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NMR Assignment of Absolute Configuration of a P-Chiral Diphosphine and Mechanics of its Stereoselective Formation

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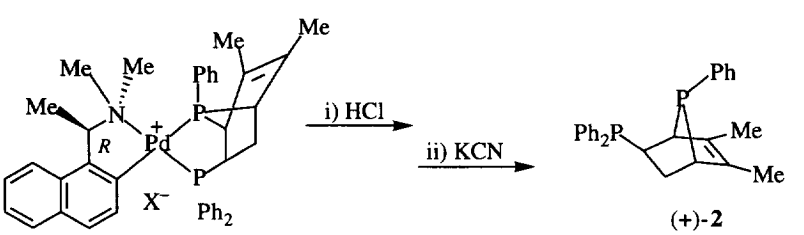
Abstract: Two-dimensional rotating-frame nuclear Overhauser enhancement (ROESY) NMR spectra are used to determine the absolute configuration of (+)-diphenyl-phosphine-2,3-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene. This diphosphine ligand is obtained from the palladium complex-promoted Diels-Alder reaction between diphenylvinylphosphine and 1-phenyl-3,3-dimethylphosphole in the presence of (*R*)-dimethyl(1-(α-naphthyl)ethylamine as the chiral auxiliary. The origin of the stereoselectivity in this asymmetric reaction is also revealed by solution NMR studies.

In connection with our studies of the asymmetric synthesis of P-chiral phosphines, we have recently reported the asymmetric Diels-Alder reaction between dimethylphenylphosphole and diphenylvinylphosphine in the presence of configurationally homogenous palladium(II) complexes containing *ortho*-metallated 1-[1-(dimethylamino)ethyl]naphthalene.[1] When the *R* form of the chiral naphthylamine auxiliary is used in this asymmetric [4+2] cycloaddition reaction, the diphosphine template product (–)-**1** is obtained stereoselectively, and the enantiomerically pure diphosphine ligand, (+)-2, can subsequently be liberated from (–)-**1** in quantitive yield.



(-)-**1** (X = Cl, ClO_4, PF_6) (+)-**2**

In this asymmetric synthesis, three carbon and one phosphorus stereogenic centres are formed stereoselectively, and ideally, the absolute configuration of the diphosphine ligand could be determined directly by an X-ray structural analysis of (–)-**1**. Unfortunately, single crystals of the complex that are suitable for structural investigation could not be produced, despite the fact that all the three salts of the cationic complex are

chemically stable and are readily crystallized from most solvent systems. These crystals generally suffer from problems of rapid desolvation and numerous capillaries are found within the lattice.

In this paper, we describe the configurational analysis of the chelating diphosphine ligand in the PF_6^- salt of (–)-**1** by means of a series of solution NMR studies. Factors that govern the stereoselectivity of the Diels-Alder reaction are also investigated. We have previously reported the development of such an NMR technique for the assignment of the absolute stereochemistry in some similar palladium(II) complexes containing (*S,S*)-chiraphos.[2]

(I) Assignment of the Absolute Stereochemistry in (–)-1.

Figure 1 shows the numbering scheme and the one-dimensional ^1H and ^{31}P NMR spectra of (–)-**1** in $CDCl_3$. Both spectra are consistent with the presence of a single isomer in solution. Selected chemical shifts of the complex are given in Table 1. The spectral assignments in the ^1H NMR spectrum are based on selective decoupling of the two types of ^{31}P nucleus, double-quantum filtered COSY spectra and NOE data from 2D-ROESY spectra.

