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SELECTIVE SYNTHESIS OF CYCLIC PHOSPHORIC ACID DIESTERS THROUGH OXORHENIUM(VII)-CATALYZED DEHYDRATIVE CONDENSATION OF PHOSPHORIC ACID WITH ALCOHOLS

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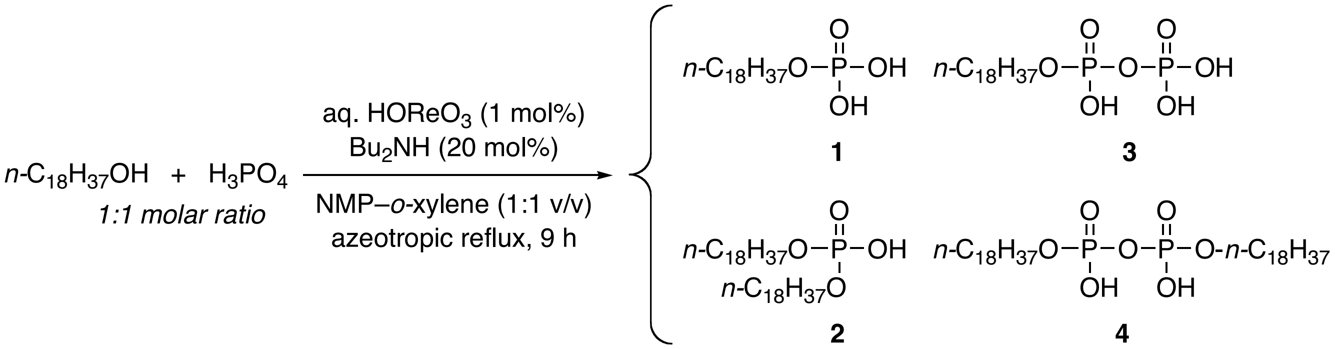
Abstract – The selective synthesis of phosphoric acid diesters has been achieved through the direct catalytic dehydrative condensation of phosphoric acid with two equivalents of alcohols. The present method works especially well for the synthesis of cyclic phosphoric acid diesters. The combination of perrhenic acid and *N*-methylbenzylamine efficiently catalyzes the dehydrative condensation of phosphoric acid with equimolar amounts of diols to give cyclic phosphoric acid diesters in excellent yields.

Many phosphoric acid esters are currently synthesized on an industrial scale and are widely used in everyday life.[1,2] Phosphoric acid diesters are important substances which have been used as liquid ion exchangers for the recovery of several valuable metals from waste liquors.[3] In particular, cyclic phosphoric acid diesters have recently been widely used in the fields of organic synthesis, materials chemistry, and so on. For example, cyclic phosphoric acid diesters of BINOL derivatives are useful chiral Brønsted acid catalysts for asymmetric synthesis.[4] Amphiphilic cyclic phosphoric acid diesters are useful surfactants with biological activities.[5,6] From the perspective of green chemistry, the direct catalytic condensation of phosphoric acid with alcohols is attractive for the synthesis of phosphoric acid esters.[7] Previously, we reported that a catalytic amount of perrhenic acid efficiently promoted the dehydrative condensation of phosphoric acid with equimolar amounts of alcohols in the presence of dibutylamine (20 mol%).[8] This reaction is usually conducted at 175–180 °C under azeotropic reflux conditions, and selectively gives phosphoric acid monoesters in excellent yields (Scheme 1).[9] After intensive studies, we found that yield of phosphoric acid diester **2** increased when the reaction of phosphoric acid with stearyl alcohol (1 equiv) was conducted at a higher reaction temperature (185–190 °C) (^{31}P NMR analysis).[10] These experimental results implied that phosphoric acid diesters may be selectively obtained when the oxorhenium(VII)-catalyzed condensation of phosphoric acid is conducted with 2 equivalents of alcohols under appropriate reaction conditions.



