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Determination of the absolute configuration of chiral cyclic alcohols using diamine derivatizing agents by ^{31}P NMR spectroscopy

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Abstract—The absolute configuration and enantiomeric excess of chiral cyclic alcohols can be predicted from the ^{31}P NMR spectra of the two diastereoisomers obtained with organophosphorus diamino-derivatizing agents (CDAs) and the chiral secondary alcohol, according to a simplified model taking into account the spatial location of the substituents of the chiral alcohol center and the ^{31}P NMR signals of the two diastereoisomers.

1. Introduction

Among the NMR methods widely used for the determination of enantiomeric purity,[1–3] based on the formation of diastereomeric complexes or derivatives, we recently reported a very efficient way of determining the enantiomeric composition and absolute configuration of chiral secondary alcohols—especially aryl and alkyl carbinols—with ^{31}P NMR, after derivatisation of these alcohols with diamine-phosphorous compounds.[4] This method has been successfully applied to 16 alcohols and three different chiral diamines, and has given a very good correlation. It relies on a simplified model (Fig. 1), established according to crystallographic structures of several diastereoisomers of chiral alcohols with CDAs, and is correlated to the sign of $\Delta\delta_{R-S}$ ($\Delta\delta_{R-S}$ representing the chemical shift difference between two diastereoisomers of the CDAs and the chiral secondary alcohol). The upfield signal corresponds to the (*R*)-alcohol enantiomer (unless the CIP rules agree with $R^1 < R^2$). We then decided to extend this work to other chiral alcohols and focused on cyclic secondary alcohols. Herein we report that a similar rule is observed so that the enantiomeric excess and absolute configuration can also be easily determined for these alcohols.

A typical procedure for the preparation of the samples with CDAs, directly into NMR tubes, is reported in Figure 2.[4–7]

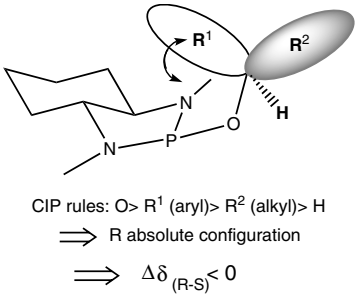

Figure 1. A model for the spatial orientation of R^1 and R^2 resulting in a shielding effect in the chemical shifts between the two diastereoisomers of the same chiral aryl-carbinol.

The formation of the chlorinated phospholidine was monitored by ^{31}P NMR. Upon the addition of the chiral alcohol, a reaction occurred instantaneously, so that the ^{31}P and ^{1}H NMR spectra could be recorded immediately. Then, sulfur may be added directly to the NMR tube and the spectra recorded again after shaking the tube, without any further purification. These stabilized P(V) compounds could also be purified by chromatography and in some cases, can be crystallized with a quality suitable enough for the determination of their structure by X-ray diffraction.

Three diamines **A**, **B**, and **C** were investigated (Fig. 3). The configuration of the cyclic secondary alcohol was known: both pure/enriched (*R*)- and (*S*)-enantiomers were alternatively used with pure (*R*,*R*)–**A**–**C** diamine. When the

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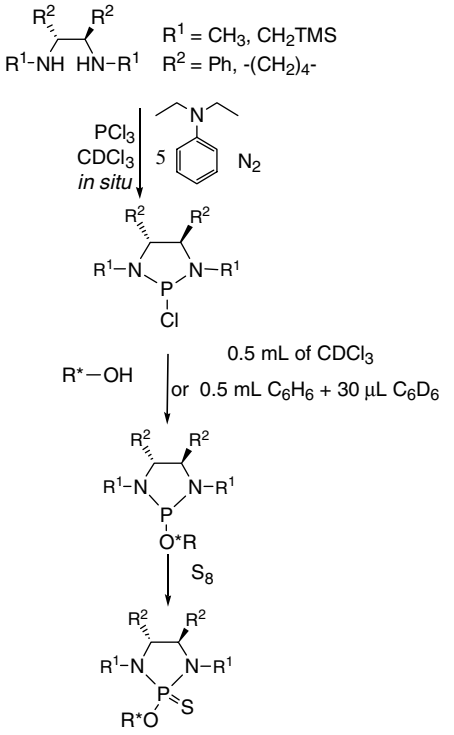


Figure 2. Preparation of the P(III) and P(V) derivatives.

