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# Synthesis and resolution of benzylisopropylphenylphosphine, a monodentate P-chiral ligand

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**Abstract**

The synthesis of benzylisopropylphenylphosphine by reaction between the benzylphenylphosphide anion and isopropyl chloride and its subsequent resolution by means of an optically active palladium metallacycle is reported. The synthesis of the organometallic complex [Pd($\eta^3$-2-Me$C_3H_4$)Cl(PBn$^i$PrPh)] is also described, as well as the assignment of the absolute configuration of the coordinated phosphine by mono- and bidimensional proton NMR spectra, using the homochiral palladacycle as a reference point. In order to estimate the height of the energy barrier corresponding to the rotation of the phosphine ligand around the Pd–P bond, several calculations were performed at the semiempirical PM3(tm) level. 

## 1. Introduction

Transition metal complexes with chiral phosphines are used as catalysts in asymmetric synthesis.[1] Among the many chiral phosphines developed for application in asymmetric catalysis, monodentate ligands possessing a stereogenic phosphorus atom are rare, even though asymmetric induction is expected to be improved if the stereogenic center is close to the metal atom in the catalyst.[2]

The asymmetric synthesis of some P-chiral phosphines, $PR^1R^2R^3$, by using borane compounds,[3] via dynamic resolution of racemic *tert*-butylphenylphosphine with (–)-sparteine[4] or by using cyclometallated derivatives,[5] has recently been published. The resolution of *tert*-butylphenyl(4-bromophenyl)phosphine[6] and benzylcyclohexylphenylphosphine[7] has also been reported. The use of P-chiral aminophosphine phosphinite ligands for the asymmetric hydrogenation or hydroformylation reactions has recently been described.[8] The catalytic results showed the predominance of the P-center chirality over the carbon backbone effect.

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Following our work on the synthesis and resolution of chiral phosphines,[7,9] we describe here the synthesis of benzylisopropylphenylphosphine, its resolution by palladium metallacycles, and the assignment of its absolute configuration by mono- and bidimensional proton NMR spectra.

## 2. Results and discussion

To the best of our knowledge, there is only one report on the synthesis of benzylisopropylphenylphosphine. This is a preliminary communication without characterization data, in which the authors describe the synthesis, with an enantiomeric excess of 20%, by reaction of $^{i}$PrLi with the phosphinite P(OCin)BnPh, where HOCin is the resolving agent cinchonine. This phosphinite was previously obtained from PClBnPh and HOCin.[10]

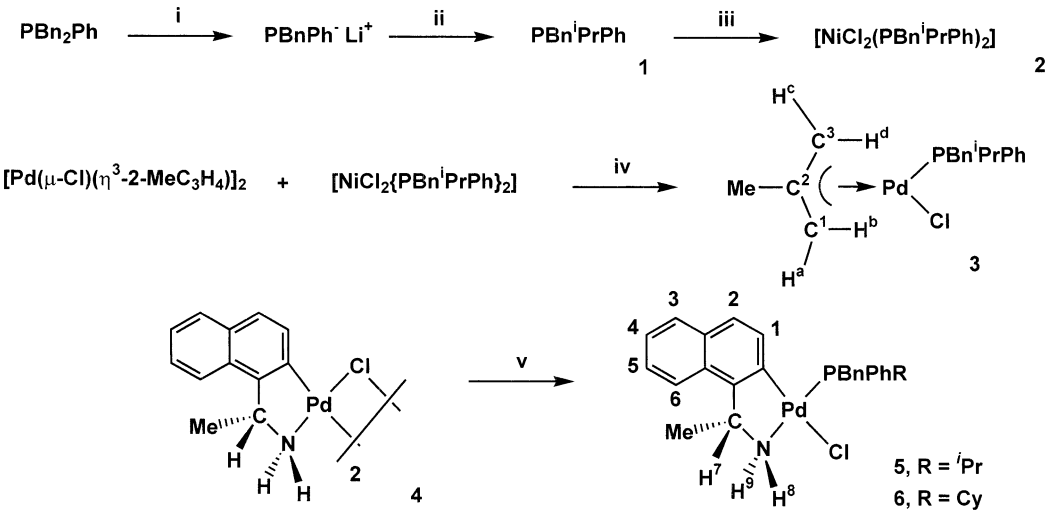
van Doorn has published a study about the reductive cleavage of carbon–phosphorus bonds with alkali metals and he reports that the cleavage of one P–$CH_2$Ph bond of $PBn_2Ph$ is selective if Li/THF is used. In contrast, the use of other reagents such as $Na/NH_3$ causes the cleavage of both benzyl groups.[11] Bearing these results in mind and following the published methodology for the synthesis of PBnCyPh,[7] we have synthesized benzylisopropylphenylphosphine. After stirring a mixture of dibenzylphenylphosphine and lithium metal in THF under a dry nitrogen atmosphere at room temperature for 20 h, complete cleavage of one of the P–$CH_2$ bonds of the dibenzylphenylphosphine was accomplished, with the formation of the benzylphenylphosphide anion. The $^{31}$P NMR spectrum, under nitrogen, illustrated the formation of this anion ($\delta = -37.1$ ppm) and was used to monitor the progress of the reaction. Isopropyl chloride was added after removing the excess lithium, affording the racemic (±)-benzylisopropylphenylphosphine. Then a saturated solution of $NiCl_2$ in absolute ethanol was added, and the resulting solution was stirred for 15 min and concentrated in vacuo to give dark red crystals of the paramagnetic complex dichlorobis[(±)-benzylisopropylphenylphosphine]nickel(II).

