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Novel Results Obtained by Freezing Berry Pseudorotation of Phosphoranes (10-P-5)

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ABSTRACT: *By freezing Berry pseudorotation of spirophosphoranes with recourse to the rigidity of the Martin bidentate ligand, we successfully prepared configurationally stable enantiomeric pairs of optically active phosphoranes, and could isolate "anti-apicophilic" C-apical O-equatorial (O-cis) phosphoranes. The effect of σ^*_{P-O} orbital of the O-cis phosphorane was investigated both experimentally and theoretically. O-cis phosphoranes were revealed to be much more electrophilic at the phosphorus atom than O-trans isomers by experimental studies. The acidity of the α-proton of an O-cis benzylphosphorane was found to be higher than that of the corresponding O-trans isomer. By the reaction of the α-carbanion of an O-cis benzylphosphorane with PhCHO, we succeeded in the first isolation and full structural characterization of a 12-P-6 phosphate bearing an oxaphosphetane ring, the intermediate in the Wittig type reaction using a 10-P-5 phosphorane.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:390–396, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10072

INTRODUCTION

Phosphorus compounds are of significance due to their important role in numerous biological processes involving phosphoryl transfer, and recently, artificial phosphorus compounds have been used in herbicides, insecticides, and medicines [1]. Thus, the mechanism of reaction involving phosphorus compounds has been a topic of interest for quite some time. Through the pioneering work of Westheimer and others [2], it is now widely accepted that the reaction process involves a pentavalent phosphorus intermediate (or transition state) formed by nucleophilic attack upon the tetracoordinate phosphorus atom, and that the stability and stereochemistry (both steric and electronic effects combined) of the transient species (or transition state) greatly influence the outcome of the process. Therefore, to deduce a basic understanding of the process, much attention has been focused on the stereochemistry by using various model compounds, and, through these studies, it has been found that the permutation of the intermediate is an important factor [3]. The permutation is usually interpreted in terms of the Berry pseudorotation [4]. Since the process requires only simultaneous bending of bonds, the energy barrier is generally very small. However, by utilizing the rigidity of the Martin bidentate ligand, we could successfully freeze Berry pseudorotation. Here we describe our recent results on the preparation of configurationally stable enantiomeric pairs of optically active phosphoranes [5], on the first isolation and full characterization of an "anti-apicophilic" (*O-cis*) phosphorane [6], on the reactivities of *O-cis*

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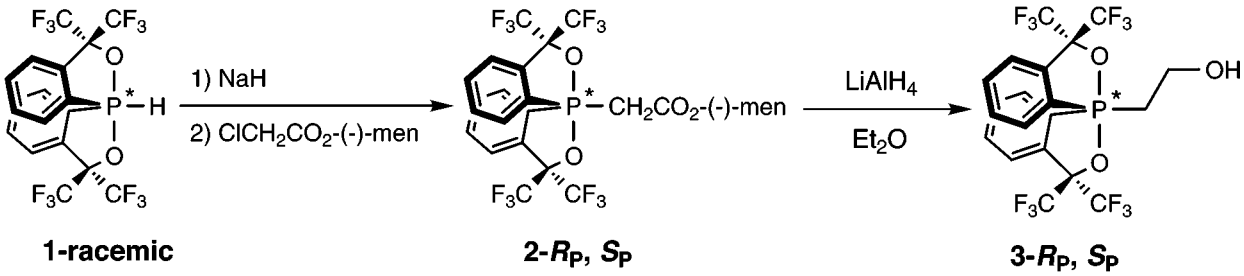


SCHEME 1

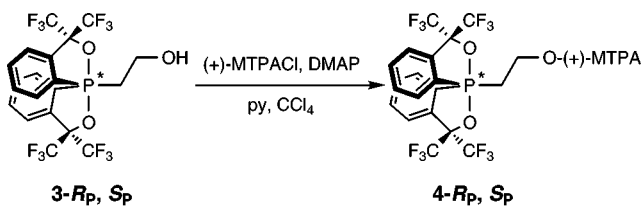
phosphoranes (S. Matsukawa, K. Kajiyama, M. Nakamoto, Y. Yamamoto, S. Kojima, and K.-y. Akiba, unpublished results), which were found to be largely different from those of regular (*O-trans*) phosphoranes, and on the stabilization of hexacoordinated anions derived from the reactions of α-anions from *O-cis* phosphoranes, including the first X-ray analysis of a 12-P-6 phosphate bearing an oxaphosphetane ring system (S. Matsukawa, K. Kajiyama, M. Nakamoto, Y. Yamamoto, S. Kojima, and K.-y. Akiba, unpublished results).

