Synthesis of $PO(OR)_2$- and PR_3^+-Disubstituted Pyridines via *N*-(Trifluoromethylsulfonyl)pyridinium Triflates

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Dedicated to Professor Welzel on the occasion of his 60th birthday

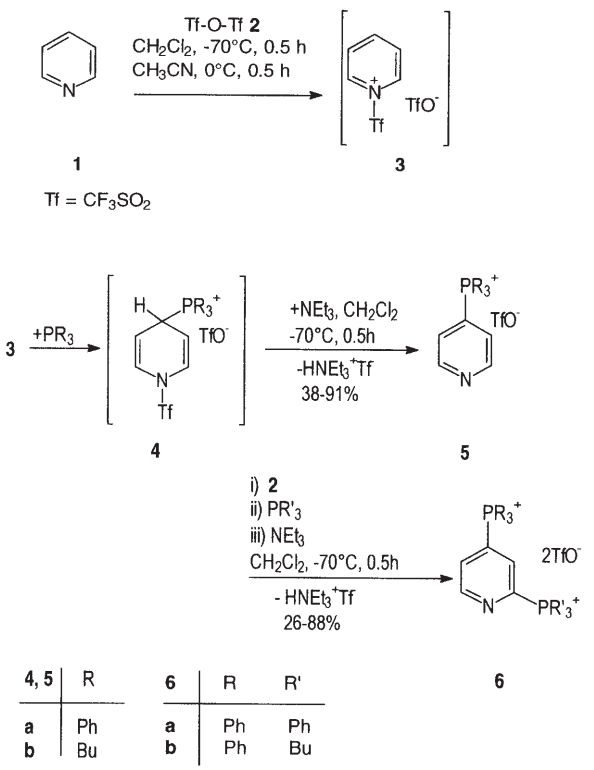
Abstract: The efficient synthesis of dialkoxyphosphoryl- and phosphonio-substituted pyridines is reported. The cationic heterocycle of *N*-(trifluoromethylsulfonyl)pyridinium triflate (**3**), or of analogous *N*-(trifluoromethylsulfonyl) compounds prepared from pyridine-4-phosphonium salts **5**, turns out to be sufficiently activated to allow attack of $P(OR)_3$ and PR_3^+ nucleophiles to give the novel compounds bis(dialkoxyphosphoryl)pyridines **11** and phosphonio(dialkoxyphosphoryl)pyridines **13**. For example, **13a–d**, with $PO(OR)_2$ at the C2 and PR_3^+ at the C4 position, represent the first examples of an N-heteroaromatic ring substituted by both dialkoxyphosphoryl and phosphonio moieties. The structure of **13b** [$PPh_3^+/PO(O\text{-}i\text{-}Pr)_2$] was confirmed by X-ray analysis. In most cases, the intermediate 1-(trifluoromethylsulfonyl)dihydropyridines, such as **7**, **8** (monosubstituted) or **10a** and b and **12a–d** (disubstituted), are sufficiently stable for isolation.

Key words: *N*-(trifluromethylsulfonyl)pyridinium triflates, regioselective nucleophilic substitution, C2- and C4-disubstituted pyridines, phosphites, phosphonium triflates

The number of synthetic procedures yielding phosphorus-substituted aromatic ring systems has significantly increased during the last decade. Nevertheless, there is a dearth of uncomplicated methods which allow the regioselective introduction of, in particular, the phosphonate [$PO(OR)_2$] moiety at several positions in heteroaromatic ring systems. In the pyridine series, this substituent deserves attention. As demonstrated by Paine et al.,[1] 2,6-bis(diethoxyphosphoryl)pyridine is a useful ligand for relatively "hard" cations such as UO_2^{2+}. Furthermore, this substituent can easily be reduced to give pyridylphosphanes. The latter serve as important ligands for relatively "soft" metal cations such as Ni, Co, Zn, Cu, Pd, Pt, etc.[2] Further, the importance of the aryl-bonded dialkoxyphosphoryl group in photostimulated $S_{RN}1$ reactions[3] and its transformations have been recently investigated.[4,5] In particular, the selective dealkylation of diisopropyl phosphonates with TMSBr in the presence of other functional groups appears to be of some importance for future applications.[6]

The C2 and the C4 ring positions of a variety of *N*-alkylpyridinium cations can be attacked by several nucleophiles to give, in the first step, the corresponding dihydropyridines. Unfortunately, in most cases these reactions rarely proceed with acceptable regioselectivity. Mixtures of isomeric substitution products are the typical result. For example, exclusive C4 attack requires bulky substituents at the C2 and C6 positions.[7–9] Redmore reported methods, which were very useful in the case of C2 substitution, but needed 2,6-dialkyl-substituted *N*-alkoxypyridinium or *N*-tritylpyridinium salts to protect both the C2 and C6 positions in order to synthesize the 4-isomer, using sodium phosphonates as nucleophiles.[8,10] Akiba synthesized the pure diisopropyl 1-(ethoxycarbonyl)-1,4-dihydropyridine-4-phosphonate,[7] while in the case of other phosphites, unpredictable molar ratios of isomeric C2/C4 dihydropyridines were also observed. Katritzky, too, used the steric demands of C2 and C6 substituents.[9] A 2,6-bis(dialkoxyphosphoryl)pyridine has been synthesized from 2,6-. dichloropyridine *N*-oxide and sodium diethyl phosphite,[1] and 3,5,6-trichloro-2,4-bis(diethoxyphosphoryl)pyridine from 2,3,4,5,6-pentachloropyridine and triethyl phosphite.[11]