Benzylisopropylphenylphosphine is easily oxidized in air, but it can be stored for months as a nickel complex. Moreover, the addition of a few drops of water to an organic solution of the nickel complex affords the free phosphine. This strategy is also a way for the purification of this ligand. This methodology was followed for the synthesis of the complex [Pd($\eta^3$-2-Me$C_3H_4$)Cl-{(±)-PBn$^{i}$PrPh)}]. The addition of a few drops of water to a THF solution of [$NiCl_2$(PBn$^{i}$PrPh)$_2$] caused the decoordination of the phosphine. Then, the organic phase was separated and dried and the addition of [Pd(μ-Cl)($\eta^3$-2-Me$C_3H_4$)]$_2$ led to the formation of **3**, which was precipitated in *n*-pentane. NMR data show that **3** occurs in two diastereomeric forms in a 5/4 ratio. Proton NMR data of the allylic group were assigned by comparison with literature values.[12] Unusually high field shifts of $H^c$ and $H^d$ were observed, showing that these protons are in close proximity to aromatic phosphine rings.

*ortho*-Palladated derivatives of optically active N-donor ligands are good resolving agents for Lewis bases.[13] The enantiomerically pure cyclopalladated dinuclear compound **4** was obtained from the optically active amine as reported.[9b] Reaction of dimer **4** with the phosphine afforded the mononuclear complex [PdCl(C–N)(PBn$^{i}$PrPh)] **5** as a 1/1 mixture of diastereomers. The high field shift of the aromatic protons of the metallated group in **5** due to the aromatic rings of the phosphine indicates the *cis* disposition of the phosphorus relative to the metallated carbon atom. The chemical shift of the phosphorus confirms this arrangement,[14] which is usual in cyclopalladated compounds containing phosphines.[15]

Compound **5** (200 mg) was eluted at room temperature in a $SiO_2$ column with $CHCl_3$–acetone (100/3) as eluent. The fractions eluted (15 mL) were concentrated in vacuo and checked by $^1H$ NMR spectroscopy. The fractions of the enantiomerically pure compound (by 200 MHz $^1H$ NMR spectroscopy) were selected using $H^1$ and $H^2$ proton signals. The first diastereomer eluted **5′** was obtained in 54% yield (54 mg), with a *d.e.* higher than 95%, and the second diastereomer **5″** was obtained in 52% yield with 77% *d.e.*

The efficiency of cyclopalladated compounds derived from 1-(1-naphthyl)ethylamine as resolving agents has been related to the locked asymmetric envelope conformation of the metallacycle, due to the fact that the methyl substituent of the stereogenic carbon atom adopts an axial disposition to avoid the unfavorable interaction with $H^6$ (see Scheme 1).[16] The NOESY spectra of both diastereomers of **5** showed that the methinic proton of the chiral carbon atom $H^7$ had strong negative off-diagonal peaks with $H^6$ and $H^8$ and, in contrast, the methyl protons of the chiral carbon atom presented only strong NOE interaction with $H^9$ and $H^7$. These data confirmed the axial disposition of this methyl group and the equatorial disposition of $H^7$ in these complexes.[17]




