

Review

Synthesis and applications of optically active metallacycles derived from primary amines

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Dedicated to Dr. José Antonio Abad on the occasion of his retirement.

Abstract

The synthesis of optically active cyclopalladated derivatives containing primary amines and their application as resolving agents of Lewis bases is reviewed. Some other applications such as the determination of the absolute configuration of coordinated chiral phosphines and the synthesis of chiral liquid crystals are also presented.

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1. Introduction

The cyclopalladation of N-donor ligands has been extensively studied [1] and as a field it has acquired great

interest because of the applications of metallacycles in many areas including organic synthesis, catalysis, the design of new metallomesogenes, and antitumoral drugs [2].

In contrast with the large number of cyclopalladated compounds described, few of them are optically active, in spite of their interesting applications. These compounds

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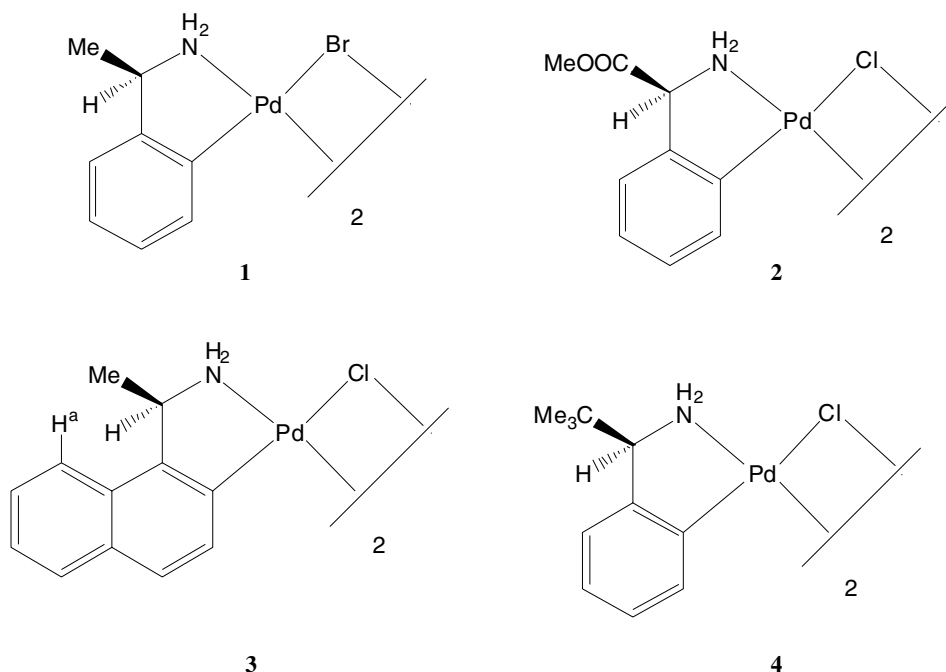
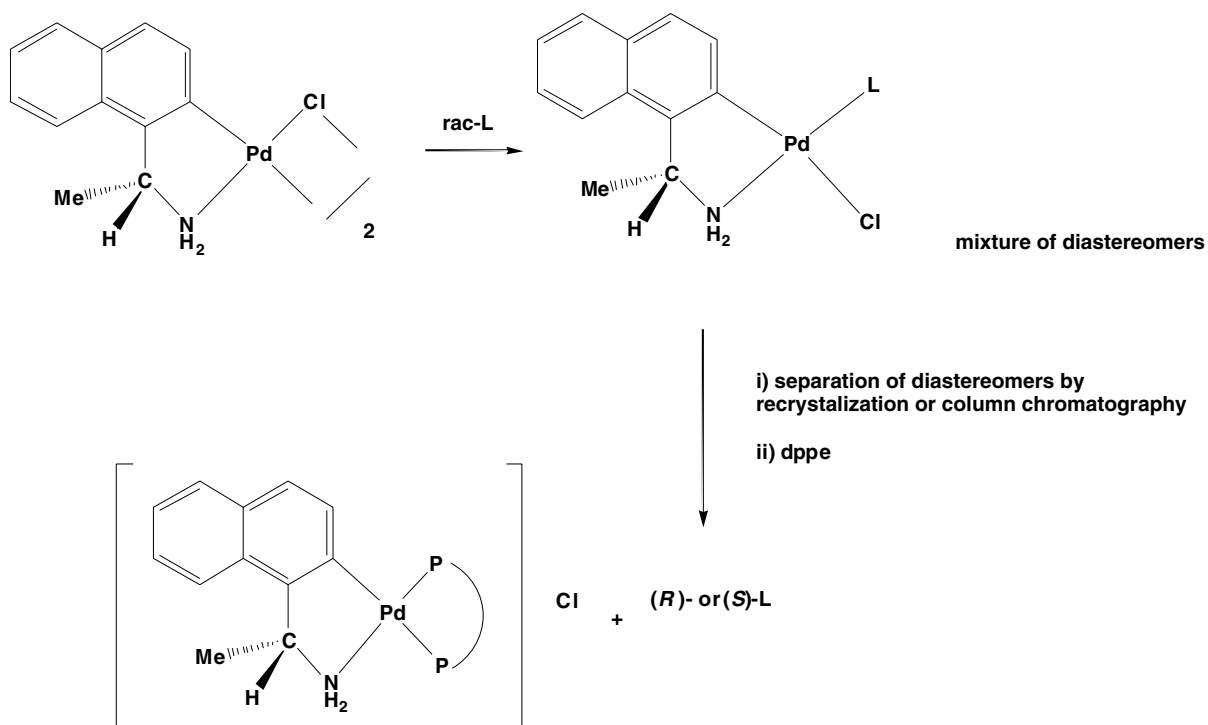


