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Bis(trifluoroacetyl)phenols and Their Derivatives in Reactions with Selected Phosphorus(III) Compounds

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ABSTRACT: *The reactivity of bis(trifluoroacetyl)-phenols toward selected λ^3P derivatives was examined. In the case of dialkyl(isocyanato)phosphites, only one of both present trifluoracetyl moieties of substrate was involved. After addition of the phenolic OH moiety across the intermediary formed P=N bond, tri-, tetra-, and pentacyclic α-(trifluoromethyl)phosphoranes were produced in a highly diastereoselective reaction. An unusual deoxygenation of the intermediary hydroxyphosphorane was observed reacting 4-methyl-2,6-bis-(trifluoroacetyl)phenol with diethyl(trimethylsilyl)-phosphite, and the subsequent hydrolysis gave γ-hydroxy-α-(trifluoromethyl)phoshonate. On the contrary, during the reaction of the O-silylated phenol with tris(trimethylsilyl)phosphite, a bis-phosphonate was obtained that underwent heterocyclization to phosphono phosphole system. The mechanistic aspects of the studied reactions, as well as structural features of the synthesized compounds are discussed, based on the multinuclear NMR spectroscopy and X-ray single crystal investigation data.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:474–482, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20451

INTRODUCTION

Fluorinated alkyl moieties, especially the CF_3 group, being incorporated into organic molecules, induce dramatic consequences on the properties of the derived compounds, with an enhanced lipophilicity, completely changed reactivity and unique metabolic behavior as the most striking aspects [1]. Thus, the species bearing a phosphorus atom and a fluorinated group at the same time is of particular interest for applications in the pharmaceutical industry, agro- and medicinal chemistry. Great attention was paid to α-fluoroalkyl phosphonates with F3-etidronic acid as the famous member of the family [2]. The most common procedure to synthesize compounds of this type consists of the addition of a phosphorus(III) nucleophile to the trifluoroacetyl group. The presence of other functions in the molecules of the reaction partners opens up further possibilities in the process proceeding, e.g., due to heterocyclization, as for the enol forms of fluorinated β-dicarbonyls [3]. Reactivity of these compounds as well as behavior of the structurally related 2-(trifluoroacetyl)phenols and their derivatives in reactions with phosphorus(III) compounds was topics of our previous work [3,4]. Therefore, our wish to involve the newly synthesized bis(trifluoroacetyl)phenols [5] in these

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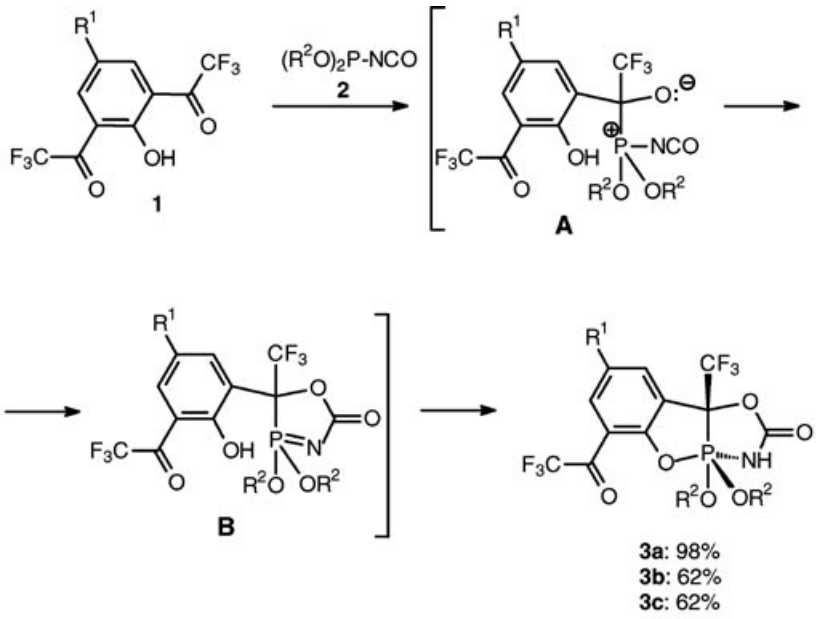
investigations is quite logical. The experimental findings are reported and analyzed in this paper.

RESULTS AND DISCUSSION

The examination of the reactivity of compounds **1** was started with dialkyl(isocyanato)phosphites **2** as phosphorus counterpart. Tricyclic phosphoranes **3**, colorless solids, were formed in 62–98% yields in a highly diastereoselective reaction (Scheme 1). Probably, the intermediate **A** generated from the attack of phosphorus on the carbonyl group provides product **B**. Finally, the phenolic OH moiety adds across the P=N double bond. Despite the presence of two chiral centers, only *one* diastereomer is obtained because of the limitation of the reaction channel numbers [6], as indicated by NMR spectroscopy, where only *one* set of signals has been observed. The reaction of 1,4-hydroquinone **4** with **2a** proceeds similarly to produce the pentacyclic bis-phosphorane **5** in 72% yield as the only diastereomer (Scheme 1). Noteworthy, (trimethylsilyl)ether **6** (easily available via protection of phenolic oxygen in **1b** with chlorotrimethylsilane) as well as 2,6-bis(trifluoroacetyl)anisol [5] do not react with phosphites **2** at all. In this context, the absence of the expected dimerization of intermediate **B** into diazadiphosphetidine [7] gets understandable: obviously, the presence of phenolic OH group is crucial for the success of the reaction.

