Highly selective *R*,*S*-coordination of non racemic (1*R*,2*R*)-(1,2-dialkyl)-1,2-diamine cyclohexane derivatives to palladium dichloride†

Esfandiar Rafii, Benjamin Dassonneville and Andreas Heumann*

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In non-racemic (1*R*,2*R*)-(1,2-dialkyl)-1,2-diaminocyclohexane palladium dichloride complexes the C_2 symmetry of the diamine ligand is broken, resulting in selective *R*,*S*-coordination.

The role of nitrogen donor ligands in controlling the reactivity, but also the selectivity, in metal-catalysed transformations has become increasingly important for organic synthesis.[1] Indeed, a great variety of amines are known and, generally, are easily available by simple organic reactions.[2] This is particularly true for chiral amines and their use for asymmetric transformations. One point that merits major attention is the possibility of making use of stereogenic nitrogen atoms upon coordination of the metal to a disymmetrically substituted amine. Such persistent *N*-chirality has recently been demonstrated with achiral 1,2-diamines in $LPdCl_2$ metal complexes.[3]

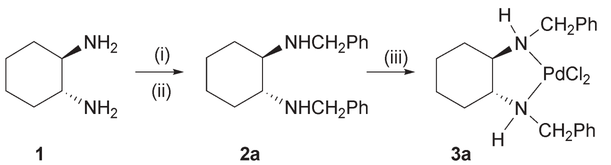
Vicinal diamines,[4] and especially enantiomerically pure *trans*-1,2-diaminocyclohexanes,[5] are convenient starting materials for highly discriminating derivatives and their metal complexes. Jacobsen's salicylidene Co(III) complexes for kinetic resolution of terminal epoxides[6] or Trost's phosphinobenzoylamides[7] for palladium catalysed allylic substitution reactions are two extremely efficient systems among others. Though numerous chiral non racemic palladium amine coordination compounds are known and are frequently applied in asymmetric catalysis, *trans*-1,2-diaminocyclohexane and derivatives are only rarely used in combination with palladium as such in NHC (*N*-heterocyclic carbene),[8,9] or hybrid imine–NHC[10] complexes. $PdCl_2$(1*R*,2*R*)-1,2-diaminocyclohexane gave good results as a reagent in the determination of the enantiomeric ratio of unprotected amino acids.[11] The enantioselective Claisen rearrangement of allyl ethers,[12] and allylic alkylation of acetates[13] are catalysed, with good to excellent selectivities, by palladium complexes with these types of C_2-symmetrical ligands. Given the ready access to chiral diamines from **1**[5] and the great interest in Pd–amine complexes as catalysts (oxidation of alcohols,[14] allylic substitution reactions,[15] *etc.*), we decided to prepare optically active $PdCl_2$–diaminocyclohexane complexes that contain variable, but identical organic groups at each nitrogen atom. In this paper we report on the synthesis of a series of *trans*-1,2-diaminocyclohexanes, their coordination to $PdCl_2$ and a structural study of these new complexes.

Among the current methods to introduce selectively one organic group into a secondary amine the reductive amination of carbonyl compounds seemed to us the most appropriate one. The palladium chloride complexes **3a** may be obtained *via* ligand exchange from L_2PdCl_2 (L = MeCN, Me_2S; L_2 = 1,5-COD). Accordingly, dialkyldiaminocyclohexanes **2a–2k** are readily prepared in this way. As a first example the bisbenzyl amine (*R*,*R*)-**2a** was coordinated to $PdCl_2$ (Scheme 1, Scheme 2).

The coordination of a metal to *trans*-1,2-diaminocyclohexanes leads to a 5-membered metallaheterocyclic ring that blocks the nitrogen in a tetrahedral position, increases the *N*-inversion barrier, and thus induces chirality provided there is non-equivalence of the nitrogen substituents.