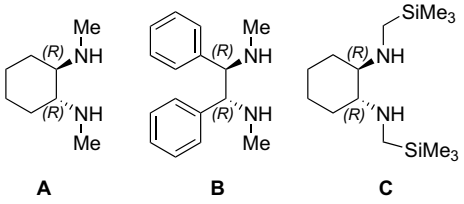


Figure 3. C_2 symmetric diamines **A**–**C** used in this study.

alcohol was a mixture of the enriched enantiomer or even a racemic mixture, two signals were observed with the (*R*,*R*)-diamine; when it was a single enantiomer two measurements had to be carried out, one with the (*R*,*R*)-diamine and one with the (*S*,*S*)-diamine (or a mixture of the two diamines), in order to obtain the chemical shift value of the second diastereoisomer.

The NMR data in Tables 1–3 are presented with all the alcohols having the same (*R*)-absolute configuration. In the first column, the derivatisation was carried out with (*R*,*R*)-1,2-diamine, whereas in the second column it was carried out with the (*S*,*S*) one. This explains why, for instance, the alcohol of entry 7, Tables 1 and 2, is the enantiomer of the ((1*S*)-*endo*)-(−)-borneol. Consequently, in order to obtain the values given in the first column of these tables, we have been working with the phospholidine obtained from *endo* borneol and the diamine of configuration (*S*,*S*), which is an enantiomer of the (*R*)-alcohol of entry 7 and the diamine with an (*R*,*R*)-configuration.

When we previously studied the crystallographic structures of diamine A with (*R*)-2-naphthyl-ethanol and compared it with the other diastereoisomer, obtained from (*S*)-2-naphthyl-ethanol, we demonstrated that the diastereoisomer resonating downshielded [the one derived from (*S*)-2-naphthyl-ethanol], had both nitrogens N1 and N2 going toward an sp^2 hybridization, while in the case of the derivative with (*R*)-2-naphthyl-ethanol, N1 had a hybridization closer to that of an sp^3 than that of an sp^2.[4] With these observations, we were able to establish the predictive model depicted in Figure 1. Regarding the cyclic alcohols, the crystallographic structure of (*R*,*R*)-1,3-dimethyl-2-(*R*)-(2-phenyl-cyclohexyloxy)-octahydro-benzo[1,3,2]diazaphosphole 2-sulfide has been elucidated, and is presented in Figure 4. The phenyl moiety of the (*R*)-2-phenyl-cyclohexanol is close to the C7 methyl of diamine A, while N1 and N2 are both closer to an sp^3 hybridization than that of an sp^2 (sum of the dihedral angles: 347.5° for N1 and 349.2 for N2, see Table 4). Despite the fact that no crystals of a suitable quality for X-ray crystallography were obtained with diamine A and (*S*)-2-phenyl-cyclohexanol, we assumed that the observed ^{31}P NMR chemical shift difference is due to the influence of the N1 hybridization, probably being closer to that of an sp^3 hybridization, and giving the upshielded signal. As a consequence, if we assume that the conformation seen in the solid state is similar to the one in solution, we can propose the model depicted in Figure 5: all the cyclic secondary alcohols whose spatial orientation of R^1 and R^2 substituents follows that spatial model will provide $\Delta\delta_{R-S} > 0$. In other words, when CIP rules are in agreement with O > –CH–R^1 > –CH–R^2 > H, the upshielded signal will be the one for which the chiral alcohol has an (*S*)-configuration. This model is, therefore, different to that proposed for the aryl–alkyl-carbinols, which lead to the (*S*) chiral alcohol downshielded compared to the other enantiomer (Fig. 1).

Experimentally, these facts were corroborated with 3 C_2-diamines **A**–**C** (see Tables 1–3), and with several cyclic alcohols, the nature of the R^1 substituents and the number of cyclic carbons being different. It was established that the rigidity of the cyclohexane ring of (*R*,*R*)-*N*,*N*′-dimethyl-cyclohexane-1,2-diamine (diamine A) generally provides larger chemical shifts compared to that of the (*R*,*R*)-*N*,*N*′-dimethyl-1,2-diphenyl-ethane-1,2-diamine (diamine B).[6,7,4] This was confirmed in all the reported examples, except for 2-naphthalen-2-yl-cyclohexanol and *endo*-norborneol (entries 2 and 6 of Tables 1 and 2) alcohols.

In the first case, the reason for the small chemical shift difference could be the rigidity and steric hindrance of the naphthyl substituent (which was not observed with 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexanol, entry 5). Additional arycyclohexanols have been previously reported by Alexakis et al.:[8,9] 19 alcohols have been synthesized by enantioselective nucleophilic opening of *meso* epoxides by organolithium reagents and the enantiomeric excess measured with the phosphorus derivative of diamine B: one can observe that in all cases $\Delta\delta_{R-S} > 0$.