As stressed above, only one set of signals was found in the ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra of compounds **3** and **5** measured at ambient temperature. Phosphorus resonances appear in the expected range −47.4 to −34.5 ppm, being typical for phosphoranes ($\lambda^5\sigma^5$P). The characteristic $^{1}J_{C\text{-}P}$ values of ca. 124 Hz suggest strongly the trigonal-bipyramidal structure with equatorial–axial–equatorial arrangement of the two fused five-membered rings and axially located $CF_3\underline{C}$ carbon [6,8], in which assignment is unambiguous due to splitting with $^{2}J_{C\text{-}F}$-coupling



SCHEME 1 Reaction of phenols **1**, **4** with dialkyl(isocyanato)phosphites **2**.

constant. In addition, these splittings allow identification of both $CF_3\underline{C}$ signals in compounds **3**; the chemical shifts (ca. 83 vs. 178.5 ppm), as well as δ_F values of the adjacent trifluoromethyl groups (ca. −72 vs. −73 ppm, respectively) are in accordance with proposed structure with a free trifluoroacetyl group and phosphorus in geminal position to the second CF_3 moiety. The axial and equatorial substituents OAlk can be easily distinguished in the ambient ^1H and ^{13}C NMR spectra, with the signals at lower field for the equatorial and at higher field for the axial position [6,8]. This fact indicates clearly that pseudorotation processes are slow on the NMR time scale. An interesting feature of compounds **3** and **5** is the spin–spin interaction of the fluorine nuclei of the trifluoroacetyl group with a carbon and proton in *o*-position ($^4J_{C\text{-}F} \approx 3$, $^5J_{F\text{-}H} \approx 1$ Hz). Probably, the "through-space" mechanism is realized, which requires a syn-periplanar arrangement of $CF_3C(O)$ group with respect to phenolic oxygen.

The asymmetric unit of **3c** consists of two discrete species **X** and **Y** and two molecules of chloroform, as revealed by X-ray diffraction analysis. In the molecule **X**, all the three phosphorus containing rings are axial-equatorial arranged, with O(2) and C(8) atoms in axial positions of the slightly distorted trigonal bipyramid (Fig. 1). The P—O distances are within the expected values for axially and equatorially bonded oxygen atoms in ring systems [9]. Remarkably, the P(1)—O(5) equatorial bond is somewhat longer than P(1)—O(2) axial bond [163.9(3) vs. 162.2(3) pm]. In the oxaphospholene framework, an angle O(5)—P(1)—C(8) of 89.19(17)° was observed, and all ring atoms are located almost coplanar with the atoms of the aromatic system (maximal deviation of 6.7 pm from the ideal plane for C(8) atom). The trifluoroacetyl moiety is something turned respective aromatic ring (torsion angle C(10)—C(16)—C(17)—O(6) 30.5°). Oxazaphosphole cycle features an "envelope" conformation, with C(8) above P(1)—N(1)—C(7)—O(4) plane by 20.4 pm (mean deviation of ca. 1.0 pm). The dioxaphosphole ring shows an "envelope" geometry with C(4) above the C(1)—O(1)—P(1)—O(2) plane by 53.4 pm (mean deviation of ca. 4.0 pm).

The reaction of **2b** with double excess on diethyl(trimethylsilyl)phosphite **7a** delivered an unexpected result. Instead of bis-phosphonate, the oxaphosphole **8** was formed (Scheme 2). From a mechanistic point of view, it can be reasonably postulated that after initial nucleophilic addition of phosphorus on the carbonyl group followed by proton transfer, a phosphorane ring closure takes place (Scheme 2, **C** → **D** → **E**). The derived hydroxyphosphorane **E** undergoes deoxygenation by an excess of

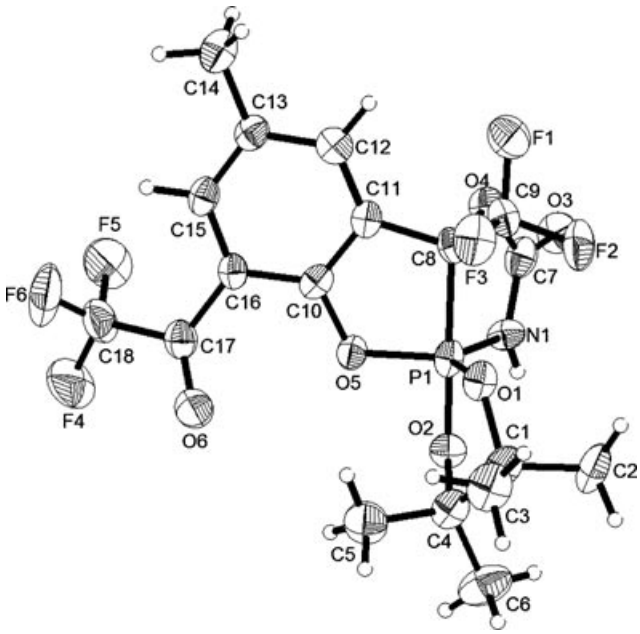
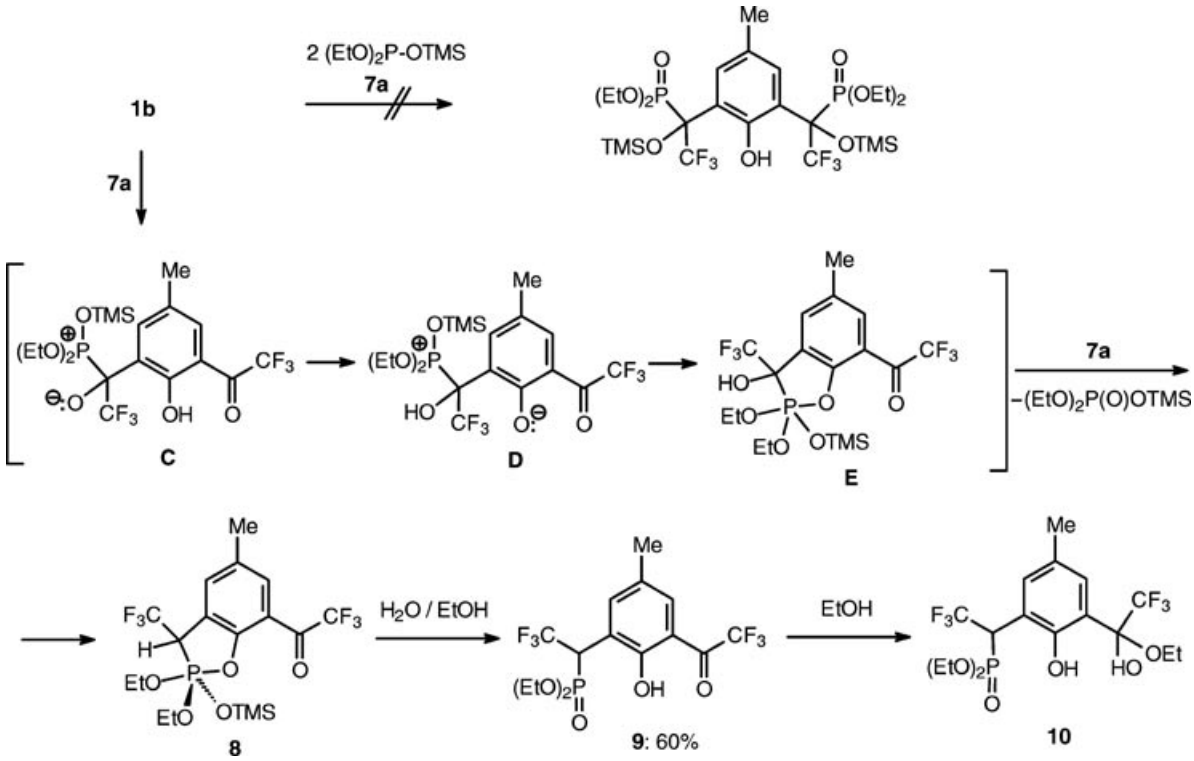


