Preparation, Reactions, and Stereochemistry of 4-*tert*-Butyl-1-chlorophosphorinane 1-Oxide and Derivatives

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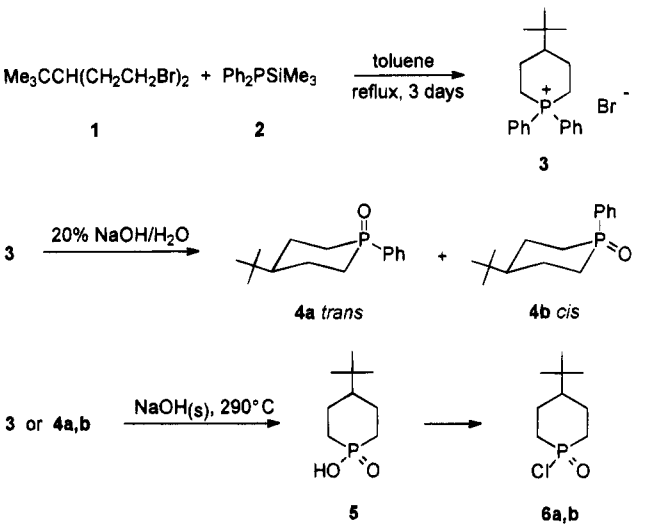
The title compound **6** was synthesized as a model structure to study the stereochemical and mechanistic aspects of nucleophilic substitution at the phosphorus atom in a six-membered ring. Several synthetic methods were used to prepare **6**, but in every case a mixture of diastereomers was obtained, in almost the same ratio. This mixture was used for the investigation of the reaction with several alcohols (methanol, ethanol, isopropyl alcohol) under acidic and/or basic conditions. Reactions with phenyllithium and two nitrogen nucleophiles, aniline and morpholine, were also carried out. The reactions led to mixtures of diastereomeric products; the ratio of these products did not always correspond to the diastereomeric ratio of starting material. Reactions of phosphinate esters were also studied, including kinetic measurements; the results strongly suggest an S_N2 reaction mechanism. 4-*tert*-Butyl-1-fluorophosphorinane 1-oxide (mixture of isomers) was synthesized and its reactions with phenoxide ions and phenyllithium were studied; the overall stereochemical results of these transformations were similar to those of the title chlorides. The stereochemical assignments of the phenyl- (**4**), methoxy- (**7**), phenoxy- (**10**), and anilino (**13**) derivatives of **6** have been firmly anchored by X-ray studies; assignments for other compounds are tentative and based on spectroscopic measurements, including ^1H, ^{13}C, ^{31}P, and ^{17}O NMR data.

Introduction

Nucleophilic substitution at tetracoordinated phosphorus has been extensively investigated.[1] The reaction routes may involve pentacoordinate transition states or intermediates; therefore, the stereochemical outcome of substitution can be complicated by intervening pseudorotation.[2] For example, alkaline hydrolysis of benzylethylmethylphenylphosphonium iodide proceeds with inversion,[3] whereas the hydrolysis of benzyl substituted phosphetanium[4] and phospholanium[5] salts goes with retention of configuration at phosphorus. Only limited stereochemical research on phosphinate esters has been done; transesterification of acyclic esters proceeds with inversion of configuration;[6] four-membered phosphinate esters react with retention of configuration.[7] Five- and six-membered phosphinate esters have not been investigated. In this work, derivatives of the parent substrate, 4-*tert*-butyl-1-chlorophosphorinane 1-oxide (**6**), were selected to probe the stereochemical details of nucleophilic substitution at a phosphorus center in six-membered rings. We wish to report the results of these experiments[8] together with their stereochemical and mechanistic implications.

Scheme 1



Results and Discussion

Synthesis and Stereochemistry (Scheme 1). The multiple step preparation of **6a,b** is outlined in Scheme 1. The phosphorinanium bromide **3** was prepared in 65–70% yield by treating 1,5-dibromo-3-*tert*-butylpentane (**1**) with diphenyl(trimethylsilyl)phosphine (**2**) in boiling toluene for three days. Heating finely powdered **3** with an excess of sodium hydroxide at 290–320 °C gave 4-*tert*-butyl-1-hydroxyphosphorinane 1-oxide (**5**) in high yield. Traces of the *trans/cis*[9] mixture of 4-*tert*-butyl-1-phenylphosphorinane 1-oxide (**4a,b**, 75:25 isomer ratio) were

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1995.

(1) For a recent reference, see Savelova, V. A.; Solomoichenko, T. N.; Ved', T. V.; Sadovskii, Yu. S.; Simanenko, Yu. S. *Zh. Organicheskoi Kchimii* **1993**, *29*, 666–677.

(2) Holmes, R. R. *Pentacoordinated Phosphorus*; ACS Monograph 176, American Chemical Society, Washington, D.C., 1980; Vol. II.

(3) Kumli, K. F.; McEwen, W. E.; VanderWerf, C. A. *J. Am. Chem. Soc.* **1959**, *81*, 3805.

(4) Cremer, S. E.; Chorvat, R. J.; Trivedi, B. C. *J. Chem. Soc., Chem. Commun.* **1969**, 769.

(5) Marsi, K. L. *J. Am. Chem. Soc.* **1969**, *91*, 4724.

(6) Green, M.; Hudson, R. F. *Proc. Chem. Soc.* **1962**, 307.

(7) Cremer, S. E.; Trivedi, B. C. *J. Am. Chem. Soc.* **1969**, *91*, 7200.

(8) Preliminary results have been published: Cremer, S. E.; Cowles, J. D.; Gamliel, A. *Phosphorus Sulfur* **1987**, *30*, 369.

(9) The *cis/trans* nomenclature refers to the relationship between the *tert*-butyl group and the substituent at the phosphoryl (P=O) group, see ref 8.

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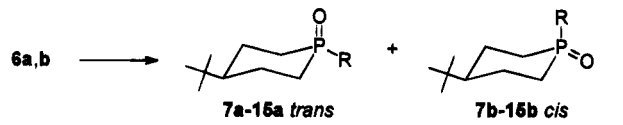
Table 1. Reactions of 6a,b with Nucleophiles



compd	R	method	yield [%]	*trans*/*cis* ratio
7	MeO	a	78	91:9
7	MeO	b	98	98:2
7	MeO	c	93	98:2
8	EtO	a	77	79:21
8	EtO	b	95	96:4
9	*i*-PrO	a	87	72:28
9	*i*-PrO	b	91	96:4
10	PhO	d	76	91:9–64:36[h]
11	4-NO_2PhO	d	73	20:80
12	F	e	58	20:80[h]
13	NHPh	f	>95[i]	68:32
14	$N(CH_2CH_2)_2O$	g	98	95:5
15	NEtPh	f,g	>95[i]	90:10[j]

[a] ROH. [b] RONa/ROH. [c] ROH/$AgNO_3$. [d] ArONa/CH_3CN. [e] NaF/CH_3CN. [f] Amine/CH_2Cl_2. [g] Amine/toluene. [h] The ratio depends on the reaction time and conditions, see text. [i] Yield from ^{31}P NMR. [j] Uncertain stereochemistry.

also observed. The phosphine oxides **4** can be obtained as sole products with nearly the same isomer ratio (70:30) if an aqueous 20% sodium hydroxide solution is used. The stereochemistry of the phosphine oxides **4** is known from a previous X-ray study,[10] and the identity of isomers may be determined from the corresponding ^{13}C NMR spectra. In turn, **4** was converted to the phosphinic acid **5** when heated with solid, powdered NaOH.

