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SYNTHESIS OF 2-ANILINO-2,4,4,6,6-PENTACHLOROCYCLOTRIPHOSPHAZENES ($N_3P_3Cl_5(NAr(R))$)

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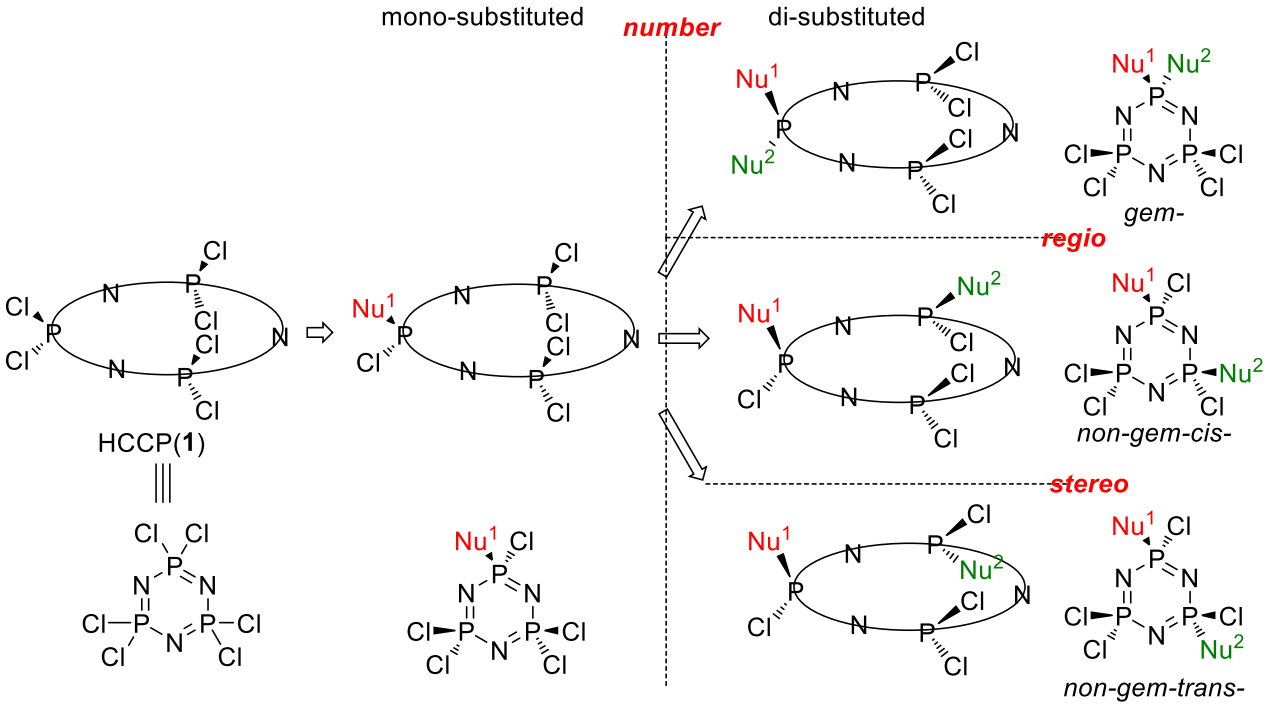
Abstract – Hexachlorocyclotriphosphazene (HCCP, $N_3P_3Cl_6$, **1**) was treated with anilines in THF at 0 ºC to give a corresponding mono-substituted 2-anilino-2,4,4,6,6-pentachlorocyclotriphosphazenes ($N_3P_3Cl_5(NAr(R))$, **2**) in good to moderate yield. Multi-substituted products $N_3P_3Cl_{6-n}(NAr(R))_n$ ($n \geq 2$)) were not detected in ^{31}P NMR spectra of the reaction mixture.

