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Cyclopalladation of the primary amine (*R*)-(+)-1-(1-naphthyl)ethylamine: a new resolving agent for monodentate phosphines

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Abstract: The cyclopalladation of the primary amine (*R*)-(+)-1-(1-naphthyl)ethylamine, available commercially, is described. The resolution of the monodentate phosphine *trans*-$PPh_2(2\text{-}HOC_6H_{10})$ by means of the dinuclear cyclopalladated derivative is also reported © 1997 Elsevier Science Ltd

The versatility of *ortho*-palladated derivatives of optically active dimethyl(1-ethyl-α-naphthyl)amine as resolving agents for Lewis bases has been convincingly demonstrated. These complexes are widely used for the resolution of bidentate and monodentate ligands.[1] They have also been used as agents for the determination of the enantiomeric purity of 1,2-diamines[2] and as chiral auxiliaries in the synthesis of optically active diphosphines.[3] Palladium metallacycles derived from this ligand are, in general, better resolving agents for bidentate ligands than the phenylethylamine analogues. This fact has been related to the increased conformational rigidity of the naphthylethylamine derivatives.[4] Surprisingly, the metallation of the corresponding primary amine (*R*)-(+)-1-(1-naphthyl)ethylamine, available commercially, has not been described. It is generally accepted that primary amines are inert towards cyclometallation reactions.[5] Nevertheless, they can undergo the cyclopalladation in good yields, if the experimental conditions are appropriate.[6] This fact prompted us to study the cyclopalladation of the optically active primary amine (*R*)-(+)-1-(1-naphthyl)ethylamine.

The homochiral cyclopalladated dinuclear compound **2** was obtained from the optically active amine by reaction with palladium acetate, in acetic acid at 60°C for 4 hours, and subsequent treatment with LiCl of the acetate dimer. Reaction of dimer **2** with the monodentate phosphines L affords the mononuclear derivatives [PdCl(C–N)L], L=PPh_3 or *trans*-$PPh_2(2\text{-}HOC_6H_{10})$, compounds **3** and **4** respectively (see Scheme 1).[7]

All the new compounds obtained were characterized by elemental analysis, IR spectra, FAB-mass spectra and ^1H and ^{31}P NMR spectra.[8] In some cases NOESY experiments were carried out to complete the NMR studies. Due to the low solubility of the dinuclear cyclopalladated derivative **2**, the NMR spectrum of this compound was recorded in the presence of an excess of deuterated pyridine, which affords the mononuclear derivative [PdCl(C–N)(py-d_5)] **5**. Aromatic protons of the palladated ring appear high-field shifted in the ^1H NMR spectra, indicating a *cis* arrangement of the pyridine and the metallated carbon atom.[9] It should be noted that the two NH protons are in a quite different environment in compound **5**, as can be inferred from their δ values and coupling constants. The value of the $^3J(HH)$ between the *H*CMe proton and the NH_a (where H_a is the NH proton that resonates at δ=6.30 ppm) shows that the metallacycle adopts a quite rigid conformation and that the dihedral angle of the fragment H_aN–CH is small.[10] The high-field shift of the aromatic protons of the palladated ring in **3** and **4**, due to the aromatic rings of phosphines, shows the *cis* disposition of the phosphorus relative to the metallated carbon atom. The chemical shift of the phosphorus in **3** confirms this geometry.[9]

Attempts to separate the diastereoisomers **4a** and **4b** by recrystallization were unsuccessful, but the elution of compound **4** on an SiO_2 column, using chloroform–methanol (100/3) as an eluent,

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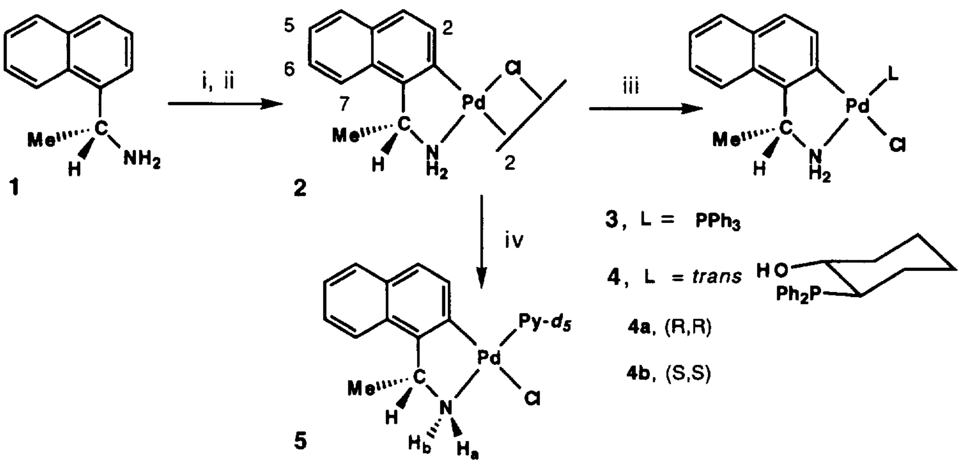

i) $Pd(AcO)_2/AcOH$, 60°, 4h; ii) LiCl/EtOH, room temperature, 30 min; iii) PPh_3, acetone room temperature, 30 min or *trans*-$PPh_2(2\text{-}OHC_6H_{10})$, THF, room temperature, 30 min; iv) py-d_5, $CDCl_3$

Scheme 1.

allows the separation of these two diastereoisomers. The first band eluted was collected in fractions of 25 ml, concentrated *in vacuo* and checked by ^1H NMR spectroscopy (250 MHz), using the methyl proton signals. From 120 mg of **4** (50/50), 40 mg of the (*R,R,R*) isomer **4a** and 30 mg of the (*R,S,S*) diastereoisomer **4b** were obtained. The *d.e.* of both diastereoisomers was more than 95%. A mixture of both diastereoisomers was also obtained in intermediate fractions.