In the second case, the chemical environment of the two –CH–R^1 and –CH–R^2 substituents seems to be insufficient to induce important chemical shift difference. However, compared to borneol and 1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol (entries 7 and 8 of Table 1 and 6 of Tables 2 and

Table 1. ^{31}P Chemical shift δ and chemical shift differences $\Delta\delta$ (ppm) of some alcohol P(III) and P(V) derivatives with (*R*,*R*)-*N*,*N*′-dimethyl-cyclohexane-1,2-diamine (in $CDCl_3$ and in C_6D_6)

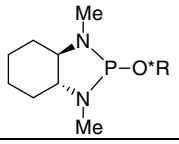
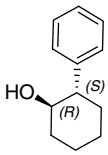
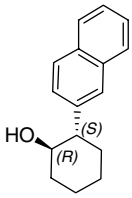
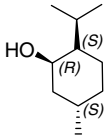
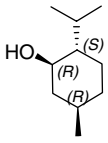
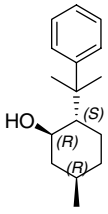
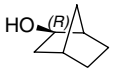
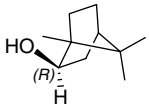
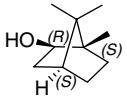
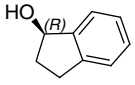
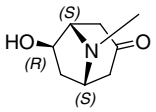
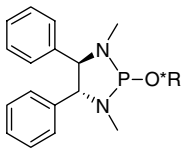
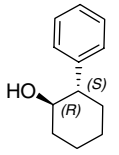
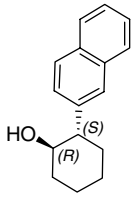
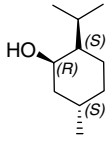
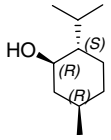
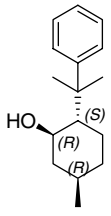
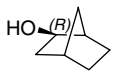
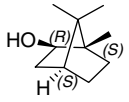
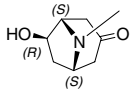
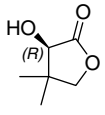
		P(III) (*R*,*R*)	P(III) (*S*,*S*)	$\Delta\delta_{(R-S)}$	P(V) (*R*,*R*)	P(V) (*S*,*S*)	$\Delta\delta_{(R-S)}$
1		$CDCl_3$: 147.44	143.89	+3.55	85.69	85.17	+0.52
		C_6D_6: 152.16	149.75	+2.41	86.02	86.57	−0.55
2		$CDCl_3$: 147.48	145.31	+0.84	85.36	84.81	+0.55
		C_6D_6: 151.06	150.46	+0.60	86.40	85.70	+0.70
3		C_6D_6: 142.35	136.17	+6.18	86.21	85.60	+0.61
4		$CDCl_3$: 148.14	141.35	+6.79	86.35	85.78	+0.57
		C_6D_6: 142.95	136.99	+5.96	86.11	85.70	+0.41
5		$CDCl_3$: 145.14	139.88	+5.26	80.08	84.38	−4.30
		C_6D_6: 151.27	145.57	+5.70	84.30	85.23	+0.32
6		139.75	138.87	+0.88	86.14	85.97	+0.17
7		C_6D_6: 130.30	139.99	+9.69	87.10	87.75	−0.65
8		$CDCl_3$: 143.16	133.09	+10.07	87.07	86.43	+0.64
9		$CDCl_3$: 146.06	139.62	+6.44	87.82	86.88	+0.94
		C_6D_6: 150.44	145.78	+4.66	88.48	87.93	+0.55
10		139.95	136.47	+3.48	86.54	86.96	−0.42

Table 2. ^{31}P chemical shift δ and chemical shift differences $\Delta\delta$ (ppm) of some alcohol P(III) and P(V) derivatives with (*R*,*R*)-*N*,*N*′-dimethyl-1,2-diphenyl-ethane-1,2-diamine (in $CDCl_3$)