The acid **5** was then used to prepare the corresponding phosphinic acid chlorides **6**. This was achieved using thionyl chloride under acidic or basic conditions, phosphorus pentachloride or triphenylphosphine/CCl_4.[11] All of these methods resulted in about same mixture of diastereomeric chlorides **6a,b**. Based on the ^{31}P NMR spectra, the average ratio was 17:83 (**6a**:**6b**)[12] and varied from 20:80 to 15:85.

The question arises as to whether the ratio in **6** corresponds to the thermodynamic equilibrium ratio. Efforts to obtain isomer enrichment or one pure isomer were made. This was achieved when a crystalline compound obtained after sublimation was partially dissolved in dry toluene. The undissolved crystals were >97% pure **6b** (by ^{31}P NMR). However, these slowly reverted to the initial **6a**:**6b** ratio if dissolved in $CDCl_3$ or toluene. A convergent approach to the equilibrium from both sides would be desirable; however, the abundance of *trans* isomer **6a** never exceeded 20%. Neither could the agent promoting the isomerization (possibly HCl?),[13] nor the precise pathway of this process be determined.

The stereochemistry of the chlorides **6** could not be established unequivocally, and the assignments remain tentative. However, some spectroscopic support (*vide infra*) for the proposed stereoassignment was obtained.

Nucleophilic Displacement of Chlorine at Phosphorus. Reactions with alcohols under acidic (HCl is produced during the reaction) and basic (alkoxide ions) conditions were performed at room temperature and

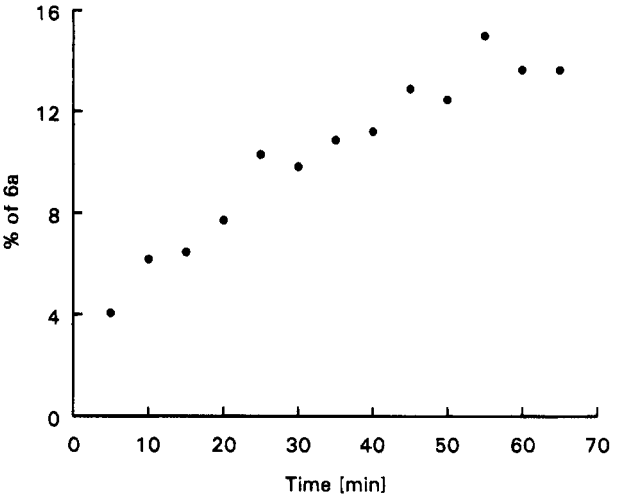


Figure 1. Time dependence of the percentage of **6a** during the reaction with isopropyl alcohol.

followed by ^{31}P NMR spectroscopy. Table 1 summarizes the results. In all experiments with alcohols, products other than the expected esters were found. Clean mixtures of the diastereomeric esters were obtained after workup.

The amount of **6a** (minor isomer) determined from the ^{31}P NMR spectrum at the beginning of the reaction was usually low; on ethanol treatment **6a** was nearly imperceptible. With isopropyl alcohol the initial amount of **6a** was more significant but still low.[14] However, the ratio **6a**:**6b** increased and was finally restored to the initial ratio during the reactions. This suggested equilibration of the chlorides under the reaction conditions. Figure 1 presents a plot of a typical change in the percentage of **6a** vs time for the reaction of mixture **6a,b** with isopropyl alcohol. The reaction with methanol was too fast to be followed by ^{31}P NMR spectroscopy.

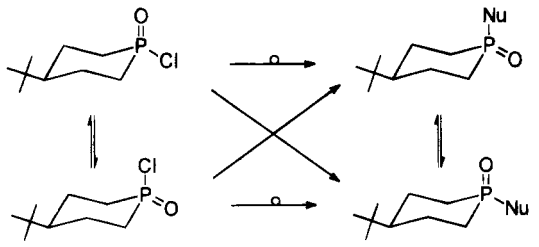
Reactions performed under basic conditions were faster and cleaner than those run in an acidic environment. The ratios of diastereomeric esters depended on the base and the reaction time. The reactions proceeded under kinetic control (the thermodynamically less stable isomers usually formed as major products, *vide infra*). However, since the equilibration of substrates occurred readily, no decisive conclusions can be made regarding the stereochemistry of the reactions.

4-*tert*-Butyl-1-methoxyphosphorinane 1-oxide (**7**) could also be obtained *via* alkylation of the phosphinic acid **5** with trimethyloxonium tetrafluoroborate (TMOTFB). This reaction yielded a 50:50 mixture of diastereomeric methyl esters **7a**:**7b**, indicating the lack of differentiation between axial and equatorial phosphoryl oxygen atoms through kinetic control. Equilibration of the mixture of diastereoisomers in CH_3ONa/CH_3OH solution leads to a mixture enriched in **7b**; this isomer crystallized from the oily mixture. Single crystal X-ray analysis of this product confirmed the *cis* stereochemical assignment.

Reactions of **6** with sodium methoxide, ethoxide, and isopropoxide afforded the same stereochemical results as the reactions with alcohols. This type of reactivity is different from that shown by 2-chloro-5-(chloromethyl)-5-methyl-1,3,2-dioxaphosphorinane 2-oxide. Wadsworth[15,16]

(10) MacDonnel, G. D.; Berlin, K. D.; Baker, J. R.; Ealick, S. E.; Helm, D. van der; Marsi, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 4535.
(11) Appel, R.; Einig, H. *Z. Anorg. Allg. Chem.* **1975**, *414*, 236.
(12) This is a tentative stereochemical assignment.
(13) Tasz, M. K.; Cremer, S. E.; Fanwick, Ph. E. *Phosphorus Sulfur* **1995** *104*, 223.
(14) If a second portion of the starting mixture of the chlorides **6** was added after completion of the reaction, this ratio of isomers remained the same as in the starting material.
(15) Wadsworth, W. S., Jr. *J. Org. Chem.* **1987**, *52*, 1748.

Scheme 2



found that methanolysis of the latter under neutral or acidic conditions proceeded *via* inversion, whereas methoxide ion led only to retention. The equilibration of alkyl esters **7**–**9** with alkoxides is slow at room temperature; therefore, the stereochemical outcome of substitution is affected primarily by equilibration of the substrates (Scheme 2). On the other hand, faster isomerization of aryl esters adds an additional degree of complication to the reaction of **6a,b** with phenols. Treatment of **6a,b** with sodium phenoxide in acetonitrile gave a 91:9 *trans:cis* ratio of phenyl esters (**10a,b**), when conducted with a deficiency or an equivalence of phenoxide ion. The concentration of the *cis* isomer **10b** increased when an excess of phenoxide was present or the reaction time increased. Isomer **10a** was isolated in pure form by recrystallization from hexanes. Its stereochemistry was established by X-ray study.[17] At equilibrium the ratio of **10a**:**10b** was 19:81, respectively.

Increased thermodynamic control of the reaction was more readily observed in the case of *p*-nitrophenoxides. The thermodynamically more stable ester predominated in a 20:80 mixture of *p*-nitrophenoxide esters (**11a,b**) from the reaction of **6** with sodium *p*-nitrophenoxide.

Reaction of **6** with aniline, benzylamine, *N*-ethylaniline, or morpholine were performed in toluene and dichloromethane. Both aniline and morpholine gave diastereoisomeric mixtures of the amides **13a,b** and **14a,b**, which were isolated and characterized. Reaction with benzylamine and *N*-ethylaniline were studied only by ^{31}P NMR spectroscopy. In all cases, the resulting ratio of diastereoisomers did not correspond to the ratio of starting chlorides.

