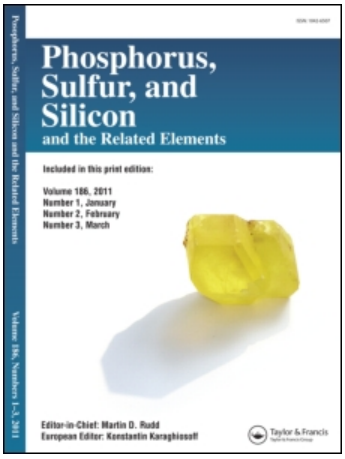

Phosphorus, Sulfur, and Silicon and the Related Elements

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Chiral Atropisomeric 2-Iodo-4,4',6,6'-tetramethyl-2'-(diphenylphosphoryl)-1,1'-biphenyl-enantiodifferentiation by $Rh_2[MTPA]_4$-Adduct Formation and Conformational Analysis

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*Enantiodifferentiation of the chiral 2-iodo-4,4′,6,6′-tetramethyl-2′-(diphenylphosphoryl)-1,1′-biphenyl (**2**) can be accomplished easily by adding one mole equivalent of the enantiopure dirhodium complex $Rh^{(II)}{}_2$[(R)-(+)-MTPA]$_4$ (**Rh***). The internal*

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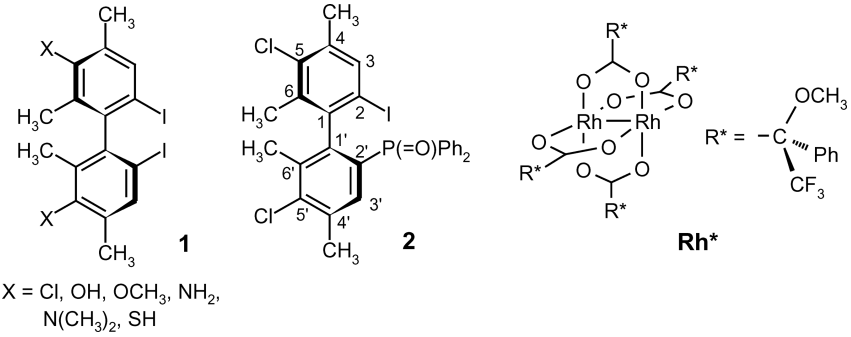
*competition of the two bindings sites in **2**, the $Ph_2P{=}O$ group, and the iodine atom was identified by variable-temperature ^{31}P NMR. Energy optimization (PM3) and ROESY spectroscopy of **2** in the absence and presence of **Rh*** reveal that **2** prefers a conformation in the adducts, which is the least stable one in the free molecule, i.e., adduct formation is accompanied by a rotation of the $Ph_2P{=}O$ group about the C-2′—P bond.*

Keywords Atropisomerism; biphenyl; chiral recognition; conformational analysis; dirhodium tetracarboxylate complex; variable-temperature NMR

Dirhodium complexes as well as their adducts, formed by adding ligands in the axial position(s), are of interest in inorganic and organic chemistry, even in medicine, for many years.[1–3] During the last decade, we have shown that the enantiomers of various low polarity ligands can easily be differentiated by adding an equimolar amount of the dirhodium complex $Rh^{(II)}_2[(R)\text{-}(+)\text{-MTPA}]_4$ (**Rh***, MTPA-H = methoxytrifluoromethylphenylacetic acid ≡ Mosher's acid; see Scheme 1) to their $CDCl_3$ solution and monitoring the diastereomeric dispersion, $\Delta\nu$, of their NMR signals at r.t.[4] This is the "dirhodium method" of chiral recognition which is complementary to the application of chiral lanthanide shift reagents (CLSR).[5]



SCHEME 1 Structures of the biphenyl derivatives **1** and **2** and the dirodium complex **Rh***.

Very recently, we have expanded our research to some atropisomeric C_2-symmetrical 2,2′-diiodobiphenyl derivatives **1** and found that even the iodine atom is able to serve as a ligating site although a very weak one.[6] In another study, it has turned out that triarylphosphine oxides are weak donors as well.[4b–c] The unsymmetrical derivative **2** (Scheme 1) is a chiral atropisomeric biphenyl in which—contrast to those reported earlier[6]—a direct intraligand competition can be studied.

RESULTS AND DISCUSSION

Signal Assignments and Parameters Obtained by Application of the Dirhodium Method

The assignment of the NMR signals of the free ligand **2** (see Scheme 1) was straightforward on the basis of routine 1D and 2D NMR correlation methods and various NOE techniques (see Experimental section). Thereby, all ^{1}H, ^{13}C and ^{31}P NMR signals could be identified (Table I).