RESULTS AND DISCUSSIONS

*Freezing Berry Pseudorotation and Isolation of Optically Active 10-P-5 Spirophosphoranes (**1** and **3**) with Asymmetry Only at Phosphorus*

By utilizing Martin's phosphorane **1**, we have succeeded in preparing and characterizing the first configurationally stable enantiomeric pairs of optically active phosphoranes **3-R_P** and **3-S_P**, and **1-R_P** and **1-S_P**, which bear asymmetry only at phosphorus. Compounds **3-R_P** and **3-S_P** were obtained from a diastereomeric pair of (*o*-$OC(CF_3)_2C_6H_4)_2P^*CH_2CO_2$(-)menthyl (**2-$R_P$** and **2-$S_P$**) which could be separated in relatively large quantities by fractional crystallization by using MeOH-H_2O as solvent. The removal of the chiral menthyl moiety was achieved by treating the diastereomers with an excess amount of $LiAlH_4$ in refluxed Et_2O, as depicted in Scheme 1, thereby generating the first enantiomeric pair of rigid optically active phosphoranes with asymmetry only at phosphorus. In order to assure the high enantiomeric purity of the chiral alcohols, the alcohols **3** were converted to their (*R*)-(+)-Mosher esters (**4-R_P** and **4-S_P**) as described in Scheme 2, using the acid chloride derived from (*R*)-(+)-2-methoxy-2-(trifluoromethyl)phenylacetic acid. A comparison of the ^{31}P NMR charts of the diastereomeric mixtures, the Mosher ester **4-S_P** derived from **3-S_P**, and the Mosher ester **4-R_P** derived from **3-R_P**, clearly shows that the crude samples of neither **4-S_P** nor **4-R_P** showed the presence of the opposing diastereomers. This implies that epimerization had not occurred either during the two consecutive transformations of esters **2-R_P** and **2-S_P** to **4-R_P** and **4-S_P**, respectively, or during the purification procedures. Thus, we could confirm the high enantiomeric purity of the alcohols **3-R_P** and **3-S_P**.

Furthermore, the first optically active pair of enantiomeric P—H phosphoranes (*o*-$OC(CF_3)_2C_6H_4)_2P^*H$ (**1-R_P** and **1-S_P**) with asymmetry only at the pentacoordinate phosphorus atom could be obtained from diastereomeric phosphoranes (*o*-$OC(CF_3)_2C_6H_4)_2P^*CH_2NHC^*H(CH_3)Ph$ (**5-R_P** and **5-S_P**), of which the absolute stereochemistry was also determined, by treatment with MeLi (Scheme 3 and 4). The high enantiomeric purities of the P—H



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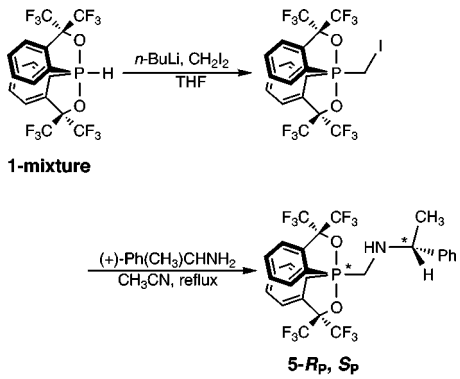