In the case of **3** with identical substituents at each nitrogen we can consider three possibilities: first, the *dl* pair *R*,*R*- and *S*,*S*-(*R*,*R*)-**3** with the substituents at nitrogen in a pseudo equatorial or pseudo axial position, respectively, and second, the isomeric structure with two different nitrogen atoms, the *R*,*S*-(*R*,*R*)-**3** with the substituents at nitrogen in both a pseudo equatorial and a pseudo axial configuration (Scheme 3). The latter situation corresponds to the *meso* compound in the case of achiral amines.

The bright yellow complex (*R*,*R*)-**3a** that we obtained from (*R*,*R*)-**2a** exhibited NMR spectra that were quite different from the picture of the free ligand.[16] All data that we obtained from the proton and carbon spectra[17] led to the conclusion that upon coordination to $PdCl_2$ the original C_2 symmetry of the diamine ligand disappeared. The aromatic signals were much more split from a quite narrow multiplet at 7.6 (less than 0.5 ppm broad) in (*R*,*R*)-**2a** to a pattern of at least three complex signals between 7.1 and 8.0 ppm in (*R*,*R*)-**3a**. Two broad NH resonances at 5.41 and 5.56 ppm in (*R*,*R*)-**3a** indicate that the two nitrogen atoms are no more equivalent compared to the C_2 symmetrical diamine (*R*,*R*)-**2a**. We also observe two well separated signals for the ring junction protons at, respectively, 2.44 and 4.14 ppm ($\Delta\delta$ 1.7 ppm), as well as two pairs of signals for the benzylic CH_2 group (3.36 and 4.22; 3.78 and 4.36 ppm). The C_1H or C_2H proton resonance at 4.14 ppm is hidden by the signal of one of the four benzylic

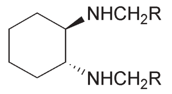


1 **2a** **3a**

Scheme 1 (i) C_6H_5CHO, CH_2Cl_2, 40 °C, 15 min; (ii) $NaBH_4$, MeOH, 4 h; (iii) $(MeCN)_2PdCl_2$, CH_2Cl_2, 25 °C, 1 h, or (finely powdered) $PdCl_2$,MeCN, 25 °C, 2–3 days.

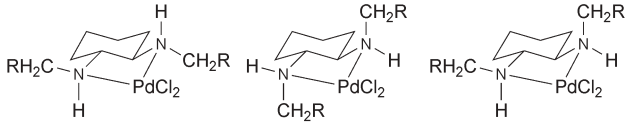
Université Paul Cézanne, UMR CNRS 6180 'Chirotechnologies: Catalyse et Biocatalyse', Faculté Saint-Jérôme, Case A 62, 13397 Marseille Cedex 20, France. E-mail: andreas.heumann@univ-cezanne.fr; Fax: 33 49128 8278; Tel: 33 49128 8278

† Electronic supplementary information (ESI) available: Experimental details, ^1H, ^{13}C and ^{19}F NMR spectra. See DOI: 10.1039/b613961b



(1*R*,2*R*)-**2a** R = Ph, **b** R = *p*-F-Ph, **c** R = *p*-CF$_3$-Ph,
d R = *p*-OMe-Ph, **e** R = *m*-CF$_3$-Ph, **f** R = *m*-NO$_2$-Ph,
g R = *o*-NO$_2$-Ph, **h** R = mesityl, **i** R = 1-naphthyl,
j R = 1-furfuryl, **k** R = 3,3-dimethylpropyl.

Scheme 2



S,*S* (1*R*,2*R*)-**3** *R*,*R* (1*R*,2*R*)-**3** *R*,*S* (1*R*,2*R*)-**3**

Scheme 3 *dl*- and *R*,*S*-coordination mode of Pd(II) to *trans*-1,2-diaminocyclohexanes.

hydrogens. This attribution was confirmed by 2D experiments, and furthermore a HMQC sequence made it possible to clearly show the relationship of the proton signal at 4.14 ppm with a tertiary carbon at 66.8 ppm. The 'loss of symmetry' was also apparent in the ^{13}C NMR spectra which showed 17 different carbon resonances corresponding to roughly one signal for every carbon atom. Upon variation of the substitutents at nitrogen a similar picture could be observed for all comparable groups in compounds **3a–3k**. Different substitution patterns at the aromatic core but also the position (*ortho*, *meta*, and *para*) of the functional groups such as CH$_3$, F, CF$_3$ and NO$_2$ are compatible with the coordination mode in (1*R*,2*R*)-**3**.[18] Also a longer aliphatic chain in (1*R*,2*R*)-**3k** gave similar NMR patterns.