As a rule, the separation of the diastereoisomers containing cyclopalladated units is based on solubility differences. In only a few cases has the separation been accomplished by column chromatography. Yoneda *et al.*[11] have described the resolution of palladium complexes containing a Pd–C*(sp^3) bond by column chromatography (150 cm high) and recently Dunina *et al.*[12] have described the purification of two diastereoisomers containing *tert*-butylmethylphenylphosphine by using several flash columns.

The action of dppe on the optically enriched cyclopalladated derivatives **4** permits us to obtain the free phosphine *trans*-$PPh_2(2\text{-}OHC_6H_{10})$ (RMN ^{31}P: $\delta = -10.4$). The ^{31}P NMR spectrum obtained when the cyclopalladated compound $[Pd(2\text{-}\{Z\text{-}(R)\text{-}CHMeN{=}CH\text{-}2',6'\text{-}Cl_2C_6H_3\}C_6H_4)Cl]_2$ is added to the solution containing the free phosphine shows that the absolute configuration of the phosphine is *1R,2R* in the first diastereoisomer eluted (δ=33.3 ppm), and also that the enantiomeric purity of these ligand is higher than 95%.[13]

In conclusion, we have shown that the primary amine (*R*)-(+)-1-(1-naphthyl)ethylamine, available commercially, can easily be metallated, if the experimental conditions are appropriate. Moreover, the dinuclear optically active metallacycle obtained can be used successfully for the resolution of the functionalized monodentate phosphine *trans*-$PPh_2(2\text{-}OHC_6H_{10})$ by a single column chromatography of the corresponding diastereomeric cyclopalladated derivative $[PdCl(C\text{–}N)\{trans\text{-}PPh_2(2\text{-}OHC_6H_{10})\}]$. The application of this dinuclear cyclopalladated derivative to the resolution of new monodentate and bidentate phosphines is currently under way.

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8. Correct C, H, N analyses were obtained for all new compounds. NMR data: **3**: ^{1}H: 7.80–7.70 [m, 5H, aromatic], 7.60–7.20 [m, 14, aromatic], 6.90 [d, J(HH)=8.5Hz, 1H, H^3], 6.55 [dd, J(HH)=8.5Hz, J(HP)=5.5Hz, 1H, H^2], 5.25 [quartet, 1H, J(HH)=5.5Hz, C*H*Me], 4.15 [br m, 1H, N*H*], 3.75 [br m, 1H, N*H*], 1.95 [br m, 1H, J(HH)=6.5Hz, 3H, CH*Me*]. ^{31}P: 40.9, s. (*R,R,R*)-**4a** : ^{1}H: 8.05–7.90 [m, 4H, aromatic], 7.65–7.25 [m, 10H, aromatic], 7.0 [d, J(HH)=8.0Hz, 1H, H^3], 6.55 [dd, J(HH)=8.5Hz, J(HP)=6.0Hz, 1H, H^2], 5.50 [br d, 1H, N*H*], 5.20 [quartet, 1H, J(HH)=6.0Hz, C*H*Me], 4.15 [br m, 1H, N*H*], 3.40 [br m, 1H, *H*O], 3.20–2.80 [br m, aliphatic], 2.60–2.30 [br m, aliphatic], 2.00 [d, J(HH)=6.5Hz, 3H, CH*Me*], 1.75–1.0 [br m, aliphatic]. ^{31}P: 45.8, s. (*R,S,S*)-**4b** : ^{1}H: 8.15–8.0 [m, 2H, aromatic], 7.95–7.85 [m, 2H, aromatic], 7.65–7.25 [m, 10H, aromatic], 7.0 [d, J(HH)=8.5Hz, 1H, H^3], 6.65 [dd, J(HH)=8.5Hz, J(HP)=6.0Hz, 1H, H^2], 5.20 [quartet, 1H, C*H*Me], 4.60 [br m, 1H, N*H*], 4.45 [br m, 1H, N*H*], 3.40 [br m, 1H, *H*O],

2.60–2.20 [br m, aliphatic], 1.85 [d, J(HH)=6.5Hz, 3H, CH*Me*], 1.75–1.0 [br m, aliphatic]. ^{31}P: 47.9, s. **5**: ^{1}H: 7.80 [m, 2 H, aromatic], 7.50–7.30 [m, 4 H, aromatic], 6.30 [dd, J(HH)=10.5, 6.5Hz; 1H, N*H*], 6.20 [d, J(HH)=8.4Hz, 1H, H^2], 5.20 [quintuplet, J(HH)=6.5Hz, 1H, C*H*Me], 3.50 [d, J(HH)=10.5Hz, 1H, N*H*], 1.90 [d, J(HH)=6.5Hz, 3H, CH*Me*].

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