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Chiral Cyclopalladated Compounds for Enantiomeric Purities of Functionalized Phosphines by means of Multinuclear NMR

J. Albert, J. Granell,* G. Muller,* D. Sainz

Departament de Química Inorgànica, Universitat de Barcelona, Diagonal 647, 08028 Barcelona, Spain

M. Font-Bardia, X. Solans

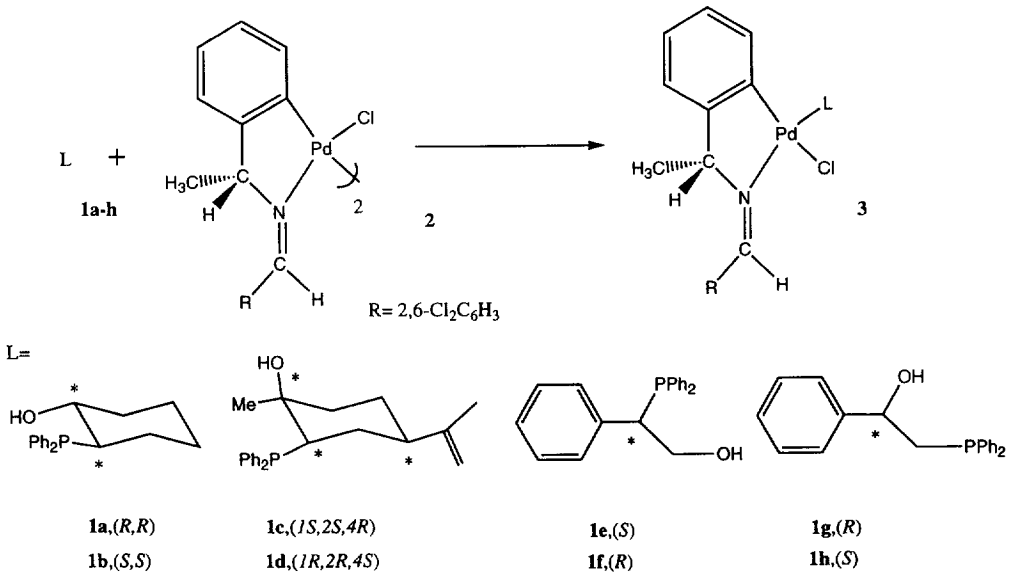
Departament de Cristal.lografia i Diposits Minerals, Universitat de Barcelona, Martí i Franquès, s/n, 08028 Barcelona (Spain)

Abstract: The application of the cyclopalladated compound [Pd(2-{Z-(*R*)-CHMeN=CH-2',6'-$Cl_2C_6H_3$}C_6H_4)Cl]$_2$ for the enantiomeric excess determination of functionalized phosphines is presented. The X-ray structure determination of diastereomeric complex [Pd(2-{Z-(*R*)-CHMeN=CH-2',6'-$Cl_2C_6H_3$}C_6H_4)Cl{*(R,R)*-PPh_2(2-OHC_6H_{10})}] is also reported.

The growing interest in asymmetric synthesis and the rapidily increasing use of enantiomerically pure compounds as auxiliary chiral building blocks require the development of fast and accurate methods for the determination of enantiomeric excess. NMR is an attractive technique for the determination of enantiomeric excess because it is usually fast and relatively simply to perform.[1] It is well known that dimeric cyclopalladated compounds react easily with a wide range of Lewis bases to afford monomeric complexes of formulae [Pd(C-N)ClL] or [Pd(C-N)ClL_2]. This simple reaction, using optically active cyclopalladated dimers, has been used successfully for the resolution and the determination of the enantiomeric excess of asymmetric chelating ligands.[2] Following our studies on the synthesis and applications of cyclometallated compounds, we expand this strategy to the determination of the enantiomeric excess of monodentated functionalized phosphines. Optically active coordination compounds, containing phosphine ligands, have been employed successfully in homogenous asymmetric catalysis,[3] and in the last few years the study of functionalized phosphine complexes has attracted considerable interest.[4] The enantiomeric purities of the functionalized phosphines **1** (see scheme) were determined by reaction with the cyclopalladated imine derivative [Pd(2-{Z-(*R*)-CHMeN=CH-2',6'-$Cl_2C_6H_3$}C_6H_4)Cl]$_2$, **2**. This optically active complex was prepared by reaction between the free imine and palladium acetate, in acetic acid at 80°C for 2 hours, and subsequent reaction with LiCl.[5] The optically pure imine was easily obtained by condensation of 2,6-dichlorobenzaldehyde and commercially available (*R*)-(+)-1-phenylethylamine. Mixing the racemic phosphine L and the dimeric complex **2** (see scheme), in a 2:1 ratio in $CHCl_3$ at room temperature affords an equimolecular mixture of the expected diastereoisomers [Pd(2-{Z-(*R*)-CHMeN=CH-2',6'-$Cl_2C_6H_3$}C_6H_4)Cl(L)], **3**.[6] The ^{1}H NMR spectra of the mixture show two sets of signals in 1 to 1 ratio. The spectra are quite complex because certain signals partially overlap, as a consequence of the high number of aromatic and aliphatic protons present, but the methinic protons appear at δ = 9 - 10 ppm, as doublets, further away from the remaining resonances[7], and showing an excellent diastereomeric peak separation (see table 1). The down-field shift of the methinic proton and its coupling constant with phosphorus of *ca.* 5 Hz confirm the Z form of the imine.[8] The protons of the metallated ring appear high-field shifted, showing a *cis* arrangement between the phosphine and the metallated carbon.