FIGURE 1 Molecular structure of compound **3c** (species **X** with arbitrary atoms numbering, thermal ellipsoids with 50% probability; molecule **Y** (being practically identical to **X** structurally) as well as the solvent ($CHCl_3$) molecule are omitted for clarity reason). Selected bond lengths of species **X** (pm): P(1)—O(1) 158.5(3), P(1)—O(2) 162.2(3), P(1)—O(5) 163.9(3), P(1)—N(1) 167.0(4), P(1)—C(8) 194.0(5); selected bond lengths of species **X** (°): O(1)—P(1)—O(5) 116.13(15), O(5)—P(1)—N(1) 117.82(17), O(2)—P(1)—N(1) 89.56(19), O(1)—P(1)—O(2) 93.39(16), O(2)—P(1)—C(8) 174.12(17), O(5)—P(1)—C(8) 89.19(17).

7a to afford heterocycle **8**. Our attempts to isolate this compound failed, but it could be characterized by NMR spectroscopy. Hydrolysis (water–ethanol) cleaved the phosphole ring to give phosphonate **9**, similar to the reaction of 2-(trifluoracetyl)phenol with trimethylphosphite [10]. After recrystallization from ethanol, compound **9** was isolated in hemi-ketal form **10** (Scheme 2), whose molecular structure was established by X-ray analysis (Fig. 2).

The δ_P values of the compounds **8** and **9** (−31.1 and 16.0, respectively) are within the usual range for the penta- and tetra-coordinated phosphorus derivatives, respectively. Similar to parent *o*-(trifluoroacetyl)phenol [11], the carbonyl group in **9** is bonded by intramolecular hydrogen bond, as indicated by δ_H shift of the OH proton (11.3 ppm). In ^{19}F NMR spectrum, the $^5J_{F\text{-}H}$ splitting found for the fluorine nuclei of the trifluoroacetyl moiety results probably from the "through-space" coupling, and is in well accordance with the *U*-type structure [12] of the intramolecularly H-bonded species. Besides



SCHEME 2 Reaction of phenol **1b** with diethyl(trimethylsilyl)phosphite **7a**.

$^3J_{F\text{-}P}$ splitting, for the second trifluoromethyl group an additional splitting in doublet with ca. 10 Hz coupling constant is evident for both compounds **8** and **9**, corresponding to the presence of a hydrogen atom in α-position.

The treatment of silyl ether **6** with a two-fold excess of **7a** or tris(trimethylsilyl)phosphite **7b** provided benz[*d*][1,2$\lambda^5\sigma^4$]oxaphospholes **11a** and **11b** in 98% and 87% yield, respectively (Scheme 3). Apparently, a double Arbuzov-type addition occurs

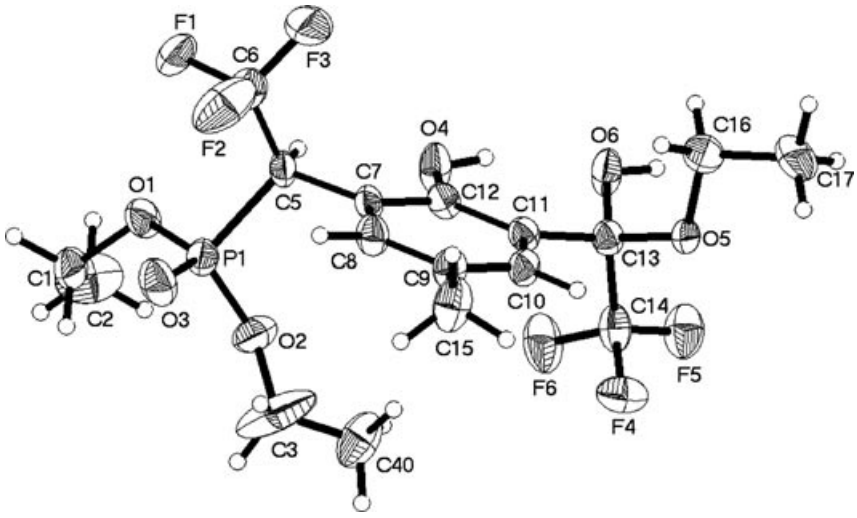
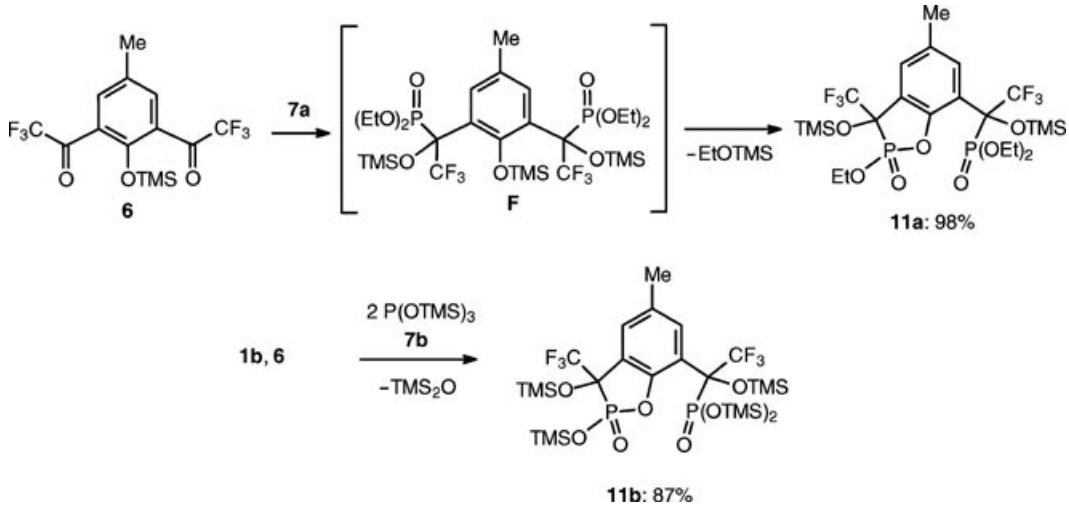


