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Applications of optically active metallacycles: new useful materials for the determination of the enantiomeric excess of Lewis bases and as resolving agents for monodentate phosphines

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Abstract

The synthesis of new optically active cyclopalladated derivatives containing imines and primary amines is described as well as their applications for the determination of the enantiomeric excess and as resolving agents of Lewis bases. The synthesis and resolution of new monodentate P-chiral tertiary phosphines is also reported, as well as the application of these new ligands to asymmetric catalysis. Besides this, some chiral secondary phosphines have been prepared and their configurational stability has been studied.

Resum

Es descriu la síntesi de nous compostos ciclopal·ladats derivats d'imines i amines primàries, òpticament actius, així com les seves aplicacions per a la determinació de l'excés enantiomèric i per a la resolució de bases de Lewis. També es comenta la síntesi i resolució de noves fosfines P-quirals, així com la seva aplicació a processos de catàlisi asimètrica. A més, es descriu la preparació d'algunes fosfines secundàries quirals i s'estudia la seva estabilitat configuracional.

Keywords: chiral, palladium, amines, resolution, enantiomeric excess

1. Introduction

The term cyclometallation was introduced by Trofimenko [1] to describe those reactions of transition metal complexes in which the ligand undergoes an intramolecular metallation with the formation of a chelate ring containing a metal-carbon σ bond. This process was one of the first known examples of C-H bond activation and cyclometallated compounds of a wide variety of ligands (containing N, P, As, O, or S as the heteroatom) have been described [2]. The cyclopalladation of N-donor ligands has been extensively studied by a number of research groups and as a field it has acquired great interest because of the applications of metallacycles in many areas including organic synthesis, homogenous catalysis, the design of new metallomesogenes, and antitumoral drugs [3].

In contrast with the large number of cyclopalladated compounds described, few of them are optically active, in spite of their interesting applications. These compounds can be used in many areas such as the determination of enantiomeric excess [4] and absolute configuration of chiral compounds [5], the asymmetric synthesis of optically active organic molecules [6] and the optical resolution of Lewis bases [7].

One of the main aims of our group is to synthesize new organometallic compounds and study their applications. We present here some of our results on the synthesis of new optically active cyclopalladated compounds derived from imines or primary amines and discuss their applications as agents for the determination of the enantiomeric excess of Lewis bases and for the resolution of monodentate chiral phosphines.

Spectacular progress has been made in the field of asymmetric catalysis by using homogeneous catalysts based on transition metal complexes modified by chiral ligands. In this way chiral phosphines have become very important in asymmetric catalysis [8]. Among the many chiral phosphines developed for application in asymmetric catalysis, examples of monodentate ligands possessing an stereogenic phosphorus atom are rare, even though metal complexes featuring marked asymmetry near the catalytic center are considered to be excellent optical inducers [9]. We describe here the synthesis of new P-chiral monodentate phosphines as well as their resolution by means of optically active metallacycles. We also report on some studies of the asymmetric hydrovinylation of styrene and 2-vinylnaphthalene, using optically active allyl complexes, containing P-chiral monodentate phosphines, as precursors of catalytic species.

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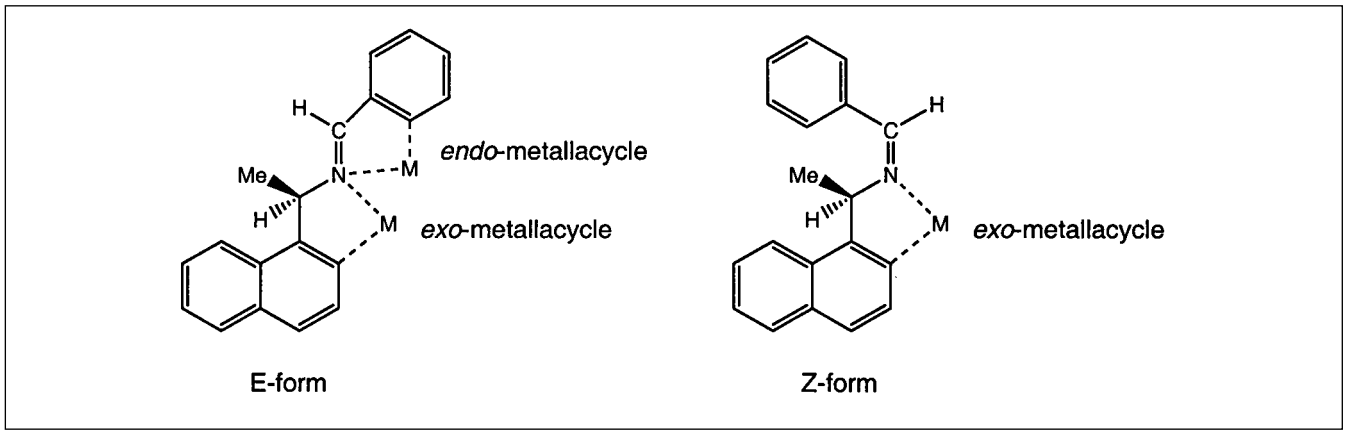
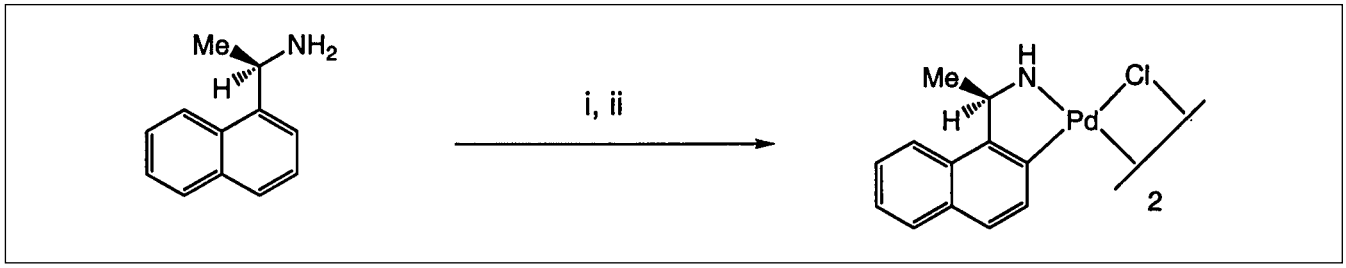


