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Stereochemistry of base-induced cleavage of methoxide ion on *cis*- and *trans*-1,4-diphenylphosphorinanium salts. A different behavior with a phenyl substituent

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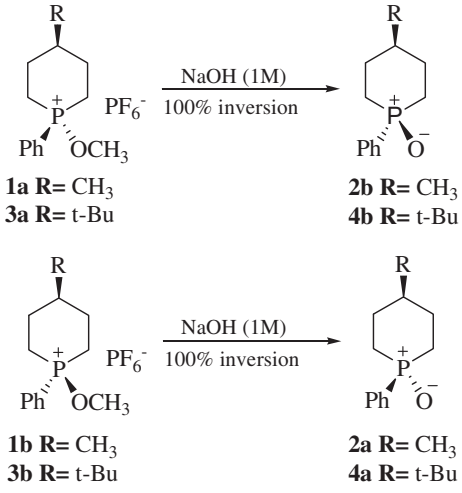
ABSTRACT

The synthesis and characterization of pure *cis*- and *trans*-1,4-diphenyl-1-methoxy-phosphorinanium tetrafluoroborate salts **11a** and **11b**, molecules designed to evaluate the effect of a phenyl substituent at C-4 on the stereochemical course of base-induced nucleophilic displacement of the methoxy group at phosphorus, was accomplished. The presence of a phenyl substituent at C-4 changes the stereochemical course of these reactions, from complete inversion with alkyl groups to products where retention of configuration at phosphorus predominates. We suggest a mechanism involving Berry pseudorotations and provide evidence that the hydroxide ion attacks the phosphorus atom through experiments with NaOH enriched with ^{17}O.

1. Introduction

Phosphorus-containing compounds and their chemistry have gained considerable attention as a result of their biological[1] and chemical profiles.[2] The most frequently encountered reactions in phosphorus chemistry are nucleophilic substitutions; such reactions at tetravalent phosphorus centers are involved in a number of cellular energetic and biosynthesis processes.[3] In this context, quaternary phosphonium salts undergo nucleophilic displacement reactions induced by aqueous hydroxide ion to yield phosphine oxides[4] and with few exceptions, these reactions have shown inversion of configuration at phosphorus as the stereochemical course.[5] In cyclic phosphonium salts, however, the stereochemical behavior is much more complex as ring size has a strong effect on the stereochemical course of these reactions. For example, phosphetanium salts[6] form the corresponding phosphine oxides with complete retention of configuration at phosphorus, whereas phospholanium salts, depending on the specific compounds, react with base to give products with complete retention of configuration at phosphorus or as a mixture of stereoisomers.[7] Both mechanistic and stereochemical arguments have been suggested to explain these differences.

In six-membered rings the most studied leaving groups have been the benzyl and the methoxy groups attached to the phosphorus atom. When the benzyl group is used as the leaving group, the reaction with base is non-stereospecific yielding phosphine oxides as mixtures of different proportions.[8] However, when the more electronegative methoxy group is used as the leaving group, pure samples of *cis* and *trans* 4-methyl (**1a** and **1b**) or 4-*tert*-butyl (**3a** and **3b**) afford the corresponding phosphine oxides **2** or **4** (Scheme 1) with complete inversion of configuration at phosphorus.[9]



Scheme 1. Stereochemical behavior of phosphorinanium salts.

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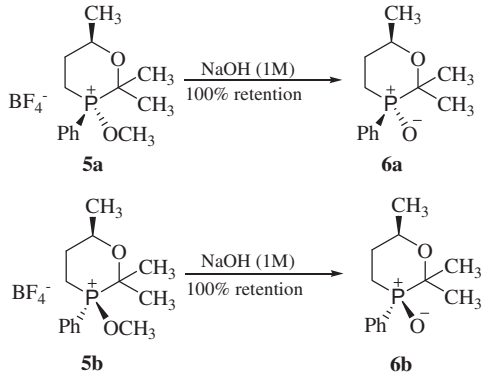
We have recently reported our results on the hydroxide-induced displacement of the methoxy groups on samples of pure cis and trans isomers of 3-methoxy-2,2,6-trimethyl-3-phenyl-1,3-oxaphosphorinanium tetrafluoroborate salts **5a** and **5b** (Scheme 2), systems designed to study the effect of a second heteroatom in the ring system on the stereochemistry of the reaction. In our study, the presence of the oxygen atom induces a different stereochemical outcome since **5a** and **5b** reacted with base to yield the phosphine oxides **6a** and **6b** with complete retention of configuration at phosphorus.[10] This study contrasts with the results observed in five-membered rings where the presence of the oxygen has no effect on the stereochemistry of the reaction.[11]



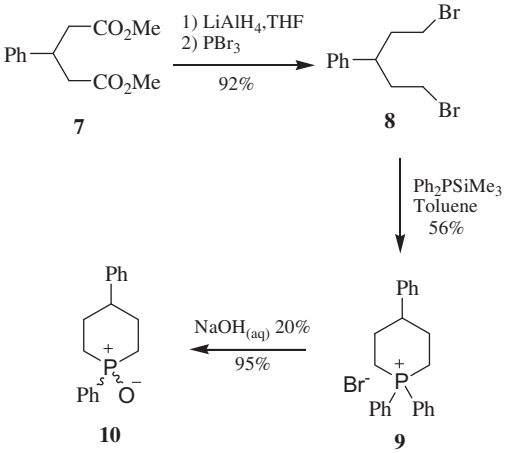
5a **6a** **5b** **6b**

Scheme 2. Stereochemical behavior of 1,3-oxaphosphorinanes.