Temperature (°C)	Conv. (%)			
	1	**2**	**3**	**4**
175–180	71	4	10	5
185–190	60	13	12	8

Scheme 1

In oxorhenium(VII)-catalyzed dehydrative condensation, 20 mol% of dibutylamine (Bu_2NH) was used to stabilize the oxorhenium(VII) catalyst under the reaction conditions.[11] Furthermore, in our recent study, we found that tetrakis[tris(dimethylamino)phosphoranilidenamino]phosphonium hydroxide, a strong organic base, also promoted the dehydrative condensation of phosphoric acid.[12] It is conceivable that the appropriate selection of organic bases is key for the selective synthesis of phosphoric acid diesters through the oxorhenium(VII)-catalyzed method. We first examined organic bases suitable for the selective synthesis of phosphoric acid diesters (Table 1). The condensation of phosphoric acid (0.5 mmol) with stearyl alcohol (2 equiv.) was conducted in the presence of perrhenic acid (10 mol%) and an organic amine (40 mol%) in *N*-methyl-2-pyrrolidone (NMP)–*o*-xylene (1:1 v/v, 10 mL) at azeotropic reflux with the removal of water. The reaction gave phosphoric acid diester **2** along with monoester **1** and triester **5**. As a result, **2** was selectively produced when a sterically less hindered secondary amine was used. In particular, *N*-methylcyclohexanemethanamine (*c*-$C_6H_{11}CH_2NHMe$, 82%), *N*-methylbenzylamine (BnNHMe, 79%) and Bu_2NH (76%) gave excellent results (entries 1, 2 and 6). Among these, commercially available BnNHMe and Bu_2NH were the most suitable. Sterically hindered secondary amines such as *N*-methyl-*tert*-butylamine (*t*-BuNHMe) and dibenzylamine (Bn_2NH) gave slightly lower yields of **2** (69 and 65%, entries 7 and 8). Tertiary amines such as tributylamine (Bu_3N)

and *N,N*-dimethylbenzylamine ($BnNMe_2$) also gave **2** in lower yield (63 and 61%, entries 9 and 10). It is conceivable that the weaker interaction between these sterically hindered amines and perrhenic acid decreased the stability of the catalyst. When the reaction was conducted with primary amines such as octylamine (n-$C_8H_{17}NH_2$), the yield of **2** significantly decreased (21%, entry 11). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), a strong organic base, gave a very poor result (9%, entry 12). The strong coordination of DBU to perrhenic acid might significantly decrease the catalytic activity. Therefore, moderate interaction between perrhenic acid and an organic base is a key to stabilizing the catalyst and effectively promoting dehydrative condensation.

The amount of the amine was also optimized under the reaction conditions in the presence of 1 mol% of perrhenic acid. The use of 20–40 mol% of BnNHMe gave similar results (entries 3 and 4). However, the yield of **2** significantly decreased when the reaction was conducted with 10 mol% of BnNHMe due to significant decomposition of the catalyst (entry 5). The use of 1 mol% of perrhenic acid and 20 mol% of BnNHMe was the most suitable for the synthesis of **2**.

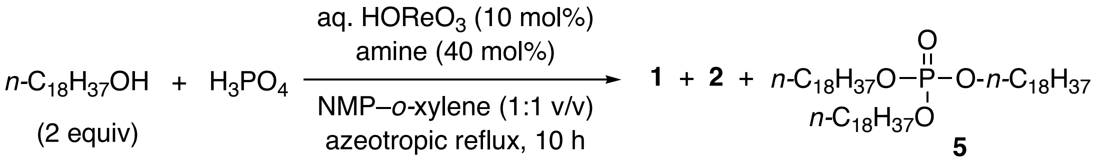


Table 1. Effect of Organic Amines for the Oxorhenium(VII)-Catalyzed Dehydrative Condensation of Phosphoric Acid with Stearyl Alcohol