Figure 1.



Scheme 1. i) PdAc2, AcH, 60°C, 24 h; ii):LiCl, EtOH, 20°C.

2. Discussion

2.1. Cyclopalladation Reactions

2.1.1. Cyclopalladation of the primary amine (R)-(+)-1-(1-naphthyl)ethylamine

The versatility of *ortho*-palladated derivatives of optically active N,N-dimethyl(1-ethyl-1-naphthyl)amine as resolving agents for Lewis bases has been convincingly demonstrated and has been related to the high conformational rigidity of the naphthylethylamine derivatives [10]. Surprisingly, the metallation of the corresponding primary amine (*R*)-(+)-1-(1-naphthyl)ethylamine, which is commercially available, has not been described. This fact prompted us to study the cyclopalladation of this primary amine.

It is generally accepted that primary amines are inert towards cyclometallation reactions, but they can undergo cyclopalladation under appropriate experimental conditions. The action of $AgClO_4$ on coordination compounds $[PdCl_2L_2]$ (L = primary amine) or the action of palladium acetate on the amines in a 1:1 ratio (usually the cyclopalladation reaction is performed in a Pd: ligand 1:2 ratio) leads to the cyclopalladation of primary amines with good yields. These results have been explained by the generation of coordinatively unsaturated species that undergo the metallation [11].

The homochiral cyclopalladated dinuclear compound of the primary amine (*R*)-(+)-1-(1-naphthyl)ethylamine was obtained from the optically active amine by reaction between the free amine and palladium acetate, in a 1:1 ratio, in acetic acid at 60°C for 4 hours. Subsequent treatment with LiCl of the acetato dimer compound affords the dinuclear chloro-bridged complex $[PdCl(C_{10}H_6CHMeNH_2)]_2$ [12].

2.1.2. Cyclopalladation of imines

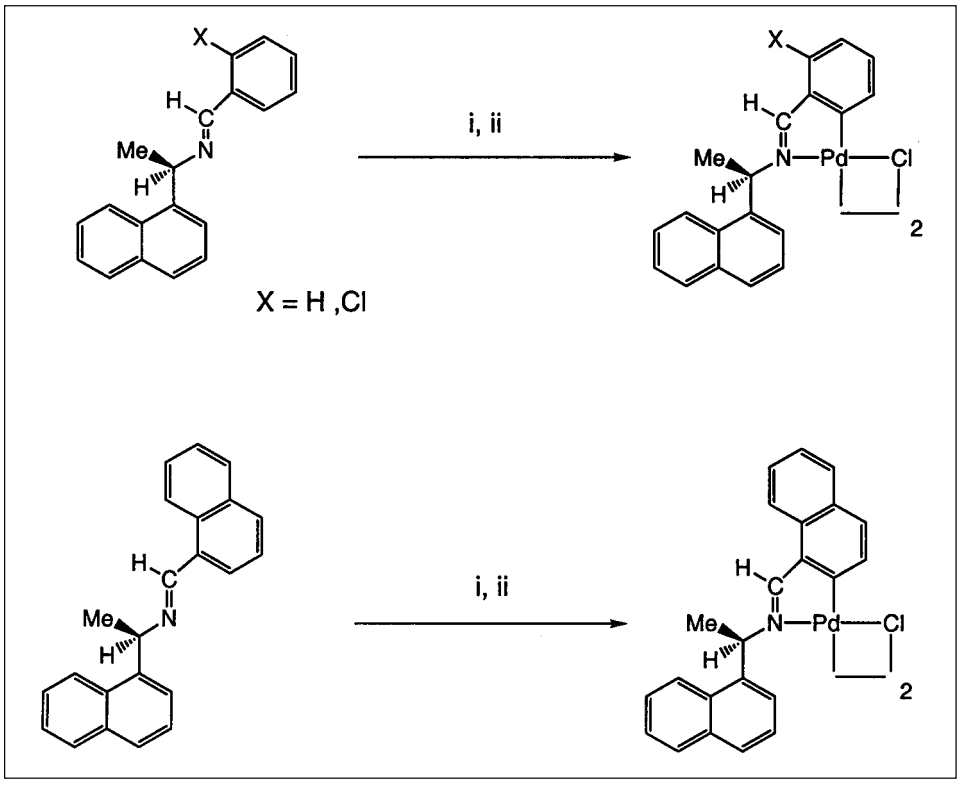
Ortho-palladated derivatives of the tertiary amines N,N-dimethyl-1-(1-naphthyl)ethylamine and N,N-dimethyl-α-methylbenzylamine have been used in nearly all the stereochemical applications of such compounds, although only over the last few years have the application of some new cyclometallated compounds in these fields been explored [13]. We have tried to prepare new cyclopalladated complexes from the reaction between palladium acetate and optically active imines. The latter were easily obtained by the condensation reaction between aromatic aldehydes and the primary amine (*R*)-(+)-1-(phenyl)ethylamine.