As part of a series of studies designed to study the effect of different structural variants on the stereochemistry of nucleophilic displacement reactions of the methoxy group in phosphorinanium salts, we herein report our results on the base-induced displacement of the methoxy groups from *cis* and *trans* 1,4-diphenylphosphorinanium tetrafluoroborate salts **11a** and **11b** in order to assess the effect of a phenyl substituent at C-4 on these cyclic systems. Whereas the effect of alkyl substituents at C-4 in phosphorinanium salts is well documented, the effect of aromatic substituents in the stereochemical course of these reactions has remained unexplored to date.

2. Results and discussion

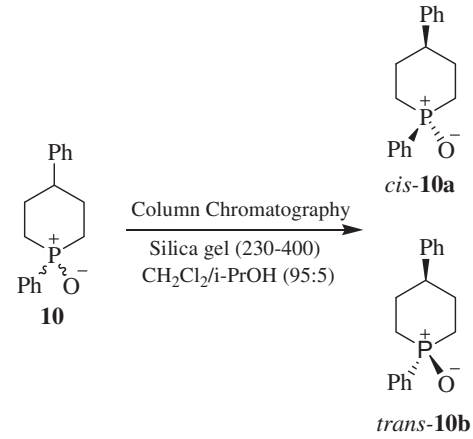
The synthesis of the 1,4-diphenylphosphorinane oxides **10**, which are the key precursors to our objective molecules, is outlined in Scheme 3 and is adapted from a similar procedure reported by Cremer et al.[12] Reduction of dimethyl 3-phenylglutarate **7**[13] with lithium aluminum hydride in THF, followed by treatment of the resulting diol with phosphorus tribromide, afforded **8** in 92% yield. The phosphorinanium bromide **9** was prepared in 56% yield by heating **8** with diphenyl(trimethylsilyl)phosphine[14] in toluene for 12 h. Subsequent treatment of salt **9** under aqueous sodium hydroxide afforded the phosphine oxides **10** as a 70:30 diastereomeric mixture (^{31}P NMR).



7 **8** **9** **10**

Scheme 3. Preparation of 1,4-diphenylphosphorinane oxides.

The separation of the diastereomeric mixture of phosphine oxides **10** was accomplished by column chromatography leading to **10a** and **10b** in a very pure form (Scheme 4). Both compounds were fully characterized by NMR spectroscopy; however, in order to carry out the stereochemical study, it was necessary to establish the relative stereochemistry of these compounds. The assignment of the relative configurations of diastereoisomers **10a** and **10b** were unambiguously established by X-ray crystal structure determinations on both.[15] Figure 1 shows the X-ray crystal structure of **10a** (cis isomer) and Figure 2 of **10b** (trans isomer). cis/trans Nomenclature is used in this work to denote the disposition of the phenyl groups at P and C-4.[16,17]



10 *cis*-**10a** *trans*-**10b**

Scheme 4. Diastereomeric separation of phosphine oxides **10a** and **10b**.

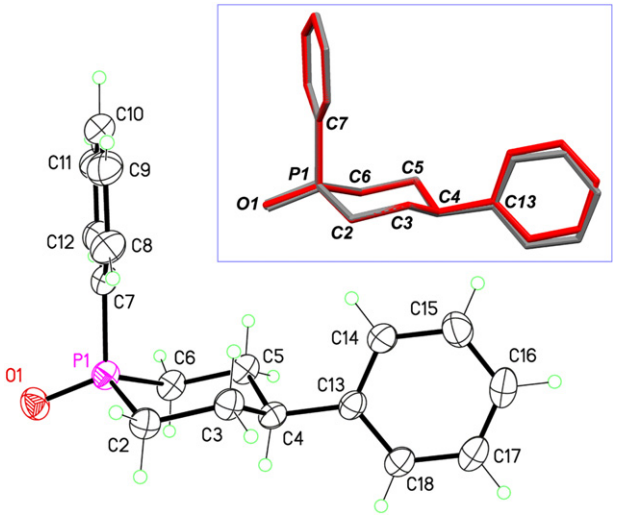


Figure 1. The molecular structure of one of the two independent molecules in **10a**, with displacement ellipsoids shown at the 30% probability level for non-H atoms. The inset is an overlay between the two independent molecules.