Entry	Amine	Conv. of **1**:**2**:**5**/%[a]	Entry	Amine	Conv. of **1**:**2**:**5**/%[a]
1	c-$C_6H_{11}CH_2NHMe$	8:82:10	7	*t*-BuNHMe	28:69:0
2	BnNHMe	13:79:8	8	Bn_2NH	31:65:4
3[b]	BnNHMe	10:74:8	9	Bu_3N	22:63:5
4[c]	BnNHMe	17:77:6	10	$BnNMe_2$	22:61:17
5[d]	BnNHMe	38:55:3	11	n-$C_8H_{17}NH_2$	70:21:1
6	Bu_2NH	13:76:8	12	DBU	72:9:0

a) Determined by ^{31}P NMR analysis.

b) The reaction was conducted with aq. $HOReO_3$ (1 mol%) and BnNHMe (40 mol%) for 20 h.

c) The reaction was conducted with aq. $HOReO_3$ (1 mol%) and BnNHMe (20 mol%) for 20 h.

d) The reaction was conducted with aq. $HOReO_3$ (1 mol%) and BnNHMe (10 mol%) for 20 h.

Next, we optimized the concentration of phosphoric acid (Figure 1). The reaction of phosphoric acid (0.5 mmol) with stearyl alcohol (2 equiv) was conducted with perrhenic acid (1 mol%) and BnNHMe (20 mol%) in NMP–*o*-xylene (1:1 v/v) at azeotropic reflux with the removal of water. The yield of **2** increased as the concentration of phosphoric acid decreased in the range of 0.05–0.2 M. A lower concentration effectively may have increased the efficiency of dehydration under azeotropic reflux conditions. However, the reaction with 0.02 M of phosphoric acid gave a rather poor result (black line). The best result was obtained with 0.05 M of phosphoric acid (red line).

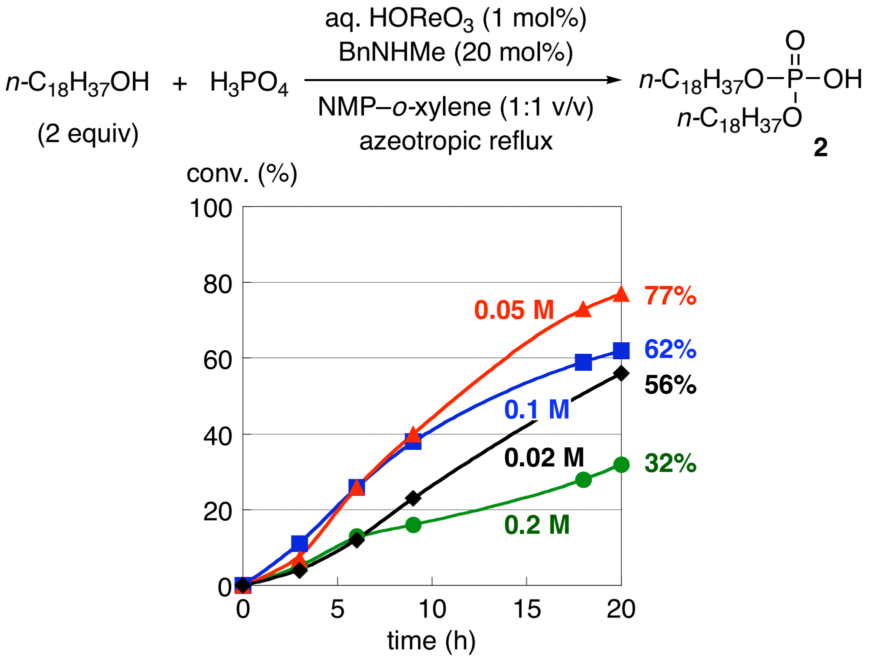


Figure 1. Plot of conversion versus time for the dehydrative condensation of phosphoric acid. Green line: 0.2 M of phosphoric acid; blue line: 0.1 M; red line: 0.05 M; black line: 0.02 M.

