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Synthesis of Pyridiniumboranephosphonate Diesters and Related Compounds using Trityl Cation as a Borane Hydride Acceptor

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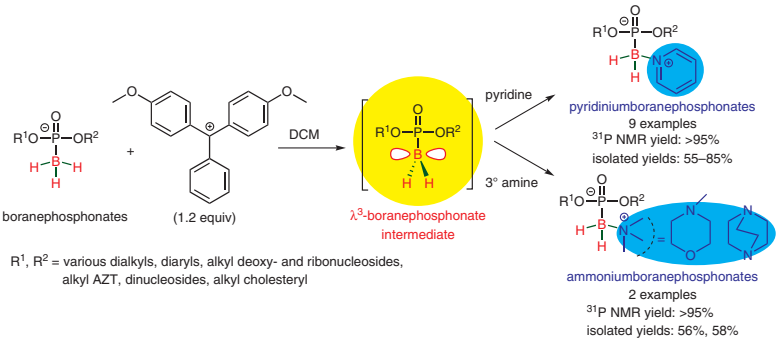

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Abstract Boranephosphonate diesters react with pyridine and some tertiary amines in the presence of dimethoxytrityl chloride used as a borane hydride acceptor, to afford the boron-modified phosphodiester analogues containing a P-B-N structural motif. The reaction provides a convenient entry to pyridinium- and ammoniumboranephosphonates derived from the corresponding alkyl, aryl, or nucleoside boranephosphonate diesters. Some aspects of the synthetic protocol, mechanistic features related to a possible intermediate involved, and the role of the solvents used, are discussed.

Key words H-phosphonates, boranephosphonates, pyridiniumboranephosphonates, trityl cation, nucleotide analogues

Boranephosphonates, analogues of natural phosphate esters in which one of the non-bridging oxygen atoms is replaced with a -BH_3 group, were introduced to nucleic acid chemistry by Sood, Shaw and Spielvogel in 1990.[1] Due to their close structural and electronic resemblance to natural phosphates (albeit with distinct differences), these compounds can,[2] on the one hand, serve as substrates for RNA and DNA polymerizing enzymes,[3] but, on the other hand, biopolymers containing this functionality are resistant to various RNA/DNA hydrolysing enzymes.[4] This constitutes the basis for the use of boranephosphonates as tools for reading, writing and modulating genetic information.[5]

Pyridiniumboranephosphonate diesters are a new class of boranephosphonate analogues[2] with a molecular complexity built around the boron center.[6] This new structural and electronic P-B-N framework of a betaine type can open new avenues for applications of nucleoside and nucleic acids boranephosphonate analogues in medicine, medicinal diagnostic or material sciences; for example, for selective deposition of metal nanostructures on the surface of oligonucleotides[6,7] or to facilitate the uptake of negatively charged oligonucleotides endowed with such a structural motif to cancer cells.[6] It is expected that the P–B–N bond system present in pyridiniumboranephosphonates and related compounds will contribute to the development of new boron-based pharmacophores[8] and may find various applications in the design of therapeutic nucleic acids.[9]

Until now there has been only one method for the synthesis of pyridiniumboranephosphonate diesters, developed by Caruthers et al.,[6] which consisted of oxidation of boranephosphonate diesters with iodine in the presence of pyridine.[6] Given the new perspectives and potential importance of this class of compounds in medicinal chemistry[2] and in material sciences,[6,7] we have been searching for new synthetic alternatives for their preparation. In this work we have been inspired by the known instability of boranephosphonates during removal of trityl protecting groups.[4b,10] This phenomenon was traced back to the generation of a trityl cation under the deprotection process, which caused partial deboronation and decomposition of boranephosphonate diesters. To remedy this problem, the detritylation protocol for protected boranephosphonates was modified to include trityl cation scavengers in a form of boraneamine complexes[4b] or alkylsilanes.[10b,11] Working towards another goal, Wada et al.[12] took advantage of the instability of boranephosphonate in the presence of the trityl cation to develop the -BH_3 group as a protection for the P-H functionality and demonstrated that boranephosphonate diesters can be efficiently converted into the parent H-phosphonate diesters using dimethoxytritanol and trifluoroacetic acid.

Since formation of pyridiniumboranephosphonates from the boranephosphonates in the presence of iodine is formally a simple substitution of a borane hydride by a pyridine moiety, for our part, we attempted to use a trityl cation as the hydride acceptor to furnish this substitution process. Our recent mechanistic studies on oxidative transformations of boranephosphonate diesters promoted by

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iodine suggested formation of highly electrophilic λ^3-boranephosphonate as a key intermediate[13] in this process. Here, we argue that trityl cation-promoted instability of boranephosphonate diesters may involve an analogous reaction pathway (shown in Scheme 1) with generation of an electrophilic λ^3-boranephosphonate as an intermediate. Such reaction, when carried out in the presence of pyridine (or 3° amines), should result in capture of the λ^3-boranephosphonate intermediate and lead to the formation of pyridiniumboranephosphonates (or the corresponding ammoniumboranephosphonates).

In this paper we describe a novel synthesis of pyridinium- and ammoniumboranephosphonate diesters from the corresponding boranephosphonates via a trityl cation-mediated abstraction of the borane hydride in the presence of pyridine and some 3° amines.

A general synthetic strategy for the preparation of pyridiniumboranephosphonate diesters **3** and related compounds **4** (structures shown in Scheme 2, Scheme 3, and Scheme 4) is depicted in Scheme 2. This consists of the synthesis of boranephosphonate diesters **2** from readily available H-phosphonate precursors **1** by using reported protocols[2] (first step, boronation), followed by oxidative transfor-

Biographical Sketches

Marta Rachwalak graduated from Adam Mickiewicz University in Poznań, Poland in 2014, and in the same year started her doctoral studies at the Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań. She received her Ph.D. in 2020 under the supervision of Prof. Jacek Stawinski and Dr. Joanna Romanowska. Her research interests include biological chemistry, especially new nucleotide analogues of biological importance.