Imines are particularly suitable ligands for the study of cyclometallation reactions since they can undergo metallation on various carbon atoms, giving organometallic complexes of different structures: *endo*-metallacycles, if the C=N bond is included in the metallacycle, or *exo*-derivatives (see Figure 1) [14]. Furthermore, imines can exist in two isomeric forms: E or Z. In general, N-substituted aldimines adopt the more stable E form in the solid state or in solution, but in some cases a significant equilibrium concentration of the less stable Z form has been found [15]. *Endo*– or *exo*-metallacycles can be obtained from imines in the E– form but *exo*-metallacycles can only be formed from the Z isomer.

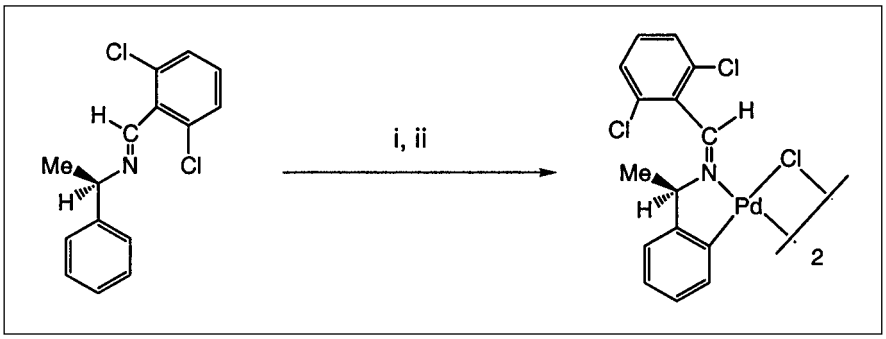
The imines shown in Scheme 2 were treated with palladium acetate in acid acetic for 24 hours at 60°C. Subsequent treatment of the reaction residues with LiCl in ethanol afforded, after purification by SiO_2 column chromatography, the corresponding chloro-bridged cyclopalladated dimers.

Overall NMR data showed that only the *endo*-derivative was formed, in agreement with studies reporting the strong tendency of imines to form *endo*-metallacycles [16]. The aromaticity of the five-membered metallacycle, involving the two conjugated bonds C=C, C=N and the filled *d* orbital of the metal of appropriate symmetry has been proposed as an explanation for the greater stability of endocyclic compounds [17].