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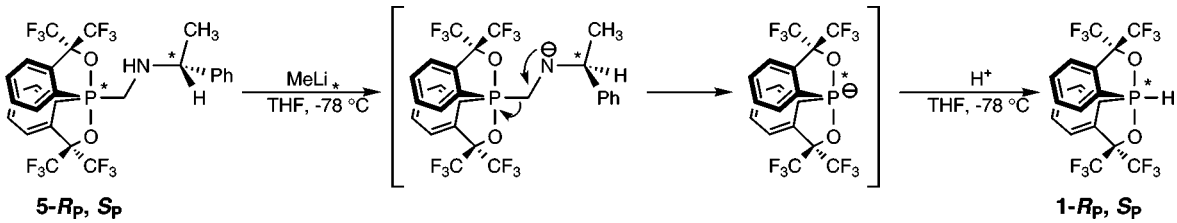


SCHEME 4

phosphoranes were confirmed by converting each of them to their corresponding (-)-menthyl esters **2-R_P** and **2-S_P** (Scheme 5). Racemization between **1-R_P** and **1-S_P** did not take place at room temperature [5].

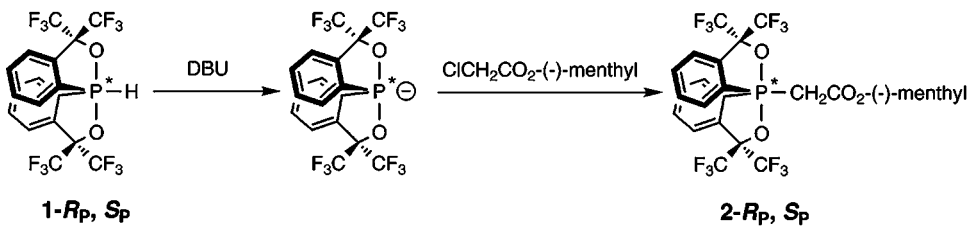
Isolation and Synthesis of Novel Anti-Apicophilic C-Apical O-Equatorial (O-cis) Spirophosphorane **6**

It is well established that trigonal bipyramidal 10-P-5 phosphoranes prefer to have the more electron-withdrawing groups of the five substituents at the apical positions on the basis of the concept of apicophilicity [7]. The only exceptions to this generality had been the case where some sort of steric constraints disallowed such configurations [8]. However, we have recently succeeded in the first isolation and full characterization of an "anti-apicophilic" phosphorane (*O-cis* **6b**) in which an oxygen atom occupies an equatorial position and a carbon atom occupies an apical position in a five-membered ring without applying restrictions that would not permit the formation of the more stable stereoisomer (*O-trans* **7b**) [6]. In the presence of pyridine, *O-cis* **6b** was formed as a major product via a unique thermal cyclization reaction of P—H (apical) phosphorane **8b** with concomitant H_2 elimination whereas **8a–c** gave *O-trans* **7a–c** in toluene and *o*-dichlorobenzene (Scheme 6) [9]. One disadvantage of this procedure is that it is not suitable for the preparation of anti-apicophilic phosphoranes that may undergo stereomutation around these temperatures. Therefore we developed mild and highly selective procedures for preparing anti-apicophilic phosphoranes *O-cis* **6**, which involves the oxidation of in situ generated dianion **9**.

The new protocol provided **6a** and **6b** exclusively at low temperatures in high yields, and aryl derivative **6f** could also be synthesized for the first time by these procedures [10]. The possible reaction mechanism is shown in Scheme 6: (i) Reaction of P—H(equatorial) phosphorane **1** with more than two equivalents of RLi provides the dianion **9**, where one equivalent of RLi works as a base and the other as a nucleophile. (ii) In the resulting dianion **9**, the lone pair electrons on the phosphorus occupy an equatorial position because of its extreme electron-donicity. Oxidant I_2 reacts with the dianion **9** to produce P—I (equatorial) phosphorane **A**, and the remaining alkoxide anion rapidly cyclizes with simultaneous elimination of I^- to form *O-cis* spirophosphorane **6**, exclusively.