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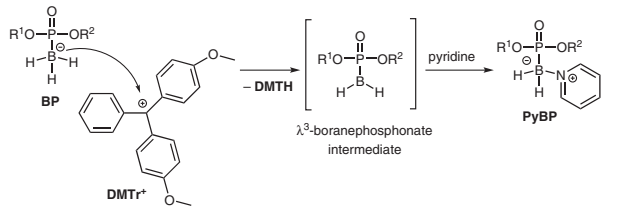
Tomasz Jakubowski studied chemistry at the University of Wrocław, Poland, and obtained his master's degree in 2011. After a few years in industry, in 2014 he became a Ph.D. student at the Institute of Bioorganic Chemistry, Polish Academy of Sciences in Poznań. He received his Ph.D. degree in 2020 working under the supervision of Prof. Jacek Stawinski. His professional interests include bioorganic chemistry, in particular the chemistry and biological properties of nucleotide analogues, and teaching chemistry.

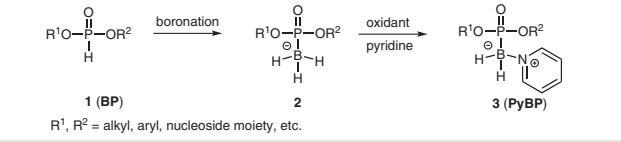
Jacek Stawinski is a Professor of Chemistry at the Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland, and Professor Emeritus at Stockholm University, Stockholm, Sweden. Since 1984, he has been conducting research and teaching in both institutions. His main research interests are in the synthetic and mechanistic chemistry of nucleic acids, bioorganic phosphorus chemistry (especially the chemistry of H-phosphates and nucleotide analogues), and the chemistry of lipids.



BP = boranephosphonate; **PyBP** = pyridiniumboranephosphonate
DMTr$^+$ = 4,4'-dimethoxytrityl cation; **DMTH** = phenyl-di(4-methoxyphenyl)methane

Scheme 1 A postulated mechanism for the formation of pyridiniumboranephosphonate diesters **PyBP** from boranephosphonates **BP** promoted by a trityl cation

mation of **2** into pyridiniumboranephosphonates **3**. For the latter step, we considered the use of a trityl cation as a borane hydride acceptor in the presence of pyridine or a 3° amine, and this is the main focus of this paper.



R^1, R^2 = alkyl, aryl, nucleoside moiety, etc.

Scheme 2 A synthetic scheme for the conversion of H-phosphonate diesters **1** into the corresponding pyridiniumboranephosphonate derivatives **3** via boranephosphonates **2** as synthetic intermediates

To provide a proof of principle for the mechanism-based transformation shown in Scheme 1, we added to the reaction mixture containing a model substrate, diethyl boranephosphonate **2a** (for compounds numbering, see Scheme 3) in pyridine, dimethoxytrityl chloride (DMTr-Cl, 1.2 equiv) as a source of a trityl cation. It was rewarding to observe that in the first ^{31}P NMR spectrum recorded (after 5 min), all the starting material **2a** (resonating at ca. 92 ppm) had disappeared, and a major signal at ca. 60 ppm due to pyridiniumboranephosphonate **3a** emerged (ca. 90%). This was confirmed by ^{11}B NMR analysis of the reaction mixture in which the signal from **2a** at ca. –39 ppm was replaced with a new resonance from **3a** at ca. –13 ppm. Apart from this desired product, small signals at ca. 27 ppm (9%) and 7.5 ppm (2%), assigned to diethyl dimethoxytritylphosphonate and diethyl H-phosphonate, respectively, could be detected by ^{31}P NMR spectroscopy.

This experiment clearly showed that DMTr$^+$ is an effective borane hydride acceptor and could be a viable alternative to iodine used as an oxidant for this purpose. We speculated that formation of the side-products in this reaction was due to incomplete capture of λ^3-boranephosphonate intermediate by pyridine. This could lead to a partial deboronation and liberation of the corresponding H-phosphonate diester (see below) that, under the reaction conditions, reacted further with DMTr-Cl to produce diethyl dimethoxytritylphosphonate as another side product.[12]

To optimize this tentative protocol for preparative purposes, additional experiments were carried out. First, we were interested to find out whether the amount of pyridine used in the reaction could be reduced without compromising the capture efficiency of the postulated λ^3-boranephosphonate intermediate. To this end we reacted diethyl boranephosphonate **2a** in acetonitrile with the added pyridine (20 equiv) in the presence of DMTr-Cl (1.2 equiv). Under these conditions we observed only a slight drop in the efficiency of formation of pyridiniumboranephosphonate **3a** (85% vs. 89%), and also the expected trend in the side products distribution; that is, more diethyl H-phosphonate (9%) and less of the corresponding dimethoxytritylphosphonate (5%). A further reduction in the amount of pyridine (10 equiv) led to a reduction in the yield of pyridinium boranephosphonate **3a** by favoring the formation of diethyl H-phosphonate (15%) and its P-dimethoxytritylated derivative (6%) (^{31}P NMR experiments). The replacement of DMTr-Cl by trityl chloride (Tr-Cl) made the reaction of **2a** with pyridine (20 equiv) rather sluggish (3.5 h vs. 5 min to reach completion) and more of the side product, diethyl H-phosphonate (20%), was observed. This apparently reflected the lower ability of Tr-Cl vs. DMTr-Cl to form ionic pairs in acetonitrile solution due to differences in the stability of the corresponding trityl cations.

Since acetonitrile is a strongly participating solvent in reactions involving the generation of electron-deficient λ^3-boranephosphonate species,[13] we anticipated that its replacement by dichloromethane (DCM) as a reaction medium may affect the outcome of this reaction. Indeed, we found that in the reaction in DCM (**2a**, 20 equiv of pyridine, 1.2 equiv of DMTr-Cl) the extent of side product formation was significantly suppressed (only 3% of the P-C side product) but the rate of the reaction remained similar to that in acetonitrile (completion within 5 min). With less pyridine used (5–10 equiv), additional amounts of diethyl H-phosphonate (ca. 3%) were formed (^{31}P NMR experiments).