A method for the regiospecific introduction of the PR_3 group into the C4 position of the unsubstituted pyridine ring system was described by our group some years ago (Scheme 1).[12, 13] This procedure takes advantage of the quantitative in situ formation of *N*-(trifluoromethylsulfonyl)pyridinium triflate (*N*-triflylpyridinium triflate, **3**), which reacted with phosphanes via dihydropyridines **4** and addition of NEt_3 to give the phosphonium salts **5**. The isomeric C2-substituted products have not been observed. Interestingly, this procedure can be repeated with the salts **5** to give the bisphosphonium salts **6**. For synthetic applications, salts such as **5** and **6** deserve interest as they allow a variety of pathways to further classes of substituted heterocyclic compounds.[13]



4, 5	R
a	Ph
b	Bu

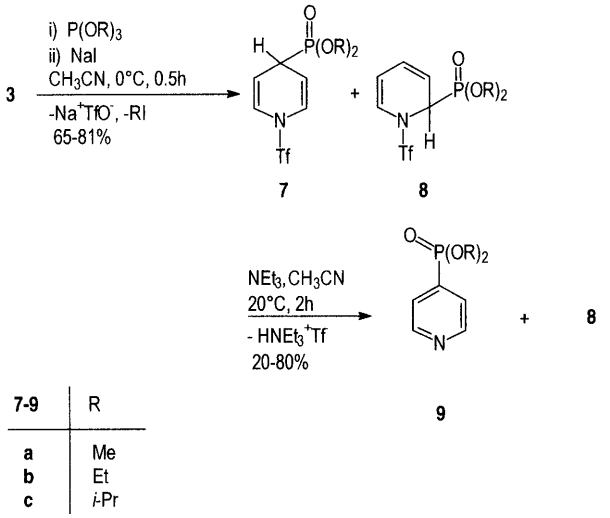
6	R	R'
a	Ph	Ph
b	Ph	Bu

Scheme 1

For reasons which are obvious from the introductory part, in the present paper we summarize our efforts which finally led to C2/C4-bis[$PO(OR)_2$]- and C2/C4-$PO(OR)_2$/PR_3^+-disubstituted pyridines. The investigation presented here takes advantage of the observation that, obviously, the *N*-SO_2CF_3 substituent plays an exceptional role (*vide supra*), which can be understood on the basis of ab initio and semiempirical MO calculations.[14]

$PO(OR)_2$-Monosubstituted 1,4- and 1,2-Dihydropyridines 7 and 8, Synthesis of the C4-$PO(OR)_2$ Compounds 9

The procedure applied (Scheme 2) reflects our efforts to extend the previously described method to phosphites under special consideration of a procedure described by Akiba.[15] From the investigations presented here, we have drawn to the conclusion that the degree of the regioselective C4 attack depends to a significant extent on small changes in the $P(OR)_3$ reactant. The extremely high C4 regioselectivity of the basic reaction (Scheme 1) was conserved in the case of the $P(OEt)_3$ nucleophile, resulting in the exclusive formation of **7b** (Table 1). Both the sterically less demanding methyl, as well as the "larger" isopropyl phosphites, yielded an excess of the corresponding C4 phosphonates (**7a** and **c**, respectively) with varying amounts of the C2-substituted isomers **8a** and **c**. Furthermore, while in the case of PR_3 nucleophiles the isolation of intermediate dihydropyridines was impossible, their $PO(OR)_2$ analogs **7** and **8** turned out to be sufficiently stable.[16] Nevertheless, at room temperature, compounds **7** slowly decompose to give product mixtures already containing **9**.



Scheme 2

This synthesis does not afford the isolation of the salt **3**; pyridine was reacted with trifluoromethanesulfonic anhydride (**2**), after 30 minutes (0 °C, CH_3CN) the trialkyl phosphites were added. To increase the yields of **7** and **8**, these reactions were performed in the presence of an equimolar amount of NaI.[17] The resulting **7**/**8** molar ratios are summarized in Table 1.

Table 1. Products **7**, **8** and **9**

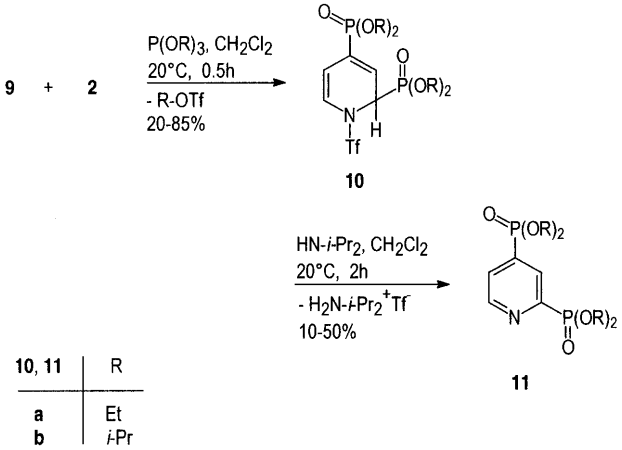
Product	R	Yield (%)	bp (°C/mbar) or mp (°C)	Ratio[a] (**7**/**8**)
7a, 8a	Me	85	100/0.39	95:5
7b, 8b	Et	65	115/0.66	100:0
7c, 8c	*i*-Pr	67	120/0.44	60:40
9a	Me	76 (30)[b]	65/0.15	–
9b	Et	80 (20)[b]	100/0.4	–
9c	*i*-Pr 5	4	43–44	

[a] Determined by ^1H NMR.
[b] Deprotonation with HN-*i*-Pr_2 in CH_2Cl_2, values in brackets: with NEt_3 in CH_3CN.

The mixtures from **7** and **8** were dissolved in CH_3CN (or CH_2Cl_2) and deprotonated with NEt_3 (or HN-***i***-Pr_2).[18] Surprisingly, and fortunately, the C2-substituted dihydropyridines **8** remain unaffected and, therefore, the C4-substituted pyridines **9** can be isolated without contamination with C2 isomers (Table 1).

