

Acetyl Chloride-Mediated Synthesis of *trans*-2-[(Diethoxyphosphoryl-amino)alkyl]-4-aryl-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide

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N-Phosphoramino-protected six-membered cyclic α-aminophosphonates *trans*-2-[(diethoxyphosphorylamino)-alkyl]-4-aryl-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide **4a–4l** were synthesized with the help of acetyl chloride. ^{31}P NMR was used to trace the reaction process. A possible reaction mechanism was proposed and the stereochemistry of the title compounds was studied. In order to confirm the structure of **4**, products **4f** and **4k** were recrystallized and determined by X-ray diffraction analysis.

α-Aminophosphonates have acquired great attention in synthetic organic chemistry due to their structural analogy to α-amino acids and their varied biological activity.[1] Many 1,3,2-dioxaphosphorinane derivatives have been designed and synthesized for the purpose of connecting with biologically active nucleoside analogs to form prodrugs with higher lipophilicity.[2,3] They also have been used as chiral resolving agents[4] due to the stereochemical properties.[5–10] Compounds containing phosphoamino groups may exhibit important biological activities.[11,12] However, studies on the synthesis and stereochemical properties of this kind of six-membered cyclic α-aminophosphonates are rare.[13,14]

Three component Mannich-type condensation of substituted aldehydes (ketones), amines, and phosphite components in one pot is a convenient method to prepare varied α-aminophosphonates.[1] A number of Lewis acid catalysts such as $InCl_3$,[15] $TaCl_5$–SiO_2,[16] and $Mg(ClO_4)_2$[17] have been used in methylene chloride or other organic solvent to promote this addition. Our group has reported the synthesis of N-protected α-aminophosphonates under refluxing benzene.[18,19] Herein, we wish to report acetyl chloride-mediated synthesis of *N*-phosphoramino-protected six-membered cyclic α-aminophosphonates bearing a P–C–N–P framework[11] via three-components, aldehydes (ketones) **2**, diethyl phosphoramidate (**1**) and 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-oxide **3**. ^{31}P NMR is an efficient method to trace the reaction process and investigate the reaction mechanisms, especially when the intermediates are unstable.[20] In this paper, ^{31}P NMR was used to trace the reaction process and a possible reaction mechanism is proposed. In order to confirm the structure of desired α-aminophosphonates **4**, products **4f** and **4k** were recrystallized and determined by X-ray diffraction analysis.

Results and Discussion

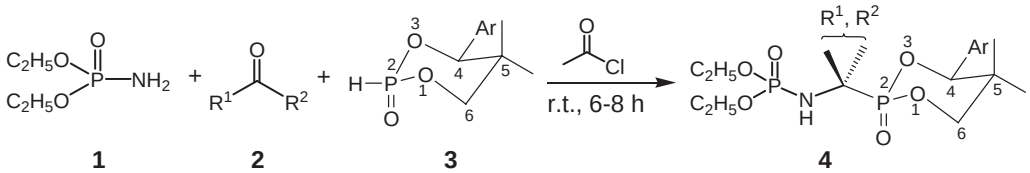
A series of new cyclic α-aminophosphonates *trans*-**4a–4l** were synthesized by a one-pot Mannich-type reaction under mild conditions in moderate yield (38–72%) (Scheme 1). Acetyl chloride was used as solvent, various aryl aldehydes or aliphatic ketones underwent the reaction smoothly (Table 1).

From the X-ray structure of **4f** and **4k** we can see that the pentane ring in the molecule is in half-chair configuration and the six-member ring's configuration P(2)–O(6)–C(10)–

Table 1. The Results of the Obtained α-Aminophosphonates **4a–4l**

4	Ar	R^1	R^2	Yield/%[a)]
4a	Ph	CH_3	CH_3	70
4b	Ph	$(CH_2)_4$		65
4c	Ph	$(CH_2)_5$		60
4d	Ph	H	4-ClC_6H_4	67[b)]
4e	4-ClC_6H_4	CH_3	CH_3	72
4f	4-ClC_6H_4	$(CH_2)_4$		66
4g	4-ClC_6H_4	$(CH_2)_5$		61
4h	4-ClC_6H_4	$(CH_2)_6$		38
4i	4-ClC_6H_4	H	C_6H_5	68[b)]
4j	4-ClC_6H_4	H	4-MeC_6H_4	70[b)]
4k	4-BrC_6H_4	$(CH_2)_4$		67
4l	4-BrC_6H_4	$(CH_2)_5$		58

a) Isolated yields. b) Total yield of two diastereoisomers.



Scheme 1. Reaction of **2**, **3**, and diethyl phosphoramidate in acetyl chloride.

Published on the web May 14, 2008; doi:10.1246/bcsj.81.630

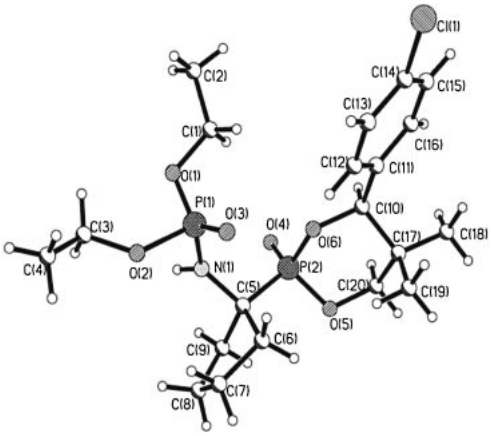


Figure 1. ORTEP plot of **4f**.

