Stereoselective coordination: a six-membered P,N-chelate tailored for asymmetric allylic alkylation

Zs. Császár, a G. Farkas, a A. Bényei, b Gy. Lendvay, c I. Tóth a and J. Bakos a

Six-membered chelate complexes [Pd(1a-b)Cl], (2a-b) and [Pd(1a-b)(η^5-PhCHCHCPh)][BF_4] (3a-b) of P,N-type ligands 1a, (2S, 4S)-2-diphenyl-phosphino-4-isopropylamino-pentane and 1b, (2S, 4S)-2-diphenyl-phosphino-4-methylamino-pentane have been prepared. The Pd-complexes have been characterized in solution by 1D and 2D NMR spectroscopy. The observed structures were confirmed by DFT calculations and in case of 2a also by X-ray crystallography. Unexpectedly, the coordination of the all-carbon-backbone aminophosphine 1a resulted in not only a stereospecific locking of the donor nitrogen atom into one of the two possible configurations but also the conformation of the six-membered chelate rings containing three alkyl substituents was forced into the same single chair structure showing axially placed isopropyl group on the coordinated N-atom. The stereodiscriminative complexation of 1a led to the formation of a palladium catalyst with a conformationally rigid chelate having a configurationally fixed nitrogen and electronically different coordination sites due to the presence of P and N donors. The stereochemically fixed catalyst provided excellent ee’s (up to 96%) and activities in asymmetric allylic alkylation reactions. In contrast, the chelate rings formed by 1b exist in two different chair conformations, both containing axial methyl groups, but with the opposite configurations of the coordinated N-atom. Pd complexes of 1b provided low enantioselectivities in similar alkylations, therefore emphasizing the importance of the stereoselective coordination of N-atom in analogous P-N chelates. The factors determining the coordination of the ligands were also studied with respect to the chelate ring conformation and the nitrogen configuration.

Introduction

In asymmetric synthesis, the application of transition metal catalysts containing chiral donor atoms is a fruitful approach for achieving high enantioselectivities.1 The potential of these systems is due to the ability of an efficient transfer of chirality from the catalyst to the substrate. A challenging direction of research in asymmetric synthesis is the design of new catalysts that are composed of metal-ligand assemblies with meta-stable stereochemistries, i.e. the ligand structure is held in a specific spatial arrangement solely due to metal coordination.2 In this respect, ligands with chiral backbone and with stereogenic N-donors are of great interest. However, it is important to note that the selectivity of the nitrogen coordination depends on a number of factors such as the effect of the cis halogen ligand in the square planar dihalogen complexes, the coordination properties of the solvent, the entropy connected with the fluxionality of the possible conformers or even the coordination sphere of the metal.3,4 The formation and control of a stereogenic nitrogen center that is directly attached to the metal increases the likelihood of effective stereochemical communication between the ligand and the reactive site. Furthermore, with heterobidentate aminoalkyl-phosphine (P,N) ligands the difference in trans influence between the P and N donor atoms differentiate the two binding sites electronically, making the ligand trans to the phosphorus more labile. The features listed above are important in asymmetric catalysis5, which can be sensitive for very fine stereoelectronic changes in the ligand nature. The coordination chemistry and catalytic properties of P,N-ligands with chiral all-carbon backbone and chiral nitrogen donor has been previously investigated for 5-membered chelates.5,6 However, the coordination behaviour of six-membered chelating P,N-ligands with stereogenic nitrogen has scarcely been studied and is far more complicated because of the configurational isomerism of nitrogen and the possible conformational changes associated with a C_2 symmetry six-membered ring. Previously, Chan and Spilling reported on the catalytic application of N-chiral six-membered chelating phosphinite-amine (POC_2N) and aminophosphine-amine (PNC_2N) ligands.6 In an extensive study, Petit et al. described the synthesis of chiral PNC_2N type ligands and investigated the importance of N-chirality in asymmetric catalysis.7 However, no clear interpretation of the factors influencing the stereoselective coordination via both the ring conformation and the nitrogen configuration has been available yet for such systems. Undoubtedly, through understanding of these factors, the coordination behaviour of the ligands could be regulated as a crucial part of structure tailoring in catalysis8 and even in medicinal chemistry.9