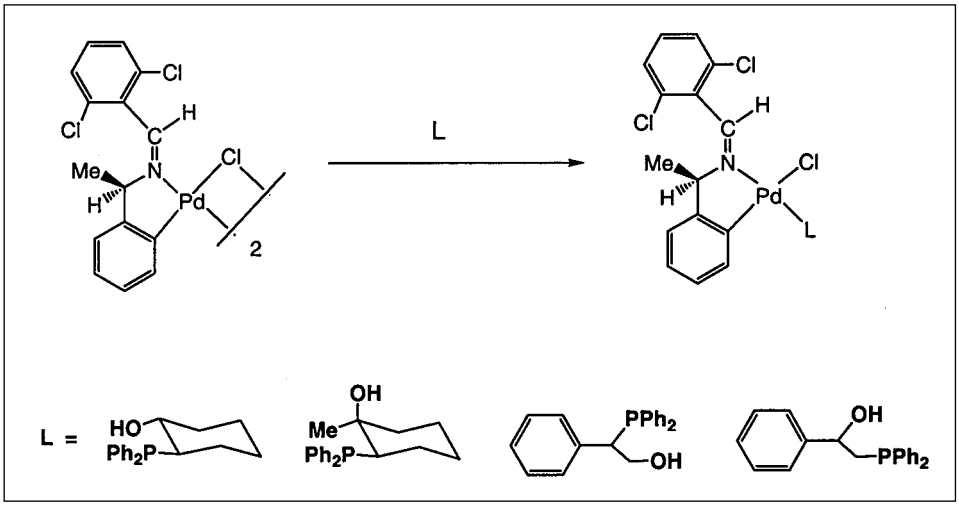
The reaction of 2,6-$Cl_2C_6H_4$CH =NCH(Me)Ph with palladium acetate acetic acid was also studied. In this ligand the *ortho* positions of the benzal ring are blocked by the chlorine atoms, and for this reason the less stable *exo*-derivative [Pd(2-{Z-(*R*)-CH MeN=CH-2',6'-$Cl_2C_6H_3$}C_6H_4)Cl $]_2$, in the Z-form, was obtained (see Scheme 3) [18].



Scheme 2. i) $PdAc_2$, AcH, 60°C, 24 h; ii):LiCl, EtOH, 20°C.



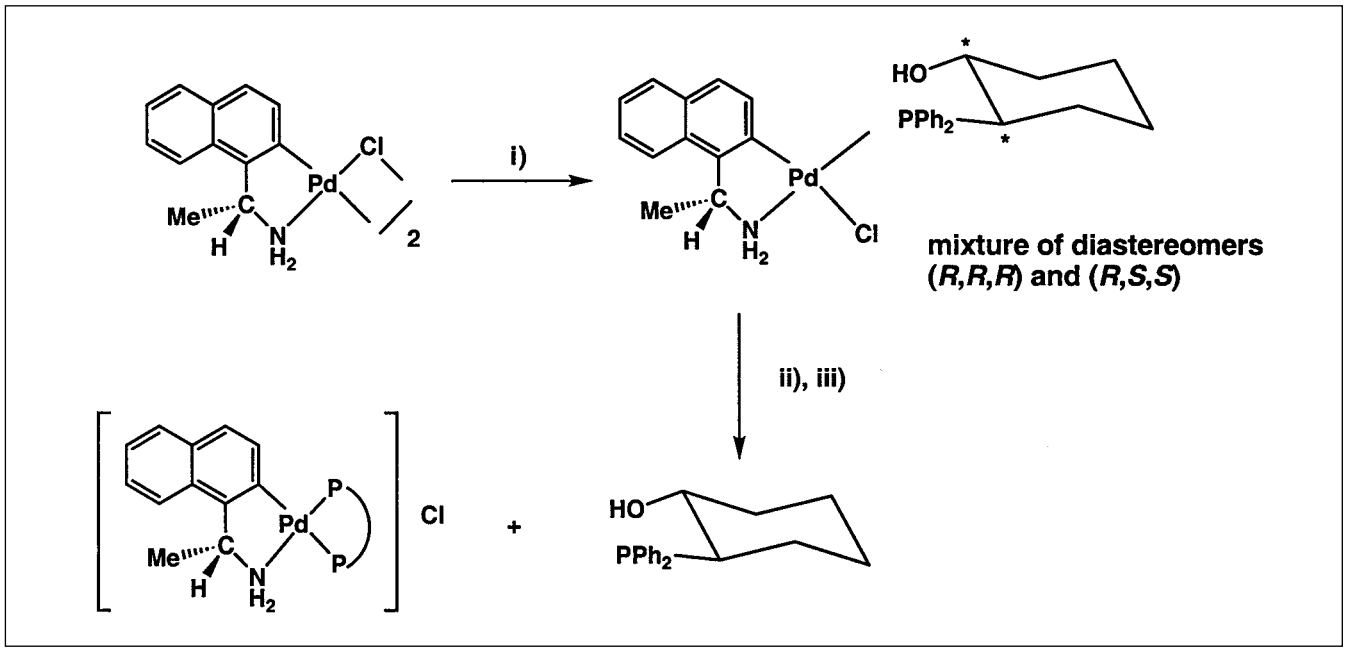
Scheme 3. i) $PdAc_2$, AcH, 80°C, 45 min; ii):LiCl, EtOH, 20°C.



Scheme 4.