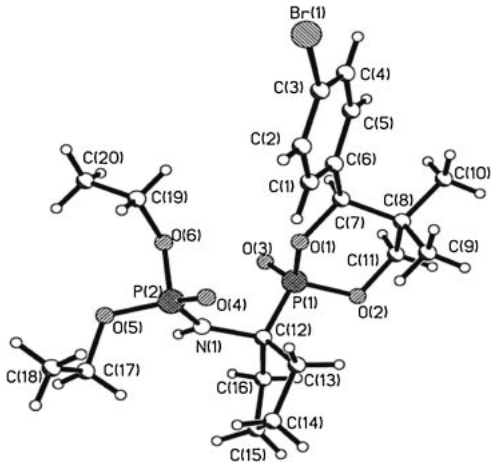


Figure 2. ORTEP plot of **4k**.

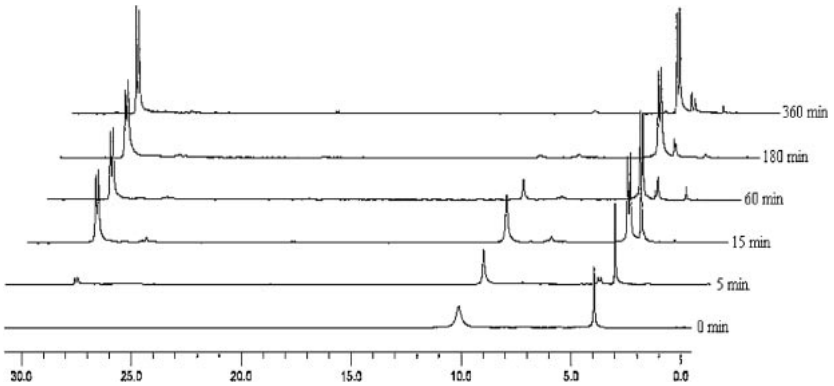


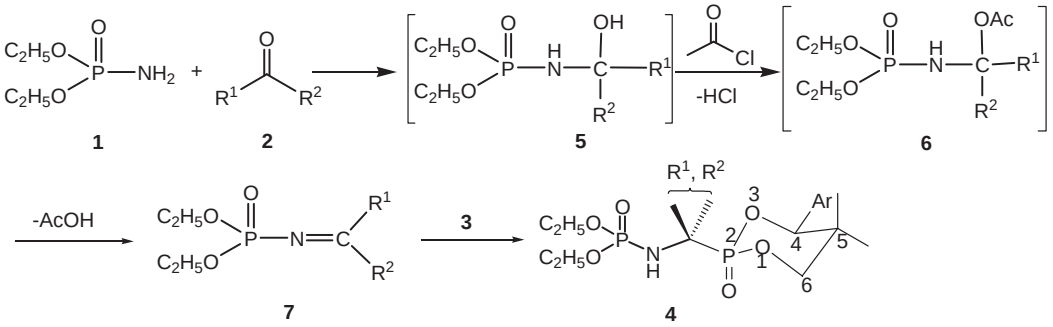
Figure 3. ^{31}P NMR stack spectra for the synthesis of **4f** (ppm).

C(17)–C(20)–O(5) is chair (take **4f** for example). There are two phosphorous atoms in this molecular, both of them are sp^3 hybridized and adopt distorted tetrahedral configurations (Figure 1 and Figure 2). The (diethoxyphosphorylamino)-cyclopentyl group as well as the aryl groups are in equatorial conformation due to steric hindrance, so only *trans*-**4** were obtained.

When symmetrical ketones **2** were used, only one isomer was obtained. When aldehydes **2** were used, because the two substituents (R^1 and R^2) of the carbonyl group are different, two diastereoisomers were formed in the cases of **4d**, **4i**, and **4j**, and the proportion of the two diastereoisomers was almost 1:1. At first, we tried to separate them through column chromatography but failed, because the polarities of the two diastereoisomers were almost the same. Subsequently, through recrystallization we obtained one or both of the two isomers.

For example, after column chromatography of **4d**, a mixture of two diastereoisomers was obtained as a white solid with four doublets in the ^{31}P NMR spectra at 21.96 (d, ^3J = 37.5 Hz), 21.33 (d, ^3J = 36.5 Hz), 8.15 (d, ^3J = 36.5 Hz), and 7.52 (d, ^3J = 37.5 Hz) ppm due to the P–P coupling. The ^{31}P NMR signals at ca. 21 and 8 ppm, are attributable to the P-atom of the diethoxyphosphinyl group and the P-atom of the *N*-phosphoryl group, respectively. The ^{31}P NMR spectra were also used for the determination of the ratio of isomers. One isomer was isolated from the mixture obtained by recrystallization at low temperature. The mother liquor was treated by column chromatography, and the other isomer was obtained in pure form. In ^{1}H NMR, the α-H of each isomer of the two diastereoisomers shows obviously multiple peaks due to the splitting of the two P atoms and the protons of the N-atoms. It is interesting that the chemical shifts of the α-H of the two diastereoisomers were obviously different due to the difference of the chemical environment.