TABLE I ^{1}H and ^{13}C Chemical Shifts of the Free Ligand 2 (δ in ppm), Complexation Shifts $\Delta\delta$ (in ppm), and Diastereomeric Dispersions $\Delta\nu$ (in Hz; at 9.4 T) in the Presence of an Equimolar Amount of Rh*.[a,b] The Numbers 1″–6″ and 1‴–6‴ refer to the 2 Diastereotopic Phenyl Rings at the Phosphorus Atom

	2[a]					
	$\delta(^{1}H)$	$\delta(^{13}H)$	$\Delta\delta(^{1}H)$	$\Delta\delta(^{13}C)$	$\Delta\nu(^{1}H)$	$\Delta\nu(^{13}C)$
CH_3-4	2.23	20.4	−0.12/−0.14	−0.2/−0.2	5.1	1.0
CH_3-6	1.84	20.0	+0.33/+0.08	−0.0/−0.0	101.2	12.1
CH_3-4′	2.39	21.2	−0.16/−0.28	−0.4/−0.4	47.2	<1
CH_3-6′	1.97	17.4	+0.02/0.00	+0.1/+0.0	9.2	3.3
1		141.1		−0.1/−0.2		8.7
2		99.7		+0.3/+0.3		4.2
3	7.32	137.7	−0.12/−0.13	+0.2/+0.2	4.8	≈0
4		137.4		+0.2/+0.2		2.1
5		135.3		+0.3/+0.3		5.4
6		136.4		+0.7/+0.7		<1
1′		146.2		−0.6/−0.7		8.2
2′		129.3		+0.6/+0.5		12.2
3′	7.30	133.7	−0.15/−0.16	+1.0/+0.9	2.3	2.1
4′		136.0		+0.7/+0.6		9.8
5′		139.6		+0.3/+0.2		9.4
6′		136.3		−0.5/−0.6		7.4
1″		133.1		+0.5/+0.3		22.3
2″/6″	7.63	132.0	+0.25/+0.24	+0.3/+0.3	6.0	5.2
3″/5″	7.40	128.1	−0.15/−0.17	−0.1/−0.1	6.4	4.8
4″	7.49	131.4	−0.09/−0.11	−0.1/−0.2	5.6	10.0
1‴		132.6		−0.2/−0.6		35.9
2‴/6‴	7.57	131.9	+0.15/+0.13	+0.1/−0.0	6.0	6.0
3‴/5‴	7.29	127.9	−0.12/−0.20	−0.3/−0.3	34.4	5.0
4‴	7.40	131.0	−0.14/−0.17	−0.5/−0.6	11.6	11.1

[a]The r.t. ^{31}P NMR data of **2** are $\delta = 27.8$ (free ligand), $\Delta\delta = +4.4$ (broadened; see Figure 1), no dispersion detectable.

[b]^{1}H and ^{13}C signal sets in the iodine-containing ring could not be correlated to those of the other ring for each enantiomer due to insufficient signal resolutions; also see text.

In the presence of **Rh*** kinetically labile adducts between the ligand(s) and **Rh*** are formed. In the standard dirhodium method experiment, equimolar amounts of both components are used, and it has been shown for a number of ligands[4] that 1:1-adducts prevail but 2:1-adducts and free **Rh*** cannot be ignored. At r.t. the NMR signals are averaged over all species revealing two parameters: (1) NMR signals shifts due to complexation ($\Delta\delta$) indicating the prefered complexation site if the donor is strong enough and (2) ligand signals split (in Hz) due to the formation of diastereomeric adducts reflecting the enantiomeric composition. In this article, the intensities within duplicated signals are 1:1 because **2** is a racemic mixture.

The identification of the ligand signals in adducts is sometimes hampered by overlapping MTPA acid signals, particularly when NMR signals of aromatic ^{1}H and ^{13}C nuclei are involved. For the signals of the ^{1}H/^{13}C pairs in the iodine-containing ring, it was not possible to state which sets of signals belong to one enantiomer and which to the other. This is due to chemical shift differences being too small in the diastereomeric adducts for discrimination by 2D NMR correlation methods.