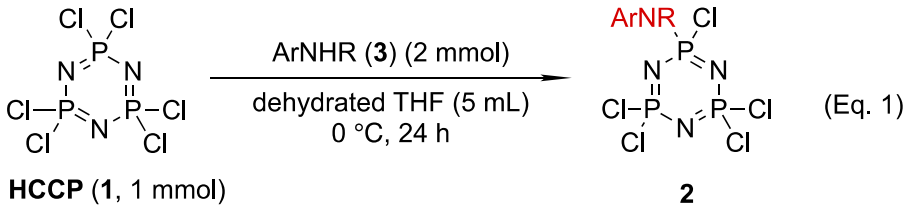
Hexachlorocyclotriphosphazene (HCCP), $N_3P_3Cl_6$ (**1**), has a six-membered ring containing three N atoms and three P atoms connecting alternately, and each P atom has two Cl atoms upper-side and lower-side of the ring.[1] Though HCCP is a stable compound, its Cl-P bond is easily substituted with several nucleophiles to give a variety of cyclotriphosphazene derivatives.[2] Multi-functionalized materials based on HCCP can be easily prepared when multi-types of nucleophiles are introduced into HCCP. However, to synthesize functionalized cyclotriphosphazenes as designed, number of the nucleophiles, regio-(*gem*/*non-gem*) and stereo-chemistry (*cis*/*trans*) should be controlled (Scheme 1).

The number, regio-, and stereo-chemistry of the introduced substituents vary and depend on the substituent and the reaction conditions. We reported that HCCP reacts with NH_3 (excess) to give 2,2-diamino-4,4,6,6-tetrachlorocyclotriphosphazene (*gem*-$N_3P_3Cl_4(NH_2)_2$) in Et_2O and 2,2,4,4-tetraamino-6,6-dichlorocyclotriphosphazene (*gem*-$N_3P_3Cl_2(NH_2)_4$) in MeCN, respectively.[3] We also reported 2,2-bis(arylthio)-4,4,6,6-tetrachlorocyclotriphosphazene (*gem*-$N_3P_3Cl_4(SAr)_2$) and 2,2,4,4-tetrakis(arylthio)-6,6-dichlorocyclotriphosphazene (*gem*-$N_3P_3Cl_2(SAr)_4$) were prepared with 2 and 4 equiv. of ArSH/NEt_3 in MeCN.[4] In these cases, neither mono-, tri-, and penta-substituted derivatives nor *non-gem*-di-substituted products were detected. Recently, we found 2-phenoxy-2,4,4,6,6-pentachlorocyclotriphsophazene $N_3P_3Cl_5(OAr)$ can be prepared in the reaction with ArOLi (excess) in THF at -40 ºC.[5]



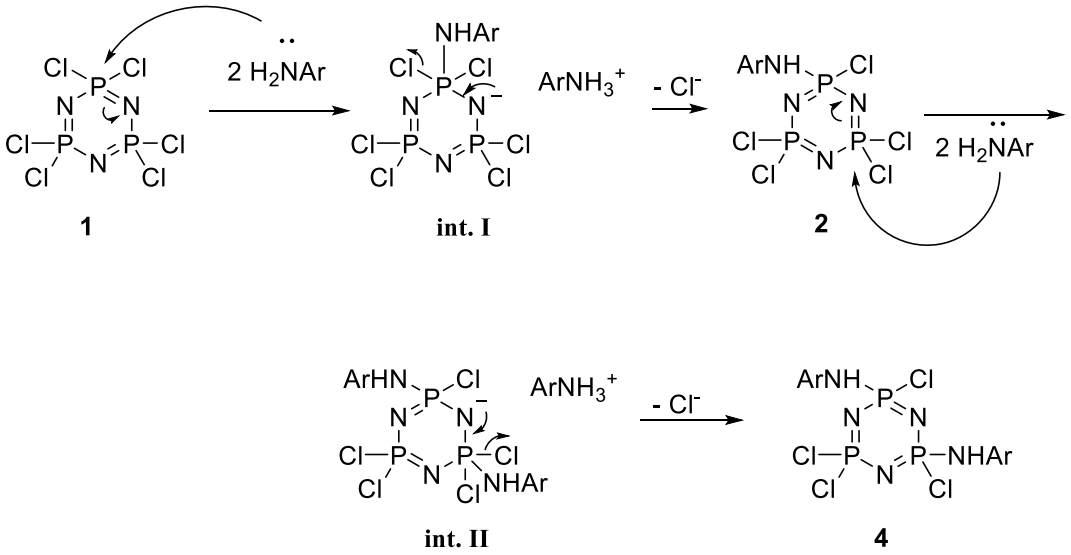
Scheme 1

In this paper, we report mono-substituted 2-anilino-2,4,4,6,6-pentachlorocyclotriphosphazenes ($N_3P_3Cl_5$(NAr(R)), **2**) was synthesized from **1** and anilines **3** (Eq. 1). Though several reports about reaction between HCCP and aniline have been published,[6-9] they mainly dealt with a distribution of the reaction mixture and/or kinetic study to reveal reaction mechanism, and optimization of the reaction conditions to obtain 2 was not reported.



