

## Stereochemistry of Nucleophilic Substitution Reactions of Sterically Rigid Phosphoranes

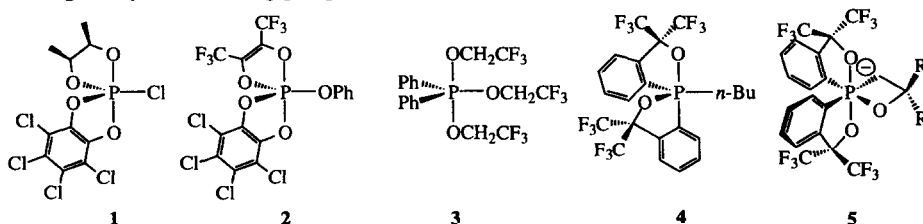
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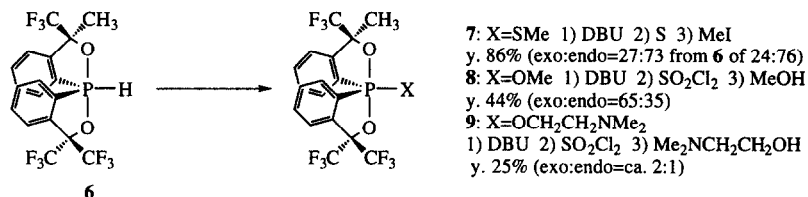
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**Abstract.** The stereomutation barriers of diastereomeric spirophosphoranes, [*o*-O(CF<sub>3</sub>)(CH<sub>3</sub>)C\**C*<sub>6</sub>H<sub>4</sub>][*o*-O(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>4</sub>]P\*X (X=OMe, SMe) were determined to be high enough to freeze the mutation at ambient temperatures [ $\Delta G^\ddagger(298\text{K})=25.0, 30.4 \text{ kcal mol}^{-1}$ ; respectively]. The nucleophilic substitution reaction of SMe compounds with alkyllithium reagents resulted in inversion of configuration, whereas that of OMe compounds gave various ratios of inversion and retention products depending on the stereochemistry of the diastereomeric reactant phosphoranes and solvent. However, the use of OCH<sub>2</sub>CH<sub>2</sub>NMe<sub>2</sub> as substituent lead to almost exclusive formation of the retention product regardless of these conditions. © 1997 Elsevier Science Ltd.

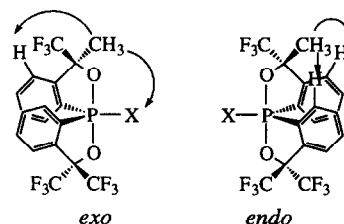
Although it is established that hexacoordinate phosphorus is involved as either an intermediate or transition state in nucleophilic substitution reactions upon pentacoordinate phosphorus,<sup>1</sup> very little stereochemical investigations of the process have been made.<sup>1e,2</sup> The stereochemistry of the substitution reaction of fluxional phosphorane **1** has been reported to depend upon the incoming nucleophile,<sup>3</sup> thus implying the presence of hexacoordinate intermediates. The addition to phosphoranes such as **2**<sup>4</sup> and **3**<sup>5</sup> has been reported to give *trans* and *cis* adducts, respectively, as the kinetic products, although pentacoordinate species were not spontaneously formed. The latter stands as an interesting case since the apparent reaction involves nucleophilic attack to the rear of a carbon substituent instead of an electronically preferred oxygen substituent. However, this reaction leaves uncertainty since the same product could also be obtained from a configuration in which a phenyl group and an alkoxy group are exchanged by stereomutation. Recently, **4** has been isolated as a stable compound, which supports the point mentioned above.<sup>6</sup> In a sterically restricted case, the ring closure of a  $\beta$ -oxidophosphorane to give **5** showed the capability of hexacoordinate phosphorus formation *anti* to a carbon atom.<sup>7,8</sup> We have found by using stereochemically rigid spirophosphoranes that rear attack to carbon is in fact feasible even in the presence of equatorial chalcogen substituents and that the stereochemistry can be diversely altered by changing the coordinating ability of the leaving group to a lithium cation.



Phosphoranes **7** (*exo* and *endo*) carrying the SMe group were prepared by treating P-H phosphorane **6** with DBU followed by elemental sulfur and MeI in THF at room temperature. The product was found to nearly retain the stereochemistry of **6**, as expected from previous findings.<sup>9</sup> Phosphoranes **8** and **9** were prepared by treating **6** with DBU then SO<sub>2</sub>Cl<sub>2</sub>, and followed by an excess of the appropriate alcohol.