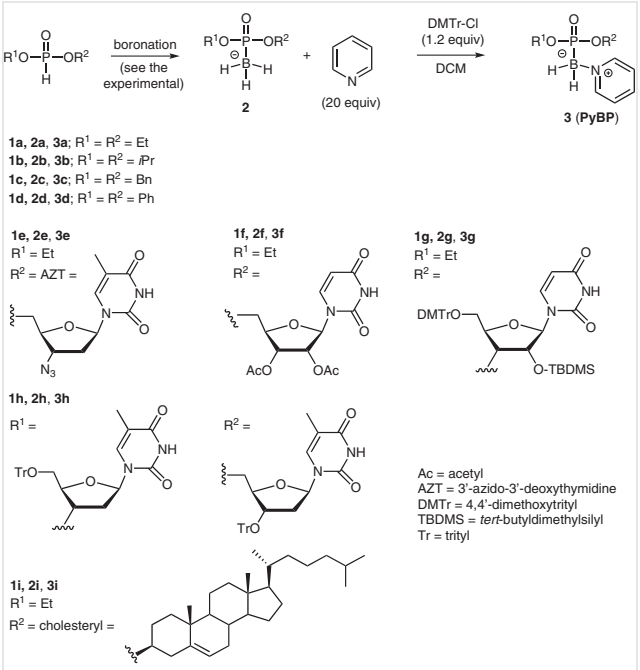
Before proceeding to preparative runs, we briefly studied some mechanistic aspects of the investigated reaction, relevant to its synthetic applications. First, we wanted to find out what products are formed when a model boranephosphonate **2a** reacts with DMTr-Cl in acetonitrile or dichloromethane without pyridine (the preactivation process), which, under normal reaction conditions, would capture the incipient electrophilic species, λ^3-boranephosphonate intermediate. To this end, **2a** was reacted with DMTr-Cl (2 equiv) in both of these solvents. We found that the preactivation in acetonitrile (NMR experiments) rapidly (ca. 30 sec) afforded an intermediate (ca. 90%; δ_P = 59 ppm and δ_B = –25 ppm) identified as an acetonitrile–diethyl λ^3-boranephosphonate adduct[13] (formed via capture of an electrophilic λ^3-boranephosphonate intermediate by acetonitrile), and diethyl H-phosphonate (10%, δ_P = 7.5 ppm).[14] Upon addition of pyridine, the acetonitrile–λ^3-boranephosphonate adduct (δ_P = 59 ppm) underwent con-

version into the desired product, pyridiniumboranephosphonate **3a**. The analogous reaction in dichloromethane was less efficient and gave a complex mixture of products containing unreacted starting material **2a** (ca. 20%), variable amounts of mono-, di- and trichloroboranephosphonates (ca. 60%), and diethyl H-phosphonate (ca. 20%). These remained practically unchanged upon addition of pyridine, indicating that chloroboranephosphonate diesters are apparently not intermediate in the formation of pyridiniumboranephosphonates **3**. An interesting observation was that when the preactivation reaction in dichloromethane was carried out in the presence of the added chloride anions (tetra-*n*-butylammonium chloride, 3 equiv) only unreacted starting material **2a** (60%) and diethyl H-phosphonate (40%) could be detected. This supported the view that generation of H-phosphonate diesters in the preactivation process and in the regular reaction with pyridine, was due to formation of chloroboranephosphonate derivatives, which collapsed to the parent H-phosphonate and the borane part[13] due to π-donation from the chlorine to the boron atom. In line with this, the addition of chloride anions (tetra-*n*-butylammonium chloride, 3 equiv) to the generated acetonitrile–λ^3-boranephosphonate adduct (δ_P = 59 ppm) caused a complete deboronation to diethyl H-phosphonate.

As to the preferred solvent for the reaction under study, DCM vs. MeCN, the above experiments pointed to DCM because of the slower oxidation of **2** by DMTr-Cl in DCM (lower polarity and less efficient ionization to $DMTr^+$ than in acetonitrile); a λ^3-boranephosphonate intermediate apparently could be more easily trapped by the pyridine present in the reaction mixture, resulting in less side products formation. In addition, since for more bulky substrates (e.g., nucleoside boranephosphonate diesters) in dichloromethane we did not observe (^{31}P NMR spectroscopy) any side product formation, we used DCM as a solvent, pyridine (20 equiv) and DMTr-Cl (1.2 equiv) for our synthetic protocol for the preparation of pyridiniumphosphonate diesters **3** (Scheme 3).

As synthetic targets for testing the generality of this approach and the utility of $DMTr^+$ as a borane hydride acceptor, we chose pyridiniumboranephosphonate diesters **3** with diverse structural features (Scheme 3).

Thus, as substrates for our reaction we selected (i) symmetrical boranephosphonate diesters **2** with simple alkyls (ethyl, **2a**), branched alkyls (isopropyl, **2b**), reactive alkyls (benzyl, **2c**), simple aryls (phenyl, **2d**), and (ii) mixed boranephosphonate diesters **2** all bearing ethyl group and an antiviral nucleoside (AZT derivative, **2e**), a protected 5′-ribonucleoside (**2f**), a protected 3′-ribonucleoside (**2g**), a cholesteryl moiety (**2i**), or two nucleoside groups (5′- and 3′-tritylated thymidine, **2h**). The entire synthesis was rather straightforward and uneventful, and proved to be effective for all compounds investigated. Progress of each of the reactions was checked by ^{31}P NMR spectroscopy, which indicated that yields of pyridiniumboranephosphonates **3** were



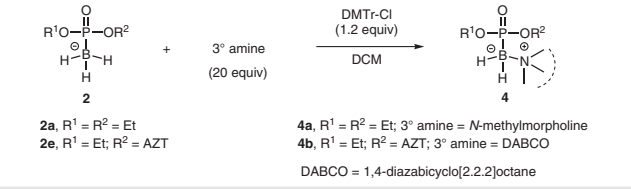
Scheme 3 A synthetic scheme for the preparation of pyridiniumboranephosphonate diesters **3** from the corresponding boranephosphonates **2** mediated by dimethoxytrityl chloride (DMTr-Cl)

>95% in all instances. One should note, however, that isolated yields of **3** depended on R^1 and R^2 (55–85%), and this we ascribed to losses during chromatography, and, possibly, a partial instability during the purification process.[15]

Since in both reaction steps in Scheme 2 and Scheme 3, the boronation of H-phosphonates **1** and oxidative transformation of boranephosphonates **2** were usually clean and efficient (^{31}P NMR experiments), we attempted to combine them into a one-pot reaction to further simplify and shorten the synthesis of pyridiniumboranephosphonates **3**. To check the efficacy of this approach, H-phosphonate diester **1e** (ethyl, AZT derivative) or **1h** (a dinucleoside derivative) was silylated in DCM using trimethylsilyl chloride (TMS-Cl, 3 equiv) to convert it into the corresponding tervalent bissilyl phosphite, and then treated with BH_3-dimethylsulfide complex (2 equiv). After quenching of the reaction mixture with aq. ammonia and evaporation to dryness, the crude product (**2e** or **2h**) was reacted in DCM with DMTr-Cl (1.2 equiv) in the presence of pyridine (20 equiv). In both instances, the ^{31}P NMR spectrum showed that formation of **2** and **3** was virtually quantitative, and the desired products, pyridiniumboranephosphonates **3e** and **3h**, were isolated in total 50 and 72% yields, respectively.