The β-hydroxyphosphines have been obtained by phosphide ion, $LiPPh_2$, attack on unsymmetrical epoxides.[9] This reaction usually takes place with inversion at the least substituted carbon atom. Since both enantiomers of *trans*-limonene and styrene oxides are commercially available it is possible to obtain the corresponding phosphines in optically pure form and, in consequence, it is easy to assign the methinic proton signals to the corresponding diastereoisomers.

The formation of diastereoisomers **3** takes place instantaneously when the phosphine and the cyclometallated compound are mixed in a 2:1 ratio in a NMR tube. Due to the high molecular weight of the chiral complexing agent, only small quantities of phosphines are required for the NMR determination. The enantiomeric ratios measured on synthetic mixtures of the different enantiomers show a good agreement with the expected values and the presence of less than 3% of the minor isomer was detected.[10] A ratio phosphine:cyclopalladated compound above 2:1 should be avoided because in some cases kinetic resolution could take place (see below). Proton NMR data show that no side products are formed and no racemization has occurred during the formation of mononuclear compounds. ^{13}C and ^{31}P NMR spectra can also be used for enantiomeric purity assignments (see table 1). All these results show that chiral cyclopalladated imine derivatives are useful derivatizing agents for the enantiomeric excess determination of phosphines.



1a,(*R,R*) **1c**,(*1S,2S,4R*) **1e**,(*S*) **1g**,(*R*)

1b,(*S,S*) **1d**,(*1R,2R,4S*) **1f**,(*R*) **1h**,(*S*)

Table 1. Selected NMR data of **3a-h**.

Compound	^{1}H NMR[a]		^{13}C NMR[a]	^{31}P NMR[b]
	HC=N	CH_3 (of imine)	HC=N	
3a	9.10 d J_{H-P} = 5.42	1.72 (d, $^3J_{H-H}$= 6.6)	162.3	33.3
3b	9.56 d J_{H-P} = 4.46	1.49 (d, $^3J_{H-H}$= 6.4)	164.6	41.8
3c	10.08 d J_{H-P}= 4.76	1.46 (d, $^3J_{H-H}$= 6.5)	166.9	49.5
3d	9.51 d J_{H-P}= 5.26	1.61 (d, $^3J_{H-H}$= 6.4)	165.2	48.2
3e	9.18 d J_{H-P}= 5.22	1.74 (d, $^3J_{H-H}$= 6.6)	162.6	41.3
3f	9.32 d J_{H-P}= 4.68	1.55 (d, $^3J_{H-H}$= 6.2)	164.1	46.4
3g	9.17 d J_{H-P}= 5.14	1.56 (d, $^3J_{H-H}$= 6.6)	163.2	27.4
3h	9.08 d J_{H-P}= 5.42	1.74 (d, $^3J_{H-H}$= 6.2)	162.4	27.0

[a] In $CDCl_3$, chemical shift in ppm with respect to internal TMS, coupling costants in Hz. [b] In $CDCl_3$, chemical shift in ppm with respect to 85% H_3PO_4.