2.2. Application of cyclopalladated compounds for the enantiomeric excess determination of Lewis bases

We have shown that the cyclopalladated compound [Pd(2-{Z-(*R*)-CHMeN=CH-2',6'-$Cl_2C_6H_3$}C_6H_4)Cl $]_2$ is a good agent for the enantiomeric excess determination of functionalized phosphines L, see Scheme 4 [19]. The formation of diastereomers [Pd(2-{Z-(*R*)-CHMeN=CH-2',6'-$Cl_2C_6H_3$}C_6H_4)Cl(L)] took place instantaneously when the racemic phosphine and the cyclometallated compound were mixed in a 2:1 ratio in a NMR tube. The ^{1}H NMR spectra of the mixture showed two sets of signals in 1:1 ratio. The spectra were quite complex because certain signals partially overlap, as a consequence of the high number of aromatic and aliphatic protons present. However, the methinic protons appeared as doublets at δ = 9 - 10 ppm further away from the remaining resonances, showing an excellent diastereomeric peak separation. The enantiomeric ratios measured on synthetic mixtures of different enantiomers agreed well with the expected values and the presence of less than 3% of the minor

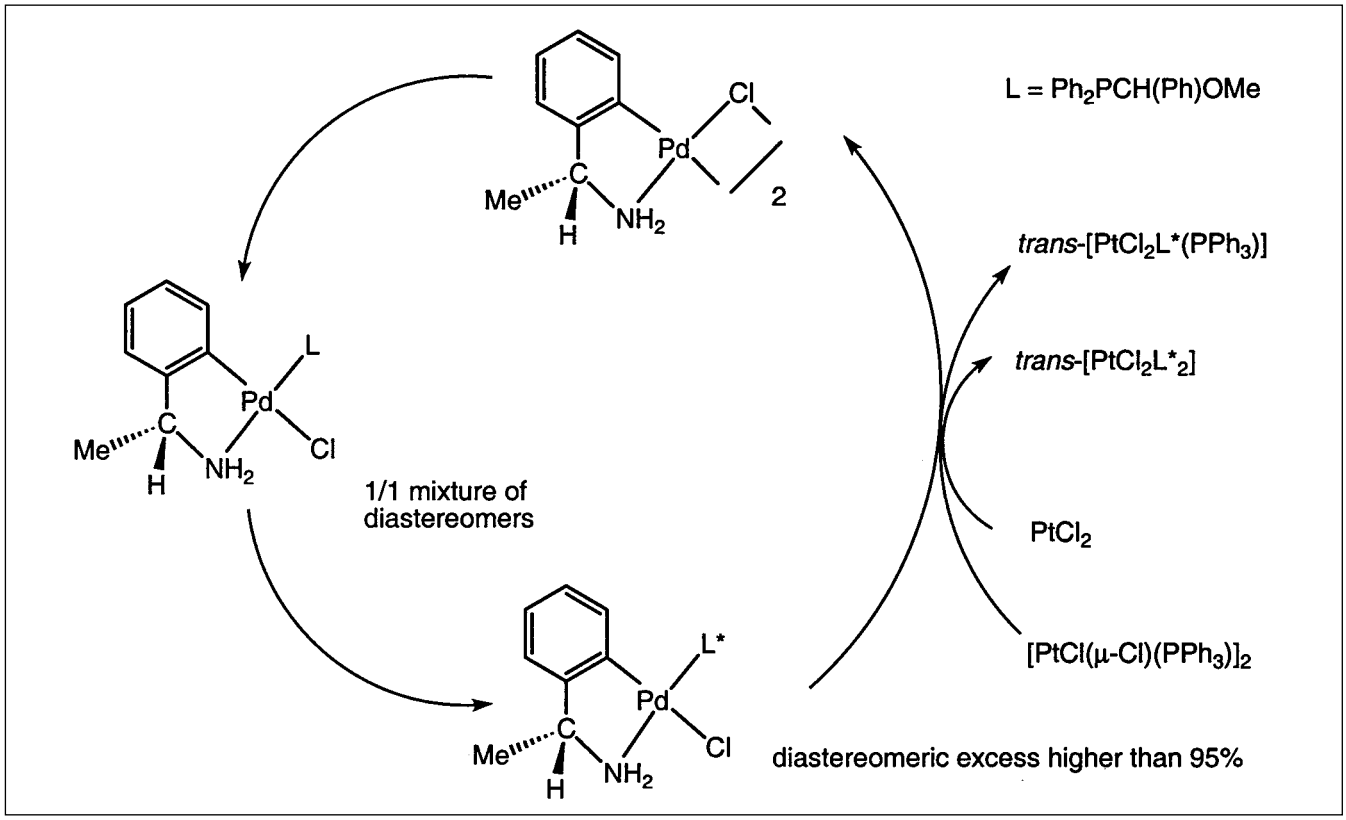


Scheme 5. i) *trans*-$PPh_2(2\text{-}OHC_6H_{10})$, THF ii) column chromatography SiO_2 iii) dppe, THF.