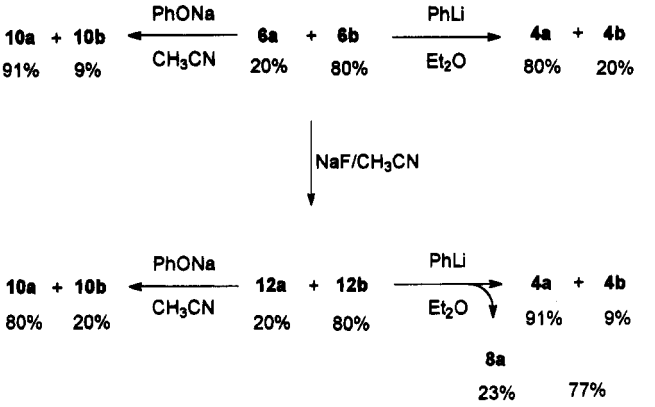
The *trans* isomer **13a** was isolated in pure crystalline form by recrystallization from chloroform/pentane and the structure confirmed by an X-ray study.[18] In the reaction with morpholine, amides were produced in a 95:5 ratio. See Note Added in Proof.

N-Ethylaniline reacted with **6** more slowly and required one week to achieve completion at room temperature (either in CH_2Cl_2 or toluene). The reaction progress was monitored by ^{31}P NMR spectroscopy. The ratio of both **6a**:**6b** and the *N*-ethylanilides (**15a**:**15b**) remained constant and without any apparent relationship.

Treatment of the mixture of diastereomeric chlorides **6a,b** with phenyllithium in diethyl ether at low temperature afforded a mixture of phosphinoxides **4a,b** in an 80:20 ratio, which was virtually the same as in starting chlorides, but inverted.

Fluoride anion was likewise found to be a useful nucleophile. A mixture of isomeric fluorides (**12a,b**) was

Scheme 3



produced in 58% yield by combining **6a,b** with sodium fluoride in acetonitrile. The product ratio corresponded to the initial ratio of chlorides (Table 1).

To obtain stereochemical information on the fluoride, the isomer mixture **12a,b** was treated with both phenyllithium and sodium phenoxide (Scheme 3). The reaction with phenoxide ion in acetonitrile afforded a mixture of phenyl phosphinates **10a,b** in a ratio corresponding to that of the starting fluorides. The major product had the same stereochemistry as that obtained from the **6a,b** mixture. Similarly, **12a,b** on treatment with phenyllithium in ether gave **4a** as the major isomer. Moreover, ethyl phosphinate (**8a**) was additionally produced, probably *via* ether cleavage by fluoride anion[19] and subsequent substitution at phosphorus by the ethoxide that was generated. Therefore, the configuration at phosphorus in the major isomers in both **6** and **12** are likely the same. A ^{31}P NMR study of the formation of the fluorides **12a,b** from the reaction of **6a,b** with F^- in acetonitrile revealed that the final mixture of isomers (~20:80 *trans:cis* ratio) was attained through equilibration. Reaction of F^- with **6a,b** *via* substitution with retention seems less probable.

Reactions of **6a,b** with methanol and fluoride ions were also conducted in acetonitrile, using the silver cation as a chloride ion scavenger. There was no significant difference between the conversions in presence or absence of silver nitrate. Chlorides **6a,b** react rapidly with silver nitrate in methanol to produce almost exclusively **7a** (see Table 1). The ratio of isomers in the mixture of fluorides **12a,b** was not influenced by the presence of silver.

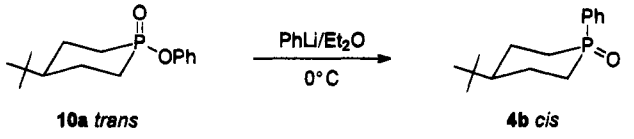
Based upon the spectroscopic analysis of **6** and both spectroscopic and X-ray data of the products, the overall results of the substitution are consistent with an inversion mechanism. However, complications arising from equilibration of either (or both) substrate and product cast doubt on the otherwise straightforward assumption that the *major* product isomer originates from the *major* substrate isomer. Therefore, substitution reactions with alkyl and aryl esters were investigated.

Substitution in Phosphinate Esters. Kinetic Evidence for Inversion. The conversion of **10a** with phenyllithium (vide infra) produced **4b** as the major product (>96% of inversion, by ^{31}P NMR). The small amount of **4a** formed in this reaction may originate from **10b**; the latter was observed in the ^{31}P NMR spectrum

(16) Wadsworth, W. S., Jr.; Larsen, S.; Horton, H. L. *J. Org. Chem.* **1973**, *38*, 256.
(17) Mazhar-ul-Haque, J. A.; Horne, W. *Acta Crystallogr.* **1987**, *C43*, 284.
(18) Mazhar-ul-Haque, J. A.; Horne, W. *Acta Crystallogr.* **1986**, *C42*, 99.

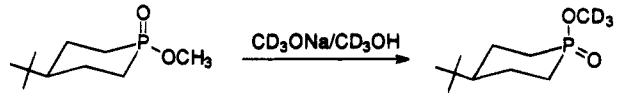
(19) Ether cleavage with fluorides was not further examined; for related references, see (a) Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivoldini, A. *Synthesis*, **1989**, 287. (b) Tyryshkin, N. I.; Vedernikov, A. N.; Solomonov, B. N.; Garifzyanowa, G. G. *Zh. Obshch. Khim.* **1992**, *62*, 375 (Russ.).

and arose from equilibration of **10a** by phenoxide anions. The ester **10a** was nearly consumed under the reaction conditions. Since the phosphinoxides **4** do not undergo equilibration under the reaction conditions, and as the stereochemistry of both substrate and product is known from X-ray investigations, this transformation constitutes clear evidence for an inversion mechanism. Similar evidence comes from an analogous reaction of a 95:5 mixture of methyl esters **7a,b** with phenyllithium to render a 10:90 *trans/cis* mixture of phosphinoxides **4a,b**.



10a *trans* **4b** *cis*

Additional evidence of the dominant role of inversion during substitution comes from a kinetic study of nucleophilic substitution at phosphorus in methyl ester **7a**.



7a **7b-*d*3**

A 95:5 mixture of **7** was treated with CD_3ONa/CD_3OD in the presence of $Ph_3P{=}O$ as an internal standard. The rate of inversion at 22 ± 1 °C was monitored by ^{31}P NMR spectroscopy. Both *protio* and *deuterio* esters were assumed to have the same ^{31}P chemical shift, since no additional signals were observed. The changes in concentration of **7a** were determined by the decrease in area of the relevant peak. A statistical analysis of the data revealed that this decrease was a first order process, with $k_{inv} = (3.7 \pm 0.1) \times 10^{-4}$ min^{-1} (for a given concentration of CD_3O^- ions). Simultaneously, ^1H NMR spectra were taken in order to independently determine the rate of substitution. Changes of the normalized integral of the signal due to the $POCH_3$ also followed a first-order rate, $k_{subst} = 3.33 \pm 0.05 \times 10^{-4}$ min^{-1} (see Figure 2). This result strongly supports the S_N2 reaction mechanism, in which every act of substitution occurs with inversion. The same mechanism was previously established in the methanolysis of the chiral, ^{14}C-methyl ester of ethylphenylphosphinic acid.[6]

Stereochemical Assignments. ^{13}C NMR spectra of the phosphorinanes are presented in Table 2. Assignments were based on the magnitude of the $^{13}C-^{31}P$ coupling constants and the chemical shifts. The directly bonded C-2 carbon atoms show the largest coupling (50–90 Hz) as expected; similar values were reported for $^1J_{PC}$ coupling constants for tetracoordinated phosphorus in phosphorinane rings.[20] The $^2J_{PC}$ values observed for C-3 are much smaller and span a narrow range of 3–7 Hz. C-3 was differentiated from C-4 ($^3J_{PC}$ coupling constants of 1–5.5 Hz) by the deshielding effect of the *tert*-butyl group, which shifted the C-4 signal downfield by about 25 ppm. Relative intensities were helpful in identification of the signals of the *tert*-butyl group. Splitting of the signal of the quaternary carbon ($^4J_{PC} \leq 1$ Hz) was sometimes observed. Peaks for the nonring carbon atoms were readily identified. Differentiation of the *endo* vs *exo* aryl carbons in the phosphonium salt **3** was arbitrary,