Internal Ligand Competition

In contrast to **1**,[6] the phosphoryl derivative **2** is a biphenyl system without C_2 symmetry because the two molecular subunits are different. One phenyl group carries an iodine atom whereas the other one (Scheme 1) bears a diphenylphosphoryl group ($Ph_2P{=}O$). This results in a full set of the NMR signals (Table I), e.g., there are four methyl signals in the free **2** and eight ones in the mixture with **Rh***. Moreover, one can expect that there is intramolecular competition between the $Ph_2P{=}O$ group and the iodine atom in the adduct formation because both the iodine atom[6] and the phosphoryl group (P=O)[4b–c] have been shown to be weak donors. Although the P=O group is polar, electrostatic attraction is attenuated by a severe steric congestion of the three aromatic groups around.[4b–c] A convenient method to identify the adduct species composed of **2** and **Rh*** is variable-temperature ^{31}P NMR spectroscopy[4b–c] showing ^{31}P NMR signal splittings on lowering the sample temperature (Figure 1).

It is obvious that all peaks **A–E** visible in the spectrum recorded at 213 K (Figure 1, bottom) emerge from one single averaged resonance that is near to its coalescence at room temperature (Figure 1, top). The ^{31}P chemical shifts of these peaks disclose their origin: Whereas signal **A** with the lowest δ-value is in the typical range of that of the free ligand **2**, those at $\delta \approx 36$–37 (**B** and **C**, comparable intensities) belong to the two diastereomeric adducts involving P=O as ligand (P=O-adducts); very

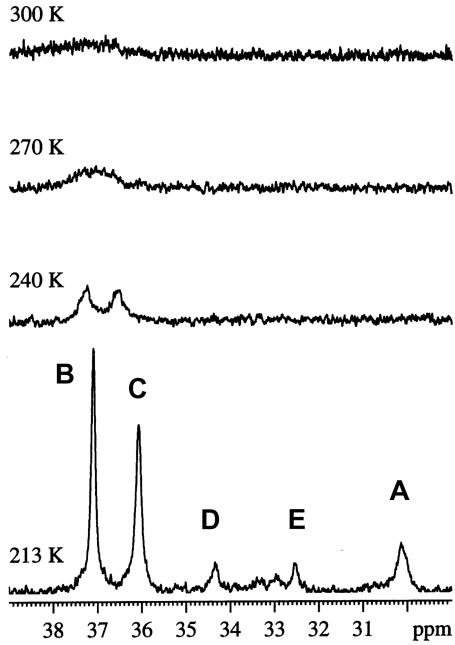


FIGURE 1 Temperature-dependent ^{31}P NMR signals; 1:1 molar ratio of **2** and **Rh***.

similar δ-values were observed for related phosphoryl compounds.[4b–c] We assigned the small signals **D** at $\delta = 34.3$ and **E** at $\delta = 32.6$, also with approximately equal intensities, to diastereomeric adducts formed by ligating the molecule **2** at the iodine atom (I-adducts); i.e., the P=O groups are free. For further support of this assignment see next section. The respective relative ratios estimated from the signal ratios are ca 15% for **A**, 75% for (**B** + **C**; P=O-adducts), and 10% for (**D** + **E**; I-adducts). This allows an estimation of the relative stabilities of the two adduct species resulting in a free energy difference ΔG_0 of 3.5 ± 0.2 kJ/mol (at 213 K).

Chiral Recognition

A large diastereomeric dispersion $\Delta\nu$ of 207 Hz is observed in the low-temperature ^{31}P NMR spectrum of **2** (Figure 1) for the P=O-adduct peaks **B** and **C** and an even larger one (365 Hz) for the I-adduct peaks **D** and **E**. Methoxy ^{1}H signals of the MTPA acid residues in **Rh*** have proven to be sensitive probes for the nature of adducts;[4b–c] Figure 2 shows the region between $\delta = 3.3$ and 2.6 with their ^{1}H resonances.