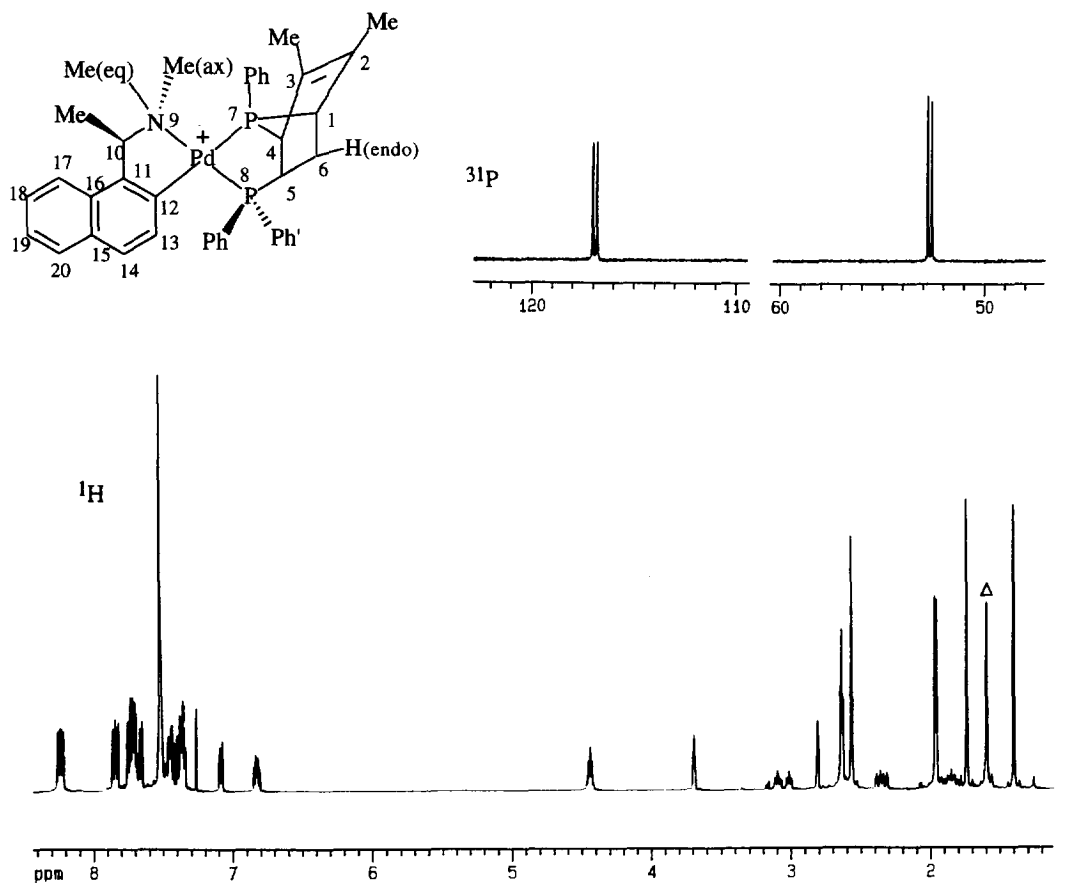


Figure 1. ^1H and ^{31}P NMR spectra of (–)-**1** in $CDCl_3$. Δ: H_2O signal.

Table 1. Selected chemical shifts in ppm in (–)-**1** in $CDCl_3$ solution.

H1	3.65	*o*-Ph8'	8.23
Me2	1.73	Me9(ax)	2.56
Me3	1.39	Me9(eq)	2.63
H4	2.81	H10	4.44
H5	3.05	Me10	1.96
H6(endo)	1.85	H13	6.83
H6(exo)	2.35	H17	7.74
Ph7	7.51	P7	116.9
o-Ph8	7.84	P8	52.7

(Ia) Internal Stereochemical References

It is well established by X-ray crystallography[3] that, in solid state, the 5-membered (*R*)-metallated naphthylamine ring adopts the δ absolute conformation with the methyl substituent on the stereogenic carbon invariably taking up the axial position above the PdCN ring, as illustrated in Figure 2. This axial rather than equatorial geometry for the methyl group is attributed to the extreme steric congestion that would otherwise be present between the proximal naphthylene proton H17 and the methyl group.[4,5] Due to the fixed ring conformation, the prochiral N-Me groups are locked into the stereochemically non-equivalent axial and equatorial positions. The NMe(ax) group projects perpendicularly below the square plane and NMe(eq) is somewhat above the plane and quite close to P. It is pertinent to note that due to their relative proximities, equatorially located donor substituents in rigid five membered rings are found to experience much more direct and severe inter-chelate repulsive forces than their axial counterparts.