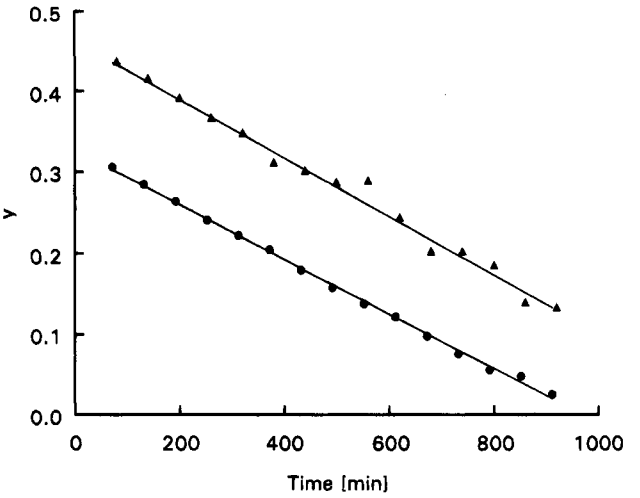


Figure 2. Kinetic study of the reaction of *trans*-4-*tert*-butyl-1-methoxyphosphorinane 1-oxide with CD_3ONa. Measured areas of the ^{31}P and ^1H peaks were normalized with respect to the corresponding areas of the reference signals. Logarithms of these values were calculated and plotted vs time. Linear regression of both data series gave the values of $k_{inv} = 3.7 \times 10^{-4}$ min^{-1} and $k_{subst} = 3.3 \times 10^{-4}$ min^{-1}, which were used to draw the best-fit lines. Series (▲) refers to the values measured in the ^{31}P NMR spectra and reflects the inversion process. Series (●) is based on the ^1H NMR spectra and represents substitution. In both cases the intercepts are arbitrary.

but the assignments were consistently patterned after the relative aryl assignments in *cis* and *trans* phosphinoxides **4**.

Isomer distinction in **6** and **12** caused a major problem. The stereochemistry of phosphinoxides **4**, methyl esters **7**, phenyl esters **10**, and anilides **13** has been confirmed by single crystal X-ray data. The stereochemistry of **8**, **9**, and **11** can be surmised from the relative ^{13}C shifts and the assumption of an inversion process in the course of their synthesis. It was also assumed that the phosphorinane ring always adopts a chair conformation and the *tert*-butyl group occupies an equatorial position. Unfortunately, the ^{31}P NMR chemical shifts were not very helpful since compounds with proven stereochemistry, such as **4a,b**, **7a,b**, **10a,b**, **13a,b** do not reveal a consistent pattern (Table 2). More information can be obtained from the ^{13}C NMR data set. Most helpful are the chemical shifts of C-2 and C-3. The difference in values in each diastereoisomeric pair was up to 1.5 ppm. For the four sets of isomers with known stereochemistry, the resonance of C-2 is always shifted downfield, and the resonance of C-3 is always shifted upfield in the isomer with an axial P=O. The upfield shift of the C-3 signal was previously observed[20] for phosphorinane derivatives containing both P=O or P=S bonds and was attributed to the γ-gauche shielding effect of an axially oriented oxygen or sulfur, respectively. Although the γ-shielding effect is assumed to be steric in nature, other factors are important. In known phosphorinane systems (including **4**, **7**, **10**, and **13**) the γ-shielding effect of a doubly bonded substituent (oxygen or sulfur) is significantly larger than the effect of other groups. When this reasoning is applied to the chlorides **6a,b**, the oxygen atom would reside in an equatorial position in structure **6b**. Assuming that the isomer ratio in **6** corresponds to the equilibrium state, this assignment is in agreement with the low (0–5%) equatorial preference of chlorine or fluorine vs P=O in phosphorinane derivatives.[21] Preliminary results of *ab*

(20) Quin, L. D. *The Heterocyclic Chemistry of Phosphorus*, John Wiley & Sons: New York, 1981.

Table 2. ^{13}C and ^{31}P NMR Chemical Shifts [ppm] (and Coupling Constants [Hz]) for 4-*tert*-Butylphosphorinane Derivatives[a]

compd	eq	ax	C-2	C-3	C-4	C-7	CMe_3	C-1′	C-2′	C-3′	C-4′	^{31}P
3	Ph	Ph	20.0	23.0	46.2	32.9	27.1	116.0[b]	131.7[b]	130.7[b]	134.4[b]	16.6
			(49)	(6)	(4)	(1)	(0)	(83)	(10)	(11)	(3)	
								120.4	132.0	129.9	134.8	
								(84)	(9)	(13)	(3)	
4a	Ph	O	28.7	22.5	49.1	33.0	27.7	133.3	129.8	127.3	131.4	32.7
			(66)	(6)	(3)	(1)	(0)	(95)	(9)	(11)	(0)	
4b	O	Ph	27.6	25.0	48.0	32.7	27.7	131.7	129.5	128.7	131.3	35.7
			(65)	(5)	(4)	(0)	(0)	(92)	(11)	(11)	(1)	
5	O	OH	27.8	24.6	48.3	32.8	27.7					53.4
			(90)	(5)	(4)	(1)	(0)					
6a	Cl	O	34.8	24.5	48.2	32.8	27.6					64.5
			(70)	(6)	(4)	(1)	(0)					
6b	O	Cl	33.6	25.1	47.5	32.7	27.6					66.7
			(70)	(6)	(5)	(1)	(0)					
7a	CH_3O	O	26.7	24.0	48.8	32.9	27.7	50.6[c]				54.4
			(84)	(7)	(5)	(0)	(0)	(6)				
7b	O	CH_3O	26.1	25.0	48.0	32.8	27.7	50.0[c]				52.5
			(86)	(5)	(5)	(0)	(0)	(7)				
8a	EtO	O	27.0	23.9	48.6	32.7	27.6	59.6[d]	16.6[e]			52.4
			(86)	(4)	(4)	(0)	(0)	(6)	(6)			
8b	O	EtO	26.6	24.8	47.9	32.6	27.5	59.1[d]	16.5[e]			50.6
			(86)	(6)	(5)	(1)	(0)	(6.)	(6)			
9a	OiPr	O	27.8	24.0	48.6	32.6	27.5	68.2[f]	24.1[g]			51.4
			(86.7)	(4.3)	(4.3)	(<1)	(0)	(6.7)	(3.7)			
9b	O	OiPr	27.3	24.3	47.9	32.5	27.4	68.0[f]	24.2[g]			49.7
			(86)	(6)	(5)	(<1)	(0)	(7)	(4)			
10a	OPh	O	27.3	24.0	48.6	32.8	27.6	150.4	120.3	129.4	124.0	52.8
			(86)	(4)	(5)	(1)	(0)	(9)	(4)	(0)	(1)	
10b	O	OPh	26.6	25.0	47.7	32.8	27.6	150.4	120.3	129.4	124.	51.1
			(85)	(6)	(5)	(1)	(0)	(9)	(4)	(0)	(1)	
11a	OPNP[h]	O	27.3	23.9	48.4	32.8	27.6	155.4	120.6	125.4	144.0	56.0
			(84)	(3)	(5)	(1)	(0)	(8)	(5)	(0)	(0)	
11b	O	OPNP[h]	26.9	25.0	47.6	32.8	27.6	155.4	120.5	125.4	144.0	54.2
			(84)	(6)	(5)	(1)	(0)	(8)	(5)	(0)	(0)	
12a	F	O	26.2	24.0	48.0	32.7	27.4					67.1
			(84)	(4)	(5)	(0)	(0)					(1044)[i]
			(10)[i]	(4)[i]								
12b	O	F	26.2	24.6	47.3	32.6	27.3					65.1
			(84)	(6)	(6)	(1)	(0)					(1010)[i]
			(15)[i]	(0)[i]								
13a	PhNH	O	28.0	23.4	48.7	32.9	27.6	140.5	118.5	129.0	121.	36.0
			(81)	(5)	(4)	(1)	(0)	(2)	(6)	(0)	(0)	
13b	O	PhNH	27.7	25.1	48.4	32.7	27.6	141.4	117.8	128.7	120.	33.7
			(82)	(5)	(1)	(1)	(1)	(1)	(6)	(0)	(1)	
14a[j]	Morph	O	25.8	23.6	49.0	32.9	27.7	43.4[k]	67.3[l]			42.2
			(81)	(5)	(4)	(0)	(0)	(0)	(6)			