The relative stereochemistry of **7-9**<sup>10</sup> was determined by <sup>1</sup>H NMR NOE experiments. The diastereomers in which irradiation of the bidentate CH<sub>3</sub> lead to intensity enhancement at the monodentate alkyl group along with the aryl proton ortho to the *i*-propoxy group could be assigned to the configuration designated *exo*, whereas the diastereomers in which irradiation of the bidentate CH<sub>3</sub> lead to intensity enhancement at the proton ortho to phosphorus in the Martin ligand and the aryl proton ortho to the *i*-propoxy group could be assigned to the configuration designated *endo*.



The interconversion rates obeyed first order kinetics and were found to be extremely slow for **7**, while **8** also required some heating to effect the isomerization. The small activation entropy is in accord with a regular Berry pseudorotation process, as found for **6**.<sup>9c</sup> The order of ease in stereomutation would be **8**(OMe)>**6**(H)>**7**(SMe). Thus, it could be confirmed that although the compounds retain some degree of fluxionality, pseudorotation process need not be considered under the present conditions (-78 °C-rt).

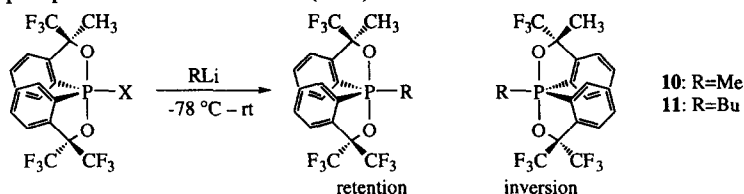
Table 1. Kinetic Parameters of the Permutation Process<sup>a</sup>

	<i>K</i> ( <i>k</i> <sub>+</sub> / <i>k</i> <sub>-</sub> )	<i>k</i> <sub>-</sub> (x10 <sup>-6</sup> s <sup>-1</sup> )	<i>endo</i> to <i>exo</i>			<i>exo</i> to <i>endo</i>			
			Δ <i>H</i> <sup>‡</sup> (kcal mol <sup>-1</sup> )	Δ <i>S</i> <sup>‡</sup> (eu)	Δ <i>G</i> <sup>‡</sup> <sub>298</sub> (kcal mol <sup>-1</sup> )	<i>k</i> <sub>+</sub> (x10 <sup>-6</sup> s <sup>-1</sup> )	Δ <i>H</i> <sup>‡</sup> (kcal mol <sup>-1</sup> )	Δ <i>S</i> <sup>‡</sup> (eu)	Δ <i>G</i> <sup>‡</sup> <sub>298</sub> (kcal mol <sup>-1</sup> )
<b>7</b>	0.27	4.55±0.02(353K)	31.5±0.8	5.9±2.2	29.8	1.25±0.01(353K)	32.3±0.9	5.4±2.6	30.7
<b>8</b>	0.47	34.5±2.1(313K)	24.0±0.5	-2.6±1.6	24.7	16.2±1.1(313K)	24.2±0.5	-3.3±1.6	25.2

<sup>a</sup> Error is given as standard deviation.

The nucleophilic substitution reaction was carried out by treating **7-9** with MeLi or BuLi at -78 °C and allowing the solution to rise to ambient temperature. The product with the alkyl group was obtained in high or quantitative yields. The stereochemistry of the products **10** and **11** was determined by <sup>1</sup>H NMR NOE. The reactions for **8** and **9** were qualitatively much faster than those for **7**, in agreement with electronegativity of the monodentate. As the data show, the stereochemistry of the reactions was completely dependent on the nucleofuge. While **7** gave predominant inversion of configuration regardless of the stereochemistry of reactant diastereomer (runs 1-4), **8** yielded large amounts of the retention product in ether, with higher selectivity for the less congested **8-*exo*** diastereomer (runs 5 and 6) compared with **8-*endo*** (runs 9 and 10), although the steric difference between the diastereomers (relative position of CH<sub>3</sub>

and  $\text{CF}_3$ ) was not very large. The size of the nucleophile (Me and Bu) seemed to affect the selectivity for **7** somewhat, but was of little significance for **8**. This could be due to the lower reactivity (higher reaction temperature) for **7**. Reaction of **8-exo** in less polar hexane also resulted in predominant retention, however with lower selectivity (run 7). This is probably due to lower reactivity in this solvent. On the other hand, the more polar THF promoted inversion for both **8-exo** and **8-endo** (runs 8 and 11). The reactions of **9** were found to be quite stereospecific as the retention product was obtained regardless of the stereochemistry of the reactant phosphoranes and even solvent (THF).