Scheme 1. (i) Li, THF, room temperature, 20 h; (ii) isopropyl chloride, THF, 0°C, 10 min; (iii) $NiCl_2$, THF/EtOH, room temperature, 15 min; (iv) THF, $D_2O$, room temperature, 30 min; (v) $[NiCl_2L_2]$ (L = (PBnRPh), THF, room temperature, 45 min

It has been demonstrated that NOE techniques[16b,17,18] or the NMR chemical shift regularities[19] can be used to determine the absolute configurations of coordinated chiral diphosphines. Dunina et al.[6] have recently extended these studies to the monodentate P-chiral ligand *tert*-butylphenyl(4-bromophenyl)phosphine. These authors have shown that it is possible to assign the absolute configuration of this phosphine by NMR techniques using the homochiral palladacycle as a reference point.

We have re-examined the NMR data of diastereomers ($R_C$,$S_P$) and ($R_C$,$R_P$) of the cyclopalladated complex **6**, containing coordinated benzylcyclohexylphenylphosphine (see Scheme 1), in order to check the possibility of assigning, by NMR techniques, the absolute configuration of phosphorus in monodentate ligands PBnRPh, coordinated to optically active cyclopalladated compounds. The absolute configuration of both diastereomers of complex **6** is known, as well as the crystal structure of the compound ($R_C$,$S_P$)-[PdCl($C_6H_4$CHMeN$Me_2$)(PBnCyPh)].[7] The crys-

tal structure of this complex shows the benzyl substituent of the phosphine widely separated from the metallacycle and on the opposite side of the coordination plane in relation to the methyl group of the chiral carbon atom. In addition, the cyclohexyl group of the phosphine is oriented towards the chloro ligand and the phenyl group is located in the proximity of the metallacycle (see Fig. 1).

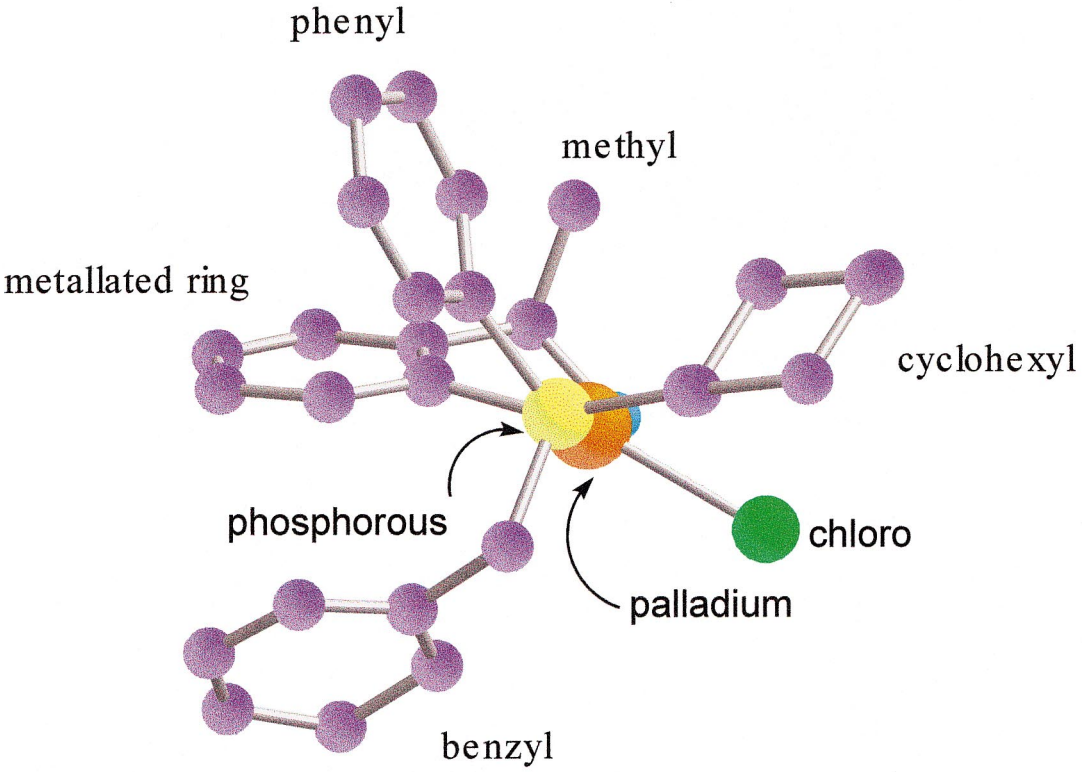



Figure 1. Structure of ($R_C$,$S_P$)-[PdCl($C_6H_4$CHMeNMe$_2$)(PBnCyPh)]