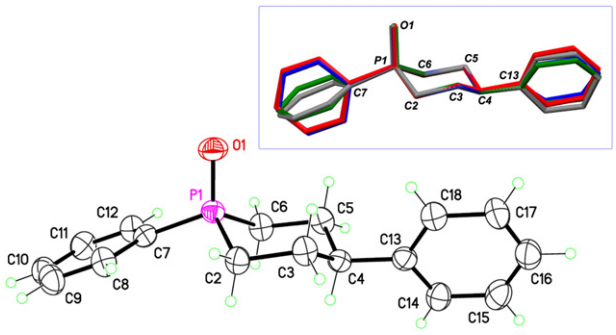


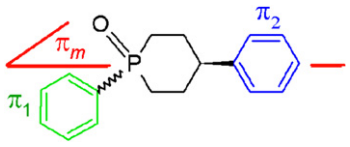
Figure 2. The molecular structure of one of the four independent molecules in **10b**, with displacement ellipsoids shown at the 30% probability level for non-H atoms. The inset is an overlay between the four independent molecules.[17]

Compound **10a** (Fig. 1) is stabilized in the solid-state with the expected chair conformation for the core phosphorinane ring, with phenyl substituents at P and C-4 atoms placed in axial and equatorial positions, respectively. The asymmetric unit contains two independent molecules and one lattice water molecule, affording a hemihydrate. The water molecule stabilizes the crystal structure, by bridging molecules P1 through strong O–H···O hydrogen bonds involving P=O groups as acceptors.

Molecular conformations may be compared for independent molecules, assuming a rigid phosphorinane ring. A fit[18] between both molecules shows that the phenyl substituting the P atom has a single orientation with respect to the phosphorinane core, while the phenyl group at C-4 experiments small libration motions, albeit limited to ca. 6° (Fig. 1, inset). Both molecules thus display almost identical conformations in the solid-state, and the crystallization with two crystallographically independent molecules is likely to be a consequence of inclusion of water in the lattice rather than a reflection of conformational flexibility. The bisected conformation about the C-4-phenyl bond is the same as that of 1,4-diphenyl-cyclohexane[19] and other related systems, and has been shown from density functional calculations to be the expected conformation for an equatorial phenyl group substituting a rigid six-membered ring.[20] In contrast, the axial phenyl group at the phosphorus atom is perpendicular to the mirror plane of the phosphorinane ring. Such an orientation avoids 1,3-*syn* diaxial repulsion between the phenyl *ortho* H atoms and the phosphorinane ring H atoms, a situation reminiscent of that described for non-sterically hindered eq-phenyl-cyclohexane derivatives.[21] It is worth mentioning that the same orientation was described in the X-ray study of 4-*tert*-butyl-1-phenylphosphorinane-1-sulfide,[22] suggesting that the stabilized conformation is mainly imposed by minimization of 1,3-*syn* diaxial interactions. This rule is obviously relaxed in the case of *O*/*S*-containing heterocycles and/or C2-subtituted phosphorinane derivatives, for which an axial phenyl substituent may be found in a bisecting orientation.[10]

A very different picture is observed for stereoisomer **10b**. The most differentiating feature is related to space group symmetry. Isomer **10a** belongs to a centrosymmetric space group while crystals of **10b** clearly lack inversion symmetry. As a consequence, the asymmetric unit for the trans isomer is duplicated compared to the **10a**. Four independent molecules are thus found in **10b**, which potentially correspond to four conformers. The substitution of the phosphorinane ring is identical for all the four molecules, with phenyl rings now placed in equatorial positions (Fig. 2). Unexpectedly, the phenyl at C-4 is twisted from the bisecting orientation observed in **10a**. The degree of rotational freedom about the C–phenyl bonds can be roughly measured by computing the angle Δ between the phenyl plane and the P1/O1/C4 mean plane, corresponding to the phosphorinane mirror plane in an ideal chair geometry: the bisecting conformer is characterized by Δ=0, while the perpendicular conformer is defined by Δ=90°. The phenyl group at C-4 is clearly bisecting the phosphorinane cycle in **10a**, while analogous Δ angles range from 22.1(3)° to 42.7(2)° in **10b** (Table 1). Regarding the equatorial phenyl bonded to the P atom, the four molecules display two totally different conformations: two molecules have the phenyl in an orientation close to perpendicular, while the others include bisecting phenyl groups (Fig. 2, inset).

Table 1
Rotational parameters for the conformation of the phenyl rings with respect to the phosphorinane chair in **10a** and **10b**



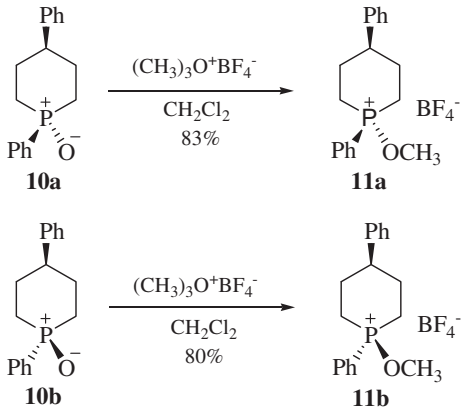
10a		**10b**			
Molecule P1	Δ_1=73.39 (7)	Molecule P1	Δ_1=87.5 (2)	Molecule P4	Δ_1=78.5 (2)
	Δ_2=1.83 (14)		Δ_2=22.1 (3)		Δ_2=39.0 (2)
Molecule P2	Δ_1=72.72 (12)	Molecule P2	Δ_1=4.1 (4)	Molecule P3	Δ_1=1.1 (4)
	Δ_2=1.9 (2)		Δ_2=42.7 (2)		Δ_2=26.0 (2)