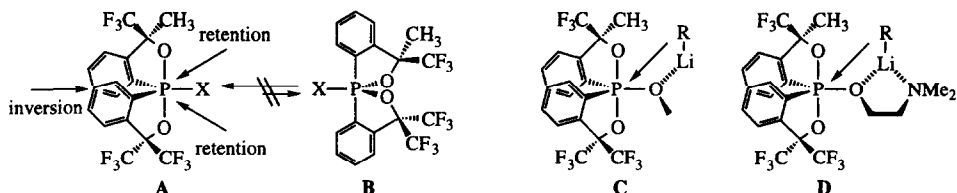


**Table 2. Stereochemistry of the Nucleophilic Substitution Reaction**

run	reactant ratio <i>exo:endo</i>	solvent	RLi	product ratio		yield (%)	configuration
				<i>exo:endo</i>			
1	<b>7</b>	ether	MeLi	10:90	>98	inversion	
2			<i>n</i> -BuLi	20:80	>98	inversion	
3			MeLi	85:15	>98	inversion	
4			<i>n</i> -BuLi	65:35	>98	inversion	
5	<b>8</b>	ether	MeLi	91:9	>98	retention	
6			<i>n</i> -BuLi	91:9	>98	retention	
7			hexane	MeLi	85:15	72	retention
8			THF	MeLi	44:56	78	inversion
9			ether	MeLi	66:34	>98	inversion
10			ether	<i>n</i> -BuLi	60:40	>98	inversion
11			THF	MeLi	94:6	93	inversion
12	<b>9</b>	ether	<i>n</i> -BuLi	95:5	90	retention	
13			THF	<i>n</i> -BuLi	98:2	95	retention
14			ether	<i>n</i> -BuLi	15:85	85	retention

Since pseudorotation between the diastereomers cannot occur at the reaction temperatures ( $-78\text{ }^{\circ}\text{C}$ –rt), **A** and **B** are the only conceivable configurations for the reaction. However, the latter is unlikely as a stationary intermediate because of previous findings<sup>6</sup> and because if **B** were the reactive species, the *S*Me compounds would also have been expected to have the same reaction stereochemistry (retention) as the *O*Me compounds since reaction *anti* to an oxygen (electronically favorable) would be reinforced for **7**. Therefore, the reactive species should be **A**. The fact that products of retention of configuration were obtained clearly indicates that attack to pentacoordinate phosphorus had occurred from the rear side of a carbon atom even in the presence of an oxygen atom to furnish hexacoordinate species from which extrusion of X had followed from the same face. This shows that electronic effects are not dominant factors in governing the stereochemistry of reactions involving pentacoordinate phosphorus. This surely stems from the ability of phosphorus to easily attain the hexacoordinate state even in the presence of P–C bonds. The intermediacy of hexacoordinate species and not ring-opened pentacoordinate species is supported by the fact that the product stereochemistry is dependent on the stereochemistry of the substrate and that a related hexacoordinate compound **5** which bears three P–C bonds has been observed as a stable species at ambient temperatures.<sup>7,8</sup> There is definitely a steric effect involved in the observed reactions, since a comparison of

diastereomers under the same reaction conditions shows that the *exo* product is always produced in larger sums. However, the difference in sizes between SMe and OMe, and CH<sub>3</sub> and CF<sub>3</sub> seem too small to account for the observed preference for retention in the case of **8**. Therefore, in addition to steric environment, attractive interaction involving the alkoxy group and nucleophile should be operative in the reactions (C). This is strongly supported by the fact that the ratio of retention products is lower in donative THF which could weaken the interaction between the reactants. In the case of **9**, it is evident from the fact that retention is predominant even in THF that the nitrogen can serve to effectively direct the reactant towards the face of the leaving group in addition to the oxygen atom (D).



In summary, we have found that nucleophilic attack *anti* to carbon is facile in phosphoranes even in the presence of equatorial P-O bonds to give retention products. We have exemplified that a directing effect by the oxygen in a leaving group is crucial to account for this stereochemistry. Furthermore, we have found that an additional directing group in the leaving group can further promote preference for retention. These results imply that nucleophilic reaction stereochemistry involving phosphorus in the biological system might also be affected in the same way since phosphorus is usually found bound to sugars including nucleic acids.

## References and Notes

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- All isolated new phosphoranes gave satisfactory elemental analyses and reasonable spectra. **7-*exo***: mp 136-137 °C; <sup>31</sup>P NMR (CDCl<sub>3</sub>) -24.1. **7-*endo***: mp 123-124 °C; <sup>31</sup>P NMR (CDCl<sub>3</sub>) -24.8. **8-*exo***: mp 128-130 °C; <sup>31</sup>P NMR (CDCl<sub>3</sub>) -16.1. **8-*endo***: mp 119-120 °C; <sup>31</sup>P NMR (CDCl<sub>3</sub>) -18.1. **9-*exo***: mp 85-87 °C; <sup>31</sup>P NMR (CDCl<sub>3</sub>) -17.4.

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