The NOESY spectrum of ($R_C$,$S_P$)-**6**, in $CDCl_3$ solution, showed that the $H^1$ proton only presented strong NOE interaction with the protons of the phosphine phenyl group ($\delta = 7.55$ ppm). In contrast the NOESY spectrum of the diastereomer ($R_C$,$R_P$)-**6**, in $CDCl_3$ solution, showed that the $H^1$ proton of this diastereomer only presented strong NOE interaction with two of the cyclohexyl protons ($\delta = 2.18$ and 1.66 ppm). It should also be noted that in no case was NOE interaction between the benzylic protons of the phosphine and the protons of the metallated ring observed. All these results show that the rotation around the Pd–P bond is rather restricted in these complexes, and that the structure of the main conformomer in solution is similar to the structure determined by X-ray diffraction of ($R_C$,$S_P$)-[PdCl($C_6H_4$CHMeNMe$_2$)(PBnCyPh)]. It is reasonable to assume that, in both diastereomers, the benzyl group is separated from the metallacycle and it is located on the opposite side of the coordination plane in relation to the methyl group of the chiral carbon atom, and the difference between the two diastereomers would be the exchange of the positions of cyclohexyl and phenyl groups. As a consequence, the NOESY spectra of such cyclometallated derivatives allow the absolute configuration of the phosphine to be revealed. Furthermore, the chemical shift of the $H^1$ proton can also be used to propose the absolute configuration of the phosphine. In the NMR

spectrum of the ($R_C$,$S_P$)-diastereomer the signal of this proton is high field shifted (it appears at $\delta = 6.05$ ppm) in relation to the signal of this proton in the ($R_C$,$R_P$)-diastereomer ($\delta = 6.48$ ppm), as a consequence of the proximity of the phenyl group of the phosphine to the metallated ring.[6]

It is reasonable to assume that in diastereomers **5**, containing the benzylisopropylphenylphosphine, the benzyl group is also placed away from the metallacycle in the major conformer and that the most significant difference between the two diastereomers is the relative positions of the isopropyl and phenyl groups. The NOESY spectrum of the first diastereomer eluted **5′**, in $CDCl_3$ solution, showed that the $H^1$ proton only presented strong NOE interaction with the protons of one of the methyl groups of the isopropyl fragment ($\delta = 1.35$ ppm). The NOESY spectrum of the second diastereomer eluted **5″**, in $CDCl_3$ solution, showed that the $H^1$ proton only presented strong NOE interaction with the *ortho*-phenyl protons of the phosphine ($\delta = 7.30$ ppm), and in none of the diastereomers was NOE interaction between the benzylic protons of the phosphine and the protons of the metallated ring observed. These data suggest the *R* and *S* configurations for the phosphorus atom in the diastereomers **5′** and **5″**, respectively. The high field shift of the signal of the metallated ring proton $H^1$ in the diastereomer **5″** ($\delta = 6.02$ ppm) in relation to the signal of this proton in the diastereomer **5′** ($\delta = 6.50$ ppm) also agrees with the ($R_C$,$S_P$) configuration proposed for **5″**.

In order to estimate the height of the energy barrier corresponding to the rotation of the phosphine ligand around the Pd–P bond, several calculations were performed on compound ($R_C$,$S_P$)-**6** at the semiempirical PM3(tm) level. The dihedral angle $C_{met}$–Pd–P–$C_{Ph}$ was increased in 18° steps, for one complete rotation. One of the features of the PM3(tm) method is the trend to overestimate the interactions between the metal and hydrogen atoms when the former has a square-planar environment, thus giving rise to artificial geometry minima.[20] This effect is especially strong when the initial geometry is far from the equilibrium, as in the case of conformational search. For this reason, no geometric optimization has been made. However, for each value of the dihedral angle, a systematic conformer search was performed, rotating each of the P–C bonds in increments of 120°. For the remaining parameters the experimental values corresponding to the X-ray diffraction have been used. Only the most stable of the 27 conformations corresponding to each value of the dihedral angle have been taken into account. According to the calculations, the most stable conformation corresponds to that determined experimentally in the solid state. The height of the barrier — taken as the difference in heat of formation between the minimum and the maximum energy systems — is 39.5 kcal/mol, which is too high to allow for a free rotation of the phosphine at room temperature. All these results confirm the information obtained in solution by means of NMR.