2,4-Bis[$PO(OR)_2$]-Disubstituted 1,2-Dihydropyridines 10a and b and the Corresponding Pyridines 11a and b

The monosubstituted C4 (dialkoxyphosphoryl)pyridines **9** exhibit sufficient N-nucleophilicity to act as acceptor for the triflyl group of **2** to yield the intermediate *N*-triflyl salts. These salts were reacted with $P(OEt)_3$ to give the 1,2-dihydropyridines **10a** (R = Et, Scheme 3). The deprotonation of the latter seems to be the limiting factor; though under the influence of the base (HN-*i*-Pr_2), the target compound **11a** was synthesized and isolated (50%), unfortunately the re-formation of **9** competes with the formation of **11**. After addition of the base, the crude reaction mixture consists of **11a** (ca. 63%) and **9a** (ca. 37%), (**11b**, **9b**: 10%, 90%).



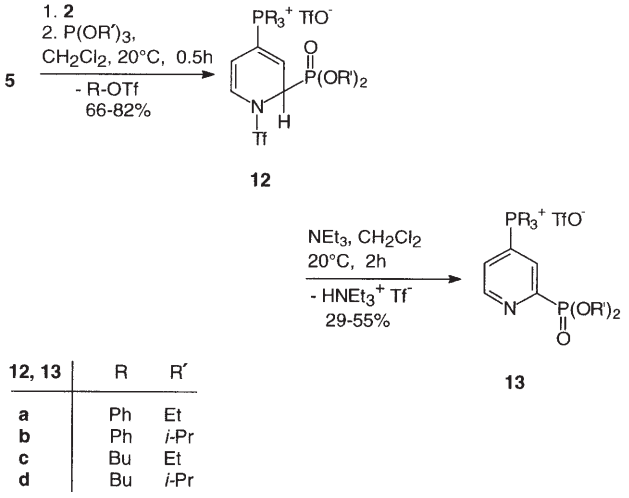
Scheme 3

C2-$PO(OR)_2$/C4-PR_3^+-Disubstituted 1,2-Dihydropyridines 12a–d and the Corresponding Pyridines 13a–d

Comparable to the preceding procedure, the phosphonium salts **5** allow (after their transformation with **2** into the cor-

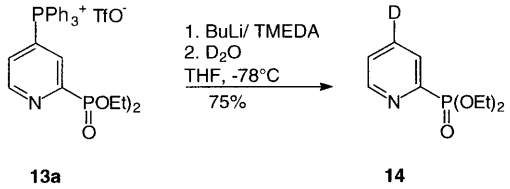
responding N^+-triflyl biscations) the regiospecific C2 attack of trialkyl phosphites giving the appropriate 1,2-dihydropyridines **12a–d** (Scheme 4). Again, this reaction was performed under very mild conditions. The instability of **12a–d** is not expressed to the extent as observed for dihydropyridines **10**. Deprotonation of compounds **12** with NEt_3 yielded the disubstituted pyridines **13**. The yields turn out to be superior to those obtained for the bis(dialkoxyphosphoryl)-substituted derivatives **11**. Minor amounts of the starting material **5a** were formed in the course of the deprotonation of the 1,2-dihydropyridines **12a** and **b**.

Interestingly, the phosphonium group of compound **13a** can be exchanged by deuterium under very mild conditions, e.g. if the salt was reacted with BuLi/TMEDA in THF at –78°C, followed by addition of D_2O (Scheme 5). Under these conditions, the (diethoxyphosphoryl) group remains unaffected and 4-deutero-2-(diethoxyphosphoryl)pyridine (**14**) was obtained in acceptable yield.



12, 13	R	R′
a	Ph	Et
b	Ph	*i*-Pr
c	Bu	Et
d	Bu	*i*-Pr

Scheme 4



Scheme 5

Attempts to synthesize related compounds from C2-PR_3^+- or C2-$PO(OR)_2$-substituted pyridine precursors,[8,19] and $P(OR)_3$ via the corresponding *N*-trifylpyridinium salts have not been successful.

As compounds **13a–d** represent the first examples of an N-heteroaromatic ring substituted by both (dialkoxyphosphoryl) and phosphonio moieties, the structure of [2-(diisopropoxyphosphoryl)-4-pyridyl]triphenylphosphonium trifluoromethanesulfonate (**13b**, Figure) was determined by X-ray single crystal diffraction. In the crystal, the conformation with the P=O bond orthogonal to the pyridine ring plane turns out to be the preferred conformer. It is noteworthy that the semiempirically (PM3) calculated structure agrees acceptably well with the X-ray data.

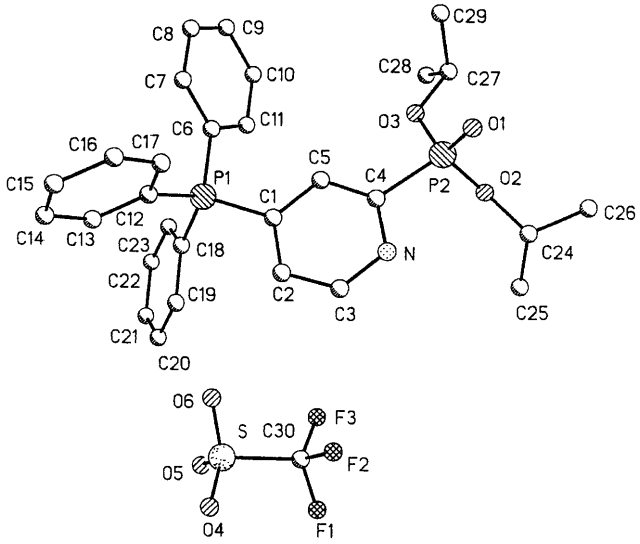


Figure. X-ray structure of **13b**. Hydrogen atoms are omitted. The Ol atom turns out to be almost orthogonal to the ring system. Selected bond lengths (Å) and angles (°): P2-C41.809(2), P1-C1 1.813(2), N-C41.337(3), N-C31.335(3), P1-C61.791(2), P2-O1 1.454(2), P2-O2 1.562(2), P1 C1 C2 C3 178.2, P2 C4 C5 C1 174.9.

