catalysis processes mediated by their transition metal complexes. Nevertheless, comparison of presented herein data leads to some general conclusions on the role of ligand structure in the processes mentioned. They may be formulated as follows:

The dependence of the properties of the transition metal catalysts and of the level of asymmetric induction on the precise control of the geometry of the ligands forming those complexes has been explicitly confirmed [23, 24, 37]

The presence of substituents at positions 3, and particularly at positions 3, 5 in $PAr_2$ function as well as at position 3,3' of biaryl core the ligand is advantageous for asymmetric induction [28, 30].

The control of the efficiency of process of transferring chirality by means of tuning of sterical properties of the ligand is still poorly studied, nevertheless in a short time it can become an excellent tool for creation of optimal catalytic systems for new substrates and reactions.

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