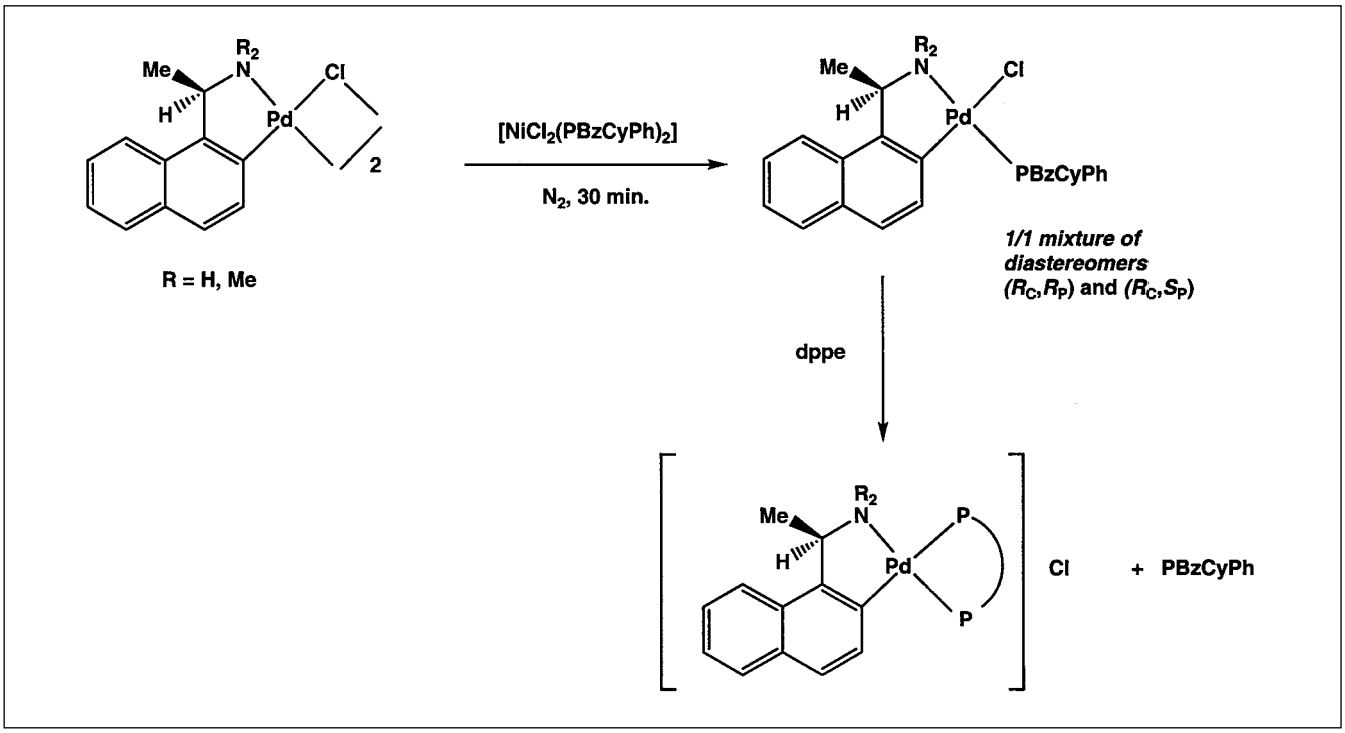
isomer was detected. It should also be noted that –due to the high molecular weight of the chiral complexing agent– only small quantities of phosphines were required for the NMR determination. In addition ^{31}P NMR spectroscopy can also be used for the enantiomeric excess determination of these ligands. All these results showed that this chiral cyclopalladated imine derivative is a useful agent for the enantiomeric excess determination of phosphines.

2.3. Application of cyclopalladated compounds for the resolution of chiral phosphines.

Reaction of the dimer (*R*)-$[PdX\{C_6H_4CH(Me)NH_2\}]_2$ [20] with the monodentate racemic phosphine *trans*-$PPh_2(2\text{-}OHC_6H_{10})$ afforded the mononuclear derivative [PdCl(C-N)L], as a mixture 1:1 of diastereomers (see Scheme 5). Attempts to separate these diastereomers by recrystallization were unsuccessful, but the elution of this mixture in an SiO_2



Scheme 6



Scheme 7

column, using chloroform-methanol (100:3) as an eluent, allowed their separation with a diastereomeric excess higher than 95% [12]. The action of dppe on the optically pure cyclopalladated derivatives allowed us to obtain the free phosphine *trans*-$PPh_2(2\text{-}OHC_6H_{10})$. The ^{31}P NMR spectrum obtained when the cyclopalladated compound $[Pd(2\text{-}\{Z\text{-}(R)\text{-}CHMeN{=}CH\text{-}2',6'\text{-}Cl_2C_6H_3\}C_6H_4)Cl]_2$ was added to the solution containing the free phosphine showed that the absolute configuration of the phosphine is *1R,2R* in the first diastereomer eluted.