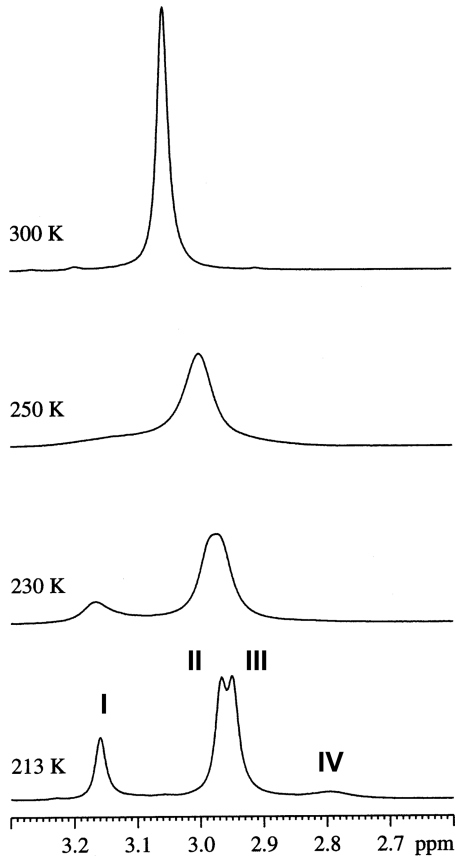


FIGURE 2 Temperature-dependent ^{1}H NMR signals of the methoxy groups in the MTPA acid residues; 1:1 molar ratio of **2** and **Rh***.

In analogy to the ^{31}P case, the methoxy ^{1}H signal with its averaged r.t. signal at $\delta = 3.08$ (Figure 2, top) splits up on going to lower temperatures. The signal **I** at $\delta = 3.16$ (at 213 K; Figure 2, bottom) is typical for free **Rh*** molecules supporting the fact that both P=O and I are weak donors and the adduct formation equilibrium contains a substantial amount of **Rh*** bearing no equatorial ligand molecule **2**.[4b–c,6] Two partially overlapping signals **II** and **III** are visible at $\delta \approx 2.95$ ($\Delta\nu = 8.8$ Hz) corresponding to the two diastereomeric 1:1-P=O-adducts of **2** and **Rh***. On the basis of the typical ^{1}H chemical shift range in other adduct species,[4,6] the weak broad signal **IV** at $\delta \approx 2.8$ has to be assigned to 2:1 adducts existing in the equilibrium in a small proportion. The relative ratio of these three signal groups is 25%, 70%, and 5%, respectively. On

the first glance, the intensity ratio for the first two resonances (**I:II/III** = 25:70) does not correspond well to that of the ^{31}P signals of the free ligand **2** *vs*. 1:1-P=O-adducts (**A:B/C** = 15:75); the proportion of the ^{1}H signal at $\delta = 3.16$ (**I**, free **Rh***) seems to be higher than expected. This discrepancy can be explained by the fact that the MTPA methoxy ^{1}H chemical shift of I-adducts is very close to that of free **Rh*** itself (**I**).[6] Therefore, the respective proportion must be added to that ^{1}H signal intensity of peak **I** as well. Taking this argument into consideration, the relative intensities in both the ^{1}H and the ^{31}P NMR spectra are in good agreement and support the existence of 1:1-I-adducts (see previous section).

It is also possible to assign all NMR signals of **2** with respect to their position within the individual phenyl rings (e.g., C-4 *vs*. C-6 and C-4′ *vs*. C-6′) as well as with respect to the two different phenyl rings (e.g., C-4 *vs*. C-4′ and C-6 *vs*. C-6′) by applying various two-dimensional NMR correlation methods, particularly HMQC, HMBC, and by inspecting ^{31}P coupling effects. For the phosphorylated ring (dashed atom numbers) even the signals belonging to each of the individual enantiomers could be identified and were arbitrarily marked by ***a*** and ***b***; an analogous differentiation could not be achieved for the iodine-containing ring due to unfortunate signal overlap and dispersion effects too small for safe differentiation (as previously noted). The horizontal 1D spectral section in Figure 3 shows the 8 ^{1}H methyl signals recorded at 320 K (at r.t.) some of which are still broadened due to coalescence associated to the exchange processes between free **2** and ligated **2** in 1:1-P=O-adducts, 1:1-I-adducts, as well as some spurious 2:1-P=O-adducts (as previously discussed). Very significant diastereomeric dispersion in each of the four signal pairs can be identified; they are between 5 and remarkable 101 Hz (see also Table I).

Conformational Analysis

Evidence on preferred adduct geometries can be deduced from the ROESY experiment of **2** and **Rh*** (1:1) as depicted in Figure 3. It is striking that positive ROESY cross peaks indicating pairwise spatial proximity could be observed for MTPA methoxy protons only with the methyl groups attached to C-6 and C-4′ in each diastereomeric adduct (encircled in Figure 4) but not for the other two methyl groups at C-4 and C-6′. This evidence can be rationalized on the basis of a conformational analysis of **2**, (Figure 4).