It is clear from the NMR data that we do not have in solution all the different structures depicted in Scheme 3. However, either we have two different species or, on the other hand, only one compound that has lost C_2-symmetry. The possible mixture of the *dl* isomers *R*,*R*- and *S*,*S*-(1*R*,2*R*)-**3a** is discarded with the following argument. In all compounds studied the integration of the different hydrogens accounts for 1 unit per hydrogen. When fluorine atoms are present two resonances appear with a 1 : 1 ratio. The *dl* isomers *R*,*R*- and *S*,*S*-(1*R*,2*R*)-**3a** are diastereomers and thus have different physical properties. It seems to us highly improbable that the coordination of all substrates **2** to PdCl$_2$ would give an exactly equimolar mixture of the *R*,*R*- and *S*,*S*-isomers. The resulting structure that we retain is *R*,*S*-(1*R*,2*R*)-**3a** with two nitrogen atoms showing opposite (*R* and *S*) configuration, respectively. To our delight, an unequivocal structure determination was obtained with the crystal structure of (1*R*,2*R*)-**3b**.

On slowly evaporating a dichloromethane solution of (1*R*,2*R*)-**3b** we obtained bright orange crystals that were suitable for an X-ray structure analysis.‡ The asymmetric unit consists of two monomers of (1*R*,2*R*)-**3b** related by a pseudo centre of symmetry. The absolute configuration was previously known since we started from enantiomerically pure diamine **2a** and it was then confirmed experimentally by the anomalous scattering of the Pd and Cl atoms and the refinement of 3506 Friedel pairs. A view of the molecule is given in Fig. 1.

This X-ray structure is consistent with the interpretation of the NMR spectra and confirms the loss of C_2 symmetry of the bisaryl(1*R*,2*R*)-diaminocyclohexane derivatives coordinated to palladium(II). The bond lengths and angles do not vary from known values (Fig. 1).[3] In the square planar Pd(II) complex the palladaheterocyclopentane ring adopts a twist conformation that is slightly out of the plane of the cyclohexane plane (C1–C2–C4–C5). As Fig. 1 shows, each substituent at nitrogen is visibly pseudo axial at one and pseudo equatorial at the other nitrogen in the coordinated (*R*,*R*)-**2**. This orientation places both benzyl groups at the same side of the cyclohexane plane and opposite to the metal. The bridgehead protons are fairly close to the palladium atom (3.231 and 3.067 Å). They now have completely different magnetic neighbourhoods: one proton is quite close to a phenyl group and consequently high-field shifted proton resonances (2.44 ppm) appear. The second CH under the cyclohexane plane is completely unaffected by the *N*-benzyl substituents and exhibits 'normal' magnetic behaviour. The high Δδ value of 1.69 ppm in (1*R*,2*R*)-**3b** reflects nicely this magnetic non-equivalence.[19] The proximity (Pd–H2 = 3.067 Å) of the Pd atom to the 'anti' hydrogen (with respect to the benzyl groups) most probably enlarges this effect.