Dihedral angles (°) between planes: Δ_1=angle (π_1, π_m); Δ_2=angle (π_2, π_m); where π_1 and π_1 are mean planes for phenyl rings and π_m is the mirror plane of the phosphorinane ring defined by atoms P, O, C4.

It is clear, from this conformational description, that **10b** is a more flexible molecule than **10a**. Although transferring this behavior for the isomers in solution is not possible, one might genuinely expect that equatorial phenyl rings in **10b** are almost free to rotate, while **10a** should be restricted to few rotational conformers.

In addition to the X-ray studies, the ^{31}P NMR of these compounds supports the stereochemical assignments given to **10a** and **10b**. Comparison of their chemical shifts shows that the phosphorus signal for **10a** appears at +35.11 ppm and that for **10b** at +31.16 ppm. This is consistent with the fact that when the oxygen occupies an axial position as in **10b**, the ^{31}P NMR shows an upfield signal and a downfield resonance when it occupies an equatorial position.[23]

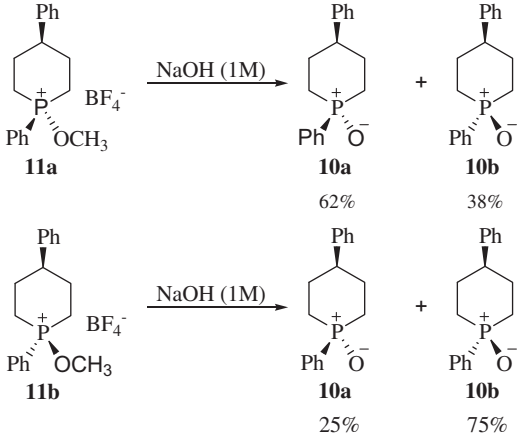
Once the configurations of the phosphine oxides **10a** and **10b** were established, the required molecules for our study **11a** and **11b** were obtained by direct methylation of **10a** and **10b** with trimethyloxonium tetrafluoroborate. The configuration of **11a** and **11b** was assumed to be the same on the basis of the established configurations of their parents **10a** and **10b**, respectively, and the known fact that methylation of cyclic phosphine oxides with this reagent proceeds with retention of configuration at phosphorus (Scheme 5).[24] Some key NMR signals were used for the structural



Scheme 5. Preparation of 1,4-diphenylphosphorinanium salts.

determination of these compounds. For example, the signals for the methoxy groups on both isomers appear as doublets centered around 3.9 ppm as a result of the coupling of these protons with the adjacent phosphorus atom. Thus the $^3J_{P-H(OCH3)}$ coupling constants have identical values of 12.6 Hz and are in agreement with those reported by Marsi[9] for phosphorus cyclic compounds substituted with methoxy groups. In addition, the ^{31}P NMR signals for each isomer appear at +79.05 ppm for **11a** and +79.44 ppm for **11b**.

The nucleophilic displacement reactions in aqueous sodium hydroxide carried out in salts **11a** and **11b** (Scheme 6) led to the



Scheme 6. Stereochemical behavior of **11a** and **11b**.

formation of mixtures of the phosphine oxides **10a** and **10b** in which the products of retention of configuration at phosphorus predominate. Specifically, salt **11a** yields 62% of the retention product **10a** and 38% of the inversion product **10b**, whereas salt **11b** affords 75% of the retention product **10b** and 25% of the inversion product **10a**. The stereochemistry observed could be easily corroborated by direct comparison of the ^1H and ^{31}P NMR spectra of the isolated phosphine oxides previously used for the synthesis of **11a** and **11b** since they are exactly the same compounds. In addition, the diastereomeric ratios of these products were determined by ^{31}P NMR data of the crude reaction mixtures.[25]