The phosphine *trans*-2-PPh_2(CyOH) is only available in racemic form,[11] nevertheless diastereoisomer **3a** could be eficiently separated[12] taking advantage of different solubilities of both diastereoisomers and partial kinetic resolution towards **3a**, when a ratio phosphine/palladium complex of 4:1 was used. The absolute configuration of the coordinated phosphine in this complex was established to be *(1R,2R)* by a crystal structure determination. The stereochemistry of **3a** is shown in Figure 1. Selected bond lengths and angles are given in table 2.

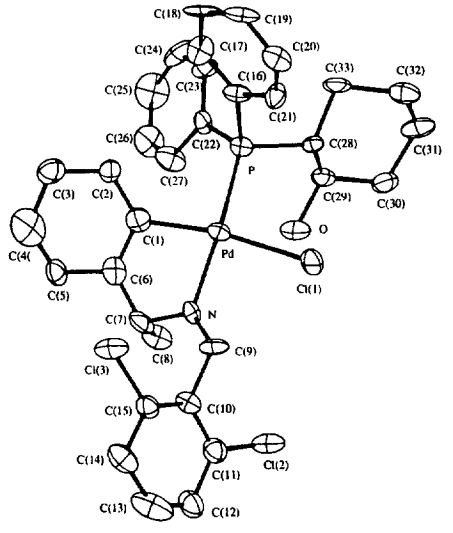


Table 2, Selected bond lengths and angles

Pd-P	2.275(1)
Cl(1)-Pd	2.414(1)
N-Pd	2.105(3)
C(1)-Pd	2.023(4)
C(7)-N	1.488(5)
C(9)-N	1.321(5)
C(29)-O	1.443(6)
Cl-Pd-P	96.2(1)
N-Pd-P	171.4(1)
N-Pd-Cl(1)	89.1(1)
C(1)-Pd-P	95.0(1)
C(1)-Pd-N	80.0(1)

Figure 1. X-ray structure of compound **3a**. $C_{33}H_{33}Cl_3NOPPd$, M = 703.37, orthorombic space group $P2_12_12_1$, a = 12.837(3), b = 13.424(3), c = 18.492(4) Å, V = 3187(2) Å^3, F(000) = 1432.0, Z = 4, D_X = 1.466 g cm^{-3}, Mo-Kα radiation, λ = 0.71069 Å, μ(Mo-Kα) = 8.99 cm^{-1}; the final R and R_W values are 0.030 and 0.032 respectively, for 3356 absorption corrected reflections with I = 2.5σ(I). Full structural details have been deposited with the Cambridge Crystallographic Center.

The crystal structure consists of discrete molecules separated by van der Waals distances. The palladium atom is in a square-planar environment, coordinated to carbon, chlorine, nitrogen and phosphorus atoms. The coordination plane shows a very slight tetrahedral distorsion, the deviation from the mean plane being: +0.062, +0.083, -0.080 and -0.102 Å for Cl1, C1, P and N respectively. The phosphorous and nitrogen atoms adopt a *trans* arrangement. The *ortho* oxygen atom of the phosphine occupies one of the apical sites in the coordination sphere, but the distance Pd···O is 3.190 Å, showing that there is no strong interaction between the two atoms. The metallated phenyl and the benzylic group are in *trans* position relative to the C=N bond, showing that the imine is in the Z form.

Acknowledgements.

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6 Correct C, H, N analyses were obtained for all new compounds.

7 Only in the ^{1}H NMR spectrum of compound **3d** the signal of the alcoholic proton appears near the methinic proton ressonance.

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10 ^{1}H NMR spectra were taken on Varian XL-500. Into an NMR tube was placed 0.044 mmol of the phosphine, 0.023 mmol (20 mg) of the palladium complex and 1.0 ml of $CDCl_3$. The NMR spectrum were recorded instantaneously (number of scans = 16). The *e.e.* determination of synthetic mixtures of the **1c** and **1d** enantiomers were attempted as the most unfavourable case (see note 7). The ratios were: 79.3/20.7 (measured), 79.5/20.5 (prepared); 89.8/10.2 (measured), 90/10 (prepared); 94.4/5.6 (measured), 94.8/5.2 (prepared); 96.6/3.4 (measured), 96.9/3.1 (prepared). The ratios were calculated using the addition of the integrals corresponding to the alcoholic and methinic proton of both isomers.

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12 Compound **3a** : mp 222-224 (with decomposition); $[\alpha]_D^{25}$ = -8.22 (c 0.36, $CHCl_3$).

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