Firstly, the solvent was optimized (Table 1). A typical procedure is as follows. To a THF (5 mL) solution of *p*-toluidine (**3a**, 2 mmol) was added HCCP (**1**, 1 mmol) at 0 ºC, and the mixture was stirred for 6 h at the same temperature. An aliquot of the reaction mixture was analyzed by ^{31}P NMR[10] to determine the products and their ratio to find that **2a** was obtained as a sole product (Entry 1). After 24 h, only **2a** and no di-substituted products were detected. When acetone (Entry 4), EtOAc (Entry 5), Et_2O (Entry 6), CH_2Cl_2 (Entry 7), and toluene (Entry 8) (medium and/or non polar solvents) were used as a solvent, the amination proceeded slowly and a mixture of **1** and **2a** was obtained. On the other hand, a mixture of **2a**

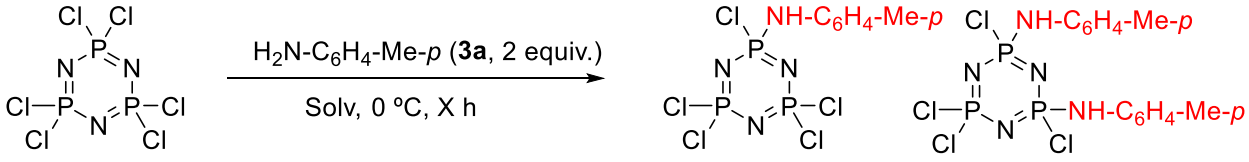
and *non-gem*-di-substituted **4a** was obtained in MeCN (Entry 3, *cis/trans* mixture), and a complex mixture of unidentified products was obtained in DMF (Entry 2) (highly polar solvents).[11] This reaction might proceed an addition/elimination mechanism, and polar solvents would stabilize an ionic intermediate **I** and **II** (Scheme 2).



Scheme 2

Next, the reaction temperature was examined in THF (Table 2). When the reaction was carried out at 0 ºC, mono-substituted product **2a** was obtained quantitatively after 6 h, and no di-substituted and/or other multi-substituted products were detected even after 96 h (Entry 3). When the reaction was carried out at lower temperature such as -40 and -20 ºC, a mixture of **1** and **2a** (52/48 after 72 h and 88/12 after 48 h, respectively) was obtained (Entries 1, 2), whereas *non-gem*-disubstituted products (*cis*/*trans* mixture) were detected (**2a**/**4a** = 85/15) at 25 ºC after 24 h (Entry 4). Therefore, reaction should be carried out at 0 ºC to obtain mono-substituted product **2a** selectively and efficiently.

Table 1. Solvent effect



1 **2a** **4a** (*cis/trans*)

Entry	Solv	time (h)	Ratio of phosphazenes[a]		
			2a (%)	**4a** (%)	**1** (%)
1	THF	6	100	0	0
		24	100	0	0
2	DMF[b]	6	0	0	0
		24	0	0	0
3	MeCN	6	82	18	0
		24	83	17	0
4	$Me_2C(=O)$	6	86	0	14
		24	93	0	7
5	EtOAc	6	60	0	40
		24	79	0	21
6	Et_2O	6	8	0	92
		24	36	0	68
7	CH_2Cl_2	6	9	0	91
		24	17	0	83
8	toluene	6	6	0	94
		24	11	0	89

[a]Determined by ^{31}P NMR of the reaction mixture. [b]Complex mixture of unidentified products was obtained.

Table 2. Effect of reaction temperature[a]

Entry	temp (ºC)	time (h)	Ratio of phosphazenes[b]		
			2a (%)	**4a** (%)	**1** (%)
1	-40	1	28	0	72
	-40	72	52	0	48
2	-20	1	21	0	79
	-20	48	88	0	12
3	0	1	68	0	32
	0	6	100	0	0
	0	96	100	0	0
4	25	24	85	15	0

[a]THF was used as a solvent. [b]Determined by ^{31}P NMR of the reaction mixture.