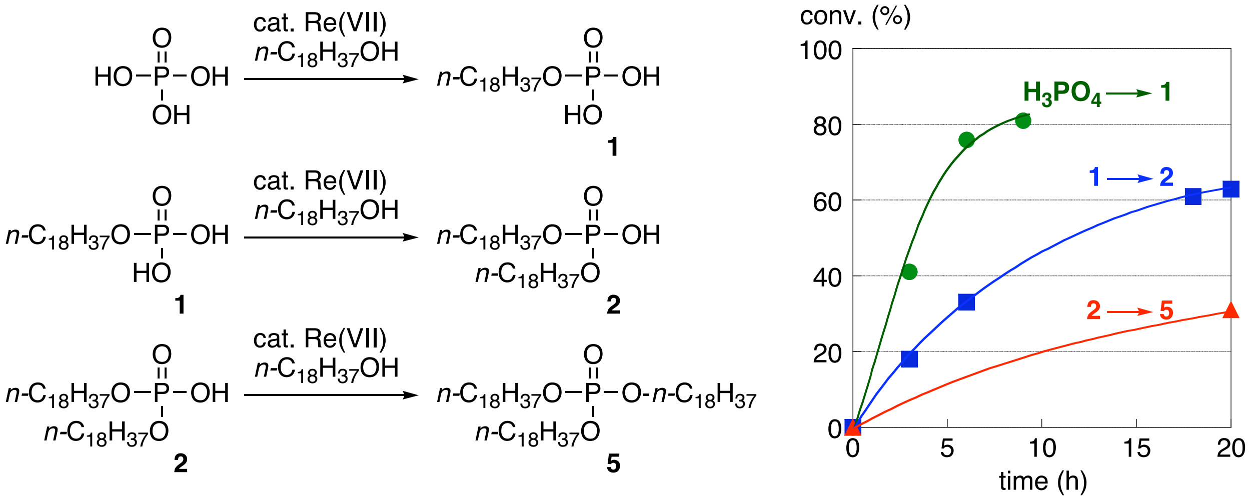


Figure 2. Comparison of the reactivities of phosphoric acids, **1** and **2**. The reaction was conducted with stearyl alcohol (1 equiv) in the presence of aq. $HOReO_3$ (1 mol%) and BnNHMe (20 mol%) in NMP–*o*-xylene (1:1 v/v) at azeotropic reflux with the removal of water.

Under the optimized conditions, the condensation reaction of phosphoric acid with stearyl alcohol (2 equiv) gave phosphoric acid diester **2** (77%) along with monoester **1** (17%) and triester **5** (6%). This selective production of **2** was attributed to the differences between the reactivities of phosphoric acid, **1**, and **2** with stearyl alcohol (1 equiv). These reactivities are compared in Figure 2. The reaction of phosphoric acid with stearyl alcohol proceeded the most rapidly to give **1** (green line). In contrast, the reactivity of phosphoric acid diester **2** was very low (red line).

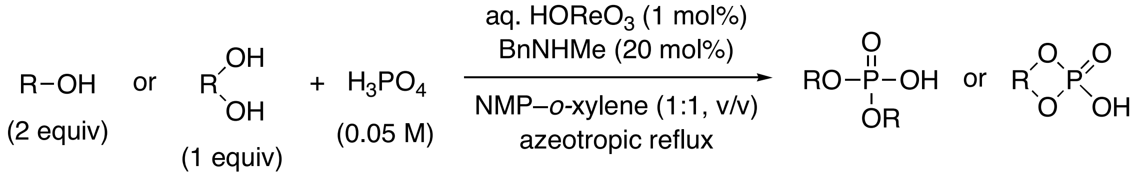
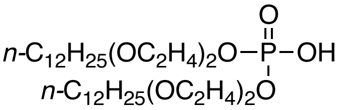
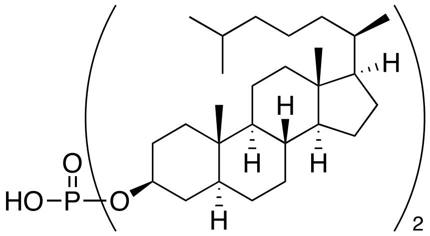
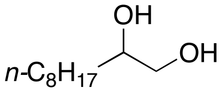
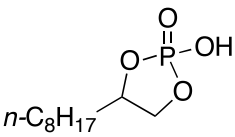
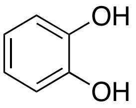
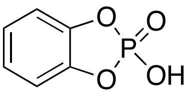
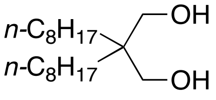
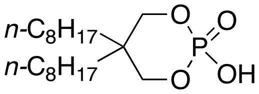
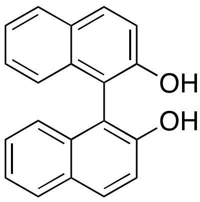
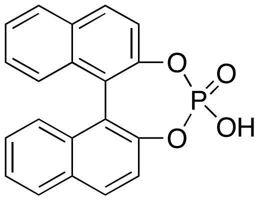