Enhanced Electrophilicity of O-cis Phosphorane **6***: Effect of* σ^*_{P-O} *Orbital in the Equatorial Plane*

O-cis phosphorane **6** has one of the two P—O bonds on the equatorial plane, and therefore has a σ^*_{P-O} orbital on the same plane. On the other hand, *O-trans* phosphorane **7** has only the corresponding P—C bonds on the equatorial plane, hence has only a σ^*_{P-C}, accordingly (Fig. 1). Since the energy level of σ^*_{P-O} should be significantly lower than that of σ^*_{P-C}, there should be an apparent effect of σ^*_{P-O} to show the difference in the reactivity between **6** and **7** toward nucleophiles (electrophilicity of phosphoranes) and in the stability of carbanions α to the phosphorus atom. Now we describe the effects of the



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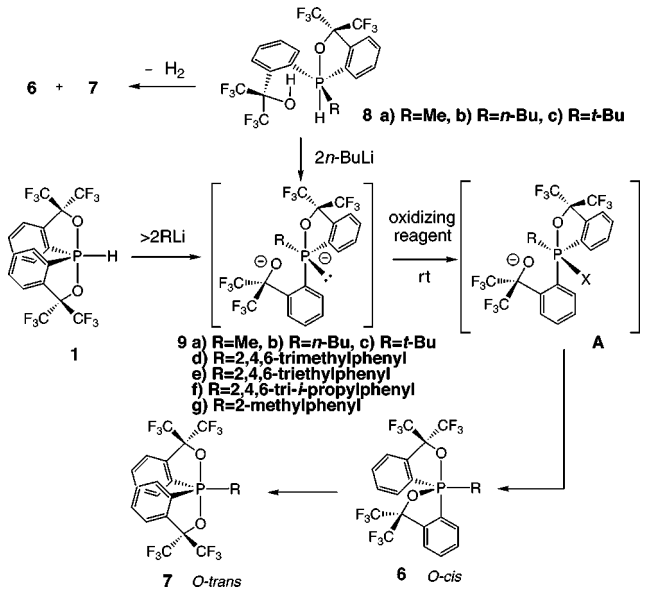


SCHEME 6

σ^*_{P-O} orbital of **6** from both experimental and theoretical viewpoints.

Reactions of *O-cis* **6b** and *O-trans* **7b** with nucleophiles were examined. Using TBAF (tetrabutylammonium fluoride; $(n\text{-Bu})_4N^+F^-$) as a nucleophile, the reaction of **6b** readily afforded a hexacoordinate phosphate bearing a P—F bond **10** ($^1J_{P-F} = 706$ Hz) while **7b** did not react at all. The configuration of phosphate **10** could not be determined with certainty because of rapid decomposition by trace amounts of H_2O. However we have already characterized the corresponding hexacoordinate fluoroantimonate with two Martin ligands by X-ray analysis [11] and therefore, in phosphate **10**, the fluorine atom is also likely to be located anti to the oxygen because of the trans influence of the fluorophosphate. These can be explained by the attack of the fluoride anti at the P—O or Sb—O (equatorial) bond of the *O-cis* isomer. Similarly, *O-cis* **6b** reacted with 1 equiv. of MeLi at 0°C for 90 min to give the corresponding adduct **11** (82% yield) after hydrolysis, while *O-trans* **7b** did not react under similar conditions (Scheme 7). Under forcing

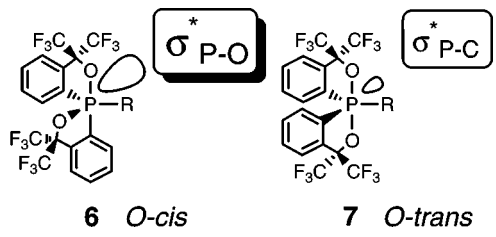
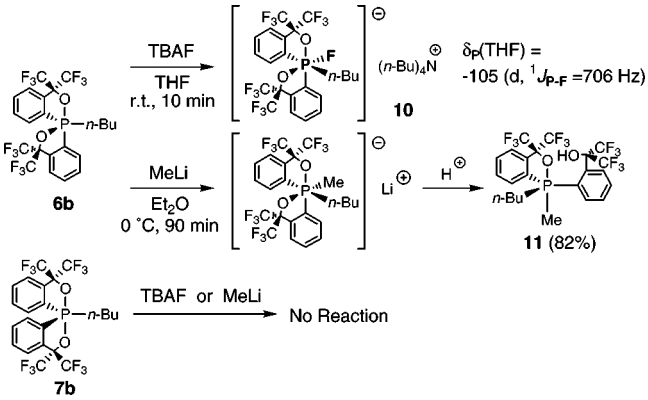


FIGURE 1 Expected enhanced electrophilicity of *O-cis* **6** due to a low-lying σ^*_{P-O} orbital.