Chart 1. Optically active cyclopalladated compounds, derived from primary amines.

can be used in many areas such as the determination of enantiomeric excess [3] and absolute configuration of chiral compounds [4], the asymmetric synthesis of optically active organic molecules [5] and the optical resolution of Lewis bases [6].

The versatility of *ortho*-palladated derivatives of optically active tertiary amines such as *N,N*-dimethyl

(1-ethyl-1-naphthyl)amine as resolving agents for Lewis bases has been convincingly demonstrated, mainly by the group of Wild [6], but, in contrast, little attention has been paid to optically active primary amines. We review here the synthesis of optically active cyclopalladated compounds, derived from primary amines, and their applications for the resolution of chiral ligands [7].



Scheme 1. General process for the resolution of Lewis bases using cyclopalladated complexes.

2. Synthesis of optically active metallacycles

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 $[\text{PdCl}_2\text{L}_2]$ (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 [8]. In a more recent paper, Vicente et al. [9] showed that the metallation of primary amines by palladium acetate occur via intermediate complexes $[\text{Pd}(\text{AcO})_2\text{L}_2]$ which react with $[\text{Pd}(\text{AcO})_2]_3$ to give the dimeric species $[\text{Pd}(\text{AcO})(\mu\text{-AcO})\text{L}]_2$, from which the *ortho*-metallated compounds are formed. The metallation of different primary amines has recently been described [10] and a comparative analysis of kinetics of cyclopalladation of primary and tertiary benzylamines has also been reported. This study suggests a common mechanism for the metallation of primary and tertiary benzylamines, involving concerted formation of the palladium–carbon bond and cleavage of carbon–hydrogen bond with a nucleophilic assistance by the coordinated acetate ligand [11].