FIGURE 2 Molecular structure of compound **10** (thermal ellipsoids with 50% probability, the disordering of C(40)H_3 methyl group is not depicted for clarity). Selected bond lengths (pm): P(1)—O(3) 146.0(2), P(1)—O(1) 155.8(2), P(1)—C(5) 182.0(3); selected bond lengths (°): O(3)—P(1)—O(1) 116.48(13), O(1)—P(1)—O(2) 105.18(13), O(3)—P(1)—C(5) 114.31(15), O(1)—P(1)—C(5) 100.75(14).



SCHEME 3 Reaction of phenol **1b** and (trimethylsilyl)ether **6** with phosphites **7**.

in this case, and bis-phosphonate **F** transforms further into the fused product. Interestingly, phenol **1b** behaves toward tris(trimethylsilyl)phosphite **7b** the same way to yield phosphono phosphole **11b**, in contrast to the reaction with diethyl(trimethylsilyl)phosphite **7a** (Scheme 3).

Two sets of signals manifest themselves in NMR spectra of **11a** to indicate the presence of two diastereomers in ca. 65:35 ratio. In ^{31}P NMR spectrum, two kinds of phosphonate resonances are obvious ($\delta_P = 11.5, 12.4$ vs. 28.3). The quartets ($^3J_{P\text{-}F} = 5.1$ Hz) in higher field were attributed to the phosphorus in oxaphosphole ring. Analogously, signals of two different trifluoromethyl moieties split with $^3J_{F\text{-}P}$ coupling constants appear in ^{19}F NMR spectra of both diastereomers. Presumably, the doublets observed in lower field ($\delta_F = -78.7$ vs. -74.8, -72.6) correspond to the trifluoromethyl group attached to heterocycle.

Only one of possible diastereomers could be detected in C_6D_6 solution of **11b**, confirmed by only one set of signals in all NMR spectra measured. Signals in the ^{31}P NMR spectrum appear in significantly higher yield when compared to **11a**, namely at -2.9 and -2.4 ppm. This difference can be explained via cumulative electron donor influence of trimethylsilyl moieties.

In summary, the behavior of bis(trifluoroacetyl)phenols and their derivatives in reactions with dialkyl(isocyanato)phosphites and (trimethylsilyl)phosphites was studied. The polyfunctional nature of starting compounds causes the synthetical manifold: a wide range of valuable phosphonates and phosphoranes bearing CF_3 substituents in α-position was obtained, among them bi-, tri-, tetra-, and pentacyclic products. In several cases, the second trifluoroacetyl group of the phenolic reaction partner remained intact. Thus, the λ^5P products appear to be promising substrates for the further organofluorine modifications, such as Perkin [13], Wittig/Horner–Wadsworth–Emmons [14] reactions, as well as biomimetic reductive amination [15].

EXPERIMENTAL

Appropriate precautions for handling moisture- and oxygen-sensitive compounds were observed throughout this work. Melting points are uncorrected. MS (*m/z*, intensity (%), species): EI (70 eV), Finnigan MAT-8200 and MAT-95 spectrometers. High-resolution mass spectra (HRMS): peak-matching method, Finnigan MAT-95 spectrometer. NMR spectra: Bruker AC-80, Bruker DPX-200, and Bruker AMX-360 spectrometers [80.1 and 200.1 (^{1}H), 50.3 (^{13}C), 75.4 and 188.3 (^{19}F), 32.4, 81.0, 145.8 (^{31}P) MHz]; Me_4Si-(^{1}H and ^{13}C), CCl_3F-(^{19}F) and H_3PO_4-(^{31}P) scales. ^{1}H NMR chemical shifts in $CDCl_3$, CD_3CN, and C_6D_6 solutions are referenced to the signal at 7.25, 1.94, and 7.15 ppm, respectively, ^{13}C-NMR chemical shifts in $CDCl_3$ solutions are referenced to the central line of solvent signal at 77.0 ppm. Reaction progress was monitored by ^{19}F and ^{31}P NMR spectroscopy for the samples from the reaction mixtures (without lock). X-ray single crystal determination for compounds **3c** and **10**: at $-100(2)^\circ$C, Siemens-P4 diffractometer with a graphite monochromated Mo K_α radiation (λ 71.073 pm) and the low-temperature device LT2. The structures were solved by direct methods and refined by full-matrix least squares at F^2 with the SHELXL-97 program package [16]. All non-H

atoms were refined anisotropically, the NH proton was refined isotropically, and the positions of the other hydrogen atoms were calculated as a riding model. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. Elemental analyses: Microanalytisches Beller Labor, Göttingen, Germany. All chemicals are commercially available and were used as purchased unless otherwise specified. Reactions in dried diethyl ether (distilled from sodium/benzophenone ketyl) were performed in oven-dried glassware under a static nitrogen atmosphere. Triethylamine was dried over KOH and distilled. Starting phenols **1** [5] and phosphites **2a** [17], **2b** [18], and **7** [19] were prepared according to the published procedures.

CCDC-657297 and CCDC-657296 contain the supplimentary crystallographic data for the structures **3c** and **10**, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieveing.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

*Standard Procedure for the Preparation of Phosphoranes (**3**)*

To a well-stirred solution of the appropriate phenol **1** (1.7 mmol) in dried diethyl ether (20 mL), freshly distilled isocyanatophosphite **2** (1.7 mmol) was added. The resulting pale yellow solution was stirred for 1 h at room temperature, and the solvent was removed under reduced pressure to afford a yellowish solid (**3b**,**c**) or yellow oil which solidified (**3a**).