To explore a possible application of a $DMTr^+$-mediated oxidation of boranephosphonate diesters **2** for the preparation of complexes of λ^3-boranephosphonate with 3° amines,[16] that is, ammoniumboranephosphonate derivatives of type **4**, we carried out ^{31}P NMR studies on the reaction shown in Scheme 4, in which pyridine was replaced

with a 3° amine. For this purpose we reacted simple diethyl boranephosphonate **2a** and *N*-methylmorpholine or boranephosphonate **2e** bearing a known antiviral nucleoside moiety (AZT) with bicylic diamine DABCO, in the presence of DMTr-Cl in DCM.



Scheme 4 Exemplary syntheses of ammoniumboranephosphonates **4** from boranephosphonates **2** and selected 3° amines

In both instances ^{31}P and ^{11}B NMR spectroscopy showed rapid (<5 min) and efficient formation of the expected ammoniumboranephosphonates **4a** and **4b**, respectively (>95%; δ_P = 59 and δ_B = –17 ppm for **4a**, and δ_P = 61 and δ_B = –13 ppm for **4b**), which were isolated in >50% yields by silica gel chromatography.

Finally, some comments related to the possible substrate scope of the investigated reaction. On mechanistic grounds, the reaction relies on the ability of a trityl cation to accept a borane hydride and thus it can be of crucial importance for any process that may be affected by the concentration of a free trityl cation or its reactivity under the reaction conditions. In this context, of significance could be formation of trityl cation complexes with pyridines[17] (or 3° amines used for the reaction) that can deplete effective concentration of a trityl cation and may themselves have different borane hydride acceptor properties.[17a] To address this issue we reacted a model boranephosphonate diester **2a** in DCM with 10 equiv of 2,6-lutidine (2,6-Lu), 3-hydroxypyridine (3-OHPy), 4-methoxypyridine (4-MeOPy), or 4-cyanopyridine (4-CNPy) in the presence of DMTr-Cl (1.2 equiv). Preliminary ^{31}P NMR experiments (spectra recorded after 5 min) showed that only for 4-cyanopyridine the reaction was almost as efficient as that for pyridine. For the other pyridine derivatives, the corresponding diethyl pyridiniumboranephosphonates of type **3** (structures not shown), were formed as minor products (20% for 2,6-Lu, 38% for 3-OHPy, and 10% for 4-MeOPy), with a significant portion of unreacted starting material **2a** (40, 25 and 60%, respectively), and the deboronation product, diethyl H-phosphonate (40, 38, and 30%, respectively). The reaction mixtures remained unchanged within an hour, indicating that apparently the DMTr-Cl was completely consumed. We interpreted these results as indicating the formation of stable complexes between dimethoxytrityl cation and 2,6-Lu, 3-OHPy and 4-MeOPy that could not act as efficient borane hydride acceptors. In line with this, no reaction was observed when 2,6-lutidine was mixed in dichloromethane with DMTr-Cl prior to the addition of boranephosphonate **2a**.[18] In contradistinction to this, the premixing of DMTr-Cl with pyridine, did not affect the oxidation efficiency of the added boranephosphonate **2a**. This apparently pointed to higher equilibrium concentration of a dimethoxytrityl cation in complexes with unsubstituted pyridine and 4-CNPy vs. pyridines with electron-donating substituents (e.g., 4-MeOPy). These studies will be the subject of further investigations in this laboratory.

To sum up, we have developed a new synthetic protocol for the preparation of pyridiniumboranephosphonates **3** under mild conditions that consists of oxidation of boranephosphonate diesters **2** in the presence of pyridine using dimethoxytrityl cation as a borane hydride acceptor. This protocol is also applicable to the synthesis of ammoniumboranephosphonate diesters **4** bearing 3° amines in place of a pyridine residue. The method is simple, efficient, and thus DMTr-Cl can be considered as a viable alternative to the iodine-promoted synthesis of this class of compounds. This protocol can be further simplified by combining the preparation of boranephosphonates **2** and their oxidative transformations towards the P-B-N derivatives of type **3** and **4** into a one-pot reaction to make the transformation more effective in terms of both time and the chemicals used.

Further studies exploring scope and limitations of $DMTr^+$ as an acceptor of borane hydrides for oxidative transformations of boranephosphonates, and its underlying mechanism, are in progress in this laboratory.

All reagents were of analytical grade, obtained from commercial suppliers, and used without further purification. The anhydrous solvents used for the reactions were stored over molecular sieves 4 Å. TLC analyses were carried out on Merck silica gel 60 F 254 precoated plates using a DCM–MeOH 9:1 (v/v) solvent system. All evaporations were carried out on rotatory evaporators under reduced pressure at 40 °C.

The NMR spectra were recorded with a Bruker Avance II 400 MHz instrument. The chemical shifts are reported in ppm, relative to solvent peaks (^1H, ^{13}C NMR), 2% H_3PO_4 solution in D_2O (^{31}P NMR), and BF_3-diethyl etherate (^{11}B NMR). Assignment of the NMR signals was accomplished based on the expected chemical shift values, splitting pattern of the signals, and 2D correlation experiments. High-resolution mass spectra (HRMS) were recorded with a Thermo Fisher Scientific Q-Exactive Orbitrap mass spectrometer.

For compounds **3e–i** and **4b**, due to the presence of two P-diastereomers and similar chemical shifts of the protons in the 3′- and 5′-nucleoside units, multiplicity and overlapping of the resonances were observed in the ^1H NMR spectra. For this reason, only selected diagnostic signals are listed. Purity of the isolated compounds was >97% (^1H NMR spectroscopy).