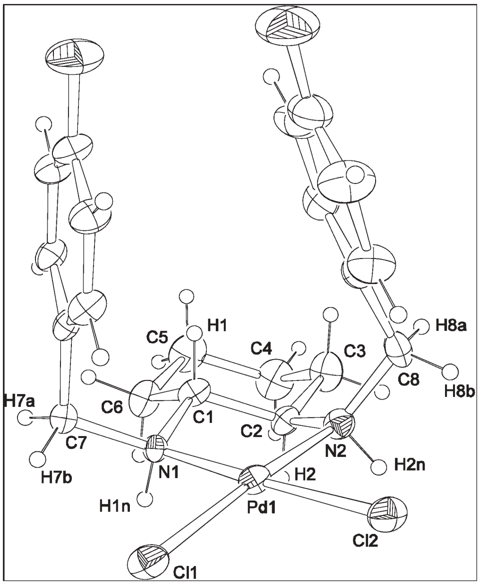


Fig. 1 X-ray structure representation (ORTEP) of (1*R*,2*R*)-**3b**. Selected structural parameters: Bond distances (Å), atom distances (Å), and angles (°) for one of the two monomers include N1–Pd = 2.059(6), N2–Pd 2.073(7), Cl1–Pd = 2.322(2), Cl2–Pd 2.324(2), H1–Pd = 3.23, H2–Pd 3.07, H7b–Pd = 3.17, H8b–Pd 3.26, H1n–Pd = 2.46, H2n–Pd 2.44, N1–Pd–N2 = 84.88, Cl1–Pd–Cl2 = 92.95. Only one of the two molecules **3b** is shown. The geometrical parameters of the second monomer are very similar to those presented for the first monomer.

The reason for the selective *R*,*S*-coordination of (1*R*,2*R*)-dialkyl-diaminocyclohexane derivatives to palladium chloride is not clear. Normally, in square planar d^8 complexes the ligand substitution is an associative process.[20] It is reasonable to assume that coordination will occur in a stepwise manner. Thus if the first nitrogen coordinates *via* the N directing the benzyl group into an equatorial position after which the approach of the second N-benzyl to the metal should occur in a position distant to the metal, that means into the pseudo-axial configuration. The size of the substituents at nitrogen might be decisive for this exclusive coordination mode, in other words: would the presence of a tertiary amine favour the *dl* isomers? The amine required for this purpose, (*R*,*R*)-**4**, could be obtained after methylation (MeI, LiOH in CH_2Cl_2)[21] of **2b**. On reacting the tertiary amine (1*R*,2*R*)-**4** with $PdCl_2$ or $(MeCN)_2PdCl_2$ under the usual conditions a mixture of three inseparable isomeric complexes (1*R*,2*R*)-**5** was observed by NMR. The NMR resonances of the fluorine atom in the ligand part of (1*R*,2*R*)-**5** allows convenient estimation of the ratios of *dl* and *R*,*S* isomers in the new complex (1*R*,2*R*)-**5**.[22] The ratios of the three components may vary depending on the reaction conditions; however, the complex *R*,*S*-(1*R*,2*R*)-**5** (see Scheme 1) is predominant together with 2 *dl* isomers of (1*R*,2*R*)-**5** (ratio *e.g.* of 5 : 2 : 2).[23]

It is interesting to note that exhaustive *N*-substitution gives rise to quite unselective *R*,*S* and *dl* coordination. This behaviour has already been observed in more flexible 1,2-diamines, such as disubstituted amines from 1,2-diaminoethane with $PdCl_2$ (*e.g.* **6a**) leading to the mixture of (*R*,*R*), (*S*,*S*) and (*R*,*S*) compounds in a ratio of about 1 : 1 : 1.[3] We also wanted to evaluate the influence of the cyclic chiral backbone upon coordination in these systems. A palladium complex without the constraint of the diequatorial position of the nitrogen atoms in the *trans* 1,2-cyclohexane and secondary nitrogen atoms (**6b**) was synthesized The bright orange compound formed easily in MeCN and the ^{19}F NMR showed two peaks in a ratio of 2 : 1.[24] Though, for the present, we cannot attribute the major compound to either the (*R*,*R*) or the *dl* series this result compares to the reactions with tertiary 1,2-diaminoethanes[3] as well with aliphatic but also with alicyclic compounds **5** and (1*R*,2*R*)-**3**.