[a] The numbering system follows the one presented in Figure 3; CMe_3 stands for the three equivalent methyl groups in the *tert*-butyl group and the prime signs denote aromatic carbons, unless otherwise stated. [b] Interchangeable with the other phenyl group. [c] Methoxy group. [d] CH_2 of the ethoxy group. [e] CH_3 of the ethoxy group. [f] CH of the isopropoxy group. [g] CH_3 of the isopropoxy group. [h] OPNP denotes the *p*-nitrophenoxy group. [i] Coupling with the fluorine atom. [j] See Note Added in Proof. [k] $N(CH_2)_2$. [l] $O(CH_2)_2$.

initio calculations on the 1-chlorophosphorinane 1-oxide indicate that the isomer with an equatorial phosphoryl is about 0.37 kcal/mol lower in energy.[22]

The ^{13}C NMR spectra of fluorides **12a,b** are nearly identical and the stereochemical assignments are uncertain. The chemical shift differences of either C-2 or C-3 are small, which implies a similar magnitude of γ-shielding for axial P–F and P=O. Caution must be exercised in this example. However, in this case the vicinal ^{13}C–^{19}F coupling constants are valuable. Although a Karplus-type magnitude–conformation relation has not been established for $^3J_{CF}$ coupling constants,[23] some evidence for their conformational dependence was found[24,25] and appeared useful in specific cases. A coupling constant for the C-3 atom in minor isomer **12a** was $^3J_{CF} = 4.2$ Hz, whereas that for the major isomer was too small to be measured. The dihedral angle F–P–C2–C3 is close to 80° in the isomer with an axial fluorine atom and 170° in the other. The coupling constant in the former was expected to be smaller than in the latter, and isomers **12a** and **12b** were assigned accordingly. The same relative magnitude of coupling constants was found for samples in $CDCl_3$ and C_6D_6. The configurations for the major isomer in **6** and in **12** therefore are the same, and their behavior in nucleophilic subtitution is consistent with the findings discussed in this investigation. The relative chemical shift differences of the C-2 and C-3 resonances in **12a,b**, while small, are also consistent with this assignment. The equatorial preference of the phosphoryl group versus fluorine is in agreement with the equilibrium position of the **12a,b** mixture.

^{17}O NMR spectroscopy was expected to provide additional proof for the stereochemical assignments. Ac-

(21) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187.
(22) Ishimura, A., Osaka City University, private communication.
(23) Emsley, J. W.; Phillips, L; Wray, V. Fluorine coupling constants. *Prog. NMR Spectrosc.* **1976**, *10*, 85.
(24) Grutzner, J. B.; Jautelat, M; Dence, J. B.; Smith, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107.
(25) Weigert, F. J. *J. Org. Chem.* **1980**, *45*, 3476.

Table 3. ^{17}O NMR Chemical Shifts and $^{1}J_{PO}$ Coupling Constants of P=O

compd	δ [ppm]	$^{1}J_{PO}$ [Hz][a]
4a	37	b
4b	70	140
6a	114	194
6b	125	176
7a	86	176
7b	94	158
10a	99	176
10b	111	158
12a	107	176
12b	115	176

[a] Digital resolution 18 Hz. [b] Could not be resolved.

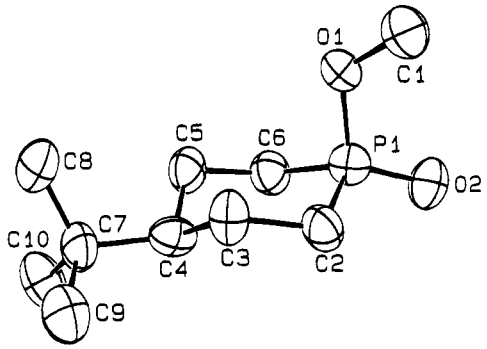


Figure 3. Molecular structure of *cis*-4-*tert*-butyl-1-methoxyphosphorinane 1-oxide **7b** (ORTEP diagram with atoms shown as 30% ellipsoids; hydrogen atoms omitted for clarity).

cording to the limited data found in the literature, an axial P=O is usually less shielded than an equatorial P=O and appears at lower field.[26] This relationship was established in a series of six-membered cyclic phosphates and phosphonates; the $^{1}J_{PO}$ coupling constants were usually smaller for an axial P=O bond.[26] ^{17}O NMR experiments for **6a,b** gave unexpected results; the more abundant *cis* isomer **6b** (equatorial P=O) showed a lower field signal. The same result was displayed by **12a,b**. Other examples supporting this trend are shown by diastereomeric pairs of unambiguous stereochemistry: **4a,b**, **7a,b**, and **10a,b**; an axially oriented P=O exhibited a higher field ^{17}O signal (35 vs 70, 86 vs 94, and 99 vs 111 ppm, respectively). Due to limited solubility the determination of ^{17}O NMR spectra of anilides **13** could not be done in toluene. An unusually broad and ill-defined ^{17}O signal of **4b** made it impossible to determine the $^{1}J_{PO}$ value. Tabulation of ^{17}O chemical shifts is summarized in Table 3.

X-ray Crystallographic Analysis. The structure of *cis*-4-*tert*-butyl-1-methoxyphosphorinane 1-oxide was confirmed by single crystal X-ray crystallography. As shown in Figure 3, the phosphorinane ring adopts a chair conformation with an equatorial *tert*-butyl group.

Crystal data: $C_{10}H_{21}O_2P$, $M_r = 204.25$, colorless needles, crystal dimensions 0.25 × 0.25 × 0.25 mm, crystallized from oil; monoclinic, space group *C2/c* (No. 15), $a = 29.352$ (4) Å, $b = 7.3554$ (7) Å, $c = 35.557$ (4) Å, $\beta = 108.728$ (9)°, $V = 7270.2$ (14) Å^3, 3 independent molecules per asymmetric unit, $Z = 24$, $d_{calc} = 1.120$ g/cm^3, λ(Cu Kα) = 1.54178 Å, μ(Cu Kα) = 18 cm^{-1}, $F(000) = 2688$. A total of 1844 reflections were measured on a Picker diffractometer at 25 °C, $2\theta_{max} = 70°$, 1192 reflections with $I > 3\sigma(I)$ used for structure solution (direct methods) and refinement (full-matrix least-squares, 353 parameters), non-hydrogen atoms refined anisotropically by means of a "riding" model; $R = 0.063$ ($R_w = 0.065$). The structure was solved using SOLVER and refined using SHELX-76.[27]

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or Midwest Microlab, Ltd., Indianapolis, IN. ^{1}H NMR spectra (300 MHz), ^{13}C NMR spectra (75 MHz), and ^{31}P NMR spectra (121 MHz) were recorded in $CDCl_3$ unless otherwise stated. ^{1}H and ^{13}C chemical shifts are referenced to the signal of solvent (7.26 and 77.0 ppm, respectively); ^{31}P chemical shifts refer to the 85% H_3PO_3 as an external standard, $\delta = 0.0$ ppm; positive values denote downfield shifts. ^{13}C and ^{31}P NMR data are reported in Table 2. ^{17}O NMR spectra (41 MHz) were measured in toluene at 70 °C; an average of 60000 scans was acquired; the acquisition time was 50 ms, with a 200 ms delay between scans. ^{17}O chemical shifts (reported in Table 3) refer to H_2O as a standard, $\delta = 0.0$ ppm; positive values denote downfield shifts. Capillary melting points are uncorrected. Reactions were conducted under a nitrogen atmosphere. Manipulation of moisture sensitive compounds was conducted in a glove box. 1,5-Dibromo-3-*tert*-butylpentane,[28] and diphenyl(trimethylsilyl)phosphine[29] were prepared according to the literature.