Formation of **4f** was traced by ^{31}P NMR spectroscopy as shown in Figure 3. The starting material diethyl phosphoramidate (**1**) and 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-oxide **3** in acetyl chloride showed ^{31}P NMR resonance at 10.46 and 4.46 ppm respectively. After aldehydes (ketones) **2** was added to the solution of **1** and **3**, the expected **4f** was produced (double peaks at 29.67 and 5.06 ppm with J = 15.2 Hz) in five minutes. As time proceeded, ^{31}P NMR signals of two starting material (δ_P at 10.46 ppm of **1** and 4.46 ppm of **3**) disappeared gradually and the signals of **4f** increased. Three intermediates appeared during the synthesis of **4f**. The signals at δ_P 3.02 and 4.30 ppm may belong to intermediate **5** and **6**[21] respectively, and the faint signals at δ_P 8.65 ppm belong to the imine **7**[22] (Scheme 2). Acetyl chloride accelerates the dehydration via formation of the intermediate **6**, and release of one molar equivalent of AcOH resulted in the formation of the corresponding Schiff's base **7**. The reaction was almost completed after 6 h according to the ^{31}P NMR spectra (Figure 3).



Scheme 2. Possible reaction mechanism for the synthesis of the α-aminophosphonates **4**.

In conclusion, we have developed an efficient method for the synthesis of *trans*-2-[(diethoxyphosphorylamino)alkyl]-4-aryl-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide **4a–4l** with the help of acetyl chloride and studied the stereochemistry. The structures of **4** were determined by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, elemental analysis, and X-ray single-crystal diffraction analysis. ^{31}P NMR was used to trace the reaction process and explore the possible reaction mechanism. Acetyl chloride is essential for this reaction and accelerates the process of intramolecular dehydration of **5** forming the corresponding Schiff's base **7**.

Experimental

4-Aryl-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxides **3** were synthesized according to a reported method,[4,23] all other reagents were purchased from Aldrich Chemical Co. Melting points were measured on a Beijing-Tech X-4 apparatus without correction. ^{1}H, ^{13}C, and ^{31}P NMR were recorded on a Bruker AV-300 and Varian AS-400 spectrometer in $CDCl_3$ and chemical shifts were express as δ (ppm). Tetramethylsilane was used as an internal standard for ^{1}H NMR, and 85% H_3PO_4 as an external standard for ^{31}P NMR spectroscopy. Mass spectra were recorded on a Polaris-Q instrument by Thermofinnigan. The crystal structure was determined on a Bruker SMART 1000 CCD diffractometer. Elemental analyses were carried out on a Yanaco CHNCORDER MT-3 analyzer. Column chromatography was performed using silica gel H (10–40 μm, Haiyang Chemical Factory of Qingdao, China).

Typical Procedure for the Synthesis of α-Aminophosphonates 4d. A dry 25-mL flask was charged with diethyl phosphoramidate (**1**) (1 mmol, 0.153 g) and 4-phenyl-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (**3**) (1 mmol, 0.226 g) in 5 mL of acetyl chloride, 4-chlorobenzaldehyde (**2**) (1 mmol, 0.140 g) was added dropwise and stirred. The resulting mixture was stirred at room temperature for 8 h (Scheme 1). The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel) with ethyl acetate–petroleum ether (bp: 60–90 °C) (v/v = 4:1) as the eluent. The title compounds were obtained (Table 1). The products **4f** and **4k** were further purified by recrystallization from ethyl acetate at room temperature to give colorless crystal suitable for X-ray analysis.

***trans*-2-[1-(Diethoxyphosphorylamino)-1-methylethyl]-5,5-dimethyl-4-phenyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4a):** Colorless oil. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 29.59 (d, $^3J_{PP}$ = 36.7 Hz), 6.60 (d, $^3J_{PP}$ = 36.7 Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.25–7.16 (m, 5H, Ph), 5.39 (s, 1H, 4-H), 4.41 (d, $^2J_{H,H'}$ = 11.1 Hz, 1H, 6-H), 4.01 (q, J = 7.1 Hz, 4H, 2OCH_2CH$_3$), 3.74 (dd, $^2J_{H,H'}$ = 11.1 Hz, $^3J_{P,H}$ = 21.3 Hz, 1H, 6-H), 3.31 (br, 1H, NH), 1.57 (d, $^3J_{P,H}$ = 3.3 Hz, 3H, α-C-CH$_3$), 1.53 (d, $^3J_{P,H}$ = 3.3 Hz, 3H, α-C-CH$_3$), 1.22 (t, J = 7.0 Hz, 6H, 2OCH$_2$CH_3), 0.94 (s, 3H, 5-C-CH$_3$), 0.69 (s, 3H, 5-C-CH$_3$); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 136.00 (d, $^3J_{P,C}$ = 7.9 Hz), 128.58, 127.97, 127.47 (Ph), 84.07 (d, $^2J_{P,C}$ = 5.9 Hz, 4-C), 75.34 (d, $^2J_{P,C}$ = 6.0 Hz, 6-C), 62.75 (d, $^2J_{P,C}$ = 5.5 Hz, 2OCH_2CH$_3$), 51.18 (d, $^1J_{P,C}$ = 155.5 Hz, α-C), 36.92 (5-C), 23.99 (α-C-CH_3), 23.74 (α-C-CH_3), 21.80 (5-C-CH_3), 17.71 (5-C-CH_3), 16.30 (d, $^2J_{P,C}$ = 7.5 Hz, 2OCH$_2$$CH_3$); Elemental analysis calculated (%) for $C_{18}H_{31}NO_6P_2$ (419.16): C, 51.55; H, 7.45; N, 3.34%. Found: C, 51.60; H, 7.47; N, 3.20%. ESI-MS: $[M + H]^+$ 420.26.