6,7-Benzo-1,1-diethoxy-12-trifluoroacetyl-5-trifluoromethyl-4,8-dioxa-2-aza-1λ^{5}σ^5-phosphabicyclo[3.3.0]-oct-6-en-3-one (**3a**): Yield 98% as yellow crystals (melting interval 68–74°C (sealed capillary)). ^{1}H NMR ($CDCl_3$): $\delta = 1.28$ (td, 3H, CH_3^{ax}, $^3J_{H\text{-}H} = 6.6$, $^4J_{H\text{-}P} \approx 1.5$ Hz), 1.32 (td, 3H, CH_3^{eq}, $^3J_{H\text{-}H} = 6.6$, $^4J_{H\text{-}P} \approx 1.6$ Hz), 3.86–4.03 (m, 1H, OC<u>H</u>H^{ax}), 4.04–4.34 (m, 3H, OCH<u>H</u>^{ax}, CH_2^{eq}), 7.01 (d, 1H, NH, $^2J_{H\text{-}P} = 9.3$ Hz), 7.27 (t, 1H, 10-H, $^3J_{H\text{-}H} = 8.1$ Hz), 7.93, 7.94 (two d, each 1H, 9,11-H, $^3J_{H\text{-}H} = 7.8$ Hz). ^{13}C{^{1}H} NMR ($CDCl_3$): $\delta = 15.6$ (d, CH_3^{ax}, $^3J_{C\text{-}P} = 8.1$ Hz), 16.1 (d, CH_3^{eq}, $^3J_{C\text{-}P} = 9.9$ Hz), 62.5 (d, CH_2^{ax}, $^2J_{C\text{-}P} = 9.9$ Hz), 67.9 (d, CH_2^{eq}, $^2J_{C\text{-}P} = 15.5$ Hz), 82.8 (dq, C-P, $^1J_{C\text{-}P} = 124.1$, $^2J_{C\text{-}F} = 31.5$ Hz), 116.0 (q, $CF_3C(O)$, $^1J_{C\text{-}F} = 291.5$ Hz), 117.1 (d, C^{Ar}, $J_{C\text{-}P} = 12.4$ Hz), 123.4, 124.2 (two s, C^{Ar}), 121.1 (q, 5-CF_3, $^1J_{C\text{-}F} = 281.2$ Hz), 133.3 (q, 9-C, $^4J_{C\text{-}F} = 2.9$ Hz), 134.7 (d, C^{Ar}, $J_{C\text{-}P} = 13.0$ Hz), 153.5 (d, 7-C, $^2J_{C\text{-}P} = 6.2$ Hz), 154.1 (d, 3-C, $^2J_{C\text{-}P} = 31.3$ Hz), 178.4 (q, $CF_3C(O)$, $^2J_{C\text{-}F} = 36.1$ Hz). ^{19}F NMR ($CDCl_3$): $\delta = -73.01$ (d, 3F, $CF_3C(O)$, $^5J_{F\text{-}H} = 1.4$ Hz), −72.01 (d, 3F, 5-CF_3, $^3J_{F\text{-}P} = 2.8$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = -46.8$ m. ^{31}P{^{1}H} NMR ($CDCl_3$): $\delta = -46.8$ (q, $^3J_{P\text{-}F} = 2.6$ Hz). MS (EI); $m/z = 449$ (20) [M$^+$], 406 (56) [M – CONH]$^+$, 404 (64) [M – EtO]$^+$, 380 (12) [M – CF_3]$^+$, 376 (100) [M – CO – EtO]$^+$, 352 (30) [M – CF_3CO]$^+$, 330 (76) [M – CF_3 – EtOH]$^+$, and other fragments. HRMS for $C_{15}H_{14}F_6NO_6P$; Calcd: 449.0463. Found: 449.0459.

6,7-Benzo-1,1-diethoxy-10-methyl-12-trifluoroacetyl-5-trifluoromethyl-4,8-dioxa-2-aza-1λ^{5}σ^5-phosphabicyclo[3.3.0]oct-6-en-3-one (**3b**): Recrystallization of crude product from heptane at −30°C yielded 62% of yellowish crystals (mp 131–133°C (sealed capillary)). ^{1}H NMR ($CDCl_3$): $\delta = 1.27$ (td, 3H, CH_3^{ax}, $^3J_{H\text{-}H} = 7.2$, $^4J_{H\text{-}P} \approx 1.4$ Hz), 1.31 (td, 3H, CH_3^{eq}, $^3J_{H\text{-}H} = 7.0$, $^4J_{H\text{-}P} \approx 1.6$ Hz), 2.40 (s, 3H, 10-CH_3), 3.85–4.03 (m, 1H, OC<u>H</u>H^{ax}), 4.07–4.32 (m, 3H, OCH<u>H</u>^{ax}, CH_2^{eq}), 7.38 (d, 1H, NH, $^2J_{H\text{-}P} = 9.3$ Hz), 7.70, 7.72 (two s, each 1H, 9,11-H). ^{13}C{^{1}H} NMR ($CDCl_3$): $\delta = 15.6$ (d, CH_3^{ax}, $^3J_{C\text{-}P} = 8.1$ Hz), 16.0 (d, CH_3^{eq}, $^3J_{C\text{-}P} = 9.9$ Hz), 20.9 (s, 10-CH_2), 62.3 (d, CH_2^{ax}, $^2J_{C\text{-}P} = 10.2$ Hz), 67.8 (d, CH_2^{eq}, $^2J_{C\text{-}P} = 15.5$ Hz), 83.0 (dq, C-P, $^1J_{C\text{-}P} = 124.2$, $^2J_{C\text{-}F} = 31.3$ Hz), 116.0 (q, $CF_3C(O)$, $^1J_{C\text{-}F} = 291.5$ Hz), 116.9 (d, C^{Ar}, $J_{C\text{-}P} = 12.0$ Hz), 124.1 (d, C^{Ar}, $J_{C\text{-}P} = 14.8$ Hz), 124.2 (q, 5-CF_3, $^1J_{C\text{-}F} = 280.7$ Hz), 133.4 (s, C^{Ar}), 135.2 (d, C^{Ar}, $J_{C\text{-}P} = 10.2$ Hz), 151.4 (d, 7-C, $^2J_{C\text{-}P} = 6.0$ Hz), 151.8 (d, 3-C, $^2J_{C\text{-}P} = 30.7$ Hz), 178.6 (q, CF_3 <u>C</u>(O), $^2J_{C\text{-}F} = 36.1$ Hz). ^{19}F NMR ($CDCl_3$): $\delta = -73.08$ (d, 3 F, $CF_3C(O)$, $^5J_{F\text{-}H} = 1.4$ Hz), −71.89 (d, 3F, 5-CF_3, $^3J_{F\text{-}P} = 2.9$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = -46.5$ m. ^{31}P{^{1}H} NMR ($CDCl_3$): $\delta = -46.5$ (q, $^3J_{P\text{-}F} = 2.9$ Hz). MS (EI): $m/z = 463$ (44) [M$^+$], 420 (64) [M – CONH]$^+$, 418 (66) [M – EtO]$^+$, 394 (20) [M – CF_3]$^+$, 390 (88) [M – CO – EtO]$^+$, 366 (40) [M – CF_3CO]$^+$, 344 (100) [M – CF_3 – EtOH]$^+$, and other fragments. HRMS for $C_{16}H_{16}F_6NO_6P$; Calcd: 463.0620. Found: 463.0612.