Recently, we have synthesized a new class of chiral pentane-2,4-diyll-based ligands, capable of forming six-membered chelate rings.10 Using these ligands we envisaged to unite (i) the relative conformational rigidity provided by the pentane-2,4-diyll backbone with (ii) the stereoselective coordination of the nitrogen, (iii) the electronic differentiation induced by the difference of donor groups and (iv) the modular ligand structure associated with a convenient
synthesis. We have found that Pd-complexes of ligand 1a (Figure 1) give high activities and enantioselectivities in asymmetric allylic alkylation reactions. Motivated by this observation, we have combined multinuclear 1D and 2D NMR spectroscopy, X-ray crystallography and electronic structure theory (DFT) calculations to characterize and understand the coordination and structural chemistry of the six-membered palladium chelates of ligands 1a and 1b, containing sterically larger N-isopropyl (N-iPr) and smaller N-methyl (N-Me) substituents, respectively (Figure 1). The importance of the stereoselective coordination of such N-atoms in asymmetric allylic alkylation is highlighted.

![Figure 1. Pentane-2,4-diyl based aminoalkyl phosphines](image)

**Results and discussion**

**Synthesis of Pd-complexes and their structural characterization**

**Synthesis.** Complexes 2a-b and 3a-b were prepared from suitably labile precursors to promote chelate formation according to Scheme 1. Considering the two possible nitrogen configurations and the conformations of the chelate, four chair, 12 twist-boat and 12 boat isomers can be drawn for complexes 2 (Figure 2). The widely used puckering parameters to describe the ring conformation have limited applicability in our case because of the large difference in the C-C covalent and M-P or M-N coordination bond distances.

![Scheme 1. Synthesis of complexes 2a-b and 3a-b](image)

**NMR analysis of complexes 2.** Complex 2a was investigated by $^1$H, $^1$C, $^3$P, $^31$P, $^13$C-H, $^3$P($^1$H), H-H-COSY, H-H NOESY and HMOC NMR methods using CDCl$_3$ or CD$_2$Cl$_2$ as solvents. According to the NMR data only one diastereomer can be found in solution. Cooling the sample in CD$_2$Cl$_2$ to -80 °C the $^{31}$P($^1$H) NMR spectrum still shows only a single line.

![Figure 2. Stereoisomers of 2 (R = iPr or Me, Cl ligands are omitted for clarity)](image)

In the $^1$H NMR spectrum the observed large $-34.5$ Hz couplings of $^3$J(P,H) (close to the Karplus maximum)$^{15}$ and the large geminal $^3$J(H,H) couplings ($-15.6$ Hz)$^{15}$ are only possible in a chair conformation (Figure 3). The relatively small $^3$J(P,H) couplings ($-12$ Hz) indicates an equatorial position of the Me groups next to R. The values of $^3$J(H,H) = 3.2 Hz, $^3$J(H,H) = 2.9 Hz and $^3$J(H,H) = 3.6 Hz suggest torsion angles of approximately 60° between the corresponding hydrogen atoms, while based on the coupling $^3$J(H,H) = 13.5 Hz a ca. 180° torsion angle can be assumed. Since only the $^3$J(H,H) is expected to be large and both $^3$J(H,H) and $^3$J(H,H) to be small, we can conclude that the methyl groups CH$_3$ and CH$_3$ are oriented as equatorial and axial, respectively. Other indications are provided from the strong cross peaks between the signals of isopropyl CH (P) and phenyl (Ph) protons, H$_1$ and H$_2$, H$_3$ and H$_4$ in the H-H NOESY spectrum of 2a. Moreover, it can be deduced that the iPr substituent occupies an axial position on the nitrogen atom whose configuration is thus (R). This is most obvious from the NOESY and $^1$H NMR spectra, where N-H shows a characteristic W-coupling with the equatorial methylene proton ($^3$J(H,H) = 1.3 Hz), which is only possible in an equatorial arrangement of H on N.$^{13}$ Another important cross peak appears in the NOESY spectrum between the signal of H$_1$ and H$_4$ indicating spatial vicinity for these protons, while a cross peak between the iPr protons and H$_2$ is absent. Accordingly, it can be stated that 2a is present in a single chair conformer in solution that is stabilized in an eaa conformation (Figure 3), i.e. the arrangement of ring alkyl substituents is equatorial-axial-axial moving from the phosphorus towards the nitrogen along the ligand backbone.$^{1}$