The novel method presented here allows access to new bis[$PO(OR)_2$]-, as well as (for the first time), mixed di-($PO(OR)_2$/PR_3^+)-substituted pyridines *without the preceding introduction of other functional groups.*

NMR spectra were recorded on a Bruker AC250 spectrometer. Chemical shifts (δ) are given in ppm downfield from TMS. Coupling constants are given in Hz. The degree of substitution of C atoms was determined from DEPT-135 spectra. Structure determinations were made with the aid of CH-COSY experiments. IR spectra were recorded on a BIO-RAD FTS-25 spectrometer. EI Mass spectra (70 eV) were recorded using a FisonsTrio 2000 spectrometer (cations were detected with FAB). Microanalyses were obtained with a LECO CHNS-932 element analyzer. Analytical TLC silica gel 60 F_{254} plates were purchased from Merck, Darmstadt. The mps are uncorrected. All solvents used were purified by distillation and dried by standard methods. Trifluoromethanesulfonic anhydride (**2**) was purchased from Merck, the phosphites from Aldrich. All operations were carried out under Ar or N_2 atmosphere. Specific details are described in the text.

4-(Dialkoxyphosphoryl)-1-(trifluoromethylsulfonyl)-1,4-dihydropyridines 7; General Procedure:

To a stirred solution of pyridine (0.79 g, 10 mmol) in CH_3CN (50 mL) was added trifluoromethanesulfonic anhydride (**2**) (2.82 g, 10 mmol) dropwise. The solution was kept at 0 °C for 0.5 h. The trialkyl phosphite (11 mmol) and NaI (1.5 g, 10 mmol) were added over 0.5 h at 0 °C. The mixture was allowed to warm to r.t. and then heated to 50 °C for 10 min. The solvent was evaporated in vacuo to dryness. The residue was treated with CH_2Cl_2 (30 mL). The suspension was filtered, the solvent was evaporated from the filtrate, and the resulting crude product mixture (**7** and **8**) was purified by bulb tube distillation, which yielded **7**.

4-(Dialkoxyphosphoryl)pyridines 9; General Procedure:

Method A: The first part of the procedure is analogous to the procedure for **7**. Specific details: after addition of the trialkyl phosphite (11 mmol) and NaI (1.5 g, 10 mmol), the solution was stirred for 1 h

Table 2. Spectroscopic Data of the Compounds **7a–c** and **9a–c**[a]

Product	IR ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ, J (Hz)	EI MS (70 eV) m/z (%)
7a	2146, 1635, 1407, 1231, 1198, 1043, 604, 589	3.45 (d, 1 H, $^2J_{PH}$ = 30, Py H-4), 3.75 (d, 6 H, J = 11, CH_3), 5.15 (m, 2 H, Py H-3/5), 6.47 (q, 2 H, Py H-2/6)	33.9 (d, 1 C, $^1J_{CP}$ = 148, Py C-4), 53.46 (d, 2 C, $^2J_{CP}$ = 7.4, CH_3), 105.35 (d, 2 C, $^3J_{CP}$ = 10, Py C-2/6), 119.455 (q, 1 C, J_{CF} = 324.7, CF_3), 123.47 (d, 2 C, $^2J_{CP}$ = 10, Py C-3/5)	321 (M^+, 2.5)
7b	1636, 1412, 1233, 1199, 1023, 603, 589	1.2 (t, 6 H, J = 7, CH_3), 3.32 (d, 1 H, $^2J_{PH}$ = 20, Py H-4), 4.02 (m, 4 H, CH_2), 5.07 (m, 2 H, Py H-3/5), 6.35 (m, 2 H, Py H-2/6)	15.98 (s, 2 C, CH_3), 33.96 (d, 1 C, $^1J_{CP}$ = 148, Py C-4), 62.22 (s, 2 C, CH_2), 105.58 (d, 2 C, $^3J_{CP}$ = 9.6, Py C-2/6), 123.03 (d, 2 C, $^2J_{CP}$ = 11, Py C-3/5), 119.3 (q, 1 C, J_{CF} = 323.71, CF_3)	349 (M^+, 24)
7c	2153, 1633, 1410, 1231, 1193, 994, 602, 565	1.29 (m, 12 H, CH_3), 3.36 (d, $^2J_{PH}$ = 30, Py H-4), 4.70 (m, 2 H, CH), 5.15 (m, 2 H, Py H-3/5), 6.42 (m, 2 H, Py H-2/6)	23.78 (m, 4 C, CH_3), 34.45 (d, 1 C, $^1J_{CP}$ = 2.4, Py C-4), 71.28 (d, 2 C, $^2J_{CP}$ = 7.4, CH), 105.87 (d, 2 C, $^3J_{CP}$ = 9.6, Py C-2/6), 122.88 (d, 1 C, $^2J_{CP}$ = 10.6, Py C-3/5), 119.40 (q, 1 C, J_{CF} = 324, CF_3)	377 (M^+, 22)
9a	1637, 1567, 1461, 1409, 1232, 1196, 1043, 783, 530	3.75 (d, 6 H, J = 11, CH_3), 7.59 (dd, 2 H, J = 4.3, $^3J_{PH}$ = 14.3, Py H-3/5), 8.73 (t, 2 H, J = 6.2, Py H-2/6)	53.00 (d, 2 C, $^2J_{CP}$ = 5.7, CH_3), 125.26 (d, 2 C, $^2J_{CP}$ = 8.2, Py C-3/5), 135.99 (d, $^1J_{CP}$ = 186.61, Py C-4), 150.12 (d, 2 C, $^3J_{C,P}$ = 14.7, Py C-2/6)	188 (M^+, 100)
9b	1654, 1589, 1478, 1403, 1253, 1142, 1020, 794, 536	1.09 (t, 6 H, J = 1 Hz, CH_3), 3.89 (m, 4H, CH_2), 7.39 (dd, 2H, J = 4.3, $^3J_{PH}$ = 13, Py H-3/5), 8.49 (t, 2 H, J = 6, Py H-2/6)	15.66 (d, 2 C, $^3J_{CP}$ = 6, CH_3-C), 62.16 (d, 2 C, $^2J_{CP}$ = 6, CH_2-C), 124.67, (d, 2C, $^2J_{CP}$ = 8, Py C-3/5), 137.45 (d, 1 C, $^1J_{CP}$ = 185.73, Py C-4), 149.98 (d, 2 C, $^3J_{CP}$ = 12, Py C-2/6)	215 (M^+, 57)
9c	1713, 1588, 1467, 1403, 1258, 1142, 983, 773, 545	1.22 (dd, 12 H, J = 5, 4^J_{PH} = 33.5, CH_3), 4.74 (m, 2 H, CH), 7.63 (dd, 2 H, J = 4.3, $^3J_{PH}$ = 13.3, Py H-3/5), 8.73 (t, 2 H, J = 6, Py H-2/6)	23.88 (d, 2 C, $^3J_{CP}$ = 13.4, CH_3-C), 71.68 (d, 1 C, $^2J_{CP}$ = 6, CH-C), 125.23 (d, 2 C, $^2J_{CP}$ = 8, Py C-3/5), 139.08 (d, 1 C, $^1J_{CP}$ = 186, Py C-4), 149.83 (d, 2 C, $^3J_{CP}$ = 12,3 Py C-2/6)	243 (M^+, 5)