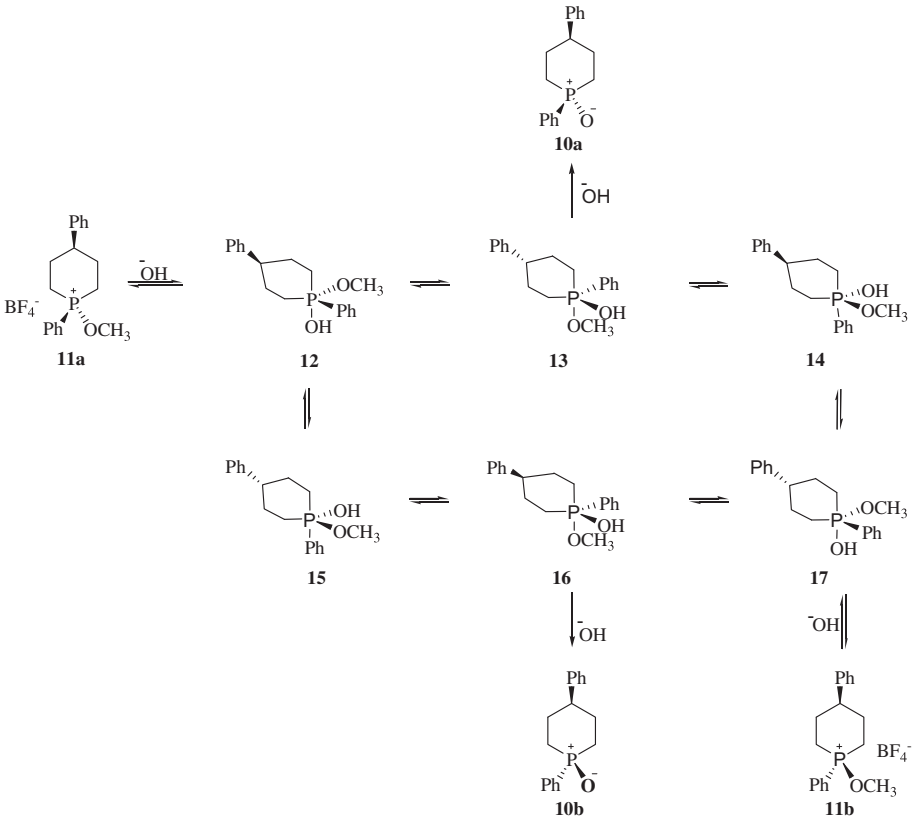
The stereochemical behavior observed in our study dramatically contrasts with the stereochemical behavior reported by Marsi[9] in phosphorinane ring systems substituted with alkyl groups at C-4 where the base-induced displacement of a methoxy group proceeds with complete inversion of configuration at phosphorus, a behavior explained on the basis of the $S_N2(P)$ mechanism. The relative preference of a substituent to occupy the apical or equatorial site in the more commonly observed trigonal bipyramid (TBP) geometry, has been a subject of intensive studies in the past.[26] In spite of the preference of the phosphorinane ring to occupy equatorial-equatorial disposition in $S_N2(P)$ mechanism, in order to explain inversion of configuration at phosphorus in phosphorinane ring systems substituted with Me or *t*-Bu groups at C-4, the non-stereospecific behavior observed in our study led us to propose that the influence of the phenyl group at C-4 on the phosphorinane ring favors a notable preference to occupy apical-equatorial disposition even in the case of an electronegative methoxy leaving group. This could be supported by the general statement in which four- to seven-membered rings at phosphorus prefer an apical-equatorial disposition unless constrained by fused rings. This behavior must be taken into an account to explain the observed stereochemistry in the studied phosphorus displacement reactions.

On the basis of the latter and on the different mechanisms that have been proposed in the literature for the nucleophilic substitution at phosphorus in cyclic compounds, the reaction mechanism that best explains the observed stereochemical behavior is the one involving Berry pseudorotation of phosphoranes.[27] This mechanism implies the initial formation of a phosphorane from an apical attack of a hydroxide ion on the phosphorus atom resulting in an apical-equatorial disposition of the phosphorinane ring.

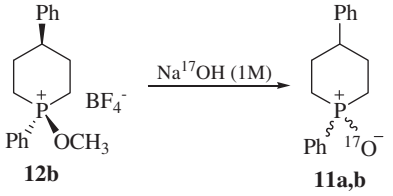
The pathway toward retention (Scheme 7) of configuration analyzing the behavior of **11b**, involves the initial formation of phosphorane **17** by an apical attack of the hydroxide ion at phosphorus atom.[28] Only one pseudorotation toward phosphorane **16** places the methoxy leaving group in an apical position, leading to the oxide **10a** with retention of configuration after the base-induced elimination of this group. The extended principle of microscopic reversibility supports the assumption of apical attack and apical departure, and establishes that apical bonds are longer and weaker. In addition, the methoxy group has a strong preference to occupy an apical position since it is the ligand bound to phosphorus with the highest relative value of apicophilicity according to Trippett's scale.[29] On the other hand, phosphoranes **17** and **16** both have a trans disposition of the phenyl groups, a condition considered favorable to avoid steric hindrance between these groups through the mechanistic pathway. The two possible pathways toward inversion of configuration, oxide **10a**, involve the formation of unfavored phosphoranes **14** or **15** placing the two electronegative substituents (OH and OCH_3) in equatorial positions and the bulky phenyl group in an apical site. According to Bent's rule,[30] these phosphoranes would be required to place the methoxy group in apical position prior to its elimination (from **14** to **13** or from **15** and **12** to **13**); to achieve this condition, this would require additional pseudorotations, as compared to the favored retention pathway.