6,7-Benzo-10-methyl-1,1-(1′,1′,2′,2′-tetramethylethylene-1′,2′-dioxy)-12-trifluoroacetyl-5-trifluoromethyl-4,8-dioxa-2-aza-1λ^{5}σ^5-phosphabicyclo[3.3.0]oct-6-en-3-one (**3c**): Recrystallization of crude product from chloroform yielded 62% of yellowish crystals (mp 180°C (sealed capillary)). ^{1}H NMR (C_6D_6): $\delta = 1.32$, 1.41 (two s, each 6H, 1′,1′,2′,2′-CH_3), 2.41 (s, 3H, 10-CH_3), 7.20 (d, 1H, NH, $^2J_{H\text{-}P} = 9.3$ Hz), 7.71 (s, 2H, 9,11-H). ^{19}F NMR (C_6D_6): $\delta = -77.36$ (s, 3F, $CF_3C(O)$), −75.19 (s, 3F, 5-CF_3). ^{31}P NMR (C_6D_6): $\delta = -34.5$ m. MS (EI): $m/z = 490$ (6) [M + H]$^+$, 446 (12) [M – CONH]$^+$, 420 (2) [M – CF_3]$^+$, 373 (18) [M – Me_2CCMe_2]$^+$, 304 (18) [M – CF_3 – Me_2CCMe_2]$^+$, and other fragments. Anal. Calcd. for $C_{18}H_{18}F_6NO_6P$ (489.31): C, 44.19; H, 3.71; F, 23.3; P, 6.33. Found: C, 44.63; H, 3.85; F, 22.8; P, 6.63.

X-ray Crystal-Structure Analysis of **3c**. Diffraction-quality crystals were selected from analytical sample obtained via recrystallization of the crude product from chloroform. Colorless prisms; $C_{19}H_{19}Cl_3F_6NO_6P$ (608.67); 0.75 × 0.30 × 0.30 mm^3, triclinic *P*-1 with $a = 964.10(10)$, $b = 1695.7(2)$, $c = 1787.7(2)$ pm, $\alpha = 61.690(10)$, $\beta = 82.160(10)$, $\gamma = 89.950(10)^\circ$, $V = 2.5421(5)$ nm^3, $D = 1.590$ g cm^{-3}, $Z = 4$, difference electron density 0.650 and −0.509 e Å^{-3}. Index range $-1 \le h \le 11$, $-17 \le k \le 17$, $-21 \le l \le 21$, 2θ range 2.62 to 25.00°, reflections measured 10,255, unique reflections 8472 (R(int) = 0.0452). Completeness to $\theta_{max} = 25.00^\circ$: 94.4%, data/restraints/parameter 8472/0/670. Goodness-of-fit at F^2 0.756; final *R*-values ($I > 2\sigma(I)$): $R_1 = 0$. 0.0507, $wR_2 = 0.1055$; *R*-value (all reflections): $R_1 = 0.1344$, $wR_2 = 0.1220$.

*6,6,15,15-Tetraethoxy-2,11-bis(trifluoromethyl)-3,7,12,16-tetraoxa-5,14-diaza-6λ^{5}σ^5,15λ^{5}σ^5-diphosphapentacyclo[13.3.0.0^{2,6}.0^{1,8}.0^{10,17}]-octadeca-1(8),9,17-trien-4,13-dione (**5**)*

A solution of freshly distilled (diethyl)isocyanatophosphite **2a** (1.1 g, 6.7 mmol) in dried diethyl ether (7 mL) was added dropwise to a well-stirred solution of hydroquinone **4** (1 g, 3.3 mmol) in diethyl ether (20 mL) maintained at 0°C. The resulting solution was allowed to warm and stirred for 1 h at room temperature. The mixture was cooled to −30°C, and dried pentane (20 mL) was added. The precipitated solid was filtered, washed with pentane (2 × 7 mL), and dried to give **5** (1.5 g, 72%) as a pale yellow moisture-sensitive powder. To obtain an analytical sample, the crude product was washed successively with acetone and diethyl ether and dried in vacuo to furnish white powder, (mp 180°C (decomp., sealed capillary)). ^{1}H NMR (CD_3CN): $\delta = 1.19$–1.32 (m, 12H, $4CH_3$), 3.81–4.07 (m, 4H, $2CH_2$), 4.08–4.29 (m, 4H, $2CH_2$), 7.18 (d, 2H, 2NH, $^2J_{H\text{-}P} = 9.8$ Hz), 7.35 (q, 2H, H^{Ar}, $^5J_{H\text{-}F} \approx 1.0$ Hz). ^{19}F NMR (acetone-d_6 + C_6D_6, ca. 3:2): $\delta = -70.88$ s. ^{31}P{^{1}H} NMR (acetone-d_6 + C_6D_6, ca. 3:2): $\delta = -47.4$ (q, $^3J_{P\text{-}F} = 2.7$ Hz). MS (EI); $m/z = 628$ (28) [M^+], 583 (50) [M – EtO]$^+$, 29 (100) [Et^+], and other fragments. HRMS for $C_{20}H_{24}F_6N_2O_{10}P_2$; Calcd: 628.0810. Found: 628.0816.