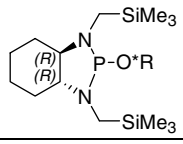
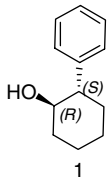
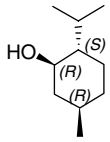
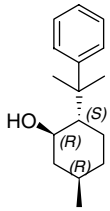
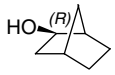
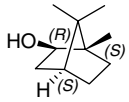
		P(III) (*R*,*R*)	P(III) (*S*,*S*)	$\Delta\delta_{(R-S)}$	P(V) (*R*,*R*)	P(V) (*S*,*S*)	$\Delta\delta_{(R-S)}$
1		142.67	141.32	1.35	83.74	81.81	1.93
2		143.42	140.94	2.48	83.94	82.14	1.80
3		142.59	140.96	1.63	82.22	81.91	1.93
4		144.53	142.84	1.69	82.96	82.60	0.36
5		145.25	137.39	7.86	81.74	80.84	0.9.
6		139.30	137.79	1.51	82.93	82.65	0.28
7		139.92	137.49	2.43	82.28	81.10	1.18
8		146.82	144.98	1.84	83.89	83.64	0.25
9		142.23	140.51	1.72	85.54	85.09	0.46

3), the presence of the methyl substituents induces chemical shift differences ten times higher than that of the *endo*-norborneol with diamines **A** and **C**, and only two times higher with diamine **B**.

For all other examples, the chemical shift difference is higher with diamines **A** and **C** compared to **B**. Even so, $\Delta\delta_{R-S}$ is often higher with the phosphorus derivatives of diamine **C** compared to **A**. This could be due to the influence on the nitrogen of the methylsilyl substituent (diamine **C**) which has a higher steric hindrance than the methyl of diamine A.

Finally, we applied our predictive model to two natural products to check whether or not it is a valuable one. Since

Table 3. ^{31}P chemical shift δ and chemical shift differences $\Delta\delta$ (ppm) of some alcohol P(III) derivatives with (*R*,*R*)-*N*,*N*′-bis-trimethylsilanylmethyl-cyclohexane-1,2-diamine (in $CDCl_3$)

		P(III) (*R*,*R*)	P(III) (*S*,*S*)	$\Delta\delta_{(R-S)}$	P(V) (*R*,*R*)	P(V) (*S*,*S*)	$\Delta\delta_{(R-S)}$
1		140.57	138.72	1.85	83.19	82.04	1.15
2		141.21	132.73	8.48	85.81	85.14	0.67
4		139.92	132.82	7.1	82.69	81.90	0.79
5		131.23	130.26	0.97	87.72	87.28	0.44
6		133.89	123.85	10.04	87.86	86.83	1.03

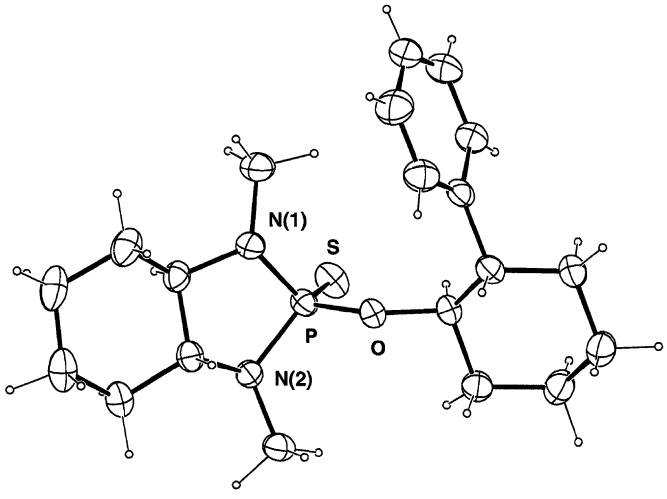


Figure 4. ORTEP view of the crystal structure of (*R*,*R*)-1,3-dimethyl-2-(*R*)-(2-phenyl-cyclohexyloxy)-octahydro-benzo[1,3,2]diazaphosphole 2-sulfide with atom numbering. Ellipsoids are represented with a 40% probability.

Table 4. Selected bond lengths, distances (Å) and bond angles (deg) for (*R*,*R*)-1,3-dimethyl-2-(*R*)-(2-phenyl-cyclohexyloxy)-octahydro-benzo[1,3,2]-diazaphosphole 2-sulfide