![Figure 3. Structure of 2a](image)

In contrast to 2a, compound 2b with sterically less demanding N-Me substituents exists in two isomeric forms at room temperature in a molar ratio of 1.7-2.3 to 1 depending slightly on the NMR solvent used. Moreover, the composition remained unchanged in the temperature range of 243-315 K in CDCl$_3$ or upon standing at room temperature. The major isomer is stabilized in eaa conformation that can be deduced from the H, $^1$C NMR (of the ring carbons) and NOESY H-H correlation spectra. In this case similar characteristic couplings and crosspeaks, respectively, were found to those of compound 2a. The minor isomer also adopts a chair conformation as indicated by the large ~30 Hz coupling of $^3$J(P,H)$^{15}$ and the ~15.8 Hz geminal $^3$J(H,H) coupling (Figure 4). Furthermore, the J(P-C) coupling constants of the minor isomer in the $^1$C NMR spectrum are similar to those of the major complex, except $^3$J(P-C-ethyl) as expected. The observed $^3$J(P,H) coupling of 16.2 Hz is typical for an axial Me next to P.$^{15}$ In the NOESY spectrum of the minor complex, cross peaks appear between the signals of H$_1$ and H$_4$, H$_3$ protons and H$_1$. The vicinity of N-Me group causes a large upfield chemical shift of the equatorial Me-group (H$_3$) in the $^1$H NMR spectrum. These together with the observed characteristic W-coupling between H$_1$ and H$_4$ on the H NMR spectrum clearly prove that the Me substituent on the nitrogen atom occupies an axial position, whose configuration is thus (S). As a consequence, it can be stated the minor 2b isomer exists in eae conformation (Figure 4).$^{1}$
Figure 4. The observed conformers of 2b

X-ray characterization of 2a. X-ray structure analysis of a single crystal grown by slow evaporation of the solvent from the solution of 2a in acetone confirms in all respects the structural data deduced from the NMR spectra. The coordination sphere of the complex has the usual distorted square planar geometry (Figure 5).‡ The Pd–Cl bond length trans to phosphorus (2.371(3) Å) is somewhat longer than that trans to the nitrogen (2.295(3) Å) reflecting the larger trans influence of the phosphine compared to the amine. Furthermore, a weak H-bond type interaction between the equatorially disposed NH and the cis chloride can further stabilize the conformation of the complex.

Figure 5. X-ray structure (ORTEP view at 50% probability level) of 2a

DFT analysis for complexes 2a-b. In order to gain deeper insight into the thermodynamic stability of the possible chair conformations, density functional theory geometry optimizations were performed for complexes 2 using the CAM-B3LYP functional combination with the SDD basis set and pseudopotential for Pd as well as the 6-31G* basis set for the rest of the atoms. The enthalpy differences between the chair conformers are shown in Diagram 1. From the four possible stereoisomers of 2a shown in Figure 2, the lowest-energy species is identical to the one observed experimentally both in solid and solution phases. The DFT calculations show that the enthalpy of the chelates containing the N-iPr group in axial position (eaa and aea) is lower (0 and 8 kJ/mol) compared to those of the equatorial derivatives (28 and 47 kJ/mol). The reason for the preference of the somewhat unexpected axial position of the N-iPr group is the smaller 1,2 inter-ligand interaction with the cis ligand (in this case a Cl atom) in the lower-energy species than in the others (Diagram 1).‡

In compound 2b the isomers with equatorial N-Me substituent also constitutes higher energy species (eae and aea isomers). However, in the case of complex 2b the theoretical calculations forecast that both the eae and aea (Diagram 1, 0 and -2 kJ/mol relative enthalpies, respectively) structures can form, where the N-substituent is in axial position (Figure 2). The formation of chelates containing only axial N-substituents underline the significance of 1,2 inter-ligand interactions in the complex formation processes.