[a] Satisfactory microanalyses obtained: C ± 0.38, H ± 0,47, N ± 0. 18; **9a**, **9b** as picrates.

Table 3. Spectroscopic Data of the Compounds **10a** and **12a–d**[a]

Product	Yield (%)	IR ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	MS (70 eV) m/z (%)
10a	85	1719, 1410, 1249, 1168, 1034, 766, 638, 588	1.33 (m, 12 H, CH_3), 4. 16 (m, 8 H, CH_2), 5.18 (dm, 1 H, $^2J_{PH}$ = 25, Py H-2), 5.96 (t, 1 H, $^3J_{PH}$ = 7.5, Py H-5), 6.50 (m, 2 H, Py H-3/6)	(EI) 486 (M^+, 12)
12a	66	3067, 1726, 1626, 1587, 1440, 1414, 1230, 1159, 1108, 1028, 634, 524	1.34 (t, 6 H, J = 7, CH_3), 4.14 (m, 4 H, CH_2), 5.48 (dd, 1 H, J = 6.7, $^2J_{PH}$ = 22, Py H-2), 5.73 (t, 1 H, J = 7, Py H-5), 6.41 (dm, 1 H, $^3J_{PH}$ = 20, Py H-3), 6.78 (d, 1 H, J = 6.7, Py H-6), 7.70 (m, 15 H, Ph H) (	(FAB) 610 M-I, 15)
12b	78	3066, 1719, 1627, 1587, 1440, 1415, 1286, 1231, 1170, 1110, 1029, 635, 524	1.28 (dd, 6 H, J = 6.4, $^4J_{PH}$ = 19, CH_3), 4.81 (m, 2 H, CH), 5.35 (m, 1 H, Py H-2), 5.82 (dd, 1 H, J = 7.5, $^3J_{PH}$ = 15, Py H-5), 6.37 (m, 1 H, Py H-3), 6.77 (d, 1 H, J = 6.5, Py H-6), 7.55 (m, 15 H, Ph H) (	(FAB) 638 M-I, 14)
12c	77	2967, 2939, 2877, 1723, 1618, 1463, 1414, 1283, 1230, 1029, 804, 638	0.90 (t, 9 H, J = 7, CH_3), 1.31 (m, 18 H, Bu CH_2 Et CH_3), 2.34 (m, 6 H, P-CH_2), 4.13 (m, 4 H, Et CH_2), 5.34 (dd, 1 H, J = 6.5, $^2J_{PH}$ = 22, Py H-2), 6.15 (t, 1 H, J = 7, H-5), 6.59 (m, 2 H, Py H-3/6)	(FAB) 550 (M-I, 100)
12d	82	2967, 2939, 2877, 1722, 1631, 1463, 1411, 1282, 1230, 1028, 805, 638	0.89 (t, 9 H, J = 6.6, Bu CH_3), 1.25 (dd, 6 H, J = 4.5, $^4J_{PH}$ = 31, *i*-Pr CH_3), 1.34 (m, 12 H, Bu CH_2), 2.33 (m, 6 H, P-CH_2), 4.76 (m, 2 H, CH), 5.25 (dd, 1 H, J = 8, $^2J_{PH}$ = 25, Py H-2), 6.08 (m, 1 H, Py H-5), 6.73 (m, 2 H, Py H-3/6)	(FAB) 578 (M-I, 14)

[a] **10b**: Yield 20%, decomposition at 160°C, MS (EI) 542 (M^+, 4).

at 0°C and NEt_3 (1.0 g, 10 mmol) was added. After another 0.5 h, the mixture was allowed to warm to r.t. The solvent was evaporated in vacuo and the residue was treated with 5% aq $NaHCO_3$ (25 mL). Extraction with CH_2Cl_2, drying ($MgSO_4$) and evaporation of the solvent yielded the crude product (brown oil) of compounds **9**, which were purified by bulb tube distillation.