***trans*-2-[1-(Diethoxyphosphorylamino)cyclopentyl]-5,5-dimethyl-4-phenyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4b):** White solid. mp 137–139 °C. ^{31}P NMR (δ, 121 MHz, $CDCl_3$): 29.59 (d, $^3J_{PP}$ = 20.2 Hz), 4.88 (d, $^3J_{PP}$ = 20.2 Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.30–7.22 (m, 5H, Ph), 5.44 (s, 1H, 4-H), 4.46 (d, $^2J_{H,H'}$ = 11.2 Hz, 1H, 6-H), 4.03 (m, 4H, 2OCH_2CH$_3$), 3.77 (dd, $^2J_{H,H'}$ = 11.2 Hz, $^3J_{P,H}$ = 21.3 Hz, 1H, 6-H), 3.01 (d, 1H, $^2J_{P,H}$ = 7.9 Hz, NH), 2.21–1.75 (m, 8H, 4CH$_2$), 1.24 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 1.21 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 0.99 (s, 3H, 5-C-CH$_3$), 0.73 (s, 3H, 5-C-CH$_3$); ^{13}C NMR (δ, 75 MHz, $CDCl_3$): 135.96 (d, $^3J_{P,C}$ = 8.3 Hz), 128.31, 127.75, 127.40 (Ph), 83.68 (d, $^2J_{P,C}$ = 5.8 Hz, 4-C), 75.05 (d, $^2J_{P,C}$ = 6.2 Hz, 6-C), 62.65 (d, $^2J_{P,C}$ = 4.0 Hz, 2OCH_2CH$_3$), 60.51 (d, $^1J_{P,C}$ = 159.4 Hz, α-C), 36.82 (5-C), 35.32 (CH$_2$), 35.19 (CH$_2$), 24.32 (d, $^3J_{P,C}$ = 4.0 Hz, α-C-CH_2), 24.18 (d, $^3J_{P,C}$ = 3.8 Hz, α-C-CH_2), 21.73 (5-C-CH_3), 17.71 (5-C-CH_3), 16.11 (d, $^2J_{P,C}$ = 6.5 Hz, OCH$_2$$CH_3$), 16.02 (d, $^2J_{P,C}$ = 6.7 Hz, OCH$_2$$CH_3$); Elemental analysis calculated (%) for $C_{20}H_{33}NO_6P_2$ (445.18): C, 53.93; H, 7.47; N, 3.14%. Found: C, 54.02; H, 7.48; N, 3.12%. ESI-MS: $[M + H]^+$ 446.21.

***trans*-2-[1-(Diethoxyphosphorylamino)cyclohexyl]-5,5-dimethyl-4-phenyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4c):** White solid. mp 175–177 °C. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 28.67 (d, $^3J_{PP}$ = 10.5 Hz), 5.72 (d, $^3J_{PP}$ = 10.5 Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.34–7.29 (m, 5H, Ph), 5.46 (s, 1H, 4-H), 4.47 (d, $^2J_{H,H'}$ = 11.4 Hz, 1H, 6-H), 4.00 (m, 4H, 2OCH_2CH$_3$), 3.79 (dd, $^2J_{H,H'}$ = 11.2 Hz, $^3J_{P,H}$ = 21.5 Hz, 1H, 6-H), 2.66 (br, 1H, NH), 2.30–1.33 (m, 10H, 5CH$_2$), 1.25 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 1.10 (t, J = 7.0 Hz, 3H, OCH_2CH$_3$), 0.98 (s, 3H, 5-C-CH$_3$), 0.74 (s, 3H, 5-C-CH$_3$); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 136.20 (d, $^3J_{P,C}$ = 7.8 Hz), 128.45, 127.95, 127.68 (Ph), 83.85 (d, $^2J_{P,C}$ = 6.5 Hz, 4-C), 75.24 (d, $^2J_{P,C}$ = 6.6 Hz, 6-C), 62.82 (d, $^2J_{P,C}$ = 5.7 Hz, 2OCH_2CH$_3$), 55.23 (d, $^1J_{P,C}$ = 154.4 Hz, α-C), 37.00 (5-C), 31.91 (CH$_2$), 31.25 (CH$_2$), 25.37 (CH$_2$), 21.92 (5-C-CH_3), 20.80 (d, $^3J_{P,C}$ = 9.3 Hz, α-C-CH_2), 20.65 (d, $^3J_{P,C}$ = 9.4 Hz, α-C-CH_2), 17.82 (5-C-CH_3), 16.36 (d, $^2J_{P,C}$ = 7.2 Hz,

OCH_2CH_3), 16.14 (d, $^2J_{P,C} = 7.3$ Hz, OCH_2CH_3); Elemental analysis calculated (%) for $C_{21}H_{35}NO_6P_2$ (459.19): C, 54.90; H, 7.68; N, 3.05%. Found: C, 54.80; H, 7.73; N, 3.06%. ESI-MS: $[M + H]^+$ 460.32.

***trans*-2-[1-(Diethoxyphosphorylamino)(*p*-chlorophenyl)-methyl]-5,5-dimethyl-4-phenyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4d):** One diastereoisomer: White solid. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 21.96 (d, $^3J_{PP} = 37.5$ Hz), 7.52 (d, $^3J_{PP} = 37.5$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.44–7.29 (m, 9H, Ph), 5.39 (s, 1H, 4-H), 4.71 (m, 1H, α-C-H), 4.30 (d, $^2J_{H,H'} = 9.7$ Hz, 1H, 6-H), 4.02 (q, $J = 7.1$ Hz, 4H, $2OCH_2CH_3$), 3.79 (dd, $^2J_{H,H'} = 9.7$ Hz, $^3J_{P,H} = 22.3$ Hz, 1H, 6-H), 2.02 (br, 1H, NH), 1.26 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.07 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 0.80 (s, 3H, 5-C-CH_3), 0.72 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 135.69 (d, $J = 7.9$ Hz), 135.02, 134.41, 129.45 (d, $J = 5.3$ Hz), 128.88, 128.69, 128.01, 127.40 (Ph), 84.84 (d, $^2J_{P,C} = 5.9$ Hz, 4-C), 75.93 (d, $^2J_{P,C} = 6.5$ Hz, 6-C), 62.86 (d, $^2J_{P,C} = 5.7$ Hz, $2OCH_2CH_3$), 52.79 (d, $^1J_{P,C} = 153.0$ Hz, α-C), 36.79 (5-C), 21.79 (5-C-CH_3), 17.56 (5-C-CH_3), 16.06 (d, $^3J_{P,C} = 2.3$ Hz, OCH_2CH_3), 15.99 (d, $^3J_{P,C} = 2.7$ Hz, OCH_2CH_3).