Apart from internal rotations of the methyl and phenyl groups, three conformations of molecule **2** are conceivable that differ in the relative orientation of the biphenyl part on one side and the phosphoryl part on the other (rotation about the P—C-2′ bond); see conformations **2a–2c**

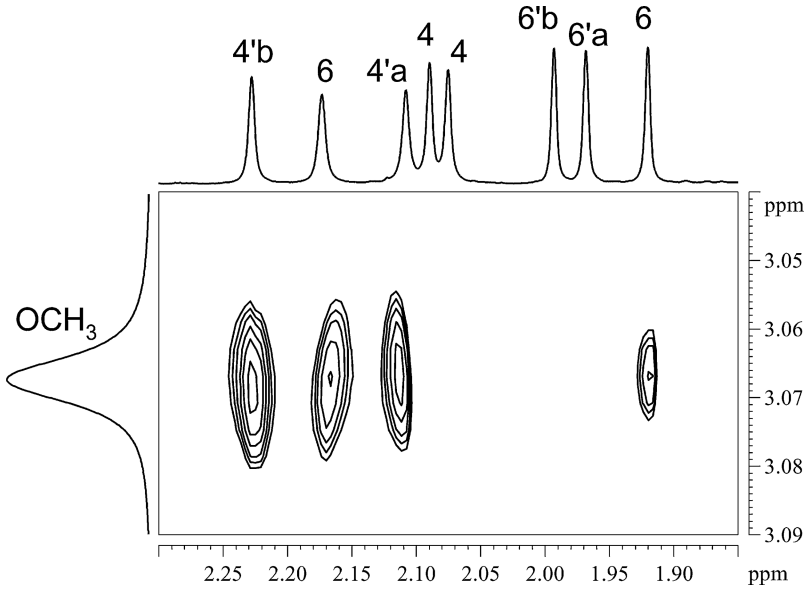


FIGURE 3 Section of the ^{1}H, ^{1}H ROESY spectrum of **2** in the presence of an equimolar amount of **Rh***, recorded at 320 K. Vertical trace: MTPA-OCH_3 signal (projection); horizontal trace: section of the methyl signals of the 1D ^{1}H NMR spectrum recorded under the same conditions. Numbers denote the carbon atoms the methyl groups are attached to.

in Figure 4, drawn from PM3-optimized structures. Whereas the conformer **2a** and **2b** have similar PM3-calculated formation enthalpies—the ΔH_f-difference is only 1–2 kJ/mol—the enthalpy of **2c** is about 9 kJ/mol higher so that these conformers do not significantly contribute to the equilibrium of the free ligand.

Turning to ROESY peaks observed for the **2**$\cdots$**Rh*** adducts (Figure 4), it is obvious that the methyl group at C-4 shows no NOE response, i.e., this methyl group apparently never reaches any MTPA methoxy group. This, however, should be possible in conformer **2a**, which is among the most stable ones in the free ligand. However, the P=O group is strongly hindered from a **Rh*** approach by the iodine-containing phenyl residue (see double arrow in Figure 4). Thus, conformation **2a** cannot play any significant role in the equilibrium and, consequently, **Rh*** can never come close to the methyl group at C-4.

Steric shielding around the P=O group is much less severe in **2b** and **2c** (Figure 4). Conformer **2b**, which is the most stable one in the free ligand **2**, would not allow a close proximity of MTPA methoxy groups to any of the methyls because the P=O bond is directed away from the biphenyl