## 3. Experimental

$^1H$ NMR at 200 MHz were recorded on a Varian Gemini 200 spectrometer and $^1H$ NMR at 500 MHz, $^{13}C$ at 75.42 MHz and $^{31}P\{^1H\}$ at 101.26 MHz were recorded, respectively, on a Varian VXR 500, a Varian 300 and a Bruker DRX 250 spectrometers. Chemical shifts (in ppm) were measured relative to $SiMe_4$ for $^1H$ and to 85% $H_3PO_4$ for $^{31}P$. Microanalyses were performed at the Institut de Química Bio-Orgànica de Barcelona and at the Serveis Científico-Tècnics de la Universitat de Barcelona. Infrared spectra were recorded as KBr disks on a Nicolet 520 FT-IR spectrometer. The optical rotations of the complexes were determined in $CHCl_3$ at 20°C using a Perkin–Elmer 241-MC polarimeter. Mass spectra were recorded on a Fisons

VG-Quattro spectrometer. The samples were introduced in a matrix of 2-nitrobenzyl alcohol for FAB analysis and then subjected to bombardment with cesium atoms.

### 3.1. Materials and synthesis

All the reactions involving free phosphines were carried out using Schlenk techniques under a nitrogen atmosphere. All solvents were dried and degassed by standard methods. Tetrahydrofuran and toluene were distilled over sodium–benzophenone, under nitrogen, before use. All chemicals were of commercial grade and used as received. $PBn_2Ph$ and compounds **4** and **6** were prepared according to procedures described elsewhere.[7,9b,21]

#### 3.1.1. Synthesis of (±)-benzylisopropylphenylphosphine, *1*

Small pieces of lithium (0.080 g, 11.53 mmol) were added to a solution of dibenzylphenylphosphine (1.4 g, 4.82 mmol) in THF (30 mL), and the reaction mixture was stirred for 20 h at room temperature. The excess of lithium was removed by decantation, the solution was cooled to 0°C and isopropyl chloride (0.45 mL, 5.11 mmol) was added and the mixture was stirred for 10 minutes. Afterwards the reaction mixture was warmed to room temperature and was stirred for a further 5 minutes. The resulting solution was cooled again to 0°C and was washed twice with 10 mL of an aqueous solution of ammonium chloride (15%), the organic layer was dried over anhydrous $Na_2SO_4$, and concentrated in vacuo to afford (±)-benzylisopropylphenylphosphine as an oil, which can be characterized by NMR spectroscopy. Characterization data: $^{31}P\{^1H\}$ NMR (101.26 MHz, $CDCl_3$): $\delta = -1.65$ s. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta = 0.90$ (dd, $J_{HP} = 13.5$ Hz, $J_{HH} = 6.9$ Hz, 3H, *Me*CHP), 1.13 (dd, $J_{HP} = 15.1$ Hz, $J_{HH} = 6.9$ Hz, 3H, *Me*CHP), 1.98 (m, 1H, *H*CP), 3.16 (d, 14.1 Hz, 1H, $H_2$CP), 3.09 (d, 14.1 Hz, 1H, $H_2$CP), 7.00–7.50 (m, 10H, *aromatic*). $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 19.18$ (d, $J_{PC} = 12.8$ Hz, *Me*CHP), 19.57 (d, $J_{PC} = 17.7$ Hz, *Me*CHP), 26.00 (d, $J_{PC} = 11.0$ Hz, *H*CP), 33.33 (d, $J_{PC} = 17.1$ Hz, $H_2$CP), 125.48 (s, *pBn*), 128.06 (s, *mBn*), 128.30 (d, $J = 10.9$ Hz, *mPh*), 128.97 (d, $J = 6.1$ Hz, *oBn*), 129.08 (s, *pPh*), 133.45 (d, $J = 18.9$ Hz, *oPh*), 136.49 (d, $J = 14.3$ Hz, *ipsoPh*), 138.28 (s, *ipsoBn*). GC-MS: 242 ($M^+$).