Other diastereoisomer: White solid. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 21.33 (d, $^3J_{PP} = 36.5$ Hz), 8.15 (d, $^3J_{PP} = 36.5$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.26–7.10 (m, 9H, Ph), 5.43 (s, 1H, 4-H), 4.80 (m, 1H, α-C-H), 4.42 (d, $^2J_{H,H'} = 10.5$ Hz, 1H, 6-H), 3.96 (q, $J = 7.3$ Hz, 4H, $2OCH_2CH_3$), 3.72 (dd, $^2J_{H,H'} = 9.3$ Hz, $^3J_{P,H} = 21.3$ Hz, 1H, 6-H), 2.04 (br, 1H, NH), 1.24 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 0.99 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 0.86 (s, 3H, 5-C-CH_3), 0.72 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 135.69 (d, $J = 7.9$ Hz), 134.90, 134.36, 129.59 (d, $J = 6.3$ Hz), 128.96, 128.74, 128.09, 127.57 (Ph), 85.04 (d, $^2J_{P,C} = 6.0$ Hz, 4-C), 76.00 (d, $^2J_{P,C} = 6.5$ Hz, 6-C), 62.93 (d, $^2J_{P,C} = 5.7$ Hz, $2OCH_2CH_3$), 52.91 (d, $^1J_{P,C} = 153.0$ Hz, α-C), 38.96 (5-C), 21.71 (5-C-CH_3), 17.61 (5-C-CH_3), 16.33 (d, $^3J_{P,C} = 2.3$ Hz, OCH_2CH_3), 16.26 (d, $^3J_{P,C} = 2.7$ Hz, OCH_2CH_3). Elemental analysis calculated (%) for $C_{22}H_{30}ClNO_6P_2$ (501.12): C, 52.65; H, 6.03; N, 2.79%. Found: C, 52.79; H, 6.30; N, 2.87%. ESI-MS: $[M + H]^+$ 502.24.

***trans*-2-[1-(Diethoxyphosphorylamino)-1-methylethyl]-4-(*p*-chlorophenyl)-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4e):** Colorless oil. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 29.51 (d, $^3J_{PP} = 36.5$ Hz), 6.30 (d, $^3J_{PP} = 36.5$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.25–7.12 (m, 4H, Ph), 5.39 (s, 1H, 4-H), 4.39 (d, $^2J_{H,H'} = 9.1$ Hz, 1H, 6-H), 3.98 (m, 4H, $2OCH_2CH_3$), 3.69 (dd, $^2J_{H,H'} = 9.1$ Hz, $^3J_{P,H} = 14.4$ Hz, 1H, 6-H), 3.44 (br, 1H, NH), 1.53 (s, 3H, α-C-CH_3), 1.49 (s, 3H, α-C-CH_3), 1.12 (m, 6H, $2OCH_2CH_3$), 0.88 (s, 3H, 5-C-CH_3), 0.65 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 134.59 (d, $^3J_{P,C} = 7.8$ Hz), 134.40, 128.86, 128.18 (Ph), 83.33 (d, $^2J_{P,C} = 4.4$ Hz, 4-C), 75.24 (d, $^2J_{P,C} = 2.6$ Hz, 6-C), 62.86 (d, $^2J_{P,C} = 5.3$ Hz, OCH_2CH_3), 62.81 (d, $^2J_{P,C} = 4.3$ Hz, OCH_2CH_3), 51.12 (d, $^1J_{P,C} = 156.8$ Hz, α-C), 36.88 (5-C), 24.06 (α-C-CH_3), 23.74 (2α-C-CH_3), 21.69 (5-C-CH_3), 17.61 (5-C-CH_3), 16.30 (d, $^2J_{P,C} = 7.5$ Hz, $2OCH_2CH_3$); Elemental analysis calculated (%) for $C_{18}H_{30}ClNO_6P_2$ (453.12): C, 47.64; H, 6.66; N, 3.09%. Found: C, 47.90; H, 6.47; N, 3.26%. ESI-MS: $[M + H]^+$ 454.30.