Diagram 1. Calculated relative enthalpies of the chair structures of 2

To substantiate this assumption we performed further DFT studies by removing the Cl substituents from 2a. Indeed, the relative enthalpy difference (ΔH°) between the eaa and eae conformations in this case is ca. 2 kJ/mol, much smaller than 28 kJ/mol found in the dichloro complex. The DFT calculations also provide information on the preference of the eaa vs. the aea conformer in 2a. In the aea conformer the torsion angle between the iPr and the adjacent ring Me group is approximately 60° (Figure 6). The steric interaction between the synclinal Me and iPr groups in this conformation is supposed to be significant. In addition, the isopropyl CH points toward the axial Ph placing the iPr methyl group in the close proximity of the backbone methyl substituent that increases the steric strain further between the two alkyl groups. In contrast to this, such interaction does not occur in the eaa conformer with antiparallel alkyl substituents. In order to support this explanation, we performed DFT studies on the ae and aa diastereomers of 1-isopropyl-2-methyloclohexane as a simple model. The enthalpy of the aa isomer with anti-positioned 1,2-substituents is approximately 8 kJ/mol lower than that of the ae structure. However, in the case of 1,2-dimethyloclohexane as a model compound for 2b, the DFT calculations showed that the diaxial isomer is ca. 5 kJ/mol less stable than the ea structure. Therefore, in the aea isomer of 2b the steric strain between the two Me groups in synclinal position is not remarkable compared to that in 2a. These observations clearly prove the fundamental role of the N-substituents in determining the stereocontrol in the complex formation.

Figure 6. Newman projections of eaa and aea isomers

Analysis of complexes 3a-b. The ¹H and ³¹P(¹H) NMR spectra of the substrate complex 3a (Figure 7) revealed two isomers at room temperature with a molar ratio of 4-7 to 1 depending moderately and reproducibly on the NMR solvent used. Furthermore, the composition remained the same in d₈-acetone cooling down to 193 K or upon standing at room temperature in each of the solvents. The ratio of major isomer was the highest in d₆-acetone and the lowest in CD₂Cl₂ by using these solvents and CDCl₃. The structure analysis of 3a by ¹H, ¹H-¹H COSY and NOESY techniques proved that the chelate ring also adopts eaa conformation both in the major and minor isomers: similar ³¹P/H, ³¹P(H) and ³¹J(H,H) couplings appear in the appropriate protons as in complex 2a. The major and
minor isomers are assigned to the exo and endo complexes that can be evidenced by referring to analogies with $^1$H chemical shifts from earlier studies or by the observed inter-ligand cross peaks in the $^1$H-$^1$H NOESY spectrum. These cross peaks appear, for example, between H and H in the endo and between H and H in the exo isomer (Figure 7). The formation of the theoretically possible syn-anti isomers can be excluded, since in both species H and H cross peaks appear as an evidence for the syn-syn geometry.† In accordance with the structure of 3a in solution, DFT calculations also proved that the exo isomer is the lower energy species.‡ As it was surmised for Pd-diphenylallyl complexes of phosphino-oxazoline (PHOX) ligands, the preference of the exo isomer over the endo originates from the face positioned equatorial P-Ph group which repels the substituent at C atom of the allyl group. In our case the same inter-ligand interaction could be proposed as a dominating factor determining the coordination mode of the allylic moiety.