4-*tert*-Butyl-1,1-diphenylphosphorinanium Bromide (3). To a solution of 8.5 g (29.7 mmol) of 1,5-dibromo-3-*tert*-butylpentane in 100 mL of benzene (or toluene) was added 10.0 g (38.8 mmol) of (trimethylsilyl)diphenylphosphine; this solution was refluxed for 3 days under nitrogen. The solution turned turbid after 25 min, and a heavy, white precipitate occurred after 3 h. The precipitate was filtered to give 9.1 g (92%) of a white powder. A small portion was recrystallized from acetonitrile-ether: mp 316–7 °C (lit.[30] 316.5–318.5 °C); ^{1}H NMR 0.79 (s, 9H), 1.23–1.44 (m, 2H), 1.78–1.90 (m, 1H), 2.30–2.55 (m, 2H), 3.08–3.26 (m, 2H), 3.48–3.64 (m, 2H), 7.45–7.62 (m, 3H), 7.67–7.80 (m, 3H), 7.92–8.02 (m, 2H), 8.05–8.15 (m, 2H).

4-*tert*-Butyl-1-phenylphosphorinane 1-Oxide (4a,b). The phosphorinanium salt **3** (3.3 g, 10.6 mmol) was refluxed overnight in 25 mL of aqueous 20% NaOH. A benzene layer appeared after 1 h. After cooling to room temperature, 35 mL of CH_2Cl_2 was added, and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 35 mL), and the combined organic layer was dried with anhydrous sodium sulfate. Upon solvent removal 2.2 g (82%) of white crystals were obtained: mp 138–40 °C (lit.[10] 136–46 °C); ^{1}H NMR (**4b**) 0.82 (s, 9H), 1.10–1.30 (m, 3H), 1.97–2.23 (m, 4H), 2.50–2.65 (m, 2H) 7.47–7.60 (m, 3H), 7.71–7.80 (m, 2H). Isomer **4a** shows the signal for the *tert*-butyl group at 0.94 ppm.

4-*tert*-Butyl-1-hydroxyphosphorinane 1-Oxide (5). Method A. Solid NaOH (4.0 g, 0.1 mol) and the mixture of phosphine oxide **4a,b** (1.8 g, 7.2 mmol) were powdered together with a mortar and pestle in a glove box. This solid mixture was heated to 250 °C in a sand bath for 1 h, and 490 mg (88%) of benzene was collected. After cooling to room temperature, 50 mL of water was added followed by 50 mL of 1:1 dilute HCl. The aqueous layer was washed with CH_2Cl_2 (6 × 20 mL), and

(26) Evans, S. A., Jr. Oxygen-17 Nuclear Magnetic Resonance (NMR) Spectroscopy of Organosulfur and Organophosphorus Compounds. In *^{17}O NMR Spectroscopy in Organic Chemistry*; Boykin, D. W., Ed.; CRC Press: Boca Raton, FL, 1991.

(27) The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(28) Sakurai, H.; Murakami, M. *Org. Prep. Proc. Int.* **1973**, *5*, 1.

(29) (a) Tunney, S. E.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 748. (b) Kremer, P. W.; Most, J. T.; Cowles, J. M.; Borsub, L.; Gamliel, A.; Cremer, S. E. *Organomet. Synth.* **1988**, *4*, 511.

(30) Most, J. T. Master's Thesis, Marquette University, Milwaukee, Wisconsin, 1979 and references cited therein.

the organic layer was dried; the solvent was removed to give 1.3 g (95%) of yellow solid: mp 187–8 °C.

Method B. Solid NaOH (63 g, 1.57 mol) and the phosphorinanium bromide **3** (44.3 g, 0.113 mol) were powdered together with a mortar and pestle in the glove box. This mixture was heated in a nickel 500 mL flask on a sand bath for 3 h at 290–320 °C. The contents of the flask were then crushed, dissolved in water, and extracted with diethyl ether to remove traces of phosphine oxides **4** formed. The basic solution was added slowly to 150 mL of concentrated hydrochloric acid, with external cooling. The slurry of the acid **5** was extracted with methylene chloride; the extract was dried and evaporated, yielding 21.0 g (97%) of **5**: ^{1}H NMR 0.88 (s, 9H); 0.95–1.1 (m, 1H), 1.4–1.7 (m, 4H), 1.85–2.20 (m, 4H), 8.2–8.4 (broad s, 1 H). Anal. Calcd for $C_9H_{19}O_2P$: C, 56.83; H, 10.07. Found: C, 56.83; H, 9.78.

4-*tert*-Butyl-1-chlorophosphorinane 1-Oxide (6a,b). Method A. To a solution of 4.5 g (23.7 mmol) of the phosphinic acid **5** in 50 mL of CCl_4 was added 5.0 g (24.0 mmol) of phosphorus pentachloride. This mixture was stirred at room temperature for two days. The solvent was removed and a bulb-to-bulb distillation under reduced pressure gave 4.2 g (84%) of a white solid: mp 113–6 °C; ^{1}H NMR 0.90 (s, 9H), 1.05–1.22 (m, 1H), 1.45–2.6 (m, 8H). Anal. Calcd for $C_9H_{18}ClOP$: C, 51.80; H, 8.69; Cl, 16.99. Found: C, 51.48; H, 8.48; Cl, 16.74.

Method B. Phosphinic acid **5** (4.01 g, 21 mmol) was dissolved in 2.5 mL (4.1 g, 34 mmol) of thionyl chloride, and the mixture was allowed to react overnight. During this time the mixture solidified; the excess of thionyl chloride was evaporated under reduced pressure and the residue was sublimed under reduced pressure, yielding 4.22 g (96%) of a 20:80 mixture of **6a**:**6b**, respectively.

Method C. Freshly distilled pyridine (2 mL, 1.96 g, 25 mmol) and thionyl chloride (1 mL 1.63 g, 14 mmol) were dissolved in 10 mL of dry toluene. A slurry of 1.90 g (10 mmol) of phosphinic acid **5** in toluene was then added slowly to this mixture; a white precipitate formed and the acid dissolved. The temperature of the mixture was maintained below 35 °C. The mixture was then heated to 65 °C for 2 h. The precipitate was filtered off under nitrogen, and the solvent and excess of reagents were evaporated under reduced pressure yielding 1.69 g (81%) of the **6a,b** mixture. The crystalline residue was then purified by sublimation under vacuum.

Reaction of 6a,b with Alcohols. General Procedure. A mixture of isomeric chlorides **6a,b** (20:80, respectively, 208 mg, 1.0 mmol) was dissolved in 5 mL of the appropriate alcohol. After the reaction was completed, the mixture was poured into 10 mL of 5% NaOH and extracted with ether. The combined organic layer was then washed with water, dried with anhydrous sodium sulfate, and evaporated. The reaction times, ^{1}H NMR spectra, results of the elemental analyses, and melting points are reported below. Table 1 illustrates the yields and isomer ratios. Table 2 summarizes the ^{13}C and ^{31}P NMR data.