H-Phosphonate diesters **1a–d** are commercial products and **1e–i** were obtained by condensation of the corresponding H-phosphonate monoesters with suitable alcohols using standard reported procedures.[19]

Synthesis of Boranephosphonate Diesters 2; General Procedure

All boranephosphonate diesters **2** were obtained by using modified reported procedures.[13a,20]

H-Phosphonate diester **1** (**1a–i**; 1 mmol) was placed in a 250 mL pear-shaped flask and dried by evaporation of the added anhydrous DCM (2 × 20 mL), and dissolved in the same solvent (30 mL). To this, trimethylsilyl chloride (3 equiv) and triethylamine (3 equiv) were added. The reaction mixture was stirred for 5 min, then dimethyl sulfide borane (BH_3-SMe_2, 2 equiv) was added to the generated silyl phosphite derivative. The reaction mixture was stirred for another 15 min, and progress of the reaction was monitored by ^{31}P NMR spectroscopy. After completion, the reaction was quenched with 25% aq. ammonia (10 mL) and the mixture was concentrated to a gum. The residue was dissolved in a small amount of DCM, applied on a silica gel column and eluted with a gradient of MeOH in DCM (0–5%, v/v). Fractions containing the desired compound were collected and evaporated, to yield **2a–i** as white, amorphous solids (Et_3N salts, 70–90% yield).

Diethyl Boranephosphonate (2a)[13a]

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 93.0 (br q, $^1J_{P-B}$ = 138.2 Hz).

^{11}B NMR (128 MHz, $CDCl_3$, 25 °C): δ = –40.3 (dq, $^1J_{P-B}$ = 138.3 Hz, $^1J_{B-H}$ = 91.3 Hz).

HRMS: *m*/*z* [M^-] calcd for $C_4H_{13}BO_3P^-$: 151.0701; found: 151.0688.

Diisopropyl Boranephosphonate (2b)

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 96.6 (br q, $^1J_{P-B}$ = 128.4 Hz).

^{11}B NMR (128 MHz, $CDCl_3$, 25 °C): δ = (dq, $^1J_{P-B}$ = 129.8 Hz, $^1J_{B-H}$ = 91.5 Hz).

HRMS: *m*/*z* [M^-] calcd for $C_6H_{17}BO_3P^-$: 179.1014; found: 179.1003.

Dibenzyl Boranephosphonate (2c)

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 97.7 (br q, $^1J_{P-B}$ = 121.4 Hz).

^{11}B NMR (128 MHz, $CDCl_3$, 25 °C): δ = –39.6 to –42.6 (br).

HRMS: *m*/*z* [M^-] calcd for $C_{14}H_{17}BO_3P^-$: 275.1014; found: 275.1017.

Diphenyl Boranephosphonate (2d)

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 90.3 (br q, $^1J_{P-B}$ = 124.1 Hz).

^{11}B NMR (128 MHz, $CDCl_3$, 25 °C): δ = –37.2 to –41.2 (br).

HRMS: *m*/*z* [M^-] calcd for $C_{12}H_{13}BO_3P^-$: 247.0701; found: 247.0700.

3′-Deoxy-3′-azidothymidin-5′-yl Ethyl Boranephosphonate (2e)

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 93.0–99.5 (br).

^{11}B NMR (128 MHz, $CDCl_3$, 25 °C): δ = –38.8 to –43.9 (br).

HRMS: *m*/*z* [M^-] calcd for $C_{12}H_{20}BN_5O_6P^-$: 372.1250; found: 372.1250.

2′,3′-*O*,*O*-Diacetyluridine-5′-yl Ethyl Boranephosphonate (2f)

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 98.5–102.9 (br).

^{11}B NMR (128 MHz, $CDCl_3$, 25 °C): δ = –39.3 to –41.5 (br).

HRMS: *m*/*z* [M^-] calcd for $C_{15}H_{23}BN_2O_{10}P^-$: 433.1189; found: 433.1190.

5′-*O*-Dimethoxytrityl-2′-*O*-*tert*-butyldimethylsilyuridin-3′-yl Ethyl Boranephosphonate (2g)

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 94.0–98.6 (br).

$^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$, 25 °C): δ = –38.2 to –42.8 (br).

HRMS: *m*/*z* [M^-] calcd for $C_{38}H_{51}BN_2O_{10}PSi^-$: 765.3149; found: 765.3156.

5′-*O*-Tritylthymidin-3′-yl 3′-*O*-Tritylthymidin-5′-yl Boranephosphonate (2h)[13a]

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 92.8–96.2 (br).

^{11}B NMR (128 MHz, $CDCl_3$, 25 °C): δ = –38.9 to –41.8 (br).

HRMS: *m*/*z* [M^-] calcd for $C_{58}H_{57}BN_4O_{11}P^-$: 1027.3860; found: 1027.3879.

Cholester-3-yl Ethyl Boranephosphonate (2i)

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 98.5–102.4 (br).

^{11}B NMR (128 MHz, $CDCl_3$, 25 °C): δ = –39.2 to –43.6 (br).

HRMS: *m*/*z* [M^-] calcd for $C_{29}H_{53}BO_3P^-$: 491.3831; found: 491.3834.

Synthesis of Pyridiniumboranephosphonate Diesters 3; General Procedure

Boranephosphonate diester **2** (**2a–i**; 0.5 mmol) was dried by evaporation of the added anhydrous DCM (2 × 20 mL) and dissolved in the same solvent (3 mL). To this, pyridine (20 equiv), followed by dimethoxytrityl chloride (1.2 equiv), were added. After stirring for 5 min, a ^{31}P NMR spectrum was recorded (a broad signal at δ_P ~60 ppm corresponding to the expected pyridiniumboranephosphonate diester **3**). After completion, the reaction mixture was evaporated to dryness, the residue was dissolved in a small amount of acetonitrile and applied on a silica gel column. Products **3** were isolated using a gradient of water in acetonitrile (0–3%, v/v). Fractions containing the desired products were collected and evaporated, to yield **3a–i** as white, amorphous solids.

Diethyl Pyridiniumboranephosphonate (3a)

Yield: 55% (63 mg).

^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.03 (t, $^3J_{H-H}$ = 7.1 Hz, 6 H, 2 × -CH_3), 3.77 (q, $^3J_{H-H}$ = 6.3 Hz, 4 H, 2 × -CH_2-), 7.47–7.53 (m, 2 H, H2Py, H6Py), 7.91–7.98 (m, 1 H, H4Py), 8.48–8.51 (m, 2 H, H3Py, H5Py).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.6 (d, $^3J_{P-C}$ = 5.6 Hz), 58.6 (d, $^2J_{P-C}$ = 6.5 Hz), 125.9 (d, *J* = 2.1 Hz), 140.6 (d, *J* = 3.2 Hz), 148.1 (d, *J* = 6.8 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 60.2 (br q, $^1J_{P-B}$ = 184.9 Hz).