![Figure 7. Endo and exo isomers of 3a: quadrant diagram for $^\eta$-diphenylallyl complexes; hydrogen is the small group (S), the iPr and the axial, edge positioned Ph are considered medium groups (M), and the equatorial Ph with face position is considered large (L).](image)

In contrast to that, complex 3b exhibits four isomers in solution in a molar ratio of 2.6/1.6/1.5/6 according to the $^1$H and $^{31}$P NMR signals in CD$_2$Cl$_2$ at room temperature. In other words the number of the complex species is doubled compared to that in the dichloro complex 2b (~2:1 isomeric molar ratio). Therefore, it is reasonable to assume that the four isomeric complex species can be assigned as the endo and exo isomers of both the eea and aea chelate conformers.

![Figure 8. Possible isomeric species of 3b: the more abundant and more reactive exo isomers of eea and aea conformations have the opposite selectivities](image)

Catalytic studies

Ligand 1a and 1b were tested in the palladium-catalyzed asymmetric allylic alkylation of benchmark substrates (4a-e) by using several nucleophiles (Scheme 2).

The catalyst modified by 1a provided excellent activities and ees (Table 1). The reactions completed in 1 h in each case at a substrate/catalyst molar ratio of 100. The best enantioselectivity (96%) was obtained by using acetylacetone as nucleophile. The products of the reactions had predominantly ($R$) configuration. This product distribution suggests that the major product enantiomer is formed upon the nucleophilic attack on the allylic termini trans to the phosphorus in the exo isomer or trans to the nitrogen in the endo species (Figure 7). Based on our results and other studies on Pd-P,N systems, it can be stated that stereochemically, the Pd-allyl terminus opposite to the more powerful acceptor atom (phosphorus) will be more susceptible to cleavage as a result of nucleophilic attack. Accordingly, it seems to be obvious that the nucleophile attacks preferentially the allylic carbon trans to the phosphorus in the exo isomer.

![Scheme 2. Asymmetric allylic alkylation by using ligand 1a](image)

The advantage of the stereoselective coordination of N in asymmetric allylic alkylation was clearly proven by using ligand 1b instead of 1a. The reaction of substrate 4a with malonate nucleophiles resulted in low enantioselectivities (up to 30%, Table 1, entries 7-9). It can be explained by the presence of four substrate complex isomers enhancing the number of competitive catalytic pathways. Based on the assumptions that the coordination mode of the allylic moiety is governed by the same interactions as in 3a and that the reaction occurs with a preferential trans-to-P nucleophilic attack of the exo isomer, it is evident that the eea conformation results in the formation of ($R$) prevailing enantiomer in contrast to aea that provides the product with ($S$)-selectivity (Figure 8). Indeed, the observed low enantioselectivity is the result of at least two competing reaction pathways. Since the number and ratio of the possible chelate conformers is strongly affected by the nature of the nitrogen substituent it can be concluded that both the stereoselective coordination of the nitrogen and the ring conformation are responsible for the high exoendo ratio that have a profound effect (Table 1) on the enantioselectivity in asymmetric allylation reactions.

The role of the ligand/palladium molar ratio was also investigated as an important factor for influencing enantioselectivity. Gradually increasing the ratio of 1a to Pd from 1 to 6 in the reaction of diphenylallyl acetate with dimethyl malonate, the enantioselectivity steadily decreases from a value of 94% to 56%. This observation can be explained by the formation of a bis-P-ligand complex in the presence of an excess amount of ligand and thus in the absence of a chelate with stereogenic nitrogen, which causes a decline in enantioselectivity.
Reaction conditions: catalyst prepared in situ from 0.5 mol% of \([\text{Pd}^{0}] - \text{C}_8\text{H}_8\text{PdCl}_2\) and 1 mol% of chiral ligand; substrate 1.25 mmol; solvent 10 mL of CH\(_2\text{Cl}_2\); KOAc 7 mg; temperature RT; reaction time 1 h. The conversion was complete in each case. Prevaling configuration of the products: (R). *Conversion is 70%.