Table 2. Synthesis of Phosphoric Acid Diesters

Entry	Alcohol	Product	Time (h)	Yield (%)[a]
1	$n\text{-}C_{12}H_{25}(OC_2H_4)_2OH$	 $n\text{-}C_{12}H_{25}(OC_2H_4)_2O-\underset{n\text{-}C_{12}H_{25}(OC_2H_4)_2O}{\overset{O}{\overset{\Vert}{P}}}-OH$ **6**	96	72[b]
2	β-cholestanol	 **7**	30	66[b]
3		 **8**	8	>99[c]
4		 **9**	20	>99[b]
5		 **10**	50	93 (100[b])
6[d] 7[d,e]		 **11**	75 48	84 (97[b]) 90[b]

a) Isolated yield.

b) Conversion yield (determined by ^{31}P NMR analysis).

c) Isolated as *N*-methylbenzylammonium salt.[13]

d) The reaction was conducted with 40 mol% of BnNHMe.

e) The reaction was conducted in the presence of 10 mol% of catecol.

With the optimized conditions in hand, we synthesized several phosphoric acid diesters (Table 2). The phosphoric acid diester of diethylene glycol dodecyl ether (**6**)[14] could be obtained in 72% yield, albeit with a prolonged reaction time (entry 1). A secondary alcohol, β-cholestanol, was also converted to the corresponding phosphoric acid diester **7** in 66% yield (entry 2). A prolonged reaction time caused decomposition of the product and the yield of **7** did not increase, although phosphoric acid monoester of β-cholestanol was obtained in an excellent yield without any decomposition.[8] The present reaction conditions worked very well for the synthesis of cyclic phosphoric acid diesters. The condensation of phosphoric acid with equimolar amounts of diols gave cyclic phosphoric acid diesters in almost quantitative yields. 1,2-Decandiol showed high reactivity to give the corresponding five-membered cyclic diester **8** in a short reaction time, which could be isolated as *N*-methylbenzylammonium form[13] (entry 3). Catechol was also converted smoothly to the corresponding five-membered cyclic phosphoric acid diester **9**[15] (>99% yield, entry 4). However, compound **9** could not be isolated since it was very labile and decomposed during purifications even as its ammonium form. A 1,3-diol such as 9,9-bis(hydroxymethyl)heptadecane was also converted into the corresponding six-membered cyclic diester **10** in 93% isolated yield (entry 5). This double-tailed cyclic phosphate **10** is in a novel class of phosphate surfactants.[5] Since the reactivity of BINOL was slightly lower than those of aliphatic alcohols, the condensation of BINOL was conducted with 40 mol% of BnNHMe. After a 75-hour reaction, binaphthylphosphoric acid **11**[16] was obtained in 84% isolated yield (entry 6). Based on the good reactivity of catechol and the lability of **9**, we proposed that catechol might promote the dehydrative condensation of phosphoric acid with BINOL. In fact, when the reaction of phosphoric acid with BINOL was conducted in the presence of catechol (10 mol%) and BnNHMe (40 mol%), the reaction proceeded smoothly and gave **11** in 90% yield (48 h) (entry 7). Compound **9** might be generated *in situ* as an active intermediate.[17]

In conclusion, we have selectively synthesized phosphoric acid diesters through the oxorhenium(VII)-catalyzed dehydrative condensation of phosphoric acid with alcohols. The present reaction was especially useful for the synthesis of cyclic phosphoric acid diesters. The condensation of phosphoric acid with equimolar amounts of diols gave cyclic phosphoric acids in almost quantitative yields.