Method B: This method does not afford the N_2 atmosphere. The resulting mixture of the dihydropyridines **7** and **8** (10 mmol) was dissolved in CH_2Cl_2 (50 mL), and HN-*i*-Pr_2 (1.0 g, 10 mmol) was added. The mixture was stirred for 2 h, and the solvent was evaporated under reduced pressure. The residue was allowed to stand for 8 h (at ca. 6°C). Then, the solution was decanted from the precipitated ammonium salt.

Table 4. Spectroscopic and Physical Data of the Compounds **11a** and **b**, and **13a–d**[a]

Product	Yield (%)	mp (°C) or bp (°C)/mbar	IR ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ, J (Hz)	MS (70 eV) m/z (%)
11a	50	175/0.05	1727, 1642, 1582, 1446, 1392, 1366, 1256, 1022, 972, 828, 794, 555	1.32 (m, 12 H, CH_3), 4.15 (m, 8H, CH_2), 7.77 (dm, 1 H, $^3J_{PH}$ = 12.5, Py H-3), 8.22 (dd, 1 H, J = 6.5, $^3J_{PH}$ = 13, Py H-5), 8.90 (t, 1 H, J = 4.8, Py H-6)	16.25, 16.35 (s, 2 C, CH_3), 62.99 (d, 1 C, $^2J_{CP}$ = 6, CH_2), 63.24 (d, 1 C, $^2J_{CP}$ = 6, CH_2), 127.51 (dd, 1 C, $^2J_{CP}$ = 8.5, Py C-3), 128.97 (dd, 1 C, $^4J_{CP}$ = 8.5, $^2J_{CP}$ = 26, Py C-5), 138.22 (dd, 1 C, $^3J_{CP}$ = 12, $^1J_{CP}$ = 186, Py C-4), 150.17 (dd, 1 C, $^3J_{CP}$ = 12, $^3J_{CP}$ = 22, Py C-6), 152.4 (dd, 1 C, $^3J_{CP}$ = 12, $^1J_{CP}$ = 228, Py C-2)	(EI) 352 (M^+, 4)
11b	10	155–l70/ 0.05	1712, 1652, 1581, 1466, 1386, 1255, 989, 888, 817, 769, 556	1.38 (dd, 12 H, J = 7.5, $^4J_{PH}$ = 42.5, CH_3), 4.67 (m, 2 H, CH), 4.89 (m, 2 H, CH), 7.73 (dm, 1 H, $^3J_{PH}$ = 12.5, Py H-3), 8.18 (dd, 1 H, J = 6.4, $^3J_{PH}$ – 13, Py H-5), 8.86 (t, 1 H, J = 4.8, Py H-6)	23.81, 24.03 (t, 2 C, $^3J_{CP}$ = 3.7, CH_3), 71.84 (d, 2 C, $^2J_{CP}$ = 6, CH), 127.12 (dd, 1 C, $^2J_{CP}$ = 3.8, $^2J_{CP}$ = 8.4, Py C-3), 128.49 (dd, 1 C, $^4J_{CP}$ = 8.5, $^2J_{CP}$ = 25, Py C-5), 139.41 (dd, 1 C, $^3J_{CP}$ = 11, $^1J_{CP}$ = 187, Py C-4), 150.35 (dd, 1 C, $^3J_{CP}$ = 12, $^3J_{CP}$ = 22, Py C-6), 153.76 (dd, 1 C, $^3J_{CP}$ = 12, $^1J_{CP}$ = 228, Py C-2)	(FAB) 408 (M^+, 100)
13a	50	128	3062, 1585, 1482, 1438, 1270, 1225, 1152, 1109, 1032, 638, 524	1.31 (t, 6 H, J = 7, CH_3), 4.23 (m, 4 H, CH_2), 7.77 (m, 16 H, Ph, H-3), 7.96 (dd, 1 H, J = 6.5, $^3J_{PH}$ = 13, H-5), 9.23 (t, 1 H, J = 5, H-6)	16.23 (d, 2 C, $^3J_{CP}$ = 6.25, CH_3), 64.03 (d, 2 C, $^2J_{CP}$ = 6.4, CH_2), 115.31 (d, 3 C, $^1J_{CP}$ = 90, Ph C-1), 120.47 (q, 1 C, J_{CF} = 320, CF_3), 130.25 (m, 3 C, Py C-3/5/4), 131.10 (d, 6 C, $^3J_{CP}$ = 13, Ph C-3/5), 134.63 (d, 6 C, $^2J_{CP}$ = 10.5, Ph C-2/6), 137.33 (d, 3 C, $^4J_{CP}$ = 3, Ph C-4), 153.60 (dd, 1 C, $^3J_{CP}$ = 12, $^3J_{CP}$ = 21.5, Py C-6)	(FAB) 476 (M-I, 85)