### Experimental

#### General experimental details
All manipulations were carried out under argon using Schlenk techniques. Solvents were purified, dried and deoxygenated by standard methods. Compounds 1a and 1b,\(^{10}\) [Pd(COD)Cl]\(_2\)\(^{11}\) and [PdPhCH2CH2PPh]\(_2\)\(^{12}\) were prepared according to literature methods. All other starting materials were purchased from Sigma Aldrich. \(^{31}\)P NMR, \(^{1}H\)-NMR and \(^{13}C\)-NMR spectra including \(^{1}H\) COSY and NOESY measurements were recorded on a BRUKER Avance 400 spectrometer (NMR Laboratory, University of Pannonia) operating at 161.98, 100.61 and 400.13 MHz respectively. \(^{1}H\) couplings were determined by using the CAM-B3LYP functional combination with the SDD basis set and potential overlap for \(^{1}H\) as well as the 6-31G** basis set for the rest of the atoms.

### Synthesis and characterization of complex 2a
Ligand 1a (109 mg, 0.3502 mmol) dissolved in CH\(_2\text{Cl}_2\) (5 mL) was added dropwise to a solution of [Pd(COD)Cl]\(_2\) (100 mg, 0.3502 mmol) in CH\(_2\text{Cl}_2\) (5 mL).

The resulting orange solution was stirred for 20 min, filtered through a short pad of celite and concentrated to ca. 2 mL. The solution was then treated with ether (10 mL) to precipitate an orange powder that was filtered and washed with ether (5 mL) to give 140 mg of 2a.

#### Yield: 87%. mp 202-205 °C. \(e_{\text{ea}}\) (major isomer) of 2b: \(^{1}H\) NMR (400 MHz, CD\(_2\text{Cl}_2\)): \(\delta = 8.21-7.32\) (m, 10H, aromatic, overlapped with the aromatic signals of the \(e_{\text{ea}}\) isomer), 4.59 (br s, 1H, H\(_e\)), 3.43 (3H, s, CH\(_3\)), 2.38 (3H, s, CH\(_3\)).

### Synthesis and characterization of complex 3a
Ligand 1a (63.4 mg, 0.2022 mmol) dissolved in CH\(_2\text{Cl}_2\) (5 mL) was added dropwise to a suspension of [Pd(n\(\text{Bu}_{2}\))\text{PCH2CH2PPh}2] (67.8 mg, 0.1011 mmol) in CH\(_2\text{Cl}_2\) (5 mL).

The resulting orange solution was stirred for 20 min and then AgBF\(_4\) (39.4 mg, 0.2022 mmol) was added. The reaction mixture was stirred for 1 h, filtered through a sort pad of celite and concentrated to ca. 2 mL. The solution was then treated with ether (10 mL) to precipitate an orange powder that was filtered and washed with ether (5 mL) to give 0.127 mg of 3a.

**Table 1.** Asymmetric allylic alkylation by using ligand 1a and 1b

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### Synthesis and characterization of 2b. Ligand 1b (90 mg, 0.3502 mmol) dissolved in CH\(_2\text{Cl}_2\) (5 mL) was added dropwise to a solution of [Pd(COD)Cl]\(_2\) (100 mg, 0.3502 mmol) in CH\(_2\text{Cl}_2\) (5 mL).

The resulting orange solution was stirred for 20 min, filtered through a sort pad of celite and concentrated to ca. 2 mL. The solution was then treated with ether (10 mL) to precipitate an orange powder that was filtered and washed with ether (5 mL) to give 140 mg of 2b.

Yield: 87%. mp 202-205 °C. \(e_{\text{ea}}\) (major isomer) of 2b: \(^{1}H\) NMR (400 MHz, CD\(_2\text{Cl}_2\)): \(\delta = 8.21-7.32\) (m, 10H, aromatic, overlapped with the aromatic signals of the \(e_{\text{ea}}\) isomer), 4.59 (br s, 1H, H\(_e\)), 3.43 (3H, s, CH\(_3\)), 2.38 (3H, s, CH\(_3\)).

### Synthesis and characterization of 3a
Ligand 1a (63.4 mg, 0.2022 mmol) dissolved in CH\(_2\text{Cl}_2\) (5 mL) was added dropwise to a suspension of [Pd(n\(\text{Bu}_{2}\))\text{PCH2CH2PPh}2] (67.8 mg, 0.1011 mmol) in CH\(_2\text{Cl}_2\) (5 mL).