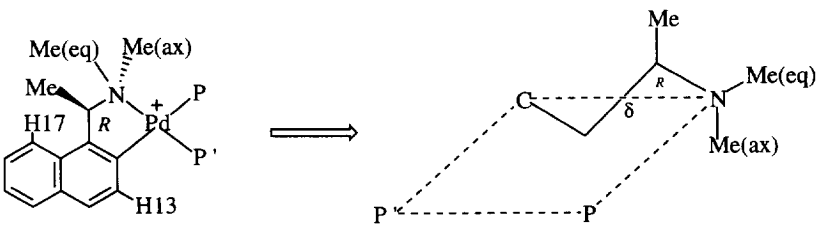


Figure 2. Absolute Conformation of the PdCN ring

In solution, the absolute stereochemistry of the PdCN ring can be unambiguously assigned by the two dimensional ^1H–^1H NOE spectroscopy (Figure 3). In this ROESY spectrum, strong NOE signals are observed for the interactions between H10 and all the three methyl groups on N9 and C10 (Signals A-C). These NOE interactions are consistent with the staggered orientation of these substituents when the (*R*)-naphthylamine ring adopts the δ conformation, as illustrated in Figure 4a. Accordingly, Me10 interacts strongly (Signal D) only with NMe(eq). The absence of a Me10–NMe(ax) NOE rules out a λ ring in solution. The driving forces for Me10 to assume the axial position, ie the H17–H10 (E) and H17–Me10 (F) repulsive interactions, are clearly reflected in the spectrum.

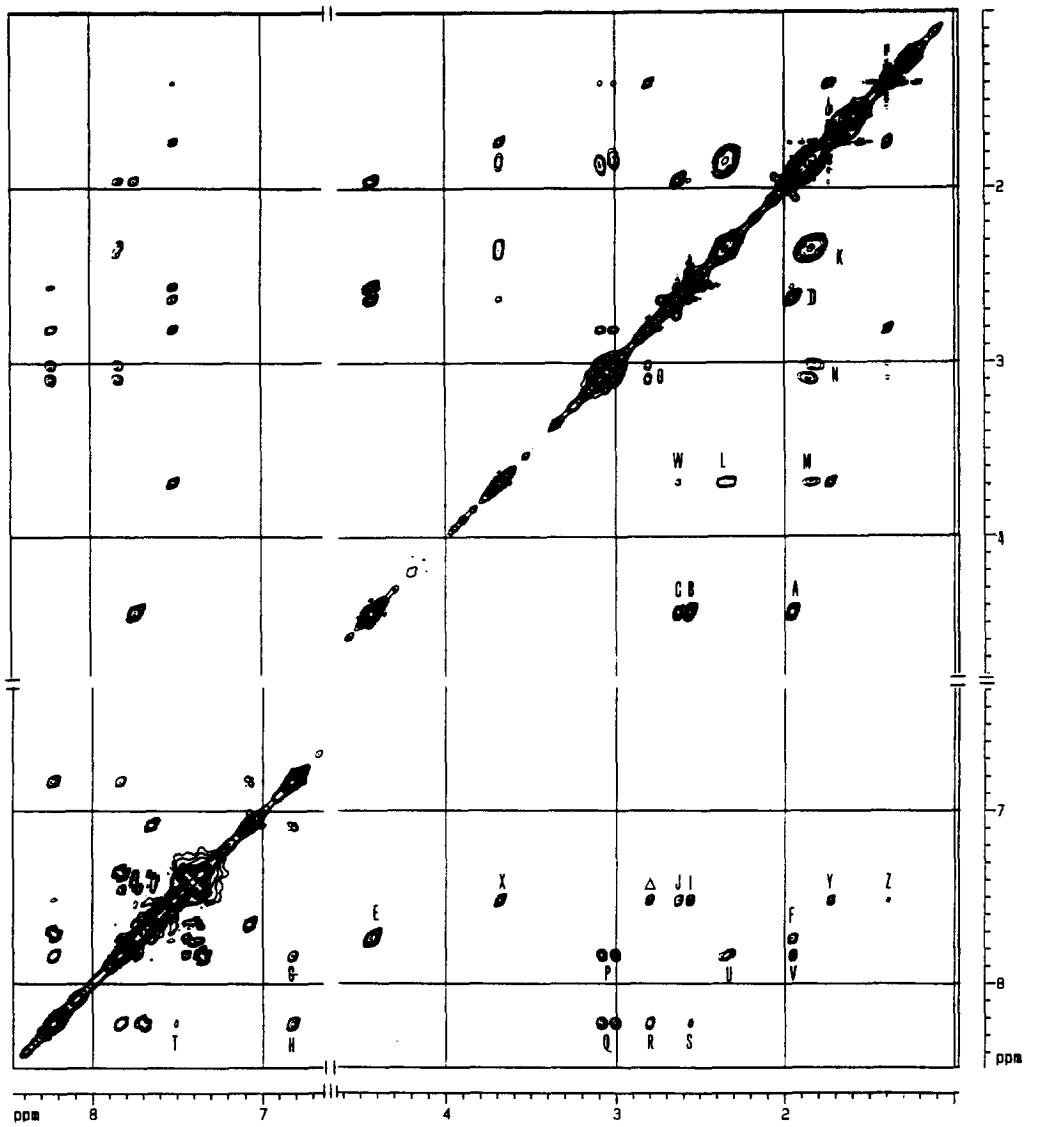


Figure 3. 2D ROESY spectrum of (–)-**1** in $CDCl_3$. Selected NOE signals:

A: H10–Me10	B: H10–Me9(ax)	C: H10–Me9(eq)	D: Me10–Me9(eq)	E: H10–H17
F: Me10–H17	G: H13–*o*-Ph8	H: H13–*o*-Ph8'	I : Me9(ax)-Ph7	J: Me9(eq)–Ph7
K: H6(exo)–H6(endo)	L: H1–H6(exo)	M: H1–H6(endo)	N: H5–H6(endo)	O: H4–H5
P: H5–*o*-Ph8	Q: H5–*o*-Ph8'	R: H4–*o*-Ph8'	S: Me9(ax)–*o*-Ph8'	T: Ph7–*o*-Ph8'
U: H6(exo)–*o*-Ph8	V: Me10–*o*-Ph8	W: H1–Me9(eq)	X: H1–Ph7	Y: Me2–Ph7
Z: Me3–Ph7	Δ : H4-Ph7			

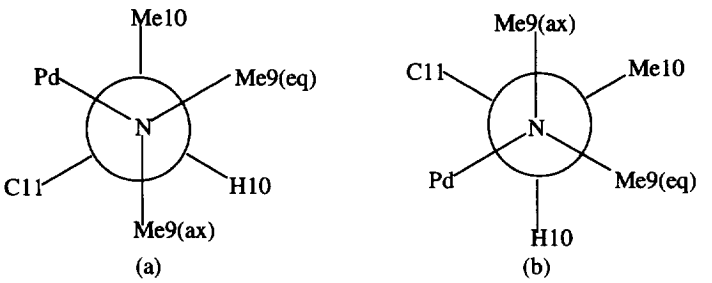


Figure 4. Staggered orientations of the N9 and C10 substituents when the PdCN ring adopts the (a) δ or (b) λ conformation.

The above ROESY signals clearly reveal that, as in the solid state, the (*R*)-naphthylamine organometallic ring adopts the δ conformation in solution. In addition, due to this rigid skew ring conformation and the strict planarity of the naphthylene ring, the H13 aromatic proton protrudes invariably toward the space just below P'. This protruding aromatic proton generally exhibits resonance signals at characteristically low chemical shifts which are readily identified. In (–)-**1**, the resonance is observed at δ 6.83. This naphthylene proton, together with the stereochemically well-defined NMe groups, are powerful chirality sensors in this naphthylaminato-palladium unit and are used as the internal references in the absolute stereochemistry assignments in the present NMR studies. We have previously reported that these protons are useful NMR probes for the enantiomeric purity determinations and, in many instances, are able to control the stereochemistry of their neighbouring coordination sites.[4]

(Ib) Regio-isomerism

The square-planar complex (–)-**1** contains one C–N and one P–P' asymmetric bidentate and thus can occur as two possible regio-isomers (Figure 5). Although the one-dimensional NMR spectra are indicative of only one isomer in solution, it is still necessary to establish the relative regio-arrangement of the four non-equivalent donor atoms prior to the absolute stereochemistry investigation.

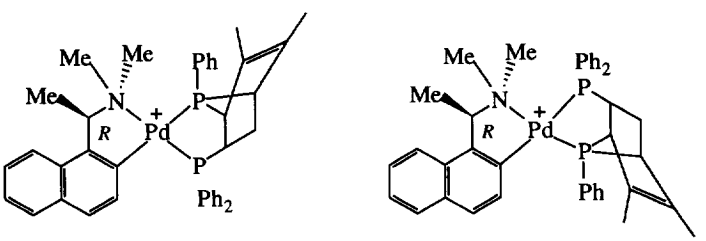


Figure 5. The two possible regio-structures of (–)-**1**.