#### 3.1.2. Synthesis of $[NiCl_2(PBn^iPrPh)_2]$, *2*

For the synthesis of the coordination compound, a solution of $NiCl_2$ (0.5 g, 2.1 mmol) in absolute ethanol (10 mL) was added to a THF solution of (±)-benzylisopropylphenylphosphine, and the resulting mixture was stirred for 15 minutes and then concentrated in vacuo. Dark red crystals of the complex were obtained, filtered and dried. The yield of the global process was 55% (0.814 g). Anal. calcd (found) for $C_{32}H_{38}Cl_2NiP_2$: C, 62.58 (62.1); H, 6.24 (6.1). IR (KBr): 1488s, 1440s, 752s, 688s.

#### 3.1.3. Synthesis of $[Pd(\eta^3\text{-}2\text{-}MeC_3H_4)Cl((\pm)\text{-}PBn^iPrPh)]$, *3*

A few drops of deoxygenated water were added to a solution of $[NiCl_2(PBn^iPrPh)_2]$ (0.293 g, 0.477 mmol) in THF (20 mL) and the mixture was stirred until the red color completely disappeared (about 10 minutes). The aqueous phase was separated and the organic layer was dried over anhydrous $Na_2SO_4$. The organic phase was separated and 0.180 g (0.457 mmol) of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}2\text{-}MeC_3H_4)]_2$ were added; the resulting suspension was stirred at room temperature for 30 minutes. THF replaced *n*-pentane, and a yellow solid precipitated as a mixture of diastereomers (in a ratio 5/4). The solid obtained, in 75% yield (300 mg), was filtered and dried

under vacuum. Characterization data: anal. calcd (found) for $C_{20}H_{26}ClPPd$: C, 54.69 (54.9); H, 5.97 (6.1). $^{31}P\{^1H\}$ NMR (101.26 MHz, $CDCl_3$): $\delta = 38.65$ s (major diastereomer) and 37.56 s (minor diastereomer). $^1H$ NMR (500 MHz, $CDCl_3$); major isomer: $\delta = 0.99$ (dd, $J_{HP} = 15.5$ Hz, $J = 7.0$ Hz, 3H, *Me*CHP), 1.22 (dd, $J_{HP} = 17.7$ Hz, $J_{HH} = 7.0$ Hz, 3H, *Me*CHP), 1.84 (s, 3H, *Me*), 2.03 (s, 1H, $H^d$), 2.47 (m, $J_{HP} = 9.5$ Hz, $J_{HH} = 7.0$, 1H, *H*CP), 2.98 (br s, 1H, $H^c$), 3.41 (d, $J_{HP} = 10.0$ Hz, 1H, $H^b$), 3.55 (m, $J_{HP} = 14.0$ Hz, $J_{HH} = 8.0$ Hz, 1H, $H_2$CP), 3.62 (m, $J_{HP} = 14.25$ Hz, $J_{HH} = 5.0$ Hz, 1H, $H_2$CP), 4.44 (d, $J_{HP} = 6.75$ Hz, 1H, $H^a$), 6.90–7.45 (m, 10H, *aromatic*); minor isomer: 1.02 (dd, $J_{HP} = 15.0$ Hz, $J_{HH} = 7.0$ Hz, 3H, *Me*CHP), 1.32 (dd, $J_{HP} = 18.0$ Hz, $J_{HH} = 7.0$ Hz, 3H, *Me*CHP), 1.76 (s, 3H, *Me*), 2.42 (s, 1H, $H^d$), 2.52 (m, $J_{HP} = 10.0$ Hz, $J_{HH} = 7.0$ Hz, 1H, *H*CP), 2.92 (br s, 1H, $H^c$), 3.44 (d, $J_{HP} = 9.5$ Hz, 1H, $H^b$), 3.50 (dd, $J_{HP} = 14.0$ Hz, $J_{HH} = 8.0$ Hz, 1H, C$H_2$), 3.60 (dd, $J_{HP} = 14.25$ Hz, $J_{HH} = 4.5$ Hz, 1H, C$H_2$), 4.46 (d, $J_{HP} = 6.5$ Hz, 1H, $H^a$), 6.90–7.45 (m, 10H). $^{13}C$ NMR (75.4 MHz, $CDCl_3$): major isomer: $\delta = 18.0$ (d, $J_{CP} = 7.0$ Hz, *Me*CHP), 18.8 (d, $J_{CP} = 7.4$ Hz, *Me*CHP), 23.0 (s, *Me*), 23.8 (d, $J_{CP} = 21.9$ Hz, *H*CP), 31.8 (d, $J_{CP} = 17.0$ Hz, $H_2$CP), 55.8 (br s, $C^3$), 78.1 (d, $J_{CP} = 31.7$ Hz, $C^1$), 126.3 (d, $J_{CP} = 3.0$ Hz, *pBn*), 127.9 (d, $J_{CP} = 4.5$ Hz, *mPh*), 128.0 (s, *mBn*), 129.8 (d, $J_{CP} = 4.6$ Hz, *oBn*), 130.5 (d, $J_{CP} = 2.4$ Hz, *pPh*), 131.2 (d, $J_{CP} = 5.2$ Hz, $C^2$), 133.4 (d, $J_{CP} = 11.6$ Hz, *oPh*), 135.1 (d, $J_{CP} = 4.8$ Hz, *ipsoBn*); minor isomer: 18.0 (d, $J_{CP} = 7.0$ Hz, *Me*CHP), 19.0 (d, $J_{CP} = 8.0$ Hz, *Me*CHP), 23.0 (s, *Me*), 24.1 (d, $J_{CP} = 22.0$ Hz, *C*HP), 31.7 (d, $J_{CP} = 17.4$ Hz, $CH_2$P), 55.6 (br s, $C^3$), 78.1 (d, $J_{CP} = 31.7$ Hz, $C^1$), 126.3 (d, $J_{CP} = 2.8$ Hz, *pBn*), 127.9 (d, $J_{CP} = 4.5$ Hz, *mPh*), 128.0 (s, *mBn*), 129.8 (d, $J_{CP} = 4.7$ Hz, *oBn)*, 130.4 (d, $J_{CP} = 2.1$ Hz, *pPh*), 131.6 (d, $J_{CP} = 5.2$ Hz, $C^2$), 133.4 (d, $J_{CP} = 11.9$ Hz, *oPh*), 134.9 (d, $J_{CP} = 5.5$ Hz, *ipsoBn*). IR (KBr): 1433s, 1100s, 1026s, 773s, 745s, 697s.