As can be seen in Scheme 7, the mechanistic pathway proposed to explain the stereochemical behavior of **11a** toward retention and inversion products, implies similar considerations as previously described for **11b**; however, the difference in the retention/inversion ratio suggests that the influence of the phenyl group at C-4 must be taken into an account. The comparison of phosphoranes involved in the retention pathways of both salts, led us to propose that the trans disposition of the phenyl groups in phosphoranes **17** and **16** avoids unfavorable interactions between them, interactions that could not be completely avoided in a cis disposition of the phenyl groups, phosphoranes **13** and **14**, and consequently having a higher net retention for **11b** than for **11a**.

Finally, evidence for a mechanism in which nucleophilic attack by the hydroxide ion occurs at phosphorus was obtained when the reaction of **12b** was carried out with NaOH enriched with ^{17}O (Scheme 8). The ^{17}O NMR of the products obtained in this reaction shows two signals, one at +28.06 ppm and another one at +55.44 ppm. This evidence supports the mechanism shown in



Scheme 7. Proposed mechanism to stereochemical outcome.



Scheme 8. Reaction with $Na^{17}OH$.

Scheme 7 and is in agreement with other studies reported in the literature where no significant attack on the methoxy carbon was observed.[9,10] In addition, the high resolution mass spectra shows that the labeled ^{17}O was incorporated in the resulting products.

3. Conclusions

In this work, we have accomplished the synthesis of *cis*- and *trans*-1-methoxy-1,4-diphenylphosphorinanium tetrafluoroborate salts **11a** and **11b**, heterocyclic organophosphorus compounds not previously reported in the literature. The base-induced cleavage of these compounds results in the formation of phosphine oxides **10a** and **10b** where the products with retention of configuration at phosphorus tend to predominate. The relative configuration of **10a** and **10b** was established by X-ray diffraction studies. We suggested a mechanism involving Berry pseudorotations on phosphoranes **12** and **17** formed after apical attack of a hydroxide ion on the phosphorus atom resulting in an apical-equatorial disposition of the phosphorinane ring system. Subsequent apical departure of the leaving group from **13** or **16** leads mainly to products where retention of configuration at phosphorus predominates. Evidence that the hydroxide ion attacks phosphorus and not carbon of the methoxy group was obtained by the reaction of **12b** with NaOH enriched with ^{17}O, ^{17}O NMR, and high resolution mass spectra showed that the labeled ^{17}O was incorporated in the resulting products.

In summary, the presence of the phenyl substituent at C-4 on **11a** and **11b** changes the stereochemical course of these reactions, from complete inversion in systems substituted with alkyl groups, such as **1a**,**b** and **3a**,**b** to products where retention of configuration at phosphorus predominates.

4. Experimental section

4.1. General experimental methods

^1H NMR spectra were recorded at 400 MHz with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 100 MHz with $CDCl_3$ as solvent. ^{31}P NMR spectra were recorded at 81 MHz with $CDCl_3$ as solvent and 85% H_3PO_4 as external standard. THF was dried by distillation over sodium benzophenone ketyl. All other solvents were used after distillation at normal pressure.

*4.1.1. 3-Phenyl-1,5-dibromopentane (**8**).* Exactly 0.408 g (10.8 mmol) of lithium aluminum hydride were suspended in 8.0 mL of anhydrous THF at 0 °C. To this suspension was added dropwise a solution of 2.0 g (8.5 mmol) of dimethyl 3-phenylglutarate dissolved in 10.0 mL of THF. When the addition was completed, the resulting mixture was refluxed for 1.5 h period. The reaction mixture was allowed to cool to room temperature, and distilled water was added very slowly until the evolution of gas ceased; then, 10.0 mL of a 20% solution of hydrochloric acid were added. The reaction mixture was extracted with dichloromethane, the organic layers were combined and dried over sodium sulfate and the solvent removed under vaccuo to produce 1.43 g (94%) of the product as a yellow oil, which was

immediately treated with 2.9 g (10.6 mmol, 1.0 mL) of phosphorus tribromide at 0 °C. When the addition was completed, the ice bath was removed and the reaction mixture was stirred overnight at room temperature. The resulting mixture was treated with 30.0 mL of distilled water and the reddish solid formed removed by filtration. The filtrate was extracted with dichloromethane, the organic layers were combined, dried over anhydrous sodium sulfate, and the solvent evaporated to give 2.37 g (98%) of **8** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.2 (m, 4H, $H_{2,4}$, $^3J_{H2,4\text{-}H3}$=8.0, $^3J_{H2,4\text{-}H1,5}$=6.0), 3.0–3.1 (m, 3H, $H_{1,3}$), 3.2–3.3 (m, 2H, H_5), 7.2–7.4 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$,100 MHz) δ 31.7 (s, $C_{2,4}$), 39.4 (s, $C_{1,5}$), 42.9 (s, C_3), 127.2 (s, C_{para}), 127.8 (s, C_{ortho}), 129.0 (s, C_{meta}), 141.5 (s, C_{ipso}). HRMS (EI) calcd for $C_{11}H_{14}Br_2$: 306.0369; found: 305.9445.