In the present series of NMR studies, it is found that resonances of *ortho*-protons in Ph8 (δ 7.84) and that in Ph8' (δ 8.23) provide crucial structural information on (–)-**1**. Both resonances show strong NOE

interactions with the protruding naphthylene proton, H13, (Signals G and H). Hence, the PPh_2 moiety occupies the coordination site which is adjacent to the metallated carbon, as depicted in Figure 5, Structure I. This regio-assignment is further supported by the selective $^1H\{^{31}P\}$ decoupling of P7 at δ 116.9. The experiment shows no effect on the quintet resonance of H10 which occurs at δ 4.44 (J_{PH} = 6.1Hz, J_{HH} = 6.4 Hz). On the other hand, selective decoupling of P8 at δ 52.7 simplifies the H10 resonance to a simple quartet. Interestingly, all the aromatic protons in Ph7 resonate as one strong signal at δ 7.51. These protons show NOE interactions with both NMe groups (I, J). In agreement with the above regio-chemistry assignment, there is no NOE contact recorded between H13 and Ph7.

(Ic) Absolute Configuration Assignment

The establishment of the regio-chemistry in (–)-**1** reduces the number of possible diastereomers to 2. Figure 6 shows the two possible diastereomeric structures for the square-planar complex cation. The diphosphine ligands in these two isomers are enantiomers. In **Isomer A**, the absolute configuration at P7 is *S*. In this isomer, the P7–C4–C5–P8 linkage may be viewed as part of the 5-membered P-Pd-P' chelate ring which adopts the rigid δ conformation. Hence, Ph8 occupies a pseudo-equatorial position above the CNPP' square-plane and Ph8' is in an axial position below the plane. The bridgehead substituent, Ph7, projects towards the space below the plane. Due to the δ conformation, significantly, H4 occupies the axial position below the plane. In **Isomer B**, the absolute configuration at P7 is *R* and the P7–C4–C5–P8 ring adopts the λ conformation. Accordingly, Ph8 occupies the axial position above the square-plane and Ph8' is equatorially disposed below it. In contrast to their counterparts in **Isomer A**, Ph7 in **Isomer B** projects to the space above the plane and, importantly, H4 is axially disposed above the plane. Thus **Isomers A** and **B** are stereochemically distinct species. The internal stereochemical reference, ie. the (*R*)-naphthylamine auxillary, is expected to interact differently with the diphosphines in these two diastereomers. Hence, an analysis of the ROESY spectrum of (–)-**1** will give directly the absolute stereochemistry of the novel asymmetric diphosphine chelate.

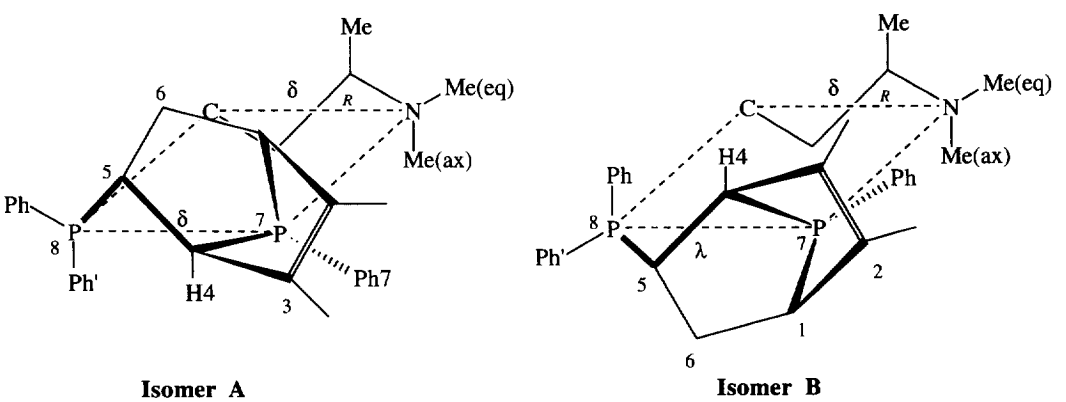


Figure 6. The two possible diastereomers of (–)-**1**.

The strongest NOE signal (K) in Figure 3 is assigned to the H6(endo)–H6(exo) interaction. Both H6 protons interact similarly with H1 (L, M) but only H6(endo) interacts with the endo-proton at C5 (N). Interestingly, H5 couples very strongly with P7 ($^3J_{PH}$ = 41.1Hz) but only moderately with P8 ($^2J_{PH}$ = 8.3 Hz).

H5 shows the expected NOE contact with its neighbouring H4 (O) as well as with the *ortho*-protons in the prochiral Ph8 and Ph8' rings (P, Q).