SCHEME 7

conditions (5 equiv. of MeLi at rt for 6 h), **7b** slowly reacted with MeLi to give **11**. These results clearly show that the electrophilicity of *O-cis* **6** is higher than that of *O-trans* **7**. This is in agreement with the rationale that the lower-lying $\sigma^*_{P-O(equatorial)}$ orbital in *O-cis* **6** should be able to accept an electrophile much more easily than the higher-lying $\sigma^*_{P-C(equatorial)}$ orbital in *O-trans* **7**.

Stabilization of Lone Pair Electrons Adjacent to the Phosphorus of O-cis **6***: Effect of the* σ^*_{P-O} *Orbital in the Equatorial Plane*

Deprotonation of *O-cis* **6h** with KHMDS (potassium hexamethyldisilazide; $(Me_3Si)_2N^-K^+$) occurred in THF at 0°C for 30 min and gave the α-deuterated product (40% deuterated) after treating the mixture with D_2O. On the other hand, *O-trans* **7h** could not be deprotonated under the same conditions. Therefore, the results clearly show that the acidity of the α-proton of *O-cis* **6h** is higher than that of *O-trans* **7h**. Moreover, the benzyl anion (**12h**) of **6h** was much more stable stereochemically than the neutral molecule of **6h**. In THF, *O-cis* **6h** was totally converted to the *O-trans* **7h** at 60°C over 5 h. Under the same conditions, the benzyl anion (**12h**) remained almost unchanged.

Theoretical Study on σ^* *Orbitals of O-cis and O-trans Phosphoranes in the Equatorial Plane*

In order to evaluate the difference in energy between the σ^*_{P-O} orbital of *O-cis* phosphorane and the σ^*_{P-C} orbital of the *O-trans* isomer, theoretical calculations for **6a** and **7a** were carried out (B3PW91/6-31G(d)). As shown in Fig. 2, the energy of σ^*_{P-O} of **6a** (LUMO + 4) is lower than that of σ^*_{P-C} of **7a** (LUMO + 5) by 18.7 kcal/mol. Other LUMOs below

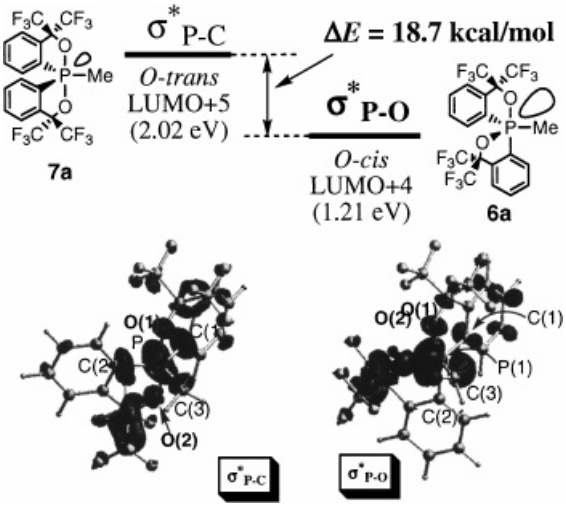
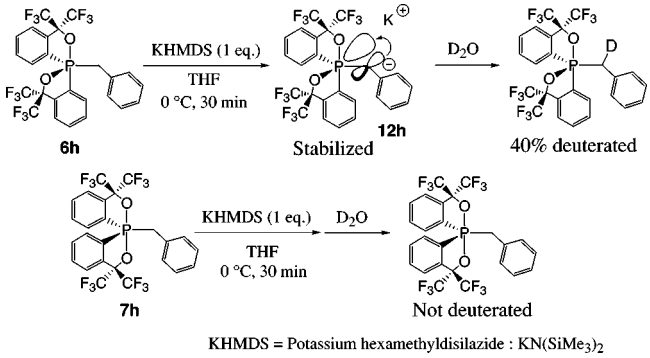


FIGURE 2 Energies of molecular orbitals for σ^*_{P-O} of *O-cis* **6a** and σ^*_{P-O} of *O-trans* **7a**.