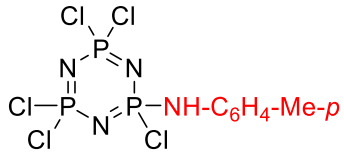
The amount of aniline was also optimized (Table 3). When 1.2 equiv. of **3a** was used in THF, a mixture of mono-substituted **2a** and HCCP (**1**) (63/37) was obtained (Entry 1), whereas **2a** was a sole product when

2 equiv. of **3a** was used (Entry 4). A similar mixture of **2a** and **1** (58/42) was obtained with 1 equiv. of **3a** together with 1 equiv. of pyridine (Entry 2). These phenomena suggested that **3a** plays both as a nucleophile and as a base. On the other hand, *non-gem*-di-substituted products **4a** were also obtained as a side product with 4 and/or 6 equiv. of **3a** (Entries 4,5). It is noteworthy that *gem*-di-substituted product **5a** was obtained in 12% as a ratio with **3a** (1 equiv.)/NEt_3 (1 equiv.), whereas **4a** was not detected (Entry 3).[6] In nucleophilic substitution of mono-substituted HCCP, the small second nucleophiles are introduced at *gem*-position of the first nucleophile, whereas sterically hindered nucleophiles are introduced at *non-gem*-position (Scheme 3).[12] In the absence of NEt_3, the second $ArNH_2$ would be introduced directly to mono-substituted HCCP at *non-gem*-position of the first ArNH. Meanwhile, elimination of HCl would occur with NEt_3 to give intermediate **III** which would give *gem*-disubstituted product **5a** (Scheme 4). Pyridine would not strong enough to eliminate HCl, and the second $ArNH_2$ would be introduced via five-coordinate intermediate.[7]

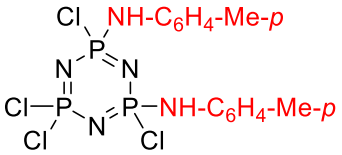
Table 3. Amount of aniline **3a**

Entry	**3a** (equiv.)	time (h)	Ratio of phosphazenes[a]			
			2a	**4a**	**5a**	**1**
1	1.2	24	63	0	0	37
2	1[b]	24	58	0	0	42
3	1[c]	24	59	0[d]	12	29
4	2	1	68	0	0	32
		6	100	0	0	0
		96	100	0	0	0
5	4	6	91	9	0	0
		24	75	25	0	0
6	6	6	84	16	0	0
		24	57	43	0	0

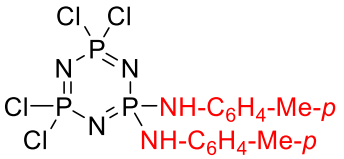
[a]Determined by ^{31}P NMR of the reaction mixture.
[b]In the presence of py (1 equiv.).
[c]In the presence of NEt_3 (1 equiv.).



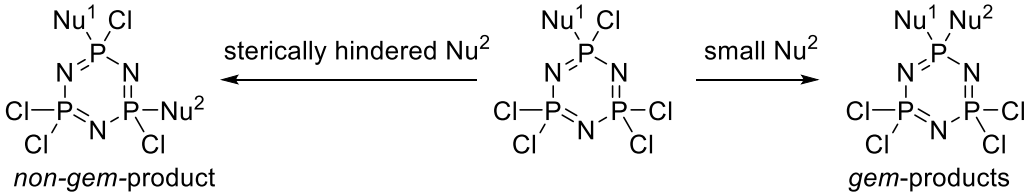
2a



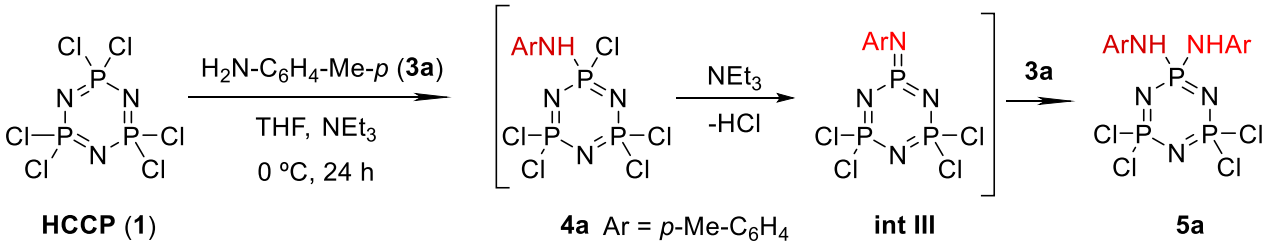
4a (*cis/trans*)