***trans*-2-[1-(Diethoxyphosphorylamino)cyclopentyl]-4-(*p*-chlorophenyl)-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4f):** White solid. mp 168–170 °C. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 29.67 (d, $^3J_{PP} = 15.2$ Hz), 5.06 (d, $^3J_{PP} = 15.2$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.33–7.23 (m, 4H, Ph), 5.46 (s, 1H, 4-H), 4.49 (d, $^2J_{H,H'} = 11.1$ Hz, 1H, 6-H), 4.11 (m, 4H, $2OCH_2CH_3$), 3.80 (dd, $^2J_{H,H'} = 11.1$ Hz, $^3J_{P,H} = 21.2$ Hz, 1H, 6-H), 3.15 (d, 1H, $^2J_{P,H} = 7.9$ Hz, NH), 2.22–1.79 (m, 8H, $4CH_2$), 1.28 (m, 6H, $2OCH_2CH_3$), 1.00 (s, 3H, 5-C-CH_3), 0.76 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 75 MHz, $CDCl_3$): 134.46 (d, $^3J_{P,C} = 8.3$ Hz), 134.17, 128.71, 127.96 (Ph), 82.96 (d, $^2J_{P,C} = 5.6$ Hz, 4-C), 74.89 (d, $^2J_{P,C} = 5.3$ Hz, 6-C), 62.66 (d, $^2J_{P,C} = 3.0$ Hz, $2OCH_2CH_3$), 60.44 (d, $^1J_{P,C} = 159.4$ Hz, α-C), 36.77 (5-C), 35.23 ($2CH_2$), 24.15 (d, $^3J_{P,C} = 4.5$ Hz, α-C-CH_2), 24.08 (d, $^3J_{P,C} = 5.9$ Hz, α-C-CH_2), 21.59 (5-C-CH_3), 17.54 (5-C-CH_3), 16.06 (d, $^2J_{P,C} = 6.8$ Hz, $2OCH_2CH_3$); Elemental analysis calculated (%) for $C_{20}H_{32}ClNO_6P_2$ (479.14): C, 50.06; H, 6.72; N, 2.92%. Found: C, 50.09; H, 6.89; N, 2.91%. ESI-MS: $[M + H]^+$ 480.14.

***trans*-2-[1-(Diethoxyphosphorylamino)cyclohexyl]-4-(*p*-chlorophenyl)-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4g):** White solid. mp 212–214 °C. ^{31}P NMR (δ, 121 MHz, $CDCl_3$): 27.65 (d, $^3J_{PP} = 9.3$ Hz), 4.67 (d, $^3J_{PP} = 9.3$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.33–7.25 (m, 4H, Ph), 5.45 (s, 1H, 4-H), 4.47 (d, $^2J_{H,H'} = 11.3$ Hz, 1H, 6-H), 4.01 (m, 4H, $2OCH_2CH_3$), 3.80 (dd, $^2J_{H,H'} = 11.3$ Hz, $^3J_{P,H} = 21.3$ Hz, 1H, 6-H), 2.64 (d, $^2J_{P,H} = 5.7$ Hz, 1H, NH), 2.41–1.33 (m, 10H, $5CH_2$), 1.28 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.12 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 0.97 (s, 3H, 5-C-CH_3), 0.76 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 134.76 (d, $^3J_{P,C} = 8.4$ Hz), 134.37, 129.03, 128.23 (Ph), 83.17 (d, $^2J_{P,C} = 6.1$ Hz, 4-C), 75.14 (d, $^2J_{P,C} = 6.6$ Hz, 6-C), 62.84 (d, $^2J_{P,C} = 5.5$ Hz, $2OCH_2CH_3$), 55.25 (d, $^1J_{P,C} = 154.9$ Hz, α-C), 36.96 (d, $^3J_{P,C} = 2.4$ Hz, 5-C), 31.94 (d, $^3J_{PC} = 5.0$ Hz, CH_2), 31.03 (CH_2), 25.37 (CH_2), 21.85 (5-C-CH_3), 20.72 (d, $^3J_{P,C} = 9.3$ Hz, α-C-CH_2), 20.51 (d, $^3J_{P,C} = 9.5$ Hz, α-C-CH_2), 17.70 (5-C-CH_3), 16.38 (d, $^2J_{P,C} = 7.4$ Hz, OCH_2CH_3), 16.16 (d, $^2J_{P,C} = 7.6$ Hz, OCH_2CH_3); Elemental analysis calculated (%) for $C_{21}H_{34}ClNO_6P_2$ (493.15): C, 51.07; H, 6.94; N, 2.84%. Found: C, 51.42; H, 7.03; N, 2.96%. ESI-MS: $[M + H]^+$ 494.39.

***trans*-2-[1-(Diethoxyphosphorylamino)cycloheptyl]-4-(*p*-chlorophenyl)-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4h):** White solid. mp 163–165 °C. ^{31}P NMR (δ, 121 MHz, $CDCl_3$): 29.96 (d, $^3J_{PP} = 17.2$ Hz), 4.99 (d, $^3J_{PP} = 17.2$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.32–7.24 (m, 4H, Ph), 5.51 (s, 1H, 4-H), 4.52 (d, $^2J_{H,H'} = 10.0$ Hz, 1H, 6-H), 4.10 (m, 4H, $2OCH_2CH_3$), 3.80 (dd, $^2J_{H,H'} = 10.0$ Hz, $^3J_{P,H} = 21.2$ Hz, 1H, 6-H), 3.06 (d, $^2J_{P,H} = 5.7$ Hz, 1H, NH), 2.26–0.82 (m, 12H, $6CH_2$), 1.25 (m, 6H, $2OCH_2CH_3$), 0.99 (s, 3H, 5-C-CH_3), 0.76 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 75 MHz, $CDCl_3$): 134.52 (d, $^3J_{P,C} = 8.1$ Hz), 134.26, 128.79, 128.06 (Ph), 83.15 (d, $^2J_{P,C} = 6.2$ Hz, 4-C), 74.98 (d, $^2J_{P,C} = 6.6$ Hz, 6-C), 62.77 (d, $^2J_{P,C} = 5.5$ Hz, $2OCH_2CH_3$), 58.15 (d, $^1J_{P,C} = 149.3$ Hz, α-C), 36.80 (d, $^3J_{P,C} = 2.8$ Hz, 5-C), 34.64 (CH_2), 34.47 (CH_2), 30.62 (CH_2), 30.53 (CH_2), 22.30 (d, $^3J_{P,C} = 6.2$ Hz, α-C-CH_2), 22.20 (d, $^3J_{P,C} = 5.8$ Hz, α-C-CH_2), 21.63 (5-C-CH_3), 17.51 (5-C-CH_3), 16.15 (d, $^2J_{P,C} = 7.4$ Hz, OCH_2CH_3), 16.05 (d, $^2J_{P,C} = 7.5$ Hz, OCH_2CH_3); Elemental analysis calculated (%) for $C_{22}H_{36}ClNO_6P_2$ (507.17): C, 52.02; H, 7.14; N, 2.76%. Found: C, 52.30; H, 7.23; N, 2.86%. ESI-MS: $[M + H]^+$ 508.29.