We have also shown that the cyclometallated compounds (*R*)-$[PdX\{3\text{-}ClC_6H_3CH{=}NCH(Me)Ph\}]_2$ and (*R*)-$[PdX\{C_6H_4CH(Me)NH_2\}]_2$ (X = Cl or Br) are useful reagents for the resolution of the phosphines *trans*-2-PPh_2(CyOH) and Ph_2PCH(OMe)Ph [21].

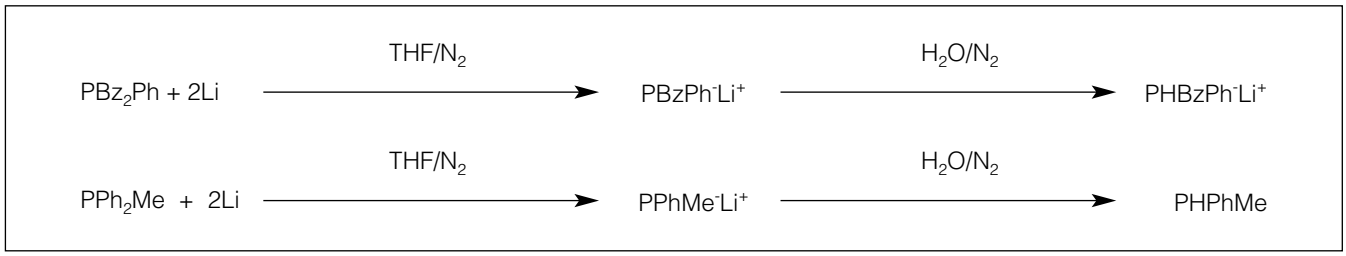
Nearly all the examples described so far for the resolution of phosphines using cyclometallated complexes result in palladacycle degradation. Only very recently a sequence of reactions that allows the regeneration of the resolving agent has been described [22]. The lability of the palladium-phosphorous bond in cyclopalladated derivatives, and the fact that the main objective of the resolution of phosphines is the synthesis of coordination compounds, which can be useful reagents for enantioselective catalysis, prompted us to study ligand transfer reactions between optically active derivatives [PdCl(C-N)L] and some platinum compounds like $PtCl_2$ or *trans*-$[PtCl(\mu\text{-}Cl)(PPh_3)]_2$ [21].

When the reactions were performed with the amine derivative (*R*)-$[PdX\{C_6H_4CH(Me)NH_2\}\{Ph_2PCH(OMe)Ph\}]$, the coordination platinum complexes *trans*-$[PtCl_2\{Ph_2PCH(OMe)Ph\}_2]$ and *trans*-$[PtCl_2\{Ph_2PCH(OMe)Ph\}(PPh_3)]$, were cleanly obtained from $PtCl_2$ and *trans*-$[PtCl(\mu\text{-}Cl)(PPh_3)]_2$, respectively, see Scheme 6. Moreover, the dinuclear cyclopalladated resolving agent (*R*)-$[PdCl\{C_6H_4CH(Me)NH_2\}]_2$ can be separated from the platinum compounds and used in a new resolution process. It should be noted that platinum complexes $[PtCl_2(PR_3)_2]$ or $[PtCl_2(P\text{-}P)]$, in the presence of $SnCl_2$, are useful catalysts in the asymmetric hydroformilation of olefins. This process is a useful approach to the subject of phosphine resolution because it allows, for the first time, the synthesis of optically active platinum complexes and the regeneration of the resolving agent in one step. Furthermore, this sequence of reactions permits the synthesis of the platinum coordination compounds without the isolation of the free phosphine preventing the racemization or decomposition of this ligand.

2.4. Synthesis and resolution of new P-chiral phosphines

2.4.1. Benzylcyclohexylphenylphosphine: synthesis, resolution and application in asymmetric hydrovinylation

Asymmetric hydrovinylation of vinyl aromatic derivatives can afford 3-phenyl-1-butene and related derivatives, which are starting materials for the synthesis of 2-arylpropionic acids, which are widely used as anti-inflammatory drugs, such as Ibuprofen and Naproxen [23]. [MCl(allyl)L] compounds (M = Ni, Pd; L = monodentate phosphine) are precursors of active species in the catalytic hydrovinylation of olefins and the activity of the catalyst increases as the bulk of the modifying ligand increases, up to a certain point beyond which a sharp decline is observed [24]. It should also be noted that, in this process, the catalyst becomes inactive in the presence of bidentate phosphines. For this reason particular attention has been given to systems containing Horner phosphines,



Scheme 8.

but unfortunately optically pure Horner phosphines are not easy to prepare [24]. These facts prompted us to prepare the benzylcyclohexylphenylphosphine, which due to its steric bulk and electronic features, seems to be a promising precursor of active species in the asymmetric hydrovinylation of olefins.