5a



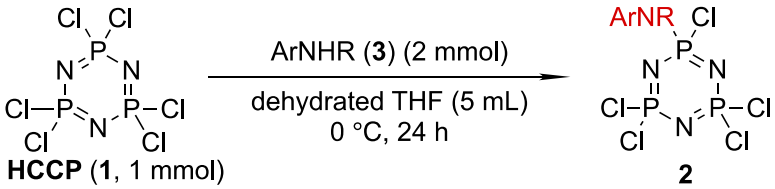
Scheme 3[7]



Scheme 4[7]

Scope and limitation of the reaction was examined (Table 4). The desired mono-substituted products **2** were obtained in good yield with anilines having an electron-donating group such as 4-MeO, 4-Me, and 3-MeO (Entries 1-3), whereas the reaction did not proceed with anilines having an electron-withdrawing group such as 4-EtOC(=O) and 4-NO_2 (Entries 5, 6). The substitution with *p*-chloroaniline (**3d**) proceeded slowly to give a mixture of **2d** and **1**. The substitution also did not proceed with secondary anilines (Entries 7, 8), probably due to their steric hindrance. Reaction of **1** under the same conditions with a primary aliphatic amine ($PrNH_2$) gave a complex mixture of unidentified products, whereas no reaction occurred with a secondary aliphatic amine (BuNHMe).

Table 4. Scope and limitation of the substitution reaction of **1** with anilines



Entry	aniline		pK_a of ArN^+H_2R	Ratio of phosphazenes/%[a]		Isolated yield of **2**/%
				2	**1**	
1	4-MeO	**3b**	5.21	100	trace	84
2	4-Me	**3a**	5.04	100	trace	85
3	3-MeO	**3c**	4.17	100	n.d.[b]	82
4	4-Cl[c,d]	**3d**	3.97	43	57	38
5	4-EtOC(=O)	**3e**	2.51	n.d.[b,e]	100	0
6	4-NO_2	**3f**	1.01	n.d.[b]	100	0
7	*N*-Me	**3g**	4.70	n.d.[b]	100	0
8	*N*-Me-4-Cl	**3h**	4.08	n.d.[b, f]	100	0

[a]Determined by ^{31}P NMR of the reaction mixture. [b]Not detected. [c]After 48, 72, and 96 h, **2e**:**1**=52/48, 58/42, and 65/35, respectively. [d]After 24 h at 24 °C, a mixture of **2e** and **1** (63/37) was obtained with a small ammount of unidentified by-products. [e]After the reaction was carried out at 24 °C for 24 h, most of **1** was remained unchanged, and trace amount of **2e** was detected in ^{31}P NMR. [f]**1** was remained unchanged at 25 °C for 24 h.

In conclusion, anilines were allowed to react with HCCP in THF at 0 ºC to give mono-substituted 2-anilino-2,4,4,6,6-pentachlorocyclotriphosphazene **2**. Electron-rich primary anilines gave the corresponding **2** in good to moderate yield, whereas electron-poor anilines and secondary anilines did not afford **2**. Primary aliphatic amine gave a complex mixture, and the substitution did not proceed with a secondary aliphatic amine. An addition-elimination mechanism was proposed.

EXPRIMENTAL

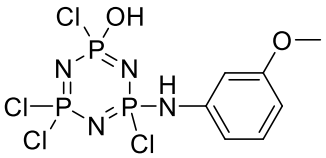
NMR was measured on JEOL ECS 400 (^{1}H, 400 MHz, ^{13}C: 100 MHz, and ^{31}P: 166 MHz) in $CDCl_3$.

To a THF (5 mL) solution of *p*-toluidine (220 mg, 2.05 mmol) was added HCCP (344 mg, 1.00 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 24 h. The mixture was poured into aq. sat. K_2CO_3, and extracted with AcOEt (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Hexane:AcOEt = 10:1) to afford 2-(4-methylanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (**2a**, 355 mg, 0.85 mmol, 85%).