***trans*-2-[1-(Diethoxyphosphorylamino)(phenyl)methyl]-4-(*p*-chlorophenyl)-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4i):** One diastereoisomer: White solid. mp 237–239 °C. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 22.56 (d, $^3J_{PP} = 38.0$ Hz), 7.53 (d, $^3J_{PP} = 38.0$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.47–7.02 (m, 9H, Ph), 5.36 (s, 1H, 4-H), 4.74 (m, 1H, α-C-H), 4.42 (d, $^2J_{H,H'} = 11.0$ Hz, 1H, 6-H), 4.10–3.66 (m, 6H, $2OCH_2CH_3$ + 6-H + NH), 1.26 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.04 (t, $J =$

7.1 Hz, 3H, OCH_2CH_3), 0.75 (s, 3H, 5-C-CH_3), 0.72 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 138.94, 136.29, 134.49, 134.39, 128.75, 128.56, 128.19, 128.03 (d, $J_{P,C} = 5.8$ Hz, Ph), 83.95 (d, $^2J_{P,C} = 5.9$ Hz, 4-C), 75.64 (d, $^2J_{P,C} = 6.2$ Hz, 6-C), 62.84 (d, $^2J_{P,C} = 5.2$ Hz, OCH_2CH_3), 62.77 (d, $^2J_{P,C} = 5.0$ Hz, OCH_2CH_3), 53.34 (d, $^1J_{P,C} = 152.3$ Hz, α-C), 36.67 (5-C), 21.70 (5-C-CH_3), 17.36 (5-C-CH_3), 16.30 (d, $^3J_{P,C} = 7.5$ Hz, OCH_2CH_3), 15.97 (d, $^3J_{P,C} = 7.6$ Hz, OCH_2CH_3).

Other diastereoisomer: White solid. mp 204–206 °C. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 21.70 (d, $^3J_{PP} = 36.4$ Hz), 7.59 (d, $^3J_{PP} = 36.4$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.47–7.13 (m, 9H, Ph), 5.40 (s, 1H, 4-H), 4.79 (m, 1H, α-C-H), 4.40 (d, $^2J_{H,H'} = 11.2$ Hz, 1H, 6-H), 4.03–3.66 (m, 6H, $2OCH_2CH_3$ + 6-H + NH), 1.24 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 1.00 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 0.78 (s, 3H, 5-C-CH_3), 0.72 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 75 MHz, $CDCl_3$): 135.97, 134.44, 134.30, 134.19, 128.64 (d, $J_{P,C} = 5.2$ Hz), 128.48, 128.07, 127.93 (d, $J_{P,C} = 6.1$ Hz, Ph), 83.98 (d, $^2J_{P,C} = 5.9$ Hz, 4-C), 75.50 (d, $^2J_{P,C} = 6.3$ Hz, 6-C), 62.62 (d, $^2J_{P,C} = 4.7$ Hz, $2OCH_2CH_3$), 53.31 (d, $^1J_{P,C} = 154.9$ Hz, α-C), 36.54 (d, $^3J_{PC} = 2.9$ Hz, 5-C), 21.46 (5-C-CH_3), 17.26 (5-C-CH_3), 16.05 (d, $^3J_{P,C} = 7.4$ Hz, OCH_2CH_3), 15.76 (d, $^3J_{P,C} = 7.5$ Hz, OCH_2CH_3). Elemental analysis calculated (%) for $C_{22}H_{30}ClNO_6P_2$ (501.12): C, 52.65; H, 6.03; N, 2.79%. Found: C, 52.70; H, 6.05; N, 2.89%. ESI-MS: $[M + H]^+$ 502.26.

***trans*-2-[1-(Diethoxyphosphorylamino)(*p*-methylphenyl)-methyl]-4-(*p*-chlorophenyl)-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4j):** One diastereoisomer: White solid. mp 199–201 °C. ^{31}P NMR (δ, 162 MHz, $CDCl_3$): 21.90 (d, $^3J_{PP} = 36.2$ Hz), 7.64 (d, $^3J_{PP} = 36.2$ Hz); ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 7.35–7.16 (m, 8H, Ph), 5.40 (s, 1H, 4-H), 4.77 (m, 1H, α-C-H), 4.40 (d, $^2J_{H,H'} = 11.3$ Hz, 1H, 6-H), 4.03–3.68 (m, 6H, $2OCH_2CH_3$ + 6-H + NH), 2.34 (s, 3H, Ph-CH_3), 1.24 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.02 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 0.83 (s, 3H, 5-C-CH_3), 0.73 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 129.54, 128.90, 128.26, 127.98 (d, $J_{P,C} = 6.5$ Hz, Ph), 84.12 (d, $^2J_{P,C} = 6.9$ Hz, 4-C), 75.71 (d, $^2J_{P,C} = 6.1$ Hz, 6-C), 62.83 (d, $^2J_{P,C} = 4.8$ Hz, OCH_2CH_3), 62.78 (d, $^2J_{P,C} = 4.5$ Hz, OCH_2CH_3), 53.20 (d, $^1J_{P,C} = 156.4$ Hz, α-C), 36.72 (5-C), 21.64 (5-C-CH_3), 21.36 (Ph-CH_3), 17.51 (5-C-CH_3), 16.23 (d, $^3J_{P,C} = 7.4$ Hz, OCH_2CH_3), 15.97 (d, $^3J_{P,C} = 7.3$ Hz, OCH_2CH_3); Elemental analysis calculated (%) for $C_{23}H_{32}ClNO_6P_2$ (515.14): C, 53.55; H, 6.25; N, 2.71%. Found: C, 52.70; H, 6.05; N, 2.89%. ESI-MS: $[M + H]^+$ 516.26.