*2,2-Diethoxy-5-methyl-7-trifluoroacetyl-3-trifluoromethyl-2-(trimethylsiloxy)benz[d]-[1,2λ^{5}σ^5]oxaphospholane (**8**) and diethyl 1-(2-hydroxy-3-trifluoroacetyl-5-methylphenyl)-2,2,2-trifluoroethylphosphonate (**9**)*

To a well-stirred solution of phenol **1b** (3 g, 10 mmol) in dried diethyl ether (10 mL), freshly distilled diethyl(trimethylsilyl)phosphite **7a** (4.2 g, 20 mmol) was added dropwise. After addition was completed, the volatile materials were removed in vacuo to leave mixture of 1,2-oxaphospholane **8** and diethyl(trimethylsilyl)phosphate ($\delta_P = 1.8$). After treatment with aqueous ethanol (ca. 90%) for 1 h at room temperature, the mixture was concentrated in vacuo to 3 mL and left overnight. The formed precipitate was collected by filtration to afford **9** as colorless crystals, 2.5 g (60%) (mp 105°C). Compound **8**. ^{1}H NMR (C_6D_6): $\delta = 0.03$ (s, 9H, $Si(CH_3)_3$), 0.80–1.85 (m, 6H, $2CH_2C\underline{H}_3$), 2.18 (s, 3H, $ArC\underline{H}_3$), 3.88 (m, 1H, *CH), 3.50–4.85 (m, 4H, $2C\underline{H}_2CH_3$), 7.22–8.00 (m, 2H, 4,6-H). ^{19}F NMR (C_6D_6): $\delta = -68.20$ (dd, 3F, 3-CF_3, $^3J_{F\text{-}P} = 14.3$, $^3J_{F\text{-}H} = 9.9$ Hz), −77.85 (d, 3F, $CF_3C(O)$, $^5J_{F\text{-}H} = 1.3$ Hz). ^{19}F{^{1}H} NMR (C_6D_6): $\delta = -68.17$ (d, 3F, 3-CF_3, $^3J_{F\text{-}P} = 14.5$ Hz), −77.85 (s, 3F, $CF_3C(O)$). ^{31}P{^{1}H} NMR (C_6D_6): $\delta = -31.1$ (q, $^3J_{P\text{-}F} = 14.8$ Hz).

Compound **9**. ^{1}H NMR (C_6D_6): 0.65–1.15 (m, 6H, 2 $CH_2C\underline{H}_3$), 2.10 (s, 3H, $ArC\underline{H}_3$), 3.55–4.45 (m, 4H, $2C\underline{H}_2CH_3$), 3.60 (dq, 1H, *CH, $^2J_{H\text{-}P} = 48.1$, $^3J_{H\text{-}F} = 11.4$ Hz), 7.14–7.98 (m, 2H, 4,6-H), 11.3 (br.s, 1H, OH). ^{19}F NMR (C_6D_6): $\delta =$ -65.60 (dd, 3F, 3-CF_3, $^3J_{F\text{-}H} = 11.4$, $^3J_{F,P} = 9.7$ Hz), −74.53 (d, 3F, $CF_3C(O)$, $^5J_{F\text{-}H} = 2.6$ Hz). ^{19}F{^{1}H} NMR (C_6D_6): $\delta = -65.60$ (d, 3F, 3-CF_3, $^3J_{F\text{-}P} = 9.7$ Hz), −74.54 (s, 3F, $CF_3C(O)$). ^{31}P{^{1}H} NMR (C_6D_6): $\delta = 16.0$ (q, $^3J_{P\text{-}F} = 9.4$ Hz). MS (EI): $m/z = 422$ (84) [M^+], 394 (18) [M – CO]$^+$, 354 (28) [M – CF_3 + H]$^+$, 353 (14) [M – CF_3]$^+$, 325 (18) [M – CF_3CO]$^+$, 284 (22) [M – $2CF_3$]$^+$, 127 (100), 45 (45) [EtO^+], and other fragments. Anal. Calcd for $C_{15}H_{17}F_6O_5P$ (422.26): C, 42.67; H, 4.06; P, 7.34. Found: C, 42.63; H, 4.61; P, 7.02.

X-ray Crystal-Structure Analysis of Hemi-ketal **10**. Diffraction-quality crystals were grown by slow crystallization of **9** from ethanol. Colorless prisms; $C_{17}H_{23}F_6O_6P$ (468.32); 0.80 × 0.80 × 0.70 mm^3, triclinic *P*-1 with $a = 818.60(10)$, $b = 1006.70(10)$, $c = 1467.1(2)$ pm, $\alpha = 70.010(10)$, $\beta = 85.680(10)$, $\gamma = 66.750(10)^\circ$, $V = 1.0414(2)$ nm^3, $D = 1.493$ g cm^{-3}, $Z = 2$, difference electron density 0.247 and −0.369 e·Å^{-3}. Index range $-1 \le h \le 9$, $-10 \le k \le 11$, $-17 \le l \le 17$, 2θ range 2.71 to 24.99°, reflections measured 4503, unique reflections 3600 (R(int) = 0.0501). Completeness to $\theta_{max} = 24.99^\circ$: 98.2%, data/restraints/parameter 3600/0/293. Goodness-of-fit at F^2 0.859; final *R*-values ($I > 2\sigma(I)$): $R_1 = 0.0491$, $wR_2 = 0.1000$; *R*-value (all reflections): $R_1 = 0.0971$, $wR_2 = 0.1121$.

*4-Trimethylsiloxy-3,5-bis(trifluoroacetyl)toluene (**6**)*

To a stirred solution of phenol **1b** (3 g, 10 mmol) in dried diethyl ether (10 mL) dried triethylamine

(1 g, 10 mmol) was added dropwise, followed by chlorotrimethylsilane (1.1 g, 10 mmol). The precipitated triethylammonium chloride was filtered off, the filtrate evaporated in vacuo to give **6** (3.6 g, 97%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): $\delta = 0.18$ (s, 9H, $Si(CH_3)_3$), 2.42 (s, 3H, $ArC\underline{H}_3$), 7.63 (s, 2H, 2,4-H). ^{19}F NMR ($CDCl_3$): $\delta = -77.01$ s. Anal. Calcd for $C_{14}H_{14}F_6O_3Si$ (372.34): C, 45.16; H, 3.79; F, 30.6. Found: C, 45.25; H, 3.96; F, 30.6.