P–N(1)	1.661(4)
P–N(2)	1.663(3)
P–S	1.941(2)
P–O	1.586(3)
N(1)–P–N(2)	94.8(2)
N(1)–P–O	104.4(2)
N(2)–P–O	108.4(2)
N(1)–P–S	119.4(1)
N(2)–P–S	115.7(1)
O–P–S	112.4(1)
P–N(1)–C	108.9(3)
P–N(1)–C_{methyl}	120.4(3)
C–N(1)–C_{methyl}	118.2(4)
Σ of angles at N(1)	347.5
N(1) $\cdots$ $plane_{(P,C,C_{methyl})}$	0.313(4)
P–N(2)–C	110.4(3)
P–N(2)–C_{methyl}	120.4(3)
C–N(2)–C_{methyl}	118.4(3)
Σ of angles at N(2)	349.2
N(2) $\cdots$ $plane_{(P,C,C_{methyl})}$	0.292(4)

the absolute configuration of *trans*-dehydroandrosterone and testosterone is (*S*) in both cases, we used pure (*R*,*R*)-diamine **A** in the first experiment and then a mixture of (*R*,*R*)- and (*S*,*S*)-diamine **A** in order to observe the two

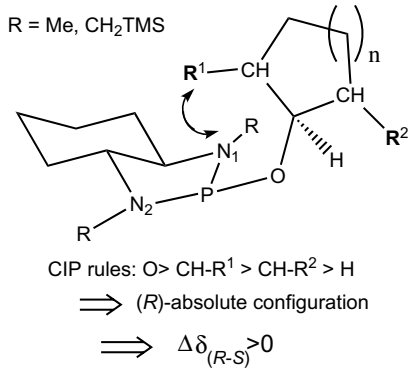


Figure 5. A model for the spatial orientation of R^1 and R^2 resulting in a shielding effect in the chemical shifts between the two diastereoisomers of the same chiral cyclic secondary alcohol. The chirality of the C_2-diamine is *R*,*R*.

diastereoisomers ^{31}P NMR signals. The results are presented in Figure 6. The predictive model has been established for a CDA having an (*R*,*R*)-configuration on the diamine, which gives the downshielded signal in the presence of the chiral alcohol having an (*R*)-configuration: in our case it is equivalent to the enantiomer obtained from the (*S*,*S*)-diamine **A** CDA and the (*S*)-alcohol. Experimentally, we obtained this downshielded signal in both cases, the chemical shift difference being much higher with derivatives of testosterone compared to that of *trans*-dehydroandrosterone. As was observed with *endo*-norborneol compared to borneol, this value can be explained by the chemical environment of the two carbon substituents, which is not so different with *trans*-dehydroandrosterone and much more inequivalent with testosterone.

It is important to note that we have never observed any kinetic resolution whatever the steric hindrance of the alcohol tested. We performed several experiments by mixing the enantiomeric forms of the alcohol or the chiral diamine in different ratios. In all cases the determination of the enantiomeric excess of the alcohols by integration of the surface of the diastereoisomer peaks was the same. The values were the same with the P(III) and with the P(V) derivatives. This points to the absence of kinetic discrimination toward the formation of both diastereoisomers, as previously reported.[4,6] As a result the enantiomeric excess of the alcohol can be carried out with accuracy (the estimated error with a 400 MHz apparatus should be less than 1%), and at the same time the absolute configuration of the major component fully attributed.