13b	55	114–118	1585, 1569, 1440, 1260, 1225, 1153, 1108, 1034, 638, 525	1.29 (dd, 6 H, J = 6, $^4J_{PH}$ = 20, CH_3), 4.84 (m, 2 H, CH), 7.7 (m, 17 H, Ph, H-3/5), 9.22 (t, 1 H, J = 5, H-6)	23.80 (dd, 2 C, J = 5, $^3J_{CP}$ = 12.4, CH_3), 73.13 (d, 2 C, $^2J_{CP}$ = 6.4, CH), 115.40 (d, 3 C, $^1J_{CP}$ = 89, Ph C-1), 122.39 (q, 1 C, J_{CF} = 320.79, CF_3), 129.32 (dd, 1 C, $^3J_{CP}$ = 12.5, $^1J_{CP}$ = 83, Py C-4), 129.44 (dd, 1 C, $^4J_{CP}$ = 8.5, $^2J_{CP}$ = 26, Py C-5), 129.94 (dd, 1 C, $^2J_{CP}$ = 3.5, $^2J_{CP}$ = 8. 1, Py C-3), 131.1 (d, 6 C, $^3J_{CP}$ = 13, Ph C-3/5), 134.61 (d, 6 C, $^2J_{CP}$ = 10.5, Ph C-2/6), 136.39 (d, 3 C, $^4J_{CP}$ = 3, Ph C-4), 152.73 (dd, 1 C, $^3J_{CP}$ = 12, $^3J_{CP}$ = 21.5, Py C-6), 155.81 (dd, 1 C, $^3J_{CP}$ = 9, $^1J_{CP}$ = 228, Py C-2)	(FAB) 504 (M-I, 12)
13c	30	oily product	2964, 2936, 2874, 1742, 1635, 1575, 1467, 1371, 1261, 1156, 1029, 638, 573	0.89 (t, 9 H, J = 5.5, Bu CH_3), 1.29 (t, 6 H, J = 7, Et CH_3), 1.45 (m, 12 H, Bu CH_2), 2.60 (m, 6 H, Bu CH_2), 4.24 (m, 4 H, Et CH_2), 8.04 (dd, 1 H, J = 6, $^3J_{PH}$ = 11, Py H-3), 8.24 (dd, 1 H, J = 5, $^3J_{PH}$ = 12, Py H-5), 9.13 (t, 1 H, J = 4.5, Py H-6)	13.27 (s, 3 C, Bu CH_3), 16.32 (d, 2 C, $^3J_{CP}$ = 6, Et CH_3), 18.83 (d, 3 C, $^1J_{CP}$ = 47.5, Bu P-CH_2), 23.72 (m, 8 C, Bu CH_2), 63.96 (d, 2 C, $^2J_{CP}$ = 6.3, Et CH_2); 123.83 (q, 1 C, J_{CF} = 318, CF_3), 127.99 (dd, 1 C, $^4J_{CP}$ = 6.4, $^2J_{CP}$ = 26, Py C-5), 128.52 (dd, 1 C, $^2J_{CP}$ = 3.3, $^2J_{CP}$ = 7. 1, Py C-3), 129. 17 (dd, 1 C, $^3J_{CP}$ = 12.4, $^1J_{CP}$ = 72.1, Py C-4), 152.45 (dd, 1 C, $^3J_{CP}$ = 8.8, $^3J_{CP}$ = 21.5, Py C-6), 154.24 (dd, 1 C, $^1J_{CP}$ = 7.9, J_{CP} = 226, Py C-2)	(FAB) 417 (M-I+1, 100)
13d	29	oily product	2965, 2936, 2874, 1725, 1633, 1575, 1467, 1379, 1260, 1224, 1154, 998, 638, 573	0.89 (t, 9 H, J = 7, Bu CH_3), 1.30 (dd, 12 H, J = 6, $^4J_{PH}$ = 22.5, *i*-Pr CH_3), 1.46 (m, 12 H, Bu CH_2), 2.63 (m, 6 H, Bu CH_2), 4.81 (m, 2 H, *i*-Pr CH), 8.02 (dd, 1 H, J = 6.5, $^3J_{PH}$ = 12, Py H-3), 8.21 (dm, 1 H, $^3J_{PH}$ = 12, Py H-5), 9.11 (t, 1 H, J = 4.5, Py H-6)	13.24 (s, 3C, Bu CH_3), 18.63 (d, 3 C, $^1J_{CP}$ = 47, Bu P-CH_2), 23.63 (m, 10 C, *i*-Pr CH_3, Bu CH_2), 72.97 (d, 2 C, $^2J_{CP}$ = 6.5, CH), 129.7 (q, 1 C, J_{CF} = 320, CF_3), 127.72 (dd, 1 C, $^4J_{CP}$ = 8.5, $^2J_{CP}$ = 26, Py C-5), 128.34 (dd, $^2J_{CP}$ = 4, $^2J_{CP}$ = 7, Py C-3), 128.96 (dd, 1 C, ^3J = 12.5, $^1J_{CP}$ = 72.5, Py C-4), 152.41 (dd, 1 C, $^3J_{CP}$ = 9, $^3J_{CP}$ = 22, Py C-6), 155.30 (dd, 1 C, $^3J_{CP}$ = 8, $^1J_{CP}$ = 227, Py C-2)	(FAB) 444 (M-I, 9)