The first optically active cyclopalladated primary amine was obtained by Vicente et al. [12] by the reaction between $[\text{PdCl}_2\{\text{NH}_2\text{CH}(\text{Me})\text{Ph}\}_2]$ and AgClO_4 in acetone and subsequent reaction with NaBr to obtain **1** (see Chart 1). This complex is obtained optically pure by using (*R*)- or (*S*)- α -methylbenzylamine as starting material. Fuchita et al. [13] described the metallation of (*R*)-2-phenylglycine methyl ester by reaction between the corresponding amino acid ester and palladium acetate in acetone under reflux for 20 h to afford compound **2**. The homochiral cyclopalladated dinuclear compound of the primary amine 1-(1-naphthyl)ethylamine (**3**) was obtained by our group by reaction between the free amine and palladium acetate, in a 1:1 ratio, in acetic acid at 60 °C for 4 h. Subsequent treatment with LiCl of the acetate dimeric compound afforded the dinuclear chloro-bridged complex $[\text{PdCl}(\text{C}_{10}\text{H}_6\text{CHMeNH}_2)]_2$ [14]. *Ortho*-palladation of $\text{Me}_3\text{CCHPhNH}_2$ was described by Dunina et al. [15,16] by using different reaction conditions to afford **4**. The best results were achieved when the reaction was performed with palladium acetate, in a 1:1 ratio, in methanol at room temperature for 1 day.

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

The typical procedure for the resolution of racemic Lewis bases by means of optically active cyclometallated complexes involves reaction between the dinuclear cyclopalladated derivative $[\text{Pd}(\mu\text{-X})(\text{C-N})_2]$ (being C–N the metallated amine and X, usually, a chloro or bromo bridging ligand) and the corresponding Lewis base to afford a

mononuclear organometallic complex $[\text{PdX}(\text{C-N})\text{L}]$. The coordination of the incoming bridge splitting ligand is usually a regioselective reaction [17] (see Scheme 1).

The mixture of diastereomers obtained can be separated by recrystallization or column chromatography and, finally, the ligand can be liberated from the metal by treating the complex with a bidentate ligand. The ligands resolved by using optically active metallacycles derived from primary amines are collected in Chart 2. This table shows that, in general, the naphthyl derivative **3** is a better resolution agent than the phenyl compound **1**. This has been explained by the fact that the methyl substituent of the chiral carbon atom adopts an axial disposition to avoid the unfavourable interaction with the aromatic hydrogen H^a , and in consequence the five-membered metallacycle has a locked asymmetric envelope conformation [6a].

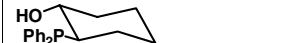
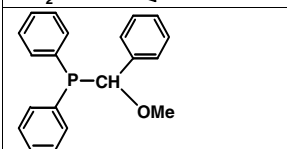
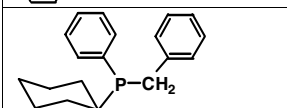
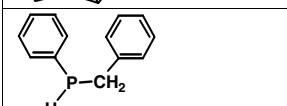
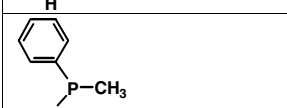
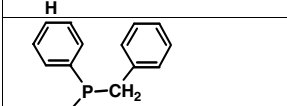
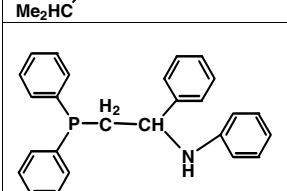
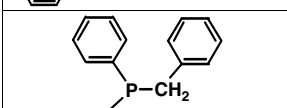
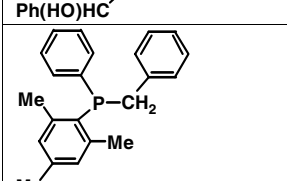
Ligand	Resolution agent	Reference
	3	14
	1	18
	3	19
	3	20
	3	20
	3	21
	1	22
	3	23
	3	24

Chart 2. Ligands resolved by using optically active metallacycles [20,22,23].

It should be noted that some of the phosphines resolved by this methodology have shown to be very useful ligands for asymmetric hydrovinylation reactions, affording an excellent selectivity and good ee values [19,24].

Nearly all the examples described for the resolution of phosphines using cyclometallated complexes result in palladacycle degradation. 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 our group to study ligand transfer reactions between optically active derivatives $[\text{PdCl}(\text{C-N})\text{L}]$ and some platinum compounds like PtCl_2 or $\text{trans-}[\text{PtCl}(\mu\text{-Cl})(\text{PPh}_3)_2]$ [18].