The stereochemically sensitive *ortho*-protons of Ph8' show a NOE contact with H4 (R) and two long range interactions with NMe(ax) (S) and Ph7 (T) indicating that these protons are located on the same side below the square-plane; as illustrated in Figure 6, **Isomer A**. On the other hand, the *ortho*-protons that resonate at δ 7.84 show a NOE proximity with H6(exo) (U) and, critically, a long range interaction with Me10 (V). Hence, these protons are both located above the plane. In agreement with this, H1 shows a NOE interaction with the equatorially disposed NMe(eq) (W). These NOE patterns (R-W), together with the closeness observed between Ph7 and NMe(ax) (I) confirm that **Isomer A** in Figure 6 is the cationic complex that is generated directly from the asymmetric Diels-Alder reaction. Hence, the absolute configuration at P7 in (–)-**1** is *S*. According to the CIP Sequences rules,[6] therefore, the free diphosphine ligand, (+)-**2**, which is liberated stereospecifically from (–)-**1**, has the *R* absolute configuration at the bridgehead P7 stereogenic centre.

(II) Origins of Stereoselectivity.

In order to evaluate the discriminating factors that inhibit the formation of **Isomer B** (in Figure 6) in the transition state of the asymmetric Diels-Alder reaction, the unfavourable diastereomer was prepared indirectly by coordinating (–)-**2** to the PF_6^- salt of bis(acetonitrile)[(*R*)-1-[1-(dimethylamino)ethyl]-2-naphthylenyl]-palladium(II).[7] This gave **Isomer B** as fluffy white crystals in 70% yield, $[\alpha]_D$ +7.0 (*c* = 1.0, $CHCl_3$).[1,8] The enantiomerically pure diphosphine (–)-**2** was prepared *via* a similar synthetic route as used for its optical antipode using the equally available (*S*)-naphthylamine as the chiral auxiliary. Figure 7 shows the 1D-^{1}H and ^{31}P NMR spectra of **Isomer B** in $CDCl_3$. Selected chemical shifts of the complex are given in Table 2. Apart from the NMe_2 signals, the 1D-NMR resonance patterns of Isomer B are similar to those of **Isomer A**. The relative NMe chemical shifts are clearly affected by the geometrical location of the neighbouring Ph7 aromatic ring. Thus, while a high field shift is observed for Me9(eq), a low field shift is detected for Me9(ax). Model studies confirm that in this diastereomer, the equatorially disposed NMe group projects toward the centre of Ph7.

Table 2. Selected chemical shifts in ppm in **Isomer B** in $CDCl_3$ solution.

H1	3.87	*o*-Ph8'	7.96
Me2	1.70	Me9(ax)	3.05
Me3	1.40	Me9(eq)	2.39
H4	2.76	H10	4.40
H5	3.02	Me10	1.69
H6(endo)	1.82	H13	6.77
H6(exo)	2.62	H17	7.71
Ph7	7.51	P7	119.4
o-Ph8	8.01	P8	51.8