*4.1.2. 1,1,4-Triphenylphosphorinanium bromide (**9**).* A mixture of 2.37 g (7.70 mmol) of 3-phenyl-1,5-dibromopentane and 1.37 mL (10.2 mmol) of trimethylsilyl (diphenylphosphine) in 25.0 mL of anhydrous toluene was heated under reflux for 30 h period. The mixture was cooled to room temperature, and the white precipitate formed was collected by filtration, the process yielded 1.78 g (56%) of **9** as a white solid, mp 174–176 °C. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.86–1.98 (m, 2H, $H_{2,6}$), 2.38–2.50 (dd, 2H, $H_{2,6}$, $^3J_{H2,6\text{-}H3,5}$=15.0), 3.10–3.20 (m, 3H, $H_{3,5,4}$), 3.46–3.53 (t, 2H, $H_{3,5}$ $^3J_{H3,5-H2,6}$=15.0), 7.14–7.30 (m, 5H, H_{arom}), 7.66–7.97 (m, 8H, H_{arom}), 8.15–8.20 (m, 2H, H_{arom}); ^{13}C NMR (CD_3OD, 100 MHz) δ 20.21 (d, $C_{2,6}$, $^1J_{C2,6-P}$=50.1), 30.11 (d, $C_{3,5}$, $^2J_{C3,5-P}$=6.1), 43.65 (d, C4, $^3J_{C4-P}$=6.1), 127.61 (s, C_{ortho}), 128.10 (s, C_{meta}), 129.86 (s, C_{para}), 131.30 (d, C_{ortho}, $^2J_{C-P}$=12.2), 132.05 (d, C_{meta}, $^3J_{Cmeta-P}$=12.2), 132.94 (d, C_{para}, $^4J_{Cpara-P}$=10.6), 136.12 (d, C_{ipso}, $^1J_{Cipso-P}$=45.6), 145.60 (s, C_{ipso}); ^{31}P NMR (CD_3OD, 81 MHz) δ +29.4. HRMS (EI) calcd for $C_{23}H_{24}BrP$: 411.3212; found: 411.3372.

*4.1.3. 1-Oxo-1,4-diphenylphosphorinane(**10**).* Exactly 1.7 g (4.13 mmol) of the bromide phosphorinanium salt **9** and 15.0 mL of a 20% solution of sodium hydroxide were heated under reflux overnight. The reaction mixture was allowed to cool to room temperature and was extracted with dichloromethane; the combined organic layers were dried over sodium sulfate and the solvent evaporated to afford 1.2 g (95%) as a 70:30 isomeric mixture of the product. ^{31}P NMR ($CDCl_3$): δ +34.1, δ +31.1. The diastereomeric mixture of **10a** and **10b** were separated through a chromatographic column (silica gel) using a 95:5 mixture of dichloromethane/isopropanol as eluent. Compound (**10a**): 0.62 g (52%), mp 125–127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70–1.85 (m, 2H, $H_{3,5ax}$), 2.14–2.42 (m, 4H, $H_{3,5,2,6eq}$), 2.67 (dd, 2H, $H_{2,6ax}$, $^3J_{H2,6ax\text{-}3,5ax}$=15.6), 2.82 (dd, 1H, 4_{ax}, $^3J_{H4ax-H3,5ax}$=11.6), 7.09–7.12 (m, 1H, H_{16para}), 7.17–7.29 (m, 4H, $H_{14,18ortho}$, $H_{15,17meta}$), 7.55–7.62 (m, 3H, $H_{8,12ortho}$, H_{10para}), 7.80–7.85 (m, 2H, $H_{9,11meta}$); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 26.9 (d, $C_{2,6}$, $^1J_{C-P}$=63.5), 31.1 (d, $C_{3,5}$, $^2J_{C-P}$=3.0), 43.7 (d, C_4, $^3J_{C-P}$=6.0), 126.7 (s, C_{16para}), 126.9 (s, $C_{14,18ortho}$), 128.8 (s, $C_{9,11,15,17meta}$), 129.5 (d, $C_{8,12ortho}$, $^2J_{C-P}$=11.0), 130.2 (d, C_{7ipso},$^1J_{C-P}$=9.0), 132.6 (s, C_{10para}), 144.7 (s, C_{13ipso}); ^{31}P NMR ($CDCl_3$, 81 MHz) δ +34.60. Anal. Calcd for $C_{17}H_{19}OP$: C, 75.53; H, 7.08. Found: C, 75.81; H, 7.17. Compound (**10b**): 0.41 g (35%), mp 183–186 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95–2.06 (m, 2H, $H_{2,6ax}$), 2.10–2.30 (m, 4H, $H_{2,6,3,5eq}$), 2.38–2.51 (m, 2H, $H_{3,5ax}$), 2.74 (dd, 1H, H_4, $^3J_{H4ax-H3,5ax}$=12.0), 7.20–7.36 (m, 5H, $H_{14,18ortho}$, H_{16para}, $H_{15,17meta}$,), 7.50–7.60 (m, 3H, $H_{8,12ortho}$, H_{10para}), 7.70–7.90 (m, 2H, $H_{9,11meta}$); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 28.35 (d, $C_{2,6}$, $^1J_{C-P}$=65.3), 28.95 (d,$C_{3,5}$, $^2J_{C-P}$=4.5), 45.26 (s, C_4), 126.79 (s, C_{16para}), 126.86 (s, $C_{14,18ortho}$), 128.78 (s, $C_{9,11,15,17meta}$), 128.90 (d, $C_{8,12ortho}$ $^2J_{C-P}$=12.1), 130.34 (d, C_{7ipso} $^1J_{C-P}$=36.4), 132.39 (s, C_{10para}), 145.58 (s, C_{13ipso}); ^{31}P NMR ($CDCl_3$, 81 MHz) δ +31.99. Anal. Calcd for $C_{17}H_{19}OP$: C, 75.53; H, 7.08. Found: C, 75.77, H, 7.11.