The resulting orange solution was stirred for 20 min and then AgBF\(_4\) (39.4 mg, 0.2022 mmol) was added. The reaction mixture was stirred for 1 h, filtered through a sort pad of celite and concentrated to ca. 2 mL. The solution was then treated with ether (10 mL) to precipitate an orange powder that was filtered and washed with ether (5 mL) to give 0.127 mg of 3a. Yield: 87%. mp 101-105 °C. \(^{1}H\) NMR (400 MHz, CD\(_2\text{Cl}_2\)): \(\delta = 7.73-6.75\) (m (partly overlaps with the analogous endo signal), 20H, aromatic), 6.58 (dd (overlap with the analogous endo signal), 2H), 7.9 (dd, 3J(H\(_h\), H\(_p\)) = 11.1 Hz, 3J(H\(_h\), H\(_m\)) = 13.5 Hz, 1H, H\(_f\)), 5.64 (dd, 3J(P,H\(_f\)) = 7.9 Hz, 3J(H\(_h\), H\(_m\)) = 11.1 Hz, 1H, H\(_f\)).
In conclusion, we have shown that a modular P,N ligand based on the chiral pentane-2,4-diylic backbone with a stereogenic nitrogen atom reacts with palladium(I)-complexes to form a conformationally and configurationally stable species. The chelate rings of 1a in complexes with Pd are stabilized in the same single chair structure displaying the alkyl substituents in equatorial-axial-axial (eaa) positions, moving from the phosphorus to the nitrogen along the ligand backbone. In contrast, complexes of ligand 1b were observed in two chelate conformations showing the alkyl substituents both in equatorial-axial-axial (eaa) and in axial-equatorial-axial positions.

**Synthesis and characterization of complex 3b.**

Ligand 1b (57.7 mg, 0.2022 mmol) dissolved in CHCl₃ (5 mL) was added dropwise to a suspension of [Pd(η⁵-C₅H₅)Cl]₂ (67.8 mg, 0.1011 mmol) in CHCl₃ (5 mL). The resulting orange solution was stirred for 20 min and then AgBF₄ (39.4 mg, 0.2022 mmol) was added. The reaction mixture was stirred for 1 h, filtered through a sorbent pad of celite and concentrated to ca. 2 mL. The solution was then treated with ether (10 mL) to precipitate an orange powder that was filtered and washed with ether (5 mL) to give 125 mg of 3b. Yield: 92%. mp. 92-95 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.02-6.70 (m, aromatic protons for the four isomers), 6.6-6.5 (m, internal allylic protons for the four isomers, overlapped), 5.87 (dd, J(P,H) = 12.9 Hz, J(H,H) = 9.1 Hz, terminal allylic H trans to P for one isomer), 5.53 (dd, J(P,H) = 13.0 Hz, J(H,P) = 8.0 Hz, terminal allylic H trans to P for one isomer), 5.41 (dd, J(P,H) = 15.1 Hz, J(H,P) = 8.0 Hz, terminal allylic proton trans to P for one isomer, overlapped), 5.40 (dd, J(P,H) = 11.9 Hz, J(H,P) = 9.6 Hz terminal allylic proton trans to P for one isomer, overlapped), 4.95 (dd, J(H,H) = 12.0 Hz, terminal allylic proton trans to N for one isomer), 4.70 (dd, J(H,H) = 11.9 Hz, terminal allylic proton trans to N for one isomer), 4.32 (dd, J(H,H) = 11.2 Hz, terminal allylic proton trans to N for one isomer), 3.71-0.91 (m, aliphatic protons for the four isomers). (Three of the N-Methyl signals can be tentatively assigned: 2.65 (d, J = 6.2 Hz, for one isomer), 2.12 (d, J = 6.4 Hz, for one isomer), 2.00 (d, J = 6.2 Hz, for one isomer).) ³¹P NMR (162 MHz, CDCl₃): δ = 27.28 (s), 24.1 % P; 26.52 (s), 14.8 % P; 26.17 (s), 9.2 % P; 25.30 (s), 51.9 % P. ESI mass spectrum: m/z 585.6 [MH – BF₄]¹, 299.0 [M – 1b – BF₄]¹, 299.1 [M – 1b – BF₄]¹, IR (KBr, cm⁻¹): 524, 637, 693, 755, 1030, 1149, 1261, 1437, 1462, 1490, 2868, 2929, 2958, 3048, 3230 (s, v(NH)).