4-*tert*-Butyl-1-methoxyphosphorinane 1-Oxide (7a,b). After 1 h reaction time: ^{1}H NMR (**7b**) 0.88 (s, 9H), 0.95–1.10 (m, 1H), 1.25–1.50 (m, 2H), 1.55–1.75 (m, 2H), 1.90–2.20 (m, 4H), 3.70 (d, 3H, J_{PH} = 10.5 Hz); mp 68–70 °C (**7b**). Anal. Calcd for $C_{10}H_{21}O_2P$: C, 58.80; H, 10.36. Found: C, 58.82; H, 10.20.

4-*tert*-Butyl-1-ethoxyphosphorinane 1-Oxide (8a,b). After 2 h reaction time: ^{1}H NMR (**8a**) 0.85 (s, 9H), 0.90–1.15 (m, 1H), 1.24 (t, 3H, J_{HH} = 7.0 Hz), 1.35–1.70 (m, 4H), 1.80–2.15 (m, 4H), 4.02 (dq, 2H, $J_{HH} \approx J_{PH} \approx$ 7.5 Hz). Anal. Calcd for $C_{11}H_{23}O_2P$: C, 60.53; H, 10.62. Found: C, 60.49; H, 10.46.

4-*tert*-Butyl-1-isopropoxyphosphorinane 1-Oxide (9a,b). After 30 h reaction time: mp 74–6 °C; ^{1}H NMR (**9a**) 0.89 (s, 9H), 0.95–1.10 (m, 1H), 1.29 (d, J_{HH} = 6.1 Hz, 6H), 1.40–1.80 (m, 4H), 1.80–2.20 (m, 4H), 4.7 (dsept, J_{HH} = 6.1 Hz, J_{PH} = 8.6 Hz, 1H). Anal. Calcd for $C_{12}H_{25}O_2P$: C, 62.04; H, 10.85. Found: C, 61.78; H, 10.64.

Reaction of 6a,b with Alkoxides. General Procedure. A mixture of isomeric chlorides **6a,b** (20:80, respectively, 208 mg, 1.0 mmol) was dissolved in 5 mL of the solution of the sodium alkoxide in the corresponding alcohol. After the reaction was completed, the mixture was poured into 10 mL of 5% HCl and extracted with ether. The combined organic layer was then washed with water, dried with anhydrous sodium sulfate, and evaporated. The yields and isomer ratios are given in Table 1.

Reaction of 6a,b with Methanol in the Presence of Silver Nitrate. To a slurry of 500 mg (2.94 mmol) of very finely ground silver nitrate in 25 mL of dry methanol was added 550 mg (2.64 mmol) of an 80:20 mixture of the acid chlorides **6b**:**6a**, respectively. A heavy white precipitate appeared on contact. This mixture was stirred at ambient temperature overnight. The precipitate was filtered, and the solvent was evaporated to give a mixture of a yellow oil and additional precipitate. Then, CH_2Cl_2 (25 mL) was added, this solution was washed with water (2 × 25 mL) and dried, and the solvent was removed to give 500 mg (93%) of a yellowish oil. ^{31}P NMR analysis showed a 98:2 mixture of **7a,b**.

4-*tert*-Butyl-1-phenoxyphosphorinane 1-Oxide (10a,b). A slurry of sodium phenoxide in 25 mL of acetonitrile was prepared from 940 mg (10 mmol) of phenol and sodium hydride (300 mg, 80% suspension in mineral oil). A solution of **6a,b** (2.08 g, 10 mmol) in 10 mL of acetonitrile was added to this slurry, with external ice-bath cooling, over 30 min. The mixture was then stirred for 2 h, filtered, evaporated, dissolved in diethyl ether, and washed with 5% NaOH and water. The organic layer was dried with anhydrous sodium sulfate, and the solvent was removed to give 1.91 g (76%) of a colorless mixture of **10a,b**, 64:36, respectively. Recrystallization from hexane gave white, fluffy crystals of **10a**: mp 89–90 °C; ^{1}H NMR (**10a**) 0.89 (s, 9H), 1.00–1.2 (m, 1H), 1.60–1.82 (m, 4H), 1.90–2.30 (m, 4H), 7.10–7.36 (m, 5H). Anal. Calcd for $C_{15}H_{23}O_2P$: C, 67.65; H, 8.70. Found: C, 67.47; H, 8.82.

4-*tert*-Butyl-1-(*p*-nitrophenoxy)phosphorinane 1-Oxide (11a,b). To a solution of 1.53 g (11.0 mmol) of *p*-nitrophenol in 10 mL of dry acetonitrile was added 260 mg (11.3 mmol) of sodium at 0 °C under a nitrogen atmosphere. The sodium salt was insoluble in the acetonitrile, and not all of the sodium reacted. To this suspension was added 2.0 g (10.0 mmol) of an 80:20 mixture of the acid chlorides **6b**:**6a**, respectively, at 0 °C and stirred at ambient temperature overnight. The orange color of the sodium salt disappeared after 1 h. To this mixture was added water and 25 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 25 mL). The combined organic layer was dried, and the solvent was removed to give 2.7 g (73%) of a yellowish powder. ^{13}C NMR analysis showed a 20:80 mixture of **11a**:**11b**, respectively. Chromatography with ethyl acetate on silica gel afforded the pure isomer **11b**: mp 105–109 °C; ^{1}H NMR (**11b**) 0.92 (s, 9H), 1.05–1.20 (m, 1H), 1.40–1.65 (m, 2H), 1.70–1.95 (m, 2H), 2.00–2.35 (m, 4H), 7.35–7.45 (m, 2H), 8.20–8.30 (m, 2H). Anal. Calcd for $C_{15}H_{22}NO_4P$: C, 57.87; H, 7.12. Found: C, 57.76; H, 7.02.

Equilibration of 4-*tert*-Butyl-1-phenoxyphosphorinane 1-Oxide (10). In an NMR tube, 20 mg of **10b** was dissolved in 0.5 mL of saturated solution of sodium phenoxide in acetonitrile. The solubility of sodium phenoxide was enhanced by addition of 260 mg of 18-crown-6 per 10 mL of the solution. After 8 days at room temperature, the ^{31}P NMR spectrum showed the presence of both isomers in a 19:81 ratio (**10a**:**10b**).

Equilibration of 4-*tert*-Butyl-1-(*p*-nitrophenoxy)phosphorinane 1-Oxide (11). In an NMR tube, 20 mg of **11b** was dissolved in 0.5 mL of saturated solution of sodium *p*-nitrophenoxide in acetonitrile. The solubility of sodium *p*-nitrophenoxide was enhanced by addition of 260 mg of 18-crown-6 per 10 mL of the solution. The ^{31}P NMR spectrum showed the presence of both isomers in 18:82 ratio (**11a**:**11b**). The tube was then heated to 77 °C for 12 h. The ratio of isomers did not change.

Reaction of 4-*tert*-Butyl-1-(*p*-nitrophenoxy)phosphorinane 1-Oxide 11b with Sodium Methoxide in Methanol. In an NMR tube, 20 mg of **11b** was dissolved in a 0.6 mL of 1 M solution of sodium methoxide in methanol. The solution was orange, which indicated the presence of *p*-

nitrophenoxide anions. ^{31}P NMR analysis showed only one compound, *trans*-4-*tert*-butyl-1-methoxyphosphorinane 1-oxide (**7a**).

Kinetic Displacement Study. Sodium (48 mg, 2.1 mmol) was dissolved in 1.544 g of CD_3OD. A portion of this solution (0.69 g) was then added to an NMR tube, containing 48 mg of 4-*tert*-butyl-1-methoxyphosphorinane 1-oxide (**7a**) and a small amount of triphenylphosphine oxide. ^1H and ^{31}P NMR spectra were recorded every hour; 15 spectra were measured.