The chiral phosphine was synthesized by reaction between dibenzylphenylphosphine and lithium metal in THF under a dry nitrogen atmosphere and subsequent reaction of the phenylbenzylphosphide anion formed with cyclohexyl bromide. This ligand can be resolved with excellent optical yields by using the cyclopalladated compounds $[PdCl(C_{10}H_6CHMeNR_2)]_2$ (R = H, Me). The absolute configuration of (R_C, R_P)-$[PdCl(C_6H_4CHMeNMe_2)(PBzCyPh)]$ has been determined by single crystal X-ray analyses [25].

Compound **5**, $[Pd(\eta^3\text{-}2\text{-}MeC_3H_4)Cl(PBzCyPh)]$, containing the phosphine in optically pure form, can be obtained by the addition of dppe to a solution of one of the optically pure diastereomers [Pd(C-N)Cl(PBzCyPh)], in a 1:1 ratio, and the subsequent reaction of the free phosphine formed with the dinuclear allyl complex $[Pd(\mu\text{-}Cl)(\eta^3\text{-}2\text{-}MeC_3H_4)]_2$.

The complex $[Pd(\eta^3\text{-}2\text{-}MeC_3H_4)(PBzCyPh)S]BF_4$, prepared *in situ* from **5** and $AgBF_4$ in CH_2Cl_2 solution was used as a catalyst precursor for asymmetric hydrovinylation of styrene and 2-vinylnaphthalene, and the results are shown in Table 4. We should emphasize the great activity of this catalyst (up to 1290 cycles per palladium atom and hour), the excellent selectivity and the low amount of dimers formed (ranging between 0.6 to 5.5%) and the *ee* values obtained, 60% for 3-phenyl-1-butene and 85% for 2-(2-naphthyl)-1-butene. It should be noted that it is the first time that good *ee* values have been obtained for this process working at room temperature. In all previous cases very low temperatures were needed in order to obtain good *ee* values [24,26].

2.4.2. Secondary phosphines: synthesis, resolution and studies on their configurational stability.

Due to the reactivity of their P-H bonds secondary phosphines are versatile synthons for the preparation of chiral mono– and bi-dentate ligands but only one secondary phosphine chiral at phosphorus has been resolved to date. Six consecutive recrystallizations from acetonitrile in the presence of sodium acetylacetonate afforded the [R_P-(1*R*,2*S*,5*R*)] diastereomer of menthylmesitylphosphine, in 94% optical purity [27]. The low configurational stability of P-chiral secondary phosphines has been explained by the acid catalyzed racemization, in which the protonation of secondary phosphines affords achiral phosphonium ions, with two enantiotopic protons that can be removed at identical rates. When the secondary phosphines are attached to metal ions, borane or chalcogens by means of the lone pair the racemization does not occur and some diastereomers containing coordinated secondary phosphines have been separated [28]. However, with the exception of the remarkable results described by Wild *et al* with menthylmesitylphosphine [27], the recovery of the free optically pure ligand has not been accomplished.

(±)-Benzylphenylphoshine was synthesized by reaction of dibenzylphenylphosphine and lithium metal in tetrahydrofuran under a dry nitrogen atmosphere and subsequent reaction of the phenylbenzylphosphide anion formed with H2O. Analogous sequence of reactions from methyldiphenylphosphine afforded (±)-methylphenylphosphine with good yield (Scheme 8) [29]. These secondary phosphines can be resolved following the previously reported methodology (see above) by using the cyclopalladated compound $[PdCl(C_{10}H_6CHMeNH_2)]_2$. When a stoichiometric amount of 1,2-bis(diphenylphosphino)ethane was added to an ether solution of the optically pure cyclopalladated derivatives the quantitative precipitation of the ionic compound [Pd(C-N)(dppe)]Cl took place and solutions of enantiopure free phosphines PHBzPh and PHMePh) in diethylether were obtained.

No racemization of benzylphenylphosphine was observed when this ligand was stored in solution for 20 minutes, as verified by ^{31}P NMR spectra. In contrast, when this experiment was carried out with methylphenylphosphine, the formation of a mixture *ca.* 1:1 of diastereomers of $[PdCl(C_{10}H_6CHMeNH_2)(PHMePh)]$ was observed in less than five minutes. The configurational stability of PHBzPh is remarkable; it should be noted that an acetonitrile solution of menthylmesitylphosphine, the only secondary phosphine resolved so far, led to immediate epimerization at phosphorus in the absence of sodium acetylacetonate [27].

Concluding remarks

The new optically active cyclopalladated derivatives containing imines and primary amines described are very useful agents for the resolution of monodentate phosphines. In addition these complexes can be used for the determination of the enantiomeric excess of Lewis bases. Some new P-chiral ligands have been prepared and resolved with good chemi-

cal and optical yields, and these phosphines have been used in the asymmetric hydrovinylation of styrene and 2-vinylnaphthalene with good results, even at room temperature. Experiments testing cyclometallated compounds for the resolution of new Lewis bases, which can be used in asymmetric catalysis, are currently in progress.

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