***trans*-2-[1-(Diethoxyphosphorylamino)cyclopentyl]-4-(*p*-bromophenyl)-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4k):** White solid. mp 149–151 °C. ^{31}P NMR (δ, 121 MHz, $CDCl_3$): 39.70 (d, $^3J_{PP} = 18.2$ Hz), 4.86 (d, $^3J_{PP} = 18.2$ Hz); ^{1}H NMR (δ, 300 MHz, $CDCl_3$): 7.55–7.18 (m, 4H, Ph), 5.48 (s, 1H, 4-H), 4.53 (d, $^2J_{H,H'} = 10.5$ Hz, 1H, 6-H), 4.10 (m, 4H, $2OCH_2CH_3$), 3.84 (dd, $^2J_{H,H'} = 10.5$ Hz, $^3J_{P,H} = 21.3$ Hz, 1H, 6-H), 3.00 (br, 1H, NH), 2.27–1.82 (m, 8H, $4CH_2$), 1.31 (m, 6H, $2OCH_2CH_3$), 1.03 (s, 3H, 5-C-CH_3), 0.78 (s, 3H, 5-C-CH_3); ^{13}C NMR (δ, 75 MHz, $CDCl_3$): 135.04 (d, $^3J_{P,C} = 8.4$ Hz), 130.99, 129.08, 122.43 (Ph), 83.05 (d, $^2J_{P,C} = 5.7$ Hz, 4-C), 74.94 (d, $^2J_{P,C} = 6.2$ Hz, 6-C), 62.73 (d, $^2J_{P,C} = 3.9$ Hz, OCH_2CH_3), 62.66 (d, $^2J_{P,C} = 3.9$ Hz, OCH_2CH_3), 60.51 (d, $^1J_{P,C} = 159.5$ Hz, α-C), 36.70 (d, $^3J_{P,C} = 2.7$ Hz, 5-C), 35.28 ($2CH_2$), 24.24 (d, $^3J_{P,C} = 5.2$ Hz, α-C-CH_2), 24.09 (d, $^3J_{P,C} = 5.2$ Hz, α-C-CH_2), 21.63 (5-C-CH_3), 17.60 (5-C-CH_3), 16.14 (d, $^2J_{P,C} = 6.8$ Hz, OCH_2CH_3), 16.05 (d, $^2J_{P,C} = 6.8$ Hz, OCH_2CH_3); Elemental analysis calculated (%) for $C_{20}H_{32}BrNO_6P_2$ (523.09): C, 45.81; H, 6.15; N, 2.67%. Found: C, 45.85; H, 6.34; N, 2.82%. ESI-MS: $[M + H]^+$ 524.21.

***trans*-2-[1-(Diethoxyphosphorylamino)cyclohexyl]-4-(*p*-bromophenyl)-5,5-dimethyl-1,3,2λ^5-dioxaphosphorinane-2-oxide (4l):** White solid. mp 210–212 °C. ^{31}P NMR (δ, 121 MHz, $CDCl_3$): 27.67 (d, $^3J_{PP} = 8.8$ Hz), 4.71 (d, $^3J_{PP} = 8.8$ Hz); ^{1}H NMR (δ, 300 MHz, $CDCl_3$): 7.32–7.21 (m, 4H, Ph), 5.46 (s, 1H, 4-H), 4.49 (d, $^2J_{H,H'} = 10.7$ Hz, 1H, 6-H), 4.04 (m, 4H, $2OCH_2CH_3$), 3.82 (dd, $^2J_{H,H'} = 11.2$ Hz, $^3J_{P,H} = 21.3$ Hz, 1H, 6-H), 2.80 (d, $^2J_{P,H} = 5.3$ Hz, 1H, NH), 2.39–1.38 (m, 10H, $5CH_2$), 1.30 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 1.15 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 1.00 (s, 3H, 5-C-CH_3), 0.78 (s, 3H, 5-C-CH_3); Elemental analysis calculated (%) for $C_{21}H_{34}BrNO_6P_2$ (537.10): C, 46.85; H, 6.37; N, 2.60%. Found: C, 46.97; H, 6.40; N, 2.87%. ESI-MS: $[M + H]^+$ 538.30.

X-ray Crystal Structure. Crystallographic data for the structural analysis of compound **4f** and **4k** have been deposited at the Cambridge Crystallographic Data Centre as Nos. CCDC 635315 and 627130 respectively. These data can be obtained free of charge by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk; or http://www.ccdc.cam.ac.uk/conts/retrieving.html.

We thank the Committee of Science and Technology of Tianjin (07JCZDJC04800) and Nankai University (J02044 to Z. W. Miao) for financial support.

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