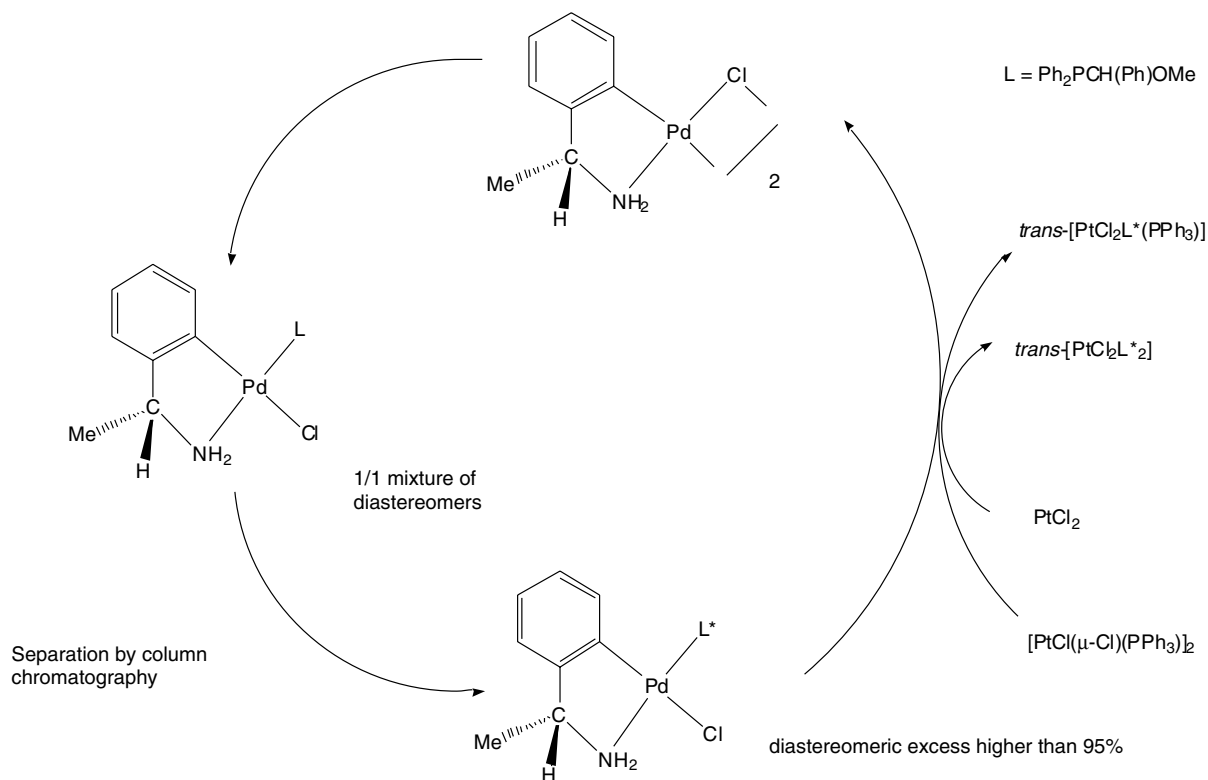
When the reactions were performed with the amine derivative $(R)\text{-}[\text{PdCl}\{\text{C}_6\text{H}_4\text{CH}(\text{Me})\text{NH}_2\}\{\text{Ph}_2\text{PCH}(\text{OMe})\text{-Ph}\}]$, the platinum complexes $\text{trans-}[\text{PtCl}_2\{\text{Ph}_2\text{PCH}(\text{OMe})\text{-Ph}\}_2]$ and $\text{trans-}[\text{PtCl}_2\{\text{Ph}_2\text{PCH}(\text{OMe})\text{Ph}\}(\text{PPh}_3)]$, were cleanly obtained from PtCl_2 and $\text{trans-}[\text{PtCl}(\mu\text{-Cl})(\text{PPh}_3)_2]$, respectively, see Scheme 2. Moreover, the dinuclear cyclopalladated resolving agent $(R)\text{-}[\text{PdCl}\{\text{C}_6\text{H}_4\text{CH}(\text{Me})\text{NH}_2\}]_2$ can be separated from the platinum compounds and used in a new resolution process. It should be noted that platinum complexes $[\text{PtCl}_2(\text{PR}_3)_2]$ or $[\text{PtCl}_2(\text{P-P})]$, in the presence of SnCl_2 , are useful catalysts in the asymmetric hydroformylation of olefins. This process is an interesting 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 oxidation of this ligand.