Reaction of the Acid Chloride 6 with Phenyllithium. To a solution of 434.6 mg (2.08 mmol) of a 20:80 mixture of the acid chloride **6a**:**6b**, respectively, in 25 mL of anhydrous ether at 0 °C was added slowly with a syringe 1.7 mL of phenyllithium (1.23M solution in ether, 2.1 mmol). The phenyllithium color discharged on contact. This solution was stirred at 0 °C for 30 min, and then 10 mL of H_2O was added. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried, and the solvent was removed to give 448.5 mg (86%) of a yellow solid. ^{13}C NMR showed an 80:20 mixture of the phosphinoxides **4a**:**4b**, respectively. Sublimation at 115 °C (0.1 mm) gave 400 mg (77%) of a white powder, which had an unaltered isomer ratio.

Preparation of Phosphinic Acid Fluorides (12). Sodium fluoride (1.0 g, 23.8 mmol) was added to a solution of **6a,b** (500 mg, 2.4 mmol) in 3 mL of acetonitrile. The mixture was stirred overnight and centrifuged and the solvent was evaporated. Upon sublimation of the residue 280 mg (58%) of a 19:81 mixture of fluorides **12a,b** was obtained, mp 100–103 °C ^1H NMR (**12b**): 0.89 (s, 9H), 1.00–1.15 (m, 1H), 1.37–1.60 (m, 2H), 1.70–1.95 (m,2H), 2.00–2.3 (m, 4H). Anal. Calcd for $C_9H_{18}FOP$: C, 56.24; H, 9.44. Found: C, 56.40; H, 9.37. The same ratio of isomers was obtained if the reaction was carried out in the presence of silver nitrate.

Reaction of Fluorides 12 with Sodium Phenoxide. A solution of 1 mmol of sodium phenoxide in 5 mL of acetonitrile was prepared from phenol and sodium hydride. To this a solution of 185 mg (0.96 mmol) of the mixture **12a,b** in 2 mL of acetonitrile was slowly added at 0 °C. After completion of the addition, water was added and the phases were separated. The water phase was extracted with ether; the combined organic layer was washed with 5% NaOH and water and dried with anhydrous sodium sulfate. Evaporation of the solvent yielded 220 mg (91%) of a crude mixture **10a,b**.

Reaction of Fluorides 12 with Phenyllithium. The sublimed fluorides **12** (0.2 g, 1 mmol) were dissolved in 10 mL of anhydrous diethyl ether and cooled to −78 °C. A solution of phenyllithium in cyclohexane/ether (1.82 M, 0.5 mL, 0.9 mmol) was added in small portions over 30 min, and the mixture was allowed to react for additional 30 min. Then, the mixture was allowed to warm to room temperature, water was added, and the phases were separated. The aqueous phase was extracted with ether, and the combined ethereal layer was dried with anhydrous sodium sulfate. ^{31}P NMR analysis of the product revealed the presence of **4a**, **4b**, and **8a** in a 30:3:10 ratio.

Incomplete Reaction of 4-*tert*-Butyl-1-methoxyphosphorinane 1-Oxide with Phenyllithium. To a solution of 278 mg (1.36 mmol) of a 95:5 mixture of *trans*/*cis*-methyl phosphinate esters **7a**:**7b**, respectively, in 25 mL of anhydrous ether was added 1.1 mL (1.23M, 1.35 mmol) of a phenyllithium solution in cyclohexane/ether at 0 °C. The color of the phenyllithium solution discharged on contact. The yellowish solution was stirred for 30 min, and 10 mL of water was added. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried, and the solvent was removed to give 265 mg (ca. 80%) of a yellow oil. ^{13}C NMR analysis revealed that the reaction had not gone to completion; the initial ester ratio had not changed, and the *cis*- and *trans*-phenylphosphorinane oxides **4a** and **4b** were obtained in a 10:90 ratio (approximately). When this reaction was repeated in ether with a large excess of phenyllithium and stirred overnight at ambient temperature or refluxed overnight in THF, the ^{13}C NMR showed, again, that the reaction had not reached completion.

Reaction of *trans*-4-*tert*-Butyl-1-phenoxyphosphorinane 1-Oxide 10a with Phenyllithium. A solution of phenyllithium (1.82 M in diethyl ether–cyclohexane, 0.65 mL, 1.2 mmol) was added at 0 °C to a solution of **10a** (0.25 g, 1mmol) in 20 mL of ether. The mixture was then stirred at 0 °C for 5 h, quenched with H_2O, and washed with 5% NaOH solution, and the organic phase was dried with anhydrous Na_2SO_4. ^{31}P NMR analysis of the mixture showed that the reaction was incomplete; both isomers of the starting phenyl phosphinates **10a,b** were present (9:91 ratio) along with a 4:96 mixture of **4a,b**.

1-Anilino-4-*tert*-butylphosphorinane 1-Oxide (13). A solution of a freshly distilled aniline (1.94 g, 21.0 mmol in 10 mL of CH_2Cl_2) was added dropwise to a solution of **6a,b** (20:80, 2.17 g, 10.4 mmol, in 20 mL of CH_2Cl_2) over 0.5 h at ambient temperature. The mixture was stirred for 1 h. A heavy white precipitate formed which was filtered to give 1.0 g (75%) of aniline hydrochloride. The solvent was removed to give a foamy solid; mp 72–82 °C. ^{13}C NMR analysis showed a 60:40 mixture of the two isomers **13a**:**13b**. This solid was redissolved in CH_2Cl_2, and the organic layer was washed with 25 mL of 5% HCl followed by 25 mL of water. The dried solvent was evaporated to give 2.61 g (94.5%) of a brown solid. ^{13}C NMR analysis showed the same isomer composition as before (mp 89–90 °C. A sample was recrystallized by dissolving it in a minimum amount of chloroform followed by the addition of petroleum ether. The first fraction consisted of colorless prisms which appeared to be a single isomer by ^{13}C NMR spectroscopy: mp 237–8 °C; ^1H NMR 0.83 (s, 9H), 0.95–1.45 (m, 1H), 1.50–1.85 (m, 4H), 1.85–2.40 (m, 4H); 6.20–6.60 (broad doublet, 1H, NH), 6.80–7.25 (m, 5H). Anal. Calcd for $C_{15}H_{24}NOP$: C, 67.90; H, 9.12. Found: C, 67.89; H, 8.94.

4-*tert*-Butyl-1-morpholinophosphorinane 1-Oxide (14). Freshly distilled morpholine (1 g, 11.5 mmol) was added to a solution of 0.42 g (2 mmol) of a diastereoisomeric mixture of chlorides **6** in 15 mL of dry toluene. A white precipitate appeared immediately. The mixture was allowed to react overnight, the salt was filtered off under nitrogen, and the filtrate was evaporated under vacuum, yielding 0.53 g (2 mmol, quantitatively) of a 95:5 isomer mixture of diastereoisomeric amides (^{31}P NMR analysis) and a small amount of phosphinic acid. Recrystallization from pentane–cyclohexane afforded the major isomer in pure form: mp 132–4 °C; ^1H NMR 0.88 (s, 9H); 1.00 (m, 1H); 1.5–1.9 (m, 6H); 2.0–2.2 (m, 2H); 3.06 (dt, J_{HH} = 6 Hz, J_{PH} = 6 Hz, 4H, $N(CH_2)_2$); 3.66 (t, J_{HH} = 6 Hz, 4H, $(CH_2)_2O$). Anal. Calcd for $C_{13}H_{26}NO_2P$: C, 60.21; H, 10.11. Found: C, 60.40; H,10.30.

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Note Added in Proof. Subsequent to acceptance of this paper, an X-ray crystal structure of **14a** confirmed its stereochemistry.

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