*Diethyl 2,2,2-trifluoro-1-[2-ethoxy-5-methyl-3-trifluoromethyl-3-(trimethylsiloxy)benz[d]-[1,2λ^{5}σ^4]oxaphospholan-2-one-7-yl]-1-(trimethylsiloxy)ethylphosphonate (**11a**)*

To a stirred solution of silyl ether **6** (3.7 g, 10 mmol) in dried diethyl ether (10 mL) freshly distilled diethyl(trimethylsilyl)phosphite **7a** (4.2 g, 20 mmol) was added dropwise at room temperature. After stirring for 1 h, the volatile materials were evaporated in vacuo to afford **11a** (6.6 g, 98%) as a yellowish oil. The NMR spectra display the presence of two diastereomers (**M** and **N**) in ca. 65:35 ratio, respectively. Isomer **M**. ^{1}H NMR (C_6D_6): $\delta = -0.18$ (s, 9H, $Si(CH_3)_3$), −0.01 (s, 9H, $Si(CH_3)_3$), 0.91–1.29 (m, 6H, $2CH_2C\underline{H}_3$), 2.15 (s, 3H, $ArC\underline{H}_3$), 3.77–4.28 (m, 4H, $2C\underline{H}_2CH_3$), 7.00–7.22 (m, 2H, 4,6-H). ^{19}F NMR (C_6D_6): $\delta = -78.66$ (d, 3F, exo-CF_3, $^3J_{F\text{-}P} = 5.3$ Hz), −72.61 (d, 3F, endo-CF_3, $^3J_{F\text{-}P} = 5.3$ Hz). ^{31}P{^{1}H} NMR (C_6D_6): $\delta = 11.5$ (q, 1P, endo-P(O), $^3J_{P\text{-}F} = 5.1$ Hz), 28.3 (unresolved q, P, exo-P(O), $^3J_{P\text{-}F} \approx 5$ Hz). Isomer **N**. ^{1}H NMR (C_6D_6): −0.01 (s, 9H, $Si(CH_3)_3$), 0.06 (s, 9H, $Si(CH_3)_3$), 0.91–1.29 (m, 6H, $2CH_2C\underline{H}_3$), 2.15 (s, 3H, $ArC\underline{H}_3$), 3.77–4.28 (m, 4H, $2C\underline{H}_2CH_3$), 7.38, 7.64 (both m, each 1H, 4,6-H). ^{19}F NMR (C_6D_6): $\delta = -78.66$ (d, 3F, exo-CF_3, $^3J_{F\text{-}P} = 5.3$ Hz), −74.86 (d, 3F, endo-CF_3, $^3J_{F\text{-}P} = 5.1$ Hz). ^{31}P{^{1}H} NMR (C_6D_6): $\delta = 12.4$ (q, 1P, endo-P(O), $^3J_{P\text{-}F} = 5.1$ Hz), 28.3 (unresolved q, 1P, exo-P(O), $^3J_{P\text{-}F} \approx 5$ Hz). MS (EI); $m/z = 674$ (6) [M^+], 659 (26) [M – Me]$^+$, 602 (26) [M – $SiMe_3$ + H]$^+$, 537 (92) [M – P(O)$(OEt)_2$]$^+$, 465 (32) [M – P(O)$(OEt)_2$ – $SiMe_3$ + H]$^+$, 421 (100), 210 (88) [TMSO-P$(OEt)_2^+$], 73 (62) [Me_3Si^+], 29 (20) [Et^+], and other fragments. Anal. Calcd for $C_{23}H_{38}F_6O_8P_2Si_2$ (674.66): C, 40.95; H, 5.68. Found: C, 40.53; H, 5.42.

*Bis(trimethylsilyl) 2,2,2-trifluoro-1-[5-methyl-3-trifluoromethyl-2,3-bis(trimethylsiloxy)benz[d]-[1,2λ^{5}σ^4]oxaphospholan-2-one-7-yl]-1-(trimethylsiloxy)ethylphosphonate (**11b**)*

To a stirred solution of phenol **1b** (3 g, 10 mmol) or silyl ether **6** (3.7 g, 10 mmol) in dried diethyl ether (10 mL), freshly distilled tris(trimethylsilyl)phosphite **7b** (6 g, 20 mmol) was added dropwise at room temperature. After stirring for 1 h, the volatile materials were evaporated in vacuo to afford **11b** (7 g, 87%) as a yellowish oil. ^{1}H NMR (C_6D_6): $\delta = -0.15$ (s, 18H, $2Si(CH_3)_3$), −0.13 (s, 9H, $Si(CH_3)_3$), 0.17 (s, 18H, $2Si(CH_3)_3$), 2.29 (s, 3H, $ArC\underline{H}_3$), 7.18–7.42 (m, 2H, 4,6-H). ^{19}F NMR (C_6D_6): $\delta = -71.83$ (d, 3F, exo-CF_3, $^3J_{F\text{-}P} = 6.4$ Hz), −70.40 (d, 3F, endo-CF_3, $^3J_{F\text{-}P} = 6.3$ Hz). ^{31}P{^{1}H} NMR (C_6D_6): $\delta = -2.8$ (q, 1P, endo-P(O), $^3J_{P\text{-}F} = 5.6$ Hz), −2.4 (q, 1P, exo-P(O), $^3J_{P\text{-}F} = 5.8$ Hz). MS (EI); $m/z = 824$ (4) [M + H_2O^+], 225 (50) [P(O)$(OTMS)_2^+$], 211 (100), 147 (98) [$Me_3SiOSiMe_2^+$], 73 (74) [Me_3Si^+], and other fragments. Anal. Calcd for $C_{26}H_{50}F_6O_8P_2Si_5$ (807.04): C, 38.70; H, 6.24; F, 14.1. Found: C, 38.68; H, 6.58; F, 13.9.

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