σ^*_{P-X} (X = O or C) were distributed on the aromatic rings of the Martin ligands. Therefore the orbitals responsible for nucleophilicity and stabilization of the α-carbanion should be the σ^*_{P-X}. This large difference in the energy between σ^*_{P-O} and σ^*_{P-C} orbitals provides theoretical evidence for the enhanced reactivity of *O-cis* spirophosphorane **6** compared with the *O-trans* isomer **7** as shown in Scheme 7.

In addition, theoretical calculations show that the energy difference between α-anion of *O-cis* (**12a**)



SCHEME 8

and the corresponding α-anion of *O-trans* (**13a**) is much smaller (4.7 kcal/mol) than the difference between **6a** and **7a** (14.1 kcal/mol) (Fig. 3). The results indicate that the equilibrium between **6a** and **12a** should be shifted much more toward the anion (**12a**) in comparison with the corresponding equilibrium between **7a** and **13a**. That is, the CH_3 protons of the *O-cis* phosphorane (**6a**) are much more acidic than the corresponding CH_3 protons of the *O-trans* phosphorane (**7a**). This is consistent with the experimental observation of enhanced acidity of the benzyl protons in *O-cis* **6h** in comparison with *O-trans* **7h** as shown in Scheme 8. Theoretical calculations were carried out by Professor Shigeru Nagase of the Institute for Molecular Science, and will be published later [12].