$^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$, 25 °C): δ = –13.2 (d, $^1J_{P-B}$ = 183.1 Hz).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{18}BNO_3P^+$: 230.1117; found: 230.1102.

Diisopropyl Pyridiniumboranephosphonate (3b)

Yield: 63% (81 mg).

^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.07 (d, $^3J_{H-H}$ = 6.2 Hz, 6 H, 2 × -CH_3*i*Pr), 1.14 (d, $^3J_{H-H}$ = 6.2 Hz, 6 H, 2 × -CH_3), 4.44–4.57 [m, 2 H, 2 × -CH(OH)-], 7.52–7.59 (m, 2 H, H2Py, H6Py), 7.96–8.04 (m, 1 H, H4Py), 8.57–8.63 (m, 2 H, H3Py, H5Py).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 24.3 (d, $^3J_{P-C}$ = 3.2 Hz), 66.1 (d, $^2J_{P-C}$ = 7.00 Hz), 125.8 (d, *J* = 2.3 Hz), 140.7 (d, *J* = 3.5 Hz), 147.9 (d, *J* = 6.9 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, 25 °C): δ = 58.3 (br).

$^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$, 25 °C): δ = –12.5 (d, $^1J_{P-B}$ = 183.9 Hz).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{22}BNO_3P^+$: 258.1430; found: 258.1412.

Dibenzyl Pyridiniumboranephosphonate (3c)

Yield: 87% (154 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.88 (dd, $^2J_{H–H}$ = 12.4 Hz, $^3J_{P–H}$ = 7.2 Hz, 2 H, -CH_2-), 4.97 (dd, $^2J_{H–H}$ = 12.35 Hz, $^3J_{P–H}$ = 7.8 Hz, 2 H, -CH_2-), 7.15–7.28 (m, 10 H, Bz), 7.35–7.41 (m, 2 H, H2Py, H6Py), 7.83–7.89 (m, 1 H, H4Py), 8.38–8.44 (m, 2 H, H3Py, H5Py).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 64.1 (d, $^2J_{P–C}$ = 6.6 Hz), 125.6 (d, *J* = 2.5 Hz), 127.1, 127.2, 127.9, 137.9 (d, *J* = 5.8 Hz), 140.5 (d, *J* = 3.5 Hz), 147.5 (d, *J* = 6.7 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, 25 °C): δ = 61.4 (br).

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C): δ = –15.7 (br).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}BNO_3P^+$: 354.1430; found: 354.1422).

Diphenyl Pyridiniumboranephosphonate (3d)

Yield: 85% (138 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.99 (m, 2 H, 2 × H4Ph), 7.11 (m, 4 H, 2 × H2Ph, 2 × H6Ph), 7.17 (m, 4 H, 2 × H3Ph, 2 × H5Ph), 7.39–7.47 (m, 2 H, H2Py, H6Py), 7.87–7.94 (m, 1 H, H4Py), 8.38–8.43 (m, 2 H, H3Py, H5Py).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 120.7 (d, $^3J_{P–C}$ = 3.9 Hz), 123.5, 125.9 (d, *J* = 2.3 Hz), 129.3, 141.0 (d, *J* = 3.5 Hz), 147.6 (d, *J* = 6.7 Hz), 151.3 (d, $^2J_{P–C}$ = 8.9 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, 25 °C): δ = 57.1 (br).

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C): δ = –15.2 (d, $^1J_{P–B}$ = 159.6 Hz).

HRMS (ESI–): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}BNO_3P^+$: 326.1117; found: 326.1100.

3′-Deoxy-3′-azidothymidin-5′-yl Ethyl Pyridiniumboranephosphonate (3e)

Yield: 71% (160 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.14–1.22 (m, 3 H, -CH_3Et), 1.86–1.93 (m, 3 H, C5-CH_3), 2.14–2.27 (m, 1 H, C2′-H_A), 2.27–2.37 (m, 1 H, C2′-H_B), 3.89–3.99 (m, 2 H, C5′-CH_2-), 4.00–4.04 (1 H, C3′-H), 4.06–4.14 (1 H, C4′-H), 4.21–4.29 (m, 1 H, -CH_2-H_AEt), 4.36–4.41 (m, 1 H, -CH_2-H_BEt), 6.23–6.30 (m, 1 H, C1′-H), 7.57 (s, 1 H, C6-H), 7.59–7.67 (m, 2 H, H2Py, H6Py), 8.02–8.10 (m, 1 H, H4Py), 8.61–8.68 (m, 2 H, H3Py, H5Py), 9.86 (s, 1 H, N3-H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.3, 16.6, 37.5, 37.6, 58.8, 59.2, 60.9, 61.0, 62.1, 62.4, 83.1, 83.3, 84.4, 111.2, 111.3, 127.1, 135.3, 140.9, 148.0, 150.5, 164.1.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, 25 °C): δ = 62.04 (br).

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C): δ = –15.9 (br).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{25}BN_6O_6P^+$: 451.1666; found: 451.1642.

2′,3′-*O*,*O*-Diacetyluridine-5′-yl Ethyl Pyridiniumboranephosphonate (3f)

Yield: 63% (161 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, diagnostic signals): δ = 1.16 (t, $^3J_{H–H}$ = 6.4 Hz, 3 H, -CH_3Et), 1.19 (t, $^3J_{H–H}$ 6.4 Hz, 3 H, -CH_3Et), 1.99–2.02 (m, 6 H, -CH_3Ac), 2.06 (s, 3 H, -CH_3Ac), 2.08 (s, 3 H, -CH_3Ac), 5.61 (d, $^3J_{H–H}$ = 8.2 Hz, 1 H, =C5-H), 5.68 (d, $^3J_{H–H}$ = 8.2 Hz, 1 H, =C5-H), 6.18 (d, $^3J_{H–H}$ = 6.9 Hz, 1 H, C1′-H), 6.22 (d, $^3J_{H–H}$ = 6.0 Hz, 1 H, C1′-H), 7.59–7.65 (m, 4 H, H2Py, H6Py), 7.76 (d, $^3J_{H–H}$ = 8.2 Hz, =C6-H), 7.83 (d, $^3J_{H–H}$ = 8.2 Hz, =C6-H), 7.98–8.08 (m, 2 H, H4Py), 8.61–8.68 (m, 4 H, H3Py, H5Py).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.5, 16.55, 16.6, 16.65, 20.3, 20.46, 20.49, 59.3, 59.36, 59.6, 59.7, 61.3, 61.4, 61.7, 61.8, 71.2, 71.4, 772.9, 81.9, 81.97, 82.0, 82.1, 85.1, 85.3, 103.1, 103.2, 126.19 (d, *J* = 2.59 Hz), 126.22 (d, *J* = 2.59 Hz), 139.6, 139.65, 140.9 (d, *J* = 3.45 Hz), 140.99 (d, *J* = 3.46 Hz), 148.0 (*J* = 7.15 Hz), 148.1 (*J* = 6.78 Hz), 150.7, 163.3, 169.5, 169.5, 169.54, 169.6, 169.65.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, 25 °C): δ = 62.3 (br).