4. Application of cyclopalladated compounds for the determination of the absolute configuration of coordinated chiral phosphines

It has been demonstrated that NOE techniques [25] or the NMR chemical shift regularities [26] can be used to determine the absolute configurations of coordinated chiral phosphines.

Our group has shown that the rotation around the Pd–P bond is rather restricted in compounds $[\text{PdCl}(\text{C-N})(\text{PBn-RPh})]$ (C–N being a chiral cyclopalladated ligand and R = isopropyl or cyclohexyl group). This fact and the locked asymmetric envelope conformation adopted by the metallacycle in the naphthalene derivatives (see before) permit the assignment of the absolute configuration of phosphorus by NMR experiments [21]. It is known that in all these complexes, the benzyl group is separated from the metallacycle and that this group is located on the opposite side of the coordination plane in relation to the methyl group of the chiral carbon atom. In consequence, the difference between the two diastereomers is the relative position of the phenyl and the R group. In one diastereomer, the



Scheme 2. Ligand transfer reactions between optically active derivatives $[\text{PdCl}(\text{C-N})\text{L}]$ and some platinum compounds.

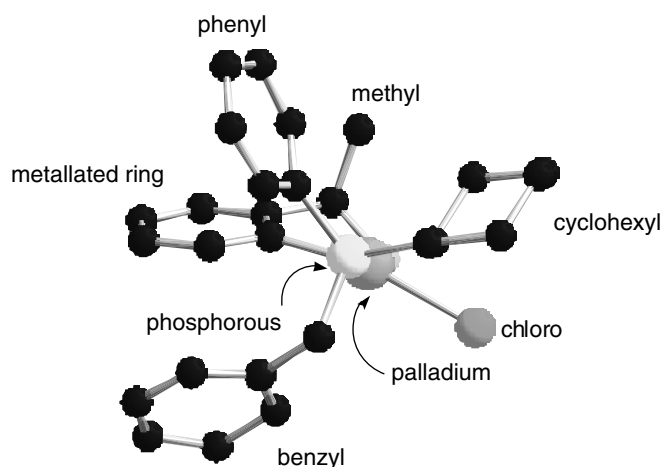


Fig. 1. Determination of the absolute configuration of (R_C, S_P)- $[\text{PdCl}\{\text{C}_{10}\text{H}_6\text{CH}(\text{Me})\text{NH}_2\}(\text{PBnCyPh})]$.

metallated ring is near to the phenyl group of the phosphine and in the other the metallated ring is near to the group R.

For example, there was a strong NOE interaction between the aromatic hydrogen adjacent to the Pd–C bond and two of the hydrogens of the cyclohexyl group in the NOESY spectra of one of the diastereomers of compound $[\text{PdCl}\{\text{C}_{10}\text{H}_6\text{CH}(\text{Me})\text{NH}_2\}(\text{PBnCyPh})]$. In contrast, in the NOESY spectra of the other diastereomer, the aromatic hydrogen adjacent to the Pd–C bond shows NOE interaction with the *ortho*-hydrogen atoms of the phenyl group of the phosphine. In conclusion, the first diastereomer of $[\text{PdCl}\{\text{C}_{10}\text{H}_6\text{CH}(\text{Me})\text{NH}_2\}(\text{PBnCyPh})]$ has the absolute