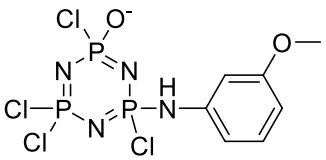
2-(4-Methylanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (2a)[6] ^{1}H NMR δ 2.32 (s, 3H), 5.98 (d, *J* = 10.8 Hz, 1H), 7.15-7.06 (m, 4H); ^{13}C NMR δ 20.93, 121.26 (d, *J* = 7.7 Hz), 130.21, 133.94, 134.64; ^{31}P NMR δ 12.50 (t, *J* = 48.3 Hz, 1P), 21.36 (d, *J* = 48.3 Hz, 2P).

2-(4-Methoxyanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (2b)[6,8] ^{1}H NMR δ 3.79 (s, 3H), 5.87 (d, *J* = 10.8 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H)); ^{13}C NMR δ 55.60, 114.85, 124.40 (d, *J* = 6.7 Hz), 128.86, 157.50; ^{31}P NMR δ 13.26 (t, *J* = 47.1 Hz, 1P), 21.39 (d, *J* = 47.1 Hz, 2P).

2-(3-Methoxyanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (2c) ^{1}H NMR δ 3.80 (s, 3H), 5.87 (d, *J* = 10.8 Hz, 1H), 6.67-6.76 (m, 3H), 7.23 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR δ 55.46, 106.66 (d, *J* = 7.7 Hz), 109.87, 112.84 (d, *J* = 8.6 Hz), 130.45, 138.05, 160.54; ^{31}P NMR δ 12.10 (dd, *J* = 49.5, 49.5 Hz, 1P), 21.87 (d, *J* = 49.5 Hz, 2P), ESI-MS During the analysis, **2c** was partially hydrolyzed to give **6c**, which ionized by deprotonation to give **6c'**. This partial hydrolysis/deprotonation is usually observed in ESI-MS of chlorophosphazenes:[5] Calcd for $C_7H_8Cl_4N_4O_2P_3$- 412.8620, Found . 412.8584.



6c



6c'

2-(4-Chloroanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (2d)[9] ^{1}H NMR δ 5.77 (d, *J* = 9.6 Hz, 1H), 7.08-7.16 (m, 2H), 7.26-7.32 (m, 2H); ^{13}C NMR δ 122.07 (d, *J* = 7.7 Hz), 129.74, 130.18, 135.37; ^{31}P NMR δ 12.26 (t, *J* = 49.5 Hz, 1P), 21.92 (d, *J* = 49.5 Hz, 2P).

2,2-Bis(4-methylanilino)-4,4,6,6-tetrachlorocyclotriphosphazene (5a)[6] ^{31}P NMR δ -1.6 (t, *J* = 48.5 Hz, 1P), 21.8 (d, *J* = 48.5 Hz, 2P).

***cis*-2,4-Bis(4-methylanilino)-2,4,6,6-tetrachlorocyclotriphosphazene (4a-*cis*)**[6] ^{31}P NMR δ 14.0 (d, *J* = 49.6 Hz, 2P), 22.5 (t, *J* = 49.6 Hz, 1P).

***trans*-2,4-Bis(4-methylanilino)-2,4,6,6-tetrachlorocyclotriphosphazene (4a-*trans*)**[6] ^{31}P NMR δ 13.9 (d, *J* = 49.6 Hz, 2P), 22.3 (t, *J* = 49.6 Hz, 1P).

ACKNOWLEDGEMENT

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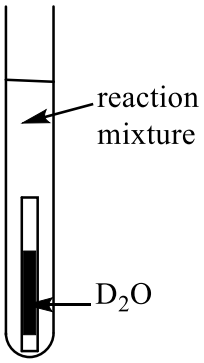
10. ^{31}P NMR analysis of the reaction mixture was one as follows. An aliquat (*ca*. 0.5 mL) of the reaction mixture was put into an NMR tube together with a capillary containing D_2O as an internal lock solvent. NMR spectra was measured at room temperature (ca. 24 ºC).



11. HCCP was decomposed in DMF swiftly even during ^{31}P NMR analysis (*ca*. 20 min) and only spectrum of a complex mixture of unidentified products was obtained.
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