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C): δ = –15.8 (br).

HRMS (ESI–): *m*/*z* [M–H]$^-$ calcd for $C_{20}H_{26}BN_3O_{10}P^-$: 510.1449; found: 510.1462.

5′-*O*-Dimethoxytrityl-2′-*O*-*tert*-butyldimethylsilyluridin-3′-yl Ethyl Pyridiniumboranephosphonate (3g)

Yield: 38% (161 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, diagnostic signals): δ = 0.23 (m, 6 H, 2 × -CH_3 *t*BDMS), 0.98 (s, 9 H, 3 × -CH_3 *t*BDMS), 3.89 (s, 6 H, 2 × -CH_3 DMTr), 5.3–5.37 (m, 1 H, =C5-H), 6.02 (d, $^3J_{H–H}$ = 5.2 Hz, 1 H, C1′-H), 7.75–7.82 (m, 2 H, H2Py, H6Py), 8.16–8.23 (m, 1 H, H4Py), 8.72–8.81 (m, 2 H, H3Py, H5Py), 9.82 (s, 1 H, N3-H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –4.96, 16.7, 18.0, 18.2, 25.3, 25.6, 25.7, 55.2, 58.1, 59.1, 59.4, 62.4, 62.7, 64.2, 70.7, 71.8, 75.3, 75.4, 82.95, 83.2, 8.2, 87.8, 87.9, 102.3, 113.2, 126.0, 127.1, 127.9, 128.1, 130.16, 130.24, 135.0, 135.1, 140.2, 141.9, 144.2, 148.1, 148.2, 150.9, 158.6, 163.3.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, 25 °C): δ = 60.55 (br).

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C): δ = –13.0 (br).

HRMS (ESI–): *m*/*z* [M–H]$^-$ calcd for $C_{43}H_{54}BN_3O_{10}PSi^-$: 842.3409; found: 842.3434.

5′-*O*-Tritylthymidin-3′-yl 3′-*O*-Tritylthymidin-5′-yl Pyridiniumboranephosphonate (3h)

Yield: 61% (337 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, diagnostic signals): δ = 1.46 and 1.48 (s, 3 H, C5-CH_3), 1.94–1.98 (s, 3 H, C5-CH_3), 6.36–6.46 (m, 1 H, C1′-H), 6.51–6.61 (m, 1 H, C1′-H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.5, 11.6, 12.3, 39.2, 39.4, 39.9, 62.6, 62.65, 63.1, 63.15, 63.8, 73.7, 75.0, 75.2, 84.2, 84.3, 84.75, 84.8, 84.9, 885.0, 85.18, 85.2, 87.56, 87.6, 87.88, 87.9, 111.1, 111.2, 111.5, 126.2, 126.3, 127.4, 127.9, 128.0, 128.1, 128.6, 128.7, 128.73, 135.3, 135.4, 135.9, 141.3, 141.4, 143.1, 143.9, 144.0, 147.7, 147.8, 147.83, 147.9, 150.5, 150.8, 163.9.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, 25 °C): δ = 61.5 (br).

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C): δ = –13.7 (br).

HRMS (ESI–): *m*/*z* [M–H]$^-$ calcd for $C_{63}H_{60}BN_5O_{11}P^-$: 1104.4120; found: 1104.4142.

Cholester-3-yl Ethyl Pyridiniumboranephosphonate (3i)

Yield: 55% (157 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, diagnostic signals): δ = 3.85–4.02 (m, 2 H, -CH_2-Et), 4.07–4.20 (m, 1 H, C3-H), 5.24–5.35 (m, 1 H, =C6-H), 7.57–7.66 (m, 2 H, H2Py, H6Py), 8.00–8.08 (m, 1 H, H4Py), 8.63–8.72 (m, 2 H, H3Py, H5Py).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.8, 16.6 (d, $^3J_{P–C}$ = 5.9 Hz), 18.6, 19.3, 20.95, 22.5, 22.8, 23.7, 24.2, 27.9, 28.2, 30.3, 31.8 (d, $^3J_{P–C}$ = 3.7 Hz), 35.7, 36.1, 36.4, 37.1, 39.4, 39.7, 40.7 (d, $^3J_{P–C}$ = 5.6 Hz), 42.2, 49.95, 56.04, 56.6, 58.4 (d, $^2J_{P–C}$ = 6.5 Hz), 72.9 (d, $^2J_{P–C}$ = 6.8 Hz), 121.9 (d, *J* = 2.6 Hz), 125.8, 140.4, 140.5 (d, *J* = 3.3 Hz), 148.1 (d, *J* = 6.95 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, 25 °C): δ = 59.1 (br).

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C): δ = –15.3 (br).

HRMS (ESI–): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{58}BNO_3P^+$: 570.4247; found: 570.4237.

One-Pot Synthesis of Pyridiniumboranephosphonates 3e and 3h from the Corresponding H-Phosphonate Diesters 1e and 1h

This synthetic protocol is a combination of a general procedure for the synthesis of boranephosphonate diesters **2** (see above) and a general procedure for the synthesis of pyridiniumboranephosphonate diesters **3** (see above), with the exception that the crude reaction mixtures containing boranephosphonates **2** were evaporated to dryness and directly subjected to the reaction with dimethoxytrityl chloride in the presence of pyridine.

After silica gel chromatography, 3′-deoxy-3′-azidothymidin-5′-yl ethyl pyridiniumboranephosphonate (**3e**) was obtained in 50% yield (from **1e**), and 5′-*O*-tritylthymidin-3′-yl 3′-*O*-tritylthymidin-5′-yl pyridiniumboranephosphonate (**3h**), in 72% yield (from **1h**). For spectral characterization of these compounds, see above.