**Catalytic experiments.** A degassed solution of [Pd(η⁵-C₅H₅)Cl]₂ (2.28 mg, 0.00625 mmol) and ligand 1a or 1b (0.0125 mmol in the case of 1/1 Pd/ligand molar ratio) in the corresponding solvent (10 mL) was stirred for 30 min, then the substrate (1.25 mmol) was added and the solution was stirred for a further 15 min. Subsequently, the nucloephile (3.75 mmol), potassium acetate (7 mg) and NaO-bis(trimethylisilyl)-acetamide (0.91 mL, 3.75 mmol) were added and the reaction mixture was stirred at room temperature. After being stirred, it was diluted with ether (10 mL) and a saturated aqueous solution of NH₄Cl was added. The mixture was extracted with ether (3x10 mL) and the extract dried over MgSO₄. The solution was then passed through a short pad of silica and was eluted with ether. The solvent was then evaporated and the residue dissolved in a mixture of n-hexane/2-propanol. The enantioselectivity and the conversion were determined by chiral HPLC (Column: Kromasil 3-AmyCoat, 4.6x150 mm). Retention times for the enantiomers of alligation products: (E)-dimethyl 2-(1,3-diphenylallyl)malonate (eluent: n-hexane-2-propanol 85/15 flow rate: 0.5 mL/min; λ: 254 nm) 10.6 and 13.7 min; (E)-diethyl 2-(1,3-diphenylallyl)malonate (eluent: n-hexane-2-propanol 85/15 flow rate: 0.5 mL/min; λ: 254 nm) 8.4 and 10.4 min; (E)-dibenzy l2-(1,3-diphenylallyl)malonate (eluent: n-hexane-2-propanol 85/15 flow rate: 0.5 mL/min; λ: 254 nm) 16.2 and 19.7 min; (E)-3-(1,3-diphenylallyl)pentane-2,4-dione (eluent: n-hexane-2-propanol 95/5 flow rate: 0.5 mL/min; λ: 254 nm) 12.5 and 13.2 min; (E)-dimethyl 2-(4-hydroxyphenyl)allylmalonate (eluent: n-hexane-2-propanol 85/15 flow rate: 0.5 mL/min; λ: 254 nm) 23.3 and 39.6 min.

**Conclusions.**

In conclusion, we have shown that a modular P,N ligand based on a chiral pentane-2,4-diylic backbone with a stereogenic nitrogen atom reacts with palladium(I)-complexes to form a conformationally and configurationally stable species. The chelate rings of 1a in complexes with Pd are stabilized in the same single chair structure displaying the alkyl substituents in equatorial-axial-axial (eaa) positions, moving from the phosphorus to the nitrogen along the ligand backbone. In contrast, complexes of ligand 1b were observed in two chelate conformations showing the alkyl substituents both in equatorial-axial-axial (eaa) and in axial-equatorial-axial positions.
Notes and references

† X-Ray structural analysis: M = 490.70, orthorhombic, a = 10.8906 (3), b = 1.9745 (3), c = 16.810 (8), A = 2175.36 (13) Å, T = 293 K, space group P212121 (no.19), Z = 4, 2294 reflections measured. The final wR(F2) was 0.112 (all data).


18 According to the 13C NMR spectrum of complex 3a, the carbon trans to the P is more eletrophilic than that trans to N. X-ray structures and DFT geometry optimizations proved that Cl-Pd or C-Pd bonds are longer trans to the P compared to that trans to N.
These observations confirm the hypothesis that the bond trans-to-P is the more susceptible to be cleaved by the nucleophile.