EXPERIMENTAL

IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) or INOVA spectrometer (500 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz) or INOVA spectrometer (125 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). ^{31}P NMR spectra were measured on a Varian Mercury-300 spectrometer (121 MHz). Chemical shifts were reported as δ value in ppm downfield from 85% H_3PO_4. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Room, Nagoya University. All experiments were carried out under an atmosphere of dry nitrogen. Chemical materials were obtained from commercial supplies and used without further purification. A 65–70 w% aqueous solution of perrhenic acid ($HOReO_3$ aq.) and a crystal form of phosphoric acid (99.999+%, Aldrich) were purchased from Aldrich.

Typical procedure for the dehydrative condensation of phosphoric acid with a diol (1 equiv): Synthesis of cyclic phosphoric acid diester 11.[16]

A 30-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 5-mL pressure-equalized addition funnel [containing a cotton plug and ca. 2 g of molecular sieves 4A (pellets)] surmounted by a reflux condenser was charged with phosphoric acid (49 mg, 0.50 mmol), 1,1'-bi-2-naphthol (143 mg, 0.50 mmol), *N*-methylbenzylamine (26 μL, 0.10 mmol) and a 65–75 w% aqueous solution of perrhenic acid (0.9 μL, ca. 1 mol %) in NMP–*o*-xylene (1:1 v/v, 10 mL). The mixture was heated for 75 hours under azeotropic reflux conditions with the removal of water. After the reaction mixture was cooled to ambient temperature, solvents were removed *in vacuo*. A solution of the residue in Et_2O–$CHCl_3$ (4:1 v/v, 50 mL) was washed with 1 M aqueous HCl (40 mL). The aqueous layer was extracted with Et_2O–$CHCl_3$ (4:1 v/v, 50 mL × 2). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g) using hexane–EtOAc–MeOH (10:10:1 → 1:1:1) as eluents, and the fractions that contained phosphoric diester **11** were collected and concentrated. A solution of the obtained compound in Et_2O–$CHCl_3$ (4:1 v/v, 50 mL) was washed with 1 M aqueous HCl (40 mL). The combined organic layer was concentrated under reduced pressure to give **11** (147 mg, 84%).

Distearyl phosphate (2).[3]

IR (KBr) 3423, 1655, 1637, 1469, 1263, 1209, 1092, 1067, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 6H), 1.16–1.49 (m, 60H), 1.67 (quint, J = 6.5 Hz, 4H), 4.01 (q, J = 6.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 29.2, 29.4, 29.6, 29.7, 29.7, 30.2, 31.9, 67.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 1.59; HRMS (FAB) calcd for $C_{56}H_{76}O_4P$ (M + H^+) 603.5481, found 603.5494.

Bis[2-(2-dodecyloxy)ethoxy]ethyl phosphate (6).[12]

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 6H), 1.16–1.46 (m, 36H), 1.58 (tt, J = 6.0 Hz, 4H), 3.45 (t, J = 6.6 Hz, 4H), 3.53–3.79 (m, 12H), 4.10–4.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 26.0, 29.3, 29.4, 29.5, 31.8, 66.3, 69.9, 70.4, 71.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 0.86.

Dicholestanyl phosphate (7).