### 3.1.4. Synthesis of **5**

A suspension formed by 0.32 mmol (200 mg) of **4**, 0.32 mmol (197 mg) of $[NiCl_2(PBn^iPrPh)_2]$ and 40 mL of THF was stirred at room temperature for 45 min and the resulting solution was concentrated in vacuo. The solid obtained was eluted by $SiO_2$ column chromatography with $CHCl_3$–acetone (100/5) as eluent. Compound **5** (1/1 mixture of diastereomers) was isolated as a yellow solid in a 70% yield. Characterization data: $^{31}P\{^1H\}$ (101.26 MHz, $CDCl_3$) $\delta = 45.2$ s and 42.3 s. Anal. calcd (found) for $C_{28}H_{31}ClNPPd$: C, 60.66 (60.8); H, 5.63 (5.5); N, 2.52 (2.4). MS-Positive FAB: 518 $[(M-Cl)^+]$.

### 3.1.5. Separation of diastereomers **5**

Compound **5** (200 mg) was carefully eluted at room temperature in a $SiO_2$ column (50 g of $SiO_2$) with $CHCl_3$–acetone (100/3) as eluent. The fractions eluted (15 mL) were concentrated in vacuo and checked by $^1H$ NMR spectroscopy. The fractions of the optically pure compound were chosen according to the aromatic proton signals. The diastereomer **5′** was obtained in 54% yield (54 mg), with a *d.e.* higher than 95%. Characterization data: $^{31}P\{^1H\}$ NMR (101.26 MHz, $CDCl_3$) $\delta = 42.3$ s. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.35$ (dd, $J_{HH} = 7.0$ Hz, $J_{HP} = 16$ Hz, 3H, *Me*CHP), 1.45 (dd, $J_{HH} = 7.0$ Hz, $J_{PH} = 17$ Hz, 3H, *Me*CHP), 1.95 (d, $J_{HH} = 6.5$ Hz, 3H, *Me*), 2.66 (m, 1H, *H*CP), 3.54 (m, 2H, $J_{HH} = 14$ Hz, $J_{PH} = 10.5$ Hz, $H_2$CP and N$H^9$), 3.86 (dd, $J_{HH} = 13.5$ Hz, $J_{HP} = 10.5$ Hz, 1H, $H_2$CP), 4.06 (br, 1H, N$H^8$), 5.20 (m, $J_{HH} = 6.5$ Hz, 1H, $H^7$), 6.50 (dd, $J_{HH} = 9$ Hz, $J_{PH} = 5.0$ Hz, 1H, $H^1$), 6.93 (d, $J_{HH} = 9$ Hz, 1H, $H^2$), 7.01–7.07 (m, 5H, *aromatic*), 7.18–7.29 (m, 3H, *aromatic*), 7.31–7.36 (m, 2H, *aromatic*), 7.40 (m, 2H, *aromatic*), 7.55 (d, $J_{HH} = 7.5$ Hz, 1H, $H^3$), 7.63 (d, $J_{HH} = 8.5$ Hz, 1H, $H^6$). Optical rotation: $[\alpha]_D^{20} = -19.7$ ($c = 1$, $CHCl_3$). The second diastereomer eluted **5″** was obtained in 52% yield with 77% *d.e.*:

$^{31}P\{^{1}H\}$ NMR (101.26 MHz, $CDCl_3$) $\delta = 45.2$, s. $^{1}H$ NMR (500 MHz, $CDCl_3$) $\delta = 0.9$ (dd, $J_{HH} = 7.0$ Hz, $J_{HP} = 14$ Hz, 3H, *Me*CHP), 1.4 (dd, $J_{HH} = 6.8$ Hz, $J_{PH} = 18.6$ Hz, 3H, *Me*CHP), 2.01 (d, $J_{HH} = 6.2$ Hz, 3H, *Me*), 2.83 (q, 1H, *H*CP), 3.51 (br, 1H, $NH_2$), 3.63–3.88 (m, 2H, $H_2CP$), 3.95 (br s, 1H, $NH_2$), 5.20 (q, $J_{HH} = 6.2$ Hz, 1H, $H^7$), 6.02 (dd, $J_{HH} = 8.8$ Hz, $J_{HP} = 5.6$ Hz, 1H, $H^1$), 6.74 (d, $J_{HH} = 8.8$ Hz, 1H, $H^2$), 7.05–7.30 (m, 7H, *aromatic*), 7.35–7.40 (m, 3H, *aromatic*), 7.43–7.64 (m, 4H, *aromatic*).

**$^{1}H$ NMR data (500 MHz, $CDCl_3$) of ($R_C$,$R_P$)-6**. $\delta = 1.95$ (d, $J_{HH} = 6.5$ Hz, 3H, *Me*), 1.25–2.35 (m, 11H, *aliphatic*), 3.54 (m, 1H, $CH_2$), 3.56 (br, 1H, N*H*), 3.88 (m, 1H, $CH_2$), 4.05 (br, 1H, N*H*), 5.2 (m, $J_{HH} = 5.5$ Hz, 1H, *H*CMe), 6.48 (dd, $J_{HH} = 9$ Hz, $J_{PH} = 5$Hz, 1H, $H^1$), 6.91 (m, 3H, *aromatic*), 7.06 (m, 3H, *aromatic*), 7.10 (m, 2H, *aromatic*), 7.20–7.35 (m, 5H, *aromatic*), 7.50 (d, $J_{HH} = 7.5$ Hz, 1H, *aromatic*), 7.60 (d, $J_{HH} = 8.5$ Hz, 1H, *aromatic*).

**$^{1}H$ NMR data (500 MHz, $CDCl_3$) of ($R_C$,$S_P$)-6.** $\delta = 1.98$ (d, $^{3}J_{HH} = 6.2$ Hz, 3H, *Me*), 0.8–2.63 (m, 11H, *aliphatic)*, 3.49–3.72 (br, 2H, N*H*, $CH_2$), 3.85–3.98 (br, 2H, N*H*, $CH_2$), 5.2 (m, $^{3}J_{HH} = 5.6$ Hz, 1H, *H*CMe), 6.05 (dd, $^{3}J_{HH} = 8.6$ Hz, $J_{PH} = 5.2$ Hz, 1H, $H^1$), 6.70 (d, $J_{HH} = 8.4$ Hz, 1H, $H^2$), 7.12–7.30 (m, 9H, *aromatic*), 7.46–7.64 (m, 5H, *aromatic*).

## 4. Computational details

The calculations were performed with the Spartan suite of programs.[22] The PM3(tm) method[23,24] was used with the default parameters supplied by the program.

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