[a] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.31, N ± 0.29, S ± 0.16.

To separate minor amounts of impurities to get analytical purity, it is useful to perform a bulb tube distillation, or TLC (silica gel, EtOAc).

Disubstituted Pyridines 11a and b, and 13a–d; General Procedure:
To a stirred solution of **9** or **5**[5] (5 mmol) in CH_2Cl_2 (50 mL), **2** (1.4 g, 5 mmol) was added dropwise at r.t. A clouding of the solution was observed in the case of **11**, and **13c** and **d**. After 0.5 h the trialkyl phosphite (6 mmol) was added. The solution became transparent after a few minutes, then NEt_3 (0.6 g, 6 mmol) was added. The mixture was stirred for 2 h, and the solvent was evaporated in vacuo. Specific details for the synthesis of compounds **11**a and **b**, **13a–d** are given below.

2,4-Bis(dialkoxyphosphoryl)pyridines 11:
Under Et_2O, the residue was cooled (6 °C) for 8 h. Then, the precipitated ammonium salt was filtered off and the solvent was evaporated. The residue (a yellow-brown oil) was purified by TLC (silica gel, EtOAc/MeOH 10:1).

[2-(Dialkoxyphosphoryl)-4-pyridyl]triphenylphosphonium Trifluoromethanesulfonates 13a and b:
The residue was treated with 5% aq $NaHCO_3$ (25 mL), extracted with CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$), and evaporated to give the crude

Table 5. ^{31}P NMR Spectral Data for Selected Compounds[a]

Product	^{31}P NMR ($CDCl_3$) δ, J (Hz) P-2	P-4
7b	–	q, 20.5, J_{PF} = 2.8
11a	d, 10.62, J_{PP} = 11.2	d, 14.49, J_{PP} = 11.2
13a	d, 8.17, J_{PP} = 9.3	d, 23.82, J_{pp} = 9.2
13b	qui, 6. 19, J = 7.4	23.81
13c	qui, 8.72, J = 7.6	33.45
14	12.04	–

[a] Shifts downfield of 85% H_3PO_4 are reported as positive.

product (white-brown solid). Unreacted **5a** was separated by fractional crystallization from EtOAc.

Tributyl[2-(dialkoxyphosphoryl)-4-pyridyl]phosphouium Trifluoromethanesulfonates 13c and d:
Similar to the procedure for **13a** and **b**, but it was necessary to transform the resulting oil to the corresponding pyridinium triflate, which separated from the solution. This material was treated with 5% aq $NaHCO_3$ (25 mL). Repeating the above procedure (extraction with CH_2Cl_2, drying with $MgSO_4$) a brown oil was separated after addition of Et_2O. The dihydropyridines **10** and **12** were isolated after completion of the addition of trialkyl phosphites. After addition of Et_2O a brown oil separated. After concentration in vacuo, the residue **12a** and b was dissolved in EtOAc. The solution was filtered off from the precipitated solid.

4-Deuterio-2-(diethoxyphosphoryl) pyridine (14):
To a stirred solution of**13a** (0.16 mmol) in THF (10mL) at –78 °C was added a cooled mixture (–78 °C) of 1.6 M BuLi in hexane (0.3mL) and TMEDA (0.48 mmol) in THF (5 mL). After 20 min, the solution was warmed to –50°C, D_2O (0.8 mmol) was added, and the mixture stirred for 30 min at this temperature. The mixture was allowed to warm to r.t. slowly before the THF was evaporated under reduced pressure. The residue was treated with 5% aq $NaHCO_3$ (10mL). Extraction with CH_2Cl_2, drying ($MgSO_4$) and evaporation of the solvent yielded the crude product **14**, which was purified by TLC (silica gel, EtOAc); oily product; yield: 75%.

^{1}H NMR ($CDCl_3$): δ = 1.35 (t, 6 H, J =7.1 Hz, CH_3), 4.21 (m, 4H, CH_2), 7.42 (m, 1 H, Py H-5), 7.98 (d, 1 H, $^3J_{P,H}$ = 6.7 Hz, Py H-3), 8.85 (d, 1 H, $^3J_{P,H}$ = 4.8 Hz, Py H-6).
^{13}C NMR ($CDCl_3$): δ = 16.27 (d, 2 C, $^3J_{C,P}$ = 6.0 Hz, CH_3), 63.03 (d, 2 C, $^2J_{C,P}$ = 5.8 Hz, CH_2), 125.95 (d, 1C, $^4J_{C,P}$ = 4.0 Hz, Py C-5), 128.06 (d, 1C,$^2J_{C,P}$ = 25.25 Hz, Py C-3), 135.85 (dt, 1 C, $J_{C,D}$ = 25.35 Hz, $^3J_{C.P}$ = 12.37 Hz, Py C-4), 150.47 (d, 1 C, $^3J_{C,P}$ = 22.9 Hz, Py C-6), 150.47 (d, 1 C, $^1J_{C,P}$ = 227.25 Hz, Py C-2).
IR (film): ν = 1637, 1567, 1461, 1409, 1232, 1196, 1043, 783, 530 cm$^{-1.}$
MS (EI): m/z (%) = 217 (M^+, 100).

X-ray Crystallographic Data of 13b:
$[C_{29}H_{32}NO_3P_2]^+$ $CF_3SO_3^-$, Mr = 653.6 g mol$^{-1,}$ colorless quader, size 0.40 × 0.40 × 0.38 mm^3, triclinic, space group *P1*, a = 9.810(1), b = 10.849(1), c = 14.943(2) Å, α = 81.76(1), β = 83.48(1), γ = 88.61(1)°, V = 1563.7 (3) Å^3, Z = 2, $p_{calcd.}$ = 1.388 g cm^{-3}, μ(Mo-Kα) = 2.67 cm^{-1}, F(000) = 680.

Data collection: The intensity data for the compound were collected on an Enraf–Nonius CAD4 diffractometer, using graphite-monochromated Mo-Kα radiation and ω-2Θ scan technique at –90°C. 6606 reflections in ±h, ±k, +l were measured in the range 2.38 ≤ Θ ≤ 26.30, of which 6352 were independent reflections (R_{int} = 0.015). 5647 reflections having I > 2σ (I). Data were corrected for Lorentz and polarization effects, but not for absorption.[20]

Structure Solution andRefinement: The structure was solved by direct methods (SHELXS[21]) and refined by full-matrix least squares techniques against F^2 (SHELXL-93[22]). The hydrogen atoms were included at calculated positions with fixed thermal parameters; all nonhydrogen atoms were refined anisotropically. The refinement converged for 388 parameters at R = 0.043, wR^2 = 0.117 and GOOF = 1.13. The difference Fourier synthesis on the basis of the final structural model showed[23] a maximum of 0.88 e Å^{-3} and a minimum of – 0.45 e Å^{-3}. XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representation.

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