IR (KBr) 3416, 1637, 1467, 1383, 1264, 1208, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (s, 6H), 0.81 (s, 6H), 0.858 (d, *J* = 6.6 Hz, 6H), 0.861 (d, *J* = 6.6 Hz, 6H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.83–1.42 (m, 38H), 1.42–1.90 (m, 18H), 1.90–2.04 (m, 6H), 4.13–4.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 12.2, 18.6, 21.2, 22.5, 22.8, 23.9, 24.2, 28.0, 28.3, 28.6, 29.3, 32.0, 35.3, 35.4, 35.7, 35.8, 36.2, 36.8, 39.5, 39.9, 42.6, 44.7, 54.2, 56.3, 56.4, 78.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 0.57; HRMS (FAB) calcd for $C_{54}H_{95}NaO_4P$ (M + Na$^+$) 861.6866, found 861.6891.

Cyclic phosphoric acid diester 8 (*N*-methybenzylammonium salt).

Compound **8** was isolated as follows: After the reaction mixture was cooled to ambient temperature, BnNHMe (64 μL, 0.50 mmol) was added, and solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (10 g) using $CHCl_3$ with a trace amount of BnNHMe and then a mixture of $CHCl_3$–MeOH–BnNHMe (2:1:trace) as eluents to give *N*-methylbenzylammonium salt of **8** (191 mg, >99%); IR (KBr) 3416, 1639, 1575, 1469, 1430, 1396, 1208, 1127, 1089, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 2H), 1.18–1.41 (m, 11H), 1.41–1.62 (m, 2H), 1.62–1.79 (m, 1H), 2.42 (s, 3H), 3.79 (ddd, *J* = 4.8, 8.7, 8.7 Hz, 1H), 3.95 (s, 2H), 4.19 (ddd, *J* = 5.7, 8.7, 16.2 Hz, 1H), 4.31–4.43 (m, 1H), 7.31–7.43 (m, 3H), 7.51 (dd, *J* = 1.8, 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.2, 29.2, 29.4, 31.4, 31.8, 33.8, 52.0, 69.7, 128.9, 130.2, 131.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 17.7; HRMS (FAB) calcd for $C_{10}H_{22}O_4P$ (M + H$^+$) 237.1256, found 237.1246.

Cyclic phosphoric acid diester 9.[15]

^{31}P NMR (121 MHz, $CDCl_3$) δ 13.7.

Cyclic phosphoric acid diester 10.

IR (neat) 1654, 1468, 1266, 1200, 1104, 1071, 1037, 1008, 989 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 6H), 1.14–1.48 (m, 28H), 4.09 (d, *J* = 12.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 22.7, 29.2, 29.3, 30.1, 30.2, 31.8, 37.0, 37.0, 75.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.30; HRMS (FAB) calcd for $C_{19}H_{40}O_4P$ (M + H$^+$) 363.2664, found 363.2666.

Binaphthylphosphoric acid 11.[16]

^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD 3:1) δ 7.26–7.34 (m, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.44–7.52 (m, 2H), 7.55 (d, *J* = 9.3 Hz, 2H), 7.95 (d, *J* = 8.1 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD 3:1) δ 120.3, 121.3, 125.4, 126.4, 126.7, 128.2, 130.8, 131.4, 132.0, 146.9, 147.0; ^{31}P NMR (121 MHz, $CDCl_3$–CD_3OD 3:1) δ 4.12.

ACKNOWLEDGEMENTS

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9. Since pyrophosphoric acid esters **3** and **4** were converted into **1** during workup and purification, **1** was obtained in 86% yield (determined by ^{31}P NMR analysis of the crude product).
10. In contrast, a phosphazenium cation-catalyzed method (ref. 11) gave only a trace amount of phosphoric acid diesters (ca. 5%) even when the reaction of phosphoric acid was conducted with 2 equivalents of an alcohol. This method could scarcely promote the condensation of phosphoric acid monoesters with alcohols.
11. Under the reaction conditions in the absence of dibutylamine, oxorhenium(VII) complexes gradually decomposed to dark insoluble, catalytically inactive species (ref. 8).
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13. The phosphoric acid form of compound **8** gradually decomposed to give a mixture of phosphoric acid monoesters, while the ammonium form of **8** was stable.
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