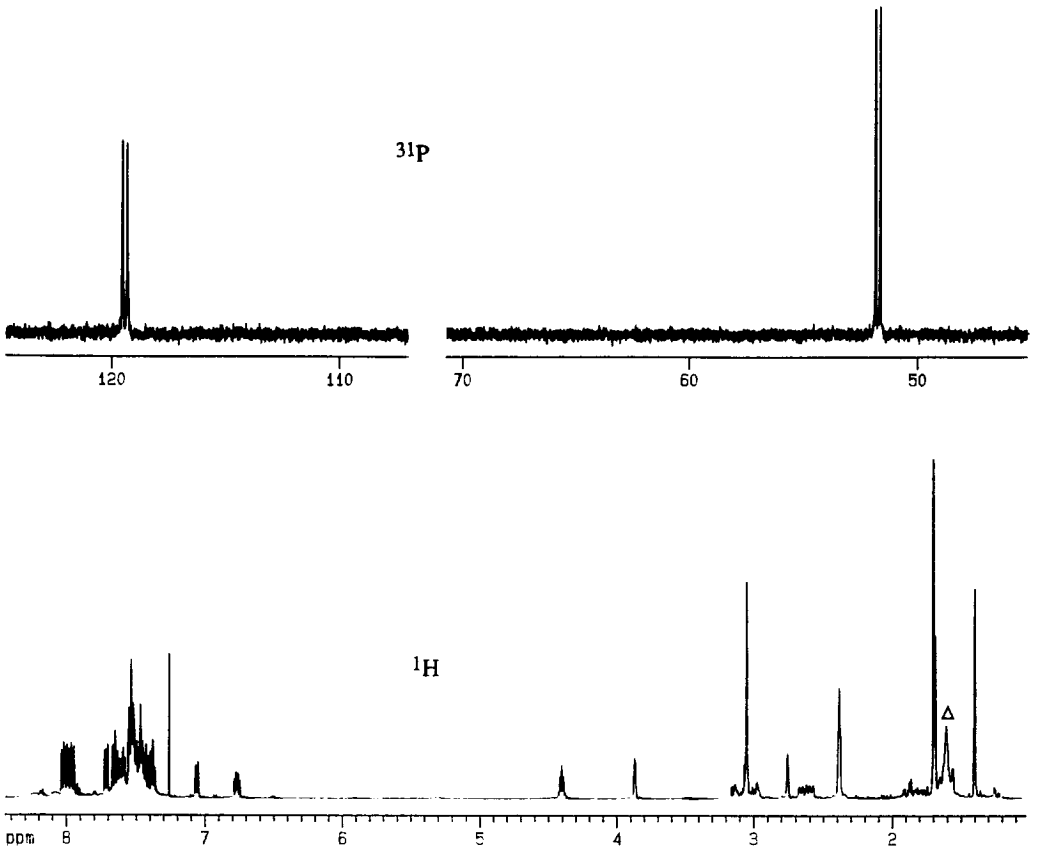


Figure 7. ^{1}H and ^{31}P NMR spectra of **Isomer B** in $CDCl_3$. Δ: H_2O signal.

The ROESY spectrum of **Isomer B** (Figure 8) shows most of the expected NOE signals for the intra-chelate contacts within the organometallic (A-F) and the diphosphine (G-O) rings. The inter-chelate interactions (P-T) are in agreement with the structure depicted in Figure 6. For example, the *ortho*-protons of Ph8 show a NOE contact with H4 (M) and a long range interaction with Me10 (S), indicating that these protons are located on the same side above the square-plane. Furthermore, the axial NMe group and Ph7 are located on opposite sides of the plane and hence there is no NOE contact observed between these two groups. Interestingly, H5 interacts only with the *ortho*-protons of Ph8 and not with those of Ph8'. This observation is in contrast to the similar NOE intensities that are recorded for the H5–*o*-Ph8 and H5–*o*-Ph8' contacts in **Isomer A**. The absence of H5–*o*-Ph8' proximity, in conjunction with the corresponding model studies, indicates that the rotational motion of the Ph8' ring must be restricted in this unfavoured isomer; clearly by the sterically protruding naphthylene proton, H13. A very similar rotational interlocking is also observed for Ph7: while in **Isomer A**, the ring is relatively free to contact with H1, Me2, Me3 and H4, there is no Ph7–Me3 interaction detected for **Isomer B**. The dynamic motion of Ph7 in the unfavourable isomer is clearly deterred by the proximal Me9(eq) steric group.