In conclusion, we have shown that easily accessible enantiomeric 1,2-diamines with cyclohexane as the chiral backbone and the nitrogens of secondary amines as the coordinating heteroatoms react with $PdCl_2$ to form stable and easily isolated metal complexes.[25] Without any exception the coordination mode corresponds to an *R*,*S*-stereochemistry, which means that the chiral nitrogens blocked in a five-membered diaza-palladacycle ring system show opposite *R* and *S* configuration. This phenomenon is, for the moment, limited to systems with square-planar ligand fields (Pd, Pt) since in the octahedral nickel complex Ni-bis[(*R*,*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine]Br_2 **7** recently described by Evans *et al.*[26] the (1*R*,2*R*)-dialkyl-diaminocyclohexane coordinates in the homochiral (*S*,*S*) fashion with both benzyl groups blocked in the pseudo-diequatorial configuration. This coordination behaviour, apart from its fundamental interest for the relation between ligand structure and coordination mode, may occur in metal catalysed transformations. As we have shown in this study, small structural changes may modify the coordination mode and the selectivity of the coordination.

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Notes and references

‡ *Single-crystal X-ray diffraction data for* (1*R*,2*R*)-**3b**: $C_{20}H_{24}Cl_2F_2N_2Pd$, M_w = 507.73, monoclinic, orange crystal (0.3 × 0.2 × 0.05 mm^3), a = 14.214(5), b = 9.039(1), c = 16.311(3) Å, β = 100.552(8)°, V = 2060.2(9) $Å^3$, space group $P2_1$, Z = 4, ρ = 1.637 g cm^{-3}, μ(MoKα) = 11.89 cm^{-1}, 14477 reflections measured at 293 K to θ_{max} = 25.97°, 7681 unique, 487 parameters refined on F^2 to final indices $R[F^2 > 4\sigma F^2$: 6291 reflections] = 0.048, wR[7681 reflections] = 0.1094 [$w = 1/[\sigma^2(F_o^{\ 2}) + (0.027P)^2 + 2.3231P]$ where $P = (F_o^{\ 2} + 2F_c^{\ 2})/3$]. The final residual Fourier positive and negative peaks were equal to 0.785 and −0.757, respectively. Absorption correction was applied to the data before the final stage of refinements. CCDC 629162 (**3b**) contains the supplementary crystallographic data for this structure. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613961b

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18 The presence of fluorine as a spectator atom in the ligand is a valuable aid in the NMR detection of the composition of the complex structure and the reaction mixtures.

19 In the complexes studied, the Δδ values vary from 1.28 to 1.71 ppm (see Table 1 in the supplementary material).

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22 ^{19}F NMR δ: −111.2 (21%, *dl*-1), −111.7 and −112.0 (55%, *R*,*S*), −111.8 (20%, *dl*-2), −114.5 (3%, unknown). The predominance of the *R*,*S* isomer is recognized by the presence of the two fluorine resonances with a ratio of 1 : 1. The analysis of the proton spectra of the mixture is also diagnostic. Theoretically we are expecting eight doublets for the benzylic protons. In reality we visualize (and attribute) seven doublets: *dl*-1 (1*R*,2*R*)-**5** δ: 4.47, 3.26; *dl*-2 (1*R*,2*R*)-**5**: 4.96, 2.96 (partially hidden); *R*,*S* (1*R*,2*R*)-**5c**: 4.23, 3.54, and 4.74, 3.67. It was possible to obtain mixtures with variable *dl* and *R*,*S* proportions *via* chromatography on silica (eluent: dichloromethane–methanol 95 : 5).

23 Conditions: $(MeCN)_2PdCl_2$, CH_2Cl_2, 25 °C, 1 h.

24 Complex **6b** is insoluble in most common solvents and we could only obtain the proton and fluorine NMR spectra in D6-DMSO. Except for the visibility of the presence of two compounds, confirmed by proton resonances, too, we are unable for the moment to analyze completely the NMR data.

25 In preliminary experiments we have obtained complexes from $PtCl_2$ with the same *R*,*S* structure comparable to *R*,*S*-(1*R*,2*R*)-**3** according to the NMR spectra.

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