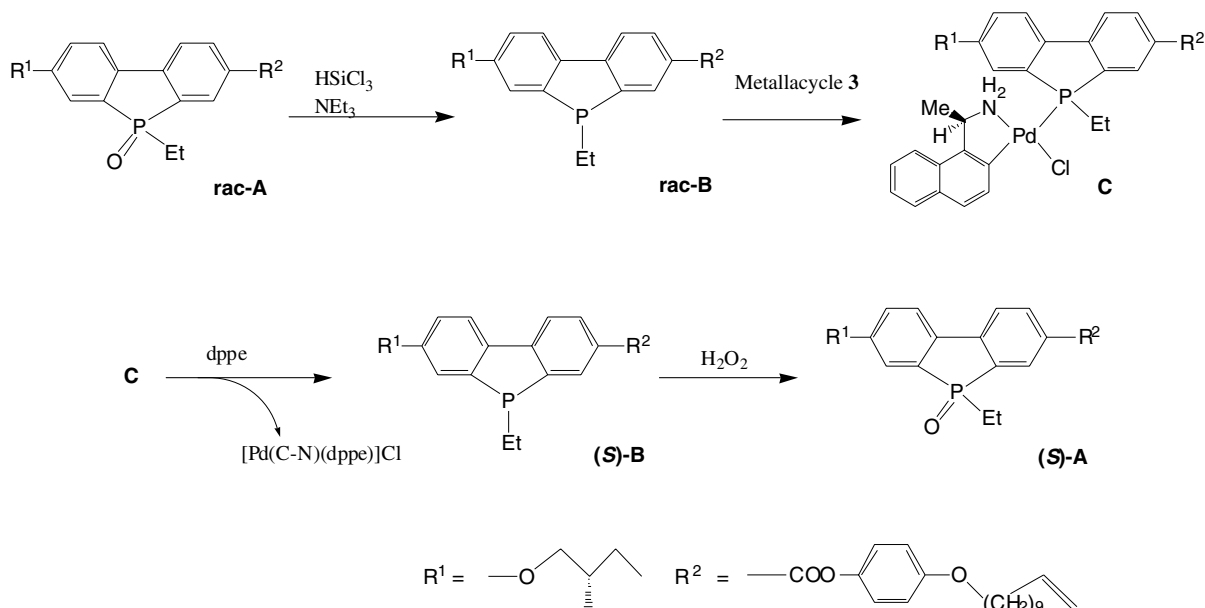
configuration (R_C, R_P) and the second diastereomer is the (R_C, S_P)-compound (see Fig. 1).

5. Chiral liquid crystals

The cyclometallated metallacycle (R)- $[\text{PdCl}\{\text{C}_{10}\text{H}_6\text{CH}(\text{Me})\text{NH}_2\}]_2$, has been used by the group of López-Calahorra [27] for the synthesis and resolution of dibenzophosphole 5-oxides. This group has also reported the synthesis of (S_P, S_C)-5-ethyl-3-(2-methylbutoxy)-7-(4-undec-10-enoxyphenoxy)carbonyl-5H-dibenzophosphole 5-oxide, the first example described of an asymmetrically substituted dibenzophosphole based group with liquid-crystal properties [28]. The first step of the process is the trichlorosilane reduction of the corresponding oxides. Subsequent reaction of the phosphines obtained with the cyclometallated derivative affords a mixture of diastereomers, that can be separated by column chromatography. Then, the phosphines are decoordinated by reaction with 1,2-bis(diphenylphosphino)ethane and the last step is the oxidation of the phosphines using hydrogen peroxide (see Scheme 3).

6. Concluding remarks

The optically active cyclopalladated derivatives containing primary amines described are very useful agents for the resolution of monodentate Lewis bases and can be, in some cases, more efficient than the tertiary amines derivatives, usually more used in this area. Besides this, these optically active metallacycles can present new and interesting applications such as the determination of the absolute configuration of coordinated chiral phosphines or the synthesis of chiral liquid crystals.



Scheme 3. Synthesis and resolution of an asymmetrically substituted dibenzophosphole based group.

Acknowledgements

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