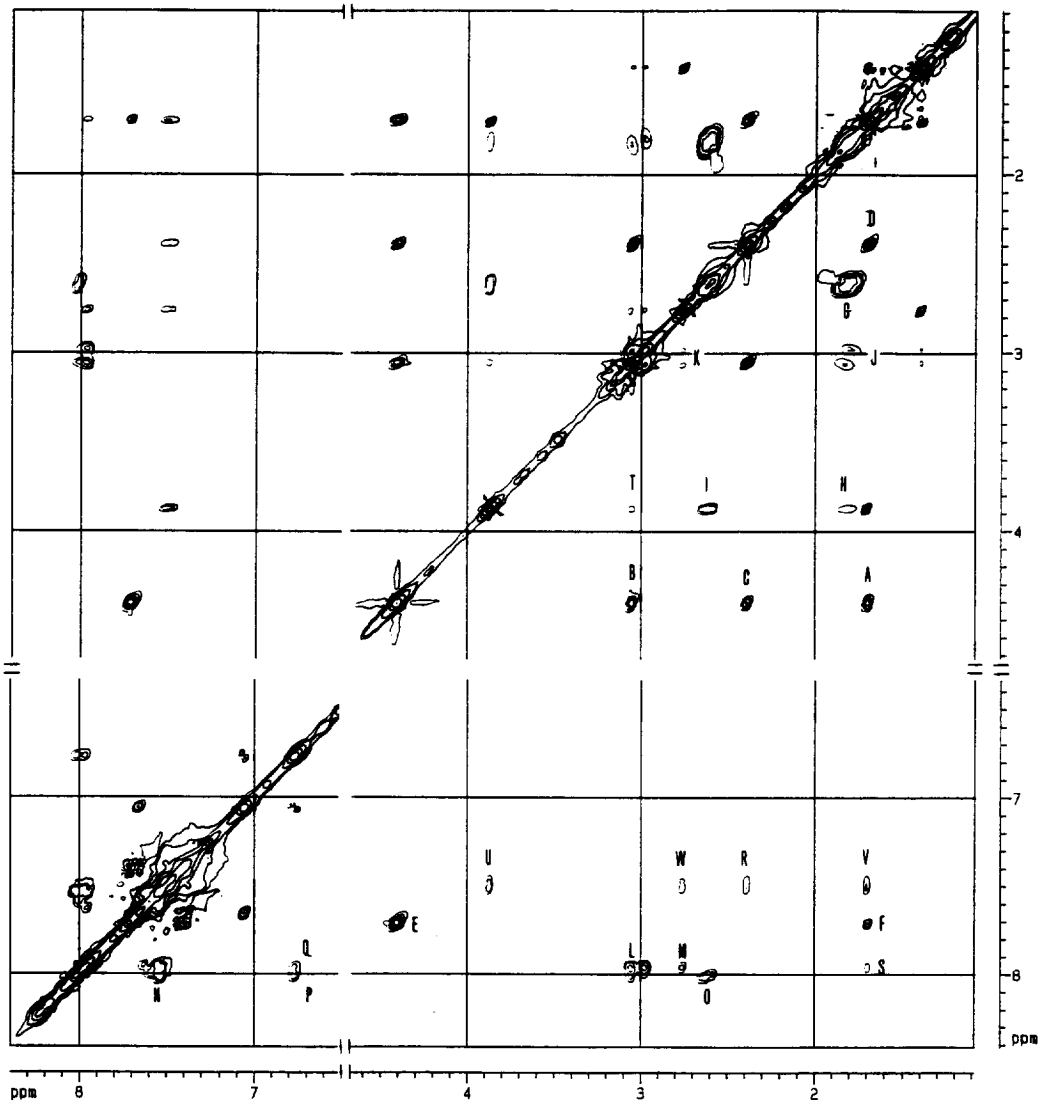


Figure 8. 2D ROESY spectrum of **Isomer B** in $CDCl_3$. Selected NOE signals:

A: H10–Me10	B: H10–Me9(ax)	C: H10–Me9(eq)	D: Me10–Me9(eq)	E: H10–H17
F: Me10–H17	G: H6(exo)–H6(endo)	H: H1–H6(exo)	I : H1–H6(endo)	J: H5–H6(endo)
K: H4–H5	L: H5–*o*-Ph8'	M: H4–*o*-Ph8	N: Ph7–*o*-Ph8	O: H6(exo)–*o*-Ph8'
P: H13–*o*-Ph8	Q: H13–*o*-Ph8'	R: Me9(eq)–Ph7	S: Me10–*o*-Ph8	T: H1–Me9(ax)
U: H1–Ph7	V: Me2–Ph7	W: H4–Ph7		

As stated earlier, donor substituents that occupy equatorial positions in 5-membered chelates show much greater inter-chelate proximities than their axial counterparts in square-planar systems. The rotational interlocking forces that observed for the Ph7 and Ph8' rings in **Isomer B** are both effective at equatorial positions. In **Isomer A**, Me9(eq) and Ph7 project toward opposite sides of the plane whereas Ph8' is located in an axial position. Hence, these rings are free to rotate along their P–C bonds in the Diels-Alder reaction product.

The formation of the diphosphine ligand in the asymmetric Diels-Alder reaction requires the coordination of both of the labile[9] precursors, ie.the modentate-diene and the monodentate-dienophile, to palladium in the proper orientation prior to the [4+2] cycloaddition process.[10] Kinetically, in such a transitional orientation, the rotational motion of the phenyl ring in DMPP and one of the phenyl rings in diphenylvinylphosphine must be impeded in the transition state which would precede the formation of **Isomer B**. In contrast, all aromatic rings may remain free to rotate in the transition state leading to **Isomer A** . We believe that the additional rotational interlocking forces that are required for the monodentate precursors in the energetically sensitive transition state are the discriminating factors that hinder the formation of **Isomer B**. In the process of preparing this unfavoured isomer by means of coordination, however, such rotational forces are relatively small compared with the powerful diphosphine chelating potential. Thermodynamically, the inter-chelate repulsive forces in **Isomer B** may be diminished simply by adjusting the orientations of the interacting phenyl rings. Therefore, once formed, both isomers are found to be chemically stable, both in solid state and in solution.

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