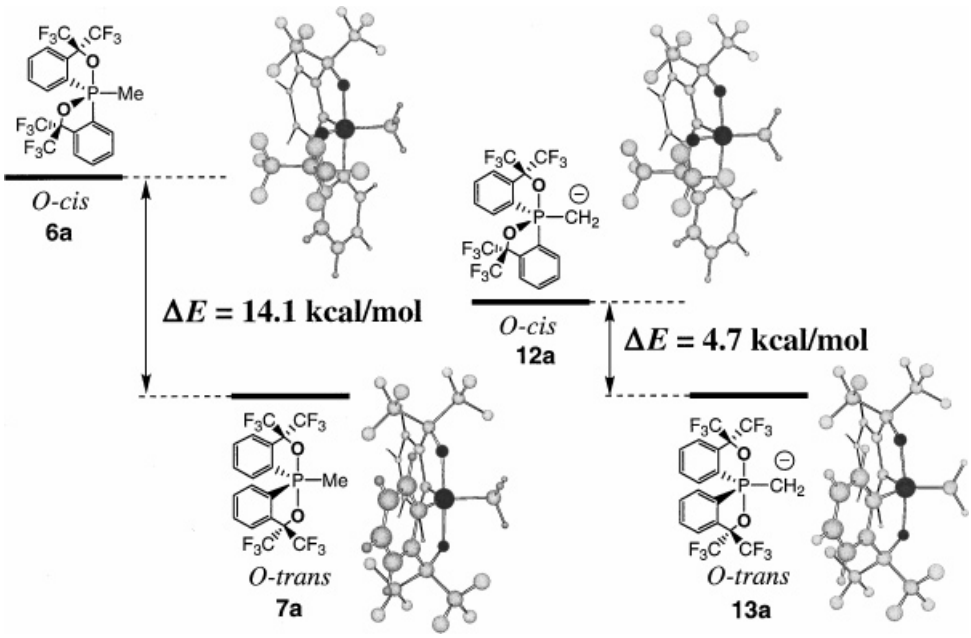


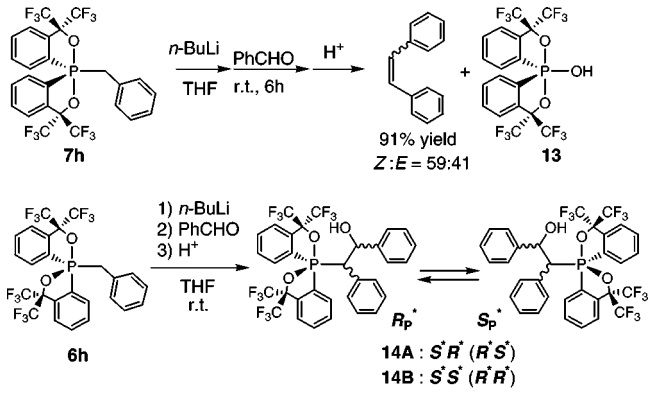
FIGURE 3 Decrease in energy difference between the anionic pair of *O-cis* **12a** and *O-trans* **13a** compared with the corresponding neutral pair of *O-cis* **6a** and *O-trans* **7a** attributable to $n_C \rightarrow \sigma^*_{P-O}$ stabilization.

Stabilization of Hexacoordinated Anions Derived from the Reactions of α-Anions from O-cis **6***: Trans Influence of the P–O Bond*

Reaction of the α-anion of *O-trans* benzylphosphorane **7h** with PhCHO proceeded smoothly to afford stilbenes and **13** in high yields (Scheme 9). *Z*-stilbene was formed preferentially (*Z*/*E* was 59:41) in the reaction with *n*-BuLi, and the *Z*/*E* ratio was up to 80:20 using KH as a base in the presence of 18-crown-6 ether. The *Z*-selectivity was lower than that of a spirophosphorane bearing an ethoxycarbonylmethyl group [13]. In contrast to the smooth formation of stilbenes from *O-trans* benzylphosphorane **7h**, the reaction of the corresponding anion of *O-cis* **6h** with PhCHO gave only the adduct, i.e., two diastereomers of **14** without the formation of stilbenes (Scheme 9).

These two diastereomers (**14A** and **14B**) could not be separated by TLC, however, a prolonged reaction time (>24 h) using *n*-BuLi as the base provided only **14B**, whose structure was confirmed by X-ray analysis to have the relative configuration of $\boldsymbol{R_P^*S^*S^*}$. We have already reported on the rapid one-step pseudorotation at the phosphorus of *O-cis* spirophosphoranes [6], similarly **14B** existed as a rapidly equilibrating mixture of $\boldsymbol{R_P^*S^*S^*}$ and $\boldsymbol{S_P^*S^*S^*}$, which showed distinct ^{31}P NMR signals at low temperatures.

Scheme 10 illustrates the possible mechanism of the reaction of the *O-cis* benzyl anion **12h–M** with PhCHO. Kinetically, the addition of PhCHO to the anion proceeds in a manner in which both phenyl groups avoid each other at the aldol condensation stage, and the resulting phosphate **Int-A**, where the two phenyl groups become overlapped by forming the oxaphosphetane ring, is the predominant intermediate. **Int-A** gives **14A** by treating it with a proton source. However, **Int-A** is expected to be unstable because of steric repulsion between the two phenyl groups on the four-membered ring, and therefore