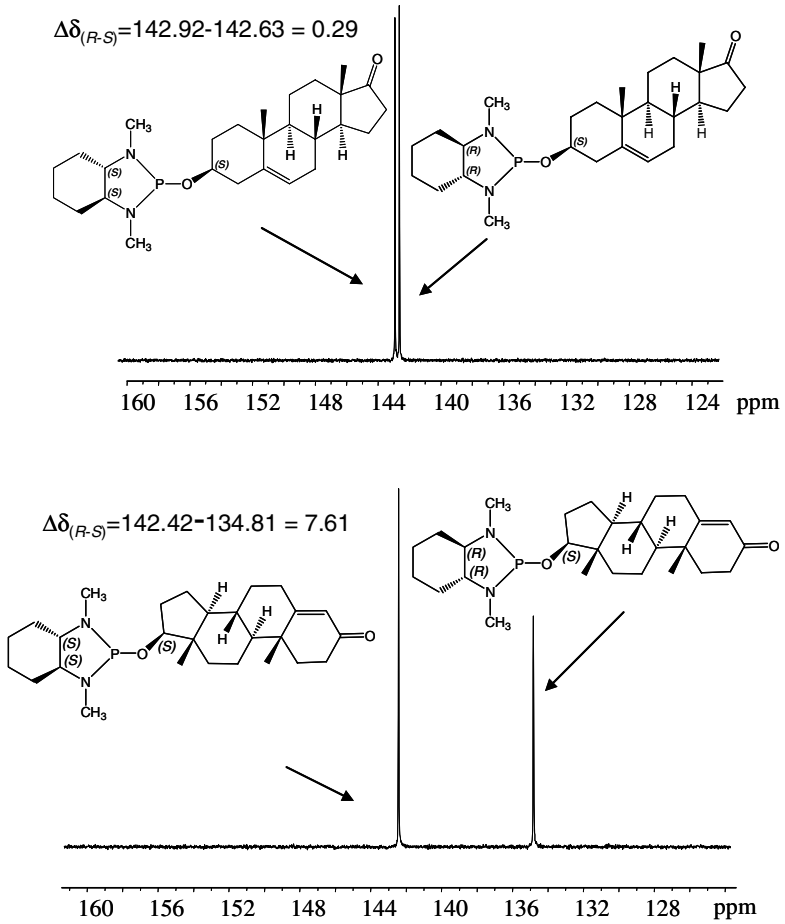


Figure 6. ^{31}P NMR spectra of phosphorus derivatives of diamine (*S*,*S*)-**A** with testosterone (upper) and *trans*-dehydroandrosterone (lower). The absolute configuration of these two alcohols is (*S*).

2. Conclusion

In conclusion, we have investigated the relationship between the chemical shift difference $\Delta\delta_{R-S}$ observed with phosphorus derivatives of cyclic alcohols and found that the upshielded signal will be the one for which the chiral alcohol has an (*S*)-configuration (unless CIP rules are not in agreement with $O > -CH-R^1 > -CH-R^2 > H$). Consequently this method can be applied to the determination of the absolute configuration of chiral cyclic alcohols and also the determination of the enantiomeric excess by integration of the surface of the peaks. Among the three C_2 diamines studied to synthesize the CDAs (Fig. 3), the preferred ones are cyclohexane-diamine (*R*,*R*)-**A** and (*R*,*R*)-**C** due to their easy and inexpensive synthesis,[10] and for which the rigidity of the cyclohexane ring generally provided the widest chemical shifts.

3. Experimental

Preparation of the phosphorus derivatives. The synthesis of diamines **A**,[10] **B**[7] and **C**[10] has already been reported, as well as the preparation of the phosphorus derivatives.[4] NMR studies were performed on a Bruker-AM-400 instrument. The enriched chiral alcohols were purchased from Acros and Fluka. An NMR tube was charged with 0.1 mmol of diamine **A** to **C**, dissolved in 0.4 mL of chloroform in the presence of freshly distillated *N*,*N*-diethylaniline or pyridine (0.5 mmol). The tube was purged with argon, followed by the addition of 0.1 mmol of freshly distilled PCl_3. The tube was shaken before the addition of the chiral alcohol (0.1 mmol), dissolved in 0.1 mL of chloroform. After performing the NMR experiment, a small amount of sulfur was added directly into the tube, which was shaken. The NMR experiments could be performed with the P(V) derivatives. Alternatively, the chloroform solution of the P(V) compound could be added to 10 mL of dichloromethane, washed twice with 10 mL of a half saturated solution of NH_4Cl and the organic phases dried over Na_2SO_4. Unreacted sulfur can be crystallized under low evaporation of the solvents. The solvent can also be easily removed and the P(V) products purified by chromatography (silica gel, CH_2Cl_2/MeOH 99.5/0.5 to 98/2 v/v). Another way of synthesizing the P(III) compound consists of making the chiral alcohol react directly with the $P-NMe_2$ derivative instead of the chlorinated one, as previously described.[4] In this case, the reaction can be directly performed in toluene, and a few drops of deuterated benzene added to allow locking of the signal.

Crystallographic data for (*R*,*R*)-1,3-dimethyl-2-(*R*)-(2-phenyl-cyclohexyloxy)-octahydro-benzo[1,3,2]diazaphosphole 2-sulfide ($C_{20}H_{31}N_2OPS$): Cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation. ($\lambda = 0.71073$ Å). Data were corrected for Lorentz and polarization effects and for absorption, $M_r = 378.6$, orthorhombic, $P2_12_12_1$, $a = 9.1013(4)$, $b = 10.6525(6)$, $c = 21.5034(11)$ Å, $V = 2084.8(2)$ Å^3, $Z = 4$, $\mu = 0.24$ mm^{-1}, $d_x = 1.206$ g cm^{-3}, $S = 1.06(2)$, $R = 0.035$, $\omega R = 0.036$, Flack parameter $x = -0.04(13)$. CDC-606438 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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