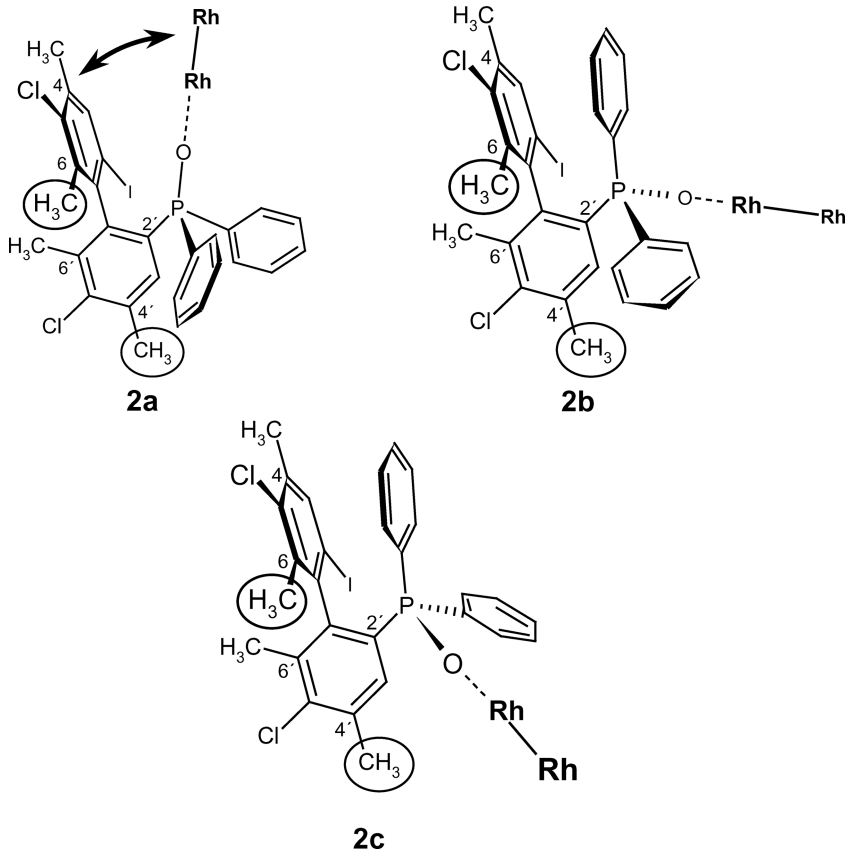


FIGURE 4 Schematic view of the conformers of **2** in the 1:1-P═O-adducts.

moiety. So, only conformer **2c**—the least stable one of the free ligand **2**—is available for allowing a simultaneous approach of both methyl groups, at C-4′ and C-6, to MTPA-OCH_3, but not for those at C-4 and C-6′. This is in perfect agreement with the ROESY results. Thus, the conformational equilibrium of **2** appears to be turned upside down by the adduct formation: Conformer **2c** dominates in the adduct although it is of very minor significance in the conformational equilibrium of the free molecule **2** itself.

CONCLUSION

(a) A sterically hindered Ph_2P═O group attached to an aromatic ring is a weak donor in **Rh***-adducts; nevertheless, it is the preferable

binding site in **2** as compared to the iodine atom. The ratio of P=O-adducts *vs*. I-adducts under standard dirhodium method conditions is 7–8:1 in favor of the P=O-adducts, the free energy difference ΔG_0 (at 213 K) being 3.5 ± 0.2 kJ/mol.

(b) Many ^{1}H and ^{13}C signals display large diastereomeric dispersion effects allowing an easy enantiodifferentiation by contact between **2** and **Rh***.

(c) ROESY contacts between some methyl signals of **2** and the methoxy protons in the MTPA residues of **Rh*** point to a strong preference of conformer **2c** in the adduct although it is the least stable one in the conformational equilibrium of the free ligand **2** itself.

EXPERIMENTAL

Substances

The synthesis of **Rh*** has been described by us earlier.[7] Racemic 2-iodo-4,4′,6,6′-tetramethyl-2′-(diphenylphosphoryl)-1,1′-biphenyl (**2**) was available from another study and was synthesized by a general procedure based on 2,2′-diiodo-4,4′,6,6′-tetramethyl-5,5′-diaminobiphenyl as precursor.[8]

NMR Spectroscopy

R.t. ^{1}H (400.1 MHz), ^{13}C (100.6 MHz), and ^{31}P (161.9 MHz) NMR measurements were performed on a Bruker Avance DPX-400 spectrometer using a QNP-probehead. The solutions were ca 50 mmolar in $CDCl_3$, and a drop of acetone-d_6 was added to the NMR sample before measurement in order to increase the solubility of **Rh***.[9] For a better comparison of chemical shifts, the same amount of acetone-d_6 was added to the $CDCl_3$-solutions of the free ligand as well. Chemical shift standards were internal tetramethylsilane ($\delta = 0$) for ^{1}H and ^{13}C and external aqueous H_3PO_4 for ^{31}P ($\delta = 0$). Signal assignments were assisted by selective 1D-NOESY, COSY, HMQC, HMBC, and ROESY (all standard Bruker software), as well as by inspecting couplings to ^{31}P.

Variable temperature ^{1}H (500.1 MHz) and ^{31}P NMR (202.4 MHz) spectra were recorded in the presence of **Rh*** on a Bruker Avance DRX-500 spectrometer.[4c] Temperatures varied from 203 to 333 K and were read from the instrument panel; no further measures for more precise temperature determinations were taken.

Calculations

Semiempirical (PM3) calculations of the free ligands were performed using Spartan '04 of the Wavefunction® software package. Hartree-Fock

ab-initio calculations were carried out additionally resulting in geometries and relative energies very similar to those obtained from PM3.

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