*4.1.4. cis- and trans-1-Methoxy-1,4-diphenylphosphorinanium tetrafluoroborates, (**11a** and **11b**).* Exactly 0.287 g (1.06 mmol) of phosphine oxide **10a** were dissolved in 25.0 mL of dichloromethane. To this solution was added a solution of 0.26 g (1.77 mmol) of trimethyloxonium tetrafluoroborate in 25.0 mL of dichloromethane, and the resulting mixture was stirred at room temperature under nitrogen for 6 h. When the reaction was completed, the solvent was evaporated and 0.33 g (83%) of the product **11a** were isolated as a white solid, mp 100–102 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.78 (m, 4H, $H_{2,6}$), 2.11(m, 4H, $H_{3,5}$), 2.75–3.14 (m, 1H, H_4, $^3J_{H4-H3,5}$=12.6), 3.91 (d, 3H, OCH_3, $^3J_{OCH3-P}$=12.6), 7.06–7.12 (m, 2H, H_{arom}), 7.17–7.29 (m, 3H, H_{arom}), 7.66–8.08(m, 5H, H_{arom}); ^{31}P NMR($CDCl_3$, 81 MHz) δ +79.05. HRMS (EI) calcd for $C_{18}H_{22}BF_4OP$: 372.1395; found: 372.1419. Compound **11b** was obtained in a similar manner yielding 0.23 g (80%) of the product as a white solid, mp 148–150 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.14–1.30 (m, 2H, $H_{2,6ax}$, $^3J_{H2,6ax-H3,5ax}$=15.0), 2.00–2.30 (m, 4H, $H_{2,6,3,5eq}$), 2.35–2.60 (m, 2H, $H_{3,5ax}$), 2.78–2.81 (m, 1H, H_4, $^3J_{H4-H3,5ax}$=15.0), 3.88 (d, 3H, OCH_3, $^3J_{OCH3-P}$=12.6), 7.18–7.40 (m, 5H, H_{arom}), 7.43–7.75 (m, 3H, H_{arom}), 7.80–8.00 (m, 2H, H_{arom}); ^{31}P NMR ($CDCl_3$, 81 MHz) δ +79.44. HRMS (EI) calcd for $C_{18}H_{22}BF_4OP$: 372.1395; found: 372.1403.

*4.1.5. Base-induced substitution reaction of 1-methoxy-cis-1,4-diphenylphosphorinanium tetrafluoroborate (**11a**).* To 0.30 g (0.81 mmol) of salt **11a** was added a 1.0 M solution of sodium hydroxide at room temperature. The mixture was stirred at room temperature for 1 h and then refluxed for an additional 2 h. The mixture was allowed to cool to room temperature and then extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate and the solvent evaporated to yield 0.19 g of a mixture of the corresponding phosphorinane oxides. Analysis of the ^{31}P NMR signals of the mixture showed 62% of **10a** and 38% of **10b**, both compounds previously characterized. The same procedure was used as for the reaction of the **11b** isomer with similar results, yielding 0.12 g of a mixture of the corresponding phosphorinane oxides. Analysis of the ^{31}P NMR signals of the mixture showed a 75% of **10b** and 25% of **10a**, both compounds previously characterized.

*4.1.6. Base substitution reaction of 1-methoxy-trans-1,4-diphenylphosphorinanium **11b** with ^{17}O-enriched sodium hydroxide.* Exactly 0.03 mL of a 1.0 M solution of $Na^{17}OH$ (prepared by adding 7.00 mg of Na° to 6.0 mg of 35% $H_2{}^{17}O$) was added to 0.047 g (0.125 mmol) of salt **11b** as previously described for base-induced substitution reactions of **11a** and **11b**. The reaction was finished and 0.024 g (71%) of the ^{17}O-enriched oxide products **10a** and **10b** were obtained. ^{17}O NMR ($CDCl_3$, 40 MHz) δ 28.08, δ 55.44. HRMS (EI) calcd for $C_{17}H_{19}{}^{17}OP$: 271.1248; found: 271.1285.

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Supplementary data

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16. CCDC-751125 (compound **10a**) and CCDC-751126 (compound **10b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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