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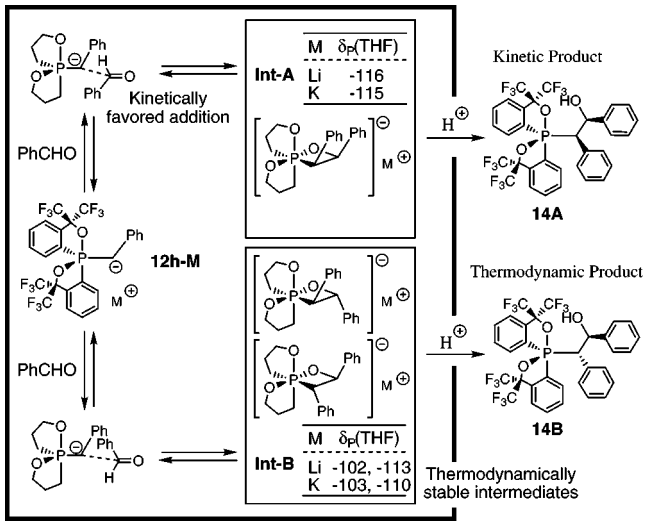
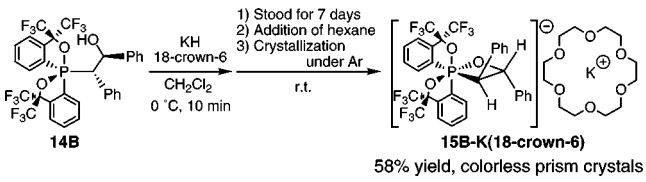


SCHEME 10

retro-aldol cleavage takes place from **Int-A** to reproduce **12h–M**. On the other hand, when the addition proceeds in an opposite manner, i.e., two phenyl groups are overlapped with each other at the aldol condensation stage, intermediates **Int-B** are generated. Both the **Int-B** are sterically less hindered, and should be more stable intermediates than **Int-A**. After equilibrium is established, only **Int-B** were observed in the reaction solution, and **14B** was obtained as the sole adduct after hydrolysis in this system.

When the thermodynamic product **14B** was deprotonated by KH in THF to form hexacoordinate phosphate, three ^{31}P NMR signals were observed in the solution at the initial stage. But finally, only a signal at −110 ppm was observed after equilibration, and the most stable phosphate **15B–K(18-crown-6)** could be isolated as single crystals by recrystallization from *n*-hexane-CH_2Cl_2 under Ar (Scheme 11). Surprisingly, these crystals were stable toward atomospheric moisture at room temperature for several months. The X-ray structure of **15B–K(18-crown-6)** is shown in Fig. 4. This became the first X-ray analysis of a 12-P-6 phosphate bearing an oxaphosphetane ring system. The structure is a slightly distorted octahedral one, and the two phenyl groups on the



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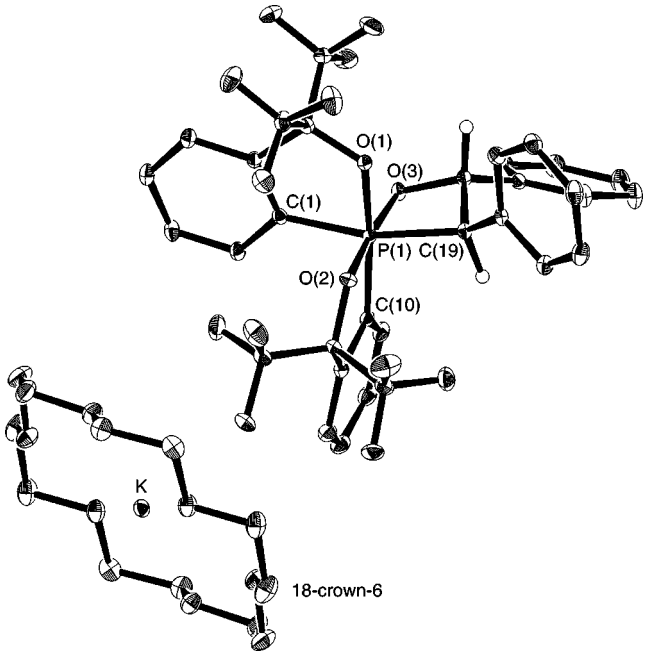

FIGURE 4 Crystal structure (30% thermal ellipsoids) of **15B–K(18-crown-6)**.

four-membered ring are located with a trans relationship to each other. The most important finding is that the structure has a configuration which could be assumed to have been formed by the attack of the alkoxide anion to the σ^*_{P-O} orbital of a *O-cis* phosphorane **14B**. This is consistent with the highly electrophilic nature of the σ^*_{P-O} orbital and stabilization of the subsequent hexacoordinate state by the trans influence of the P—O bond.

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