Synthesis of Ammoniumboranephosphonates 4

Ammoniumboranephosphonates **4a** and **4b** were obtained analogously to compounds **3** with the exception that pyridine was replaced with *N*-methylmorpholine (for **4a**, obtained from **2a**) or 1,4-diazabicyclo[2.2.2]octane (DABCO, for **4b**, obtained from **2e**).

Diethyl *N*-Methylmorpholiniumboranephosphonate (4a)

Yield: 56% (70 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, $^3J_{H–H}$ = 7.1 Hz, 6 H, 2 × -CH_3), 2.78–2.87 (m, 2 H, -CH_2-N), 2.92 (s, 3 H, -CH_3 *N*-methylmorpholine), 3.31–3.38 (m, 2 H, -CH_2-N, *N*-methylmorpholine), 3.69–3.76 (m, 2 H, -CH_2-O, *N*-methylmorpholine), 3.86–4.00 (m, 4 H, 2 × -CH_2-Et), 4.01–4.09 (m, 2 H, -CH_2-O, *N*-methylmorpholine).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.6 (d, *J* = 5.8 Hz), 51.5, 58.4 (d, *J* = 6.7 Hz), 59.6 (d, *J* = 9.7 Hz), 61.4.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, 25 °C): δ = 59.2 (br q, $^1J_{P–B}$ = 179.2 Hz).

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C): δ = –16.7 (d, $^1J_{P–B}$ = 189.5 Hz).

HRMS (ESI+): *m*/*z* [2M + H]$^+$ calcd for $(C_9H_{23}BNO_4P)_2$+H$^+$: 503.2994; found: 503.2988.

3′-Deoxy-3′-azidothymidin-5′-yl Ethyl (1,4-Diazabicyclo[2.2.2]-octane-1-ium)boranephosphonate (4b)

Yield: 58% (130.5 mg).

^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 1.31 (t, $^3J_{H–H}$ = 6.8 Hz, 3 H, -CH_3Et), 1.97 (s, 3 H, C5-CH_3), 2.53–2.61 (m, 2 H, -C2′H_2-), 3.01–3.08 (m, 6 H, -CH_2-DABCO), 3.13–3.21 (m, 6 H, -CH_2-DABCO), 3.98–4.10 (m, 2 H, -CH_2-Et), 4.14–4.24 (m, 3 H, C5′-CH_2-), 4.46–4.54 (m, 1 H, C3′-H), 6.24–6.29 (m, 1 H, C1′-H), 7.63–7.66 (s, 1 H, C6-H).

^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 11.74, 11.78, 15.77, 15.83, 36.05, 36.1, 44.3, 51.3, 51.4, 60.0, 60.2, 60.3, 60.5, 62.4, 62.6, 82.7, 82.8, 85.2, 111.37, 111.4, 137.26, 137.3, 151.8, 166.8.

^{31}P{^{1}H} NMR (162 MHz, D_2O, 25 °C): δ = 60.9 (br).

^{11}B{^{1}H} NMR (128 MHz, D_2O, 25 °C): δ = –12.8 (br).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{32}BN_7O_6P^+$: 484.2245; found: 484.2221.

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Supporting Information

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References and Notes

(1) Sood, A.; Shaw, B. R.; Spielvogel, B. F. *J. Am. Chem. Soc.* **1990**, *112*, 9000.
(2) Li, P.; Sergueeva, Z. A.; Dobrikov, M.; Shaw, B. R. *Chem. Rev.* **2007**, *107*, 4746.
(3) (a) He, K.; Porter, K. W.; Hasan, A.; Briley, J. D.; Shaw, B. R. *Nucleic Acids Res.* **1999**, *27*, 1788. (b) Porter, K. W.; Briley, J. D.; Shaw, B. R. *Nucleic Acids Res.* **1997**, *25*, 1611. (c) Li, H.; Porter, K.; Huang, F. Q.; Shaw, B. R. *Nucleic Acids Res.* **1995**, *23*, 4495.
(4) (a) Kandimalla, E. R.; Manning, A.; Zhao, Q. Y.; Shaw, D. R.; Byrn, R. A.; Sasisekharan, V.; Agrawal, S. *Nucleic Acids Res.* **1997**, *25*, 370. (b) Sergueeva, Z. A.; Sergueev, D.; Shaw, B. R. *Nucleosides, Nucleotides Nucleic Acids* **2001**, *20*, 941. (c) Hall, A. H.; Wan, J.; Shaughnessy, E. E.; Ramsay Shaw, B.; Alexander, K. A. *Nucleic Acids Res.* **2004**, *32*, 5991.
(5) (a) Summers, J. S.; Shaw, B. R. *Curr. Med. Chem.* **2001**, *8*, 1147. (b) Shaw, B. R.; Dobrikov, M.; Wang, X. I. N.; Wan, J.; He, K.; Lin, J.-L.; Li, P.; Rait, V.; Sergueeva, Z. A.; Sergueev, D. *Ann. N. Y. Acad. Sci.* **2003**, *1002*, 12.
(6) Roy, S.; Paul, S.; Roy, M.; Kundu, R.; Monfregola, L.; Caruthers, M. H. *J. Org. Chem.* **2017**, *82*, 1420.
(7) Ganguly, S.; Paul, S.; Yehezkeli, O.; Cha, J.; Caruthers, M. H. *Chem. Mater.* **2017**, *29*, 2239.
(8) (a) Coulthurst, S. J.; Whitehead, N. A.; Welch, M.; Salmond, G. P. C. *Trends Biochem. Sci.* **2002**, *27*, 217. (b) Issa, F.; Kassiou, M.; Rendina, L. M. *Chem. Rev.* **2011**, *111*, 5701. (c) Niziol, J.; Rode, W.; Ruman, T. *Mini-Rev. Org. Chem.* **2012**, *9*, 418. (d) Diaz, D. B.; Yudin, A. K. *Nat. Chem.* **2017**, *9*, 731.
(9) (a) Ni, S.; Yao, H.; Wang, L.; Lu, J.; Jiang, F.; Lu, A.; Zhang, G. *Int. J. Mol. Sci.* **2017**, 18. (b) Hara, R. I.; Saito, T.; Kogure, T.; Hamamura, Y.; Uchiyama, N.; Nukaga, Y.; Iwamoto, N.; Wada, T. *J. Org. Chem.* **2019**, *84*, 7971. (c) Smith, C. I. E.; Zain, R. *Annu. Rev. Pharmacol. Toxicol.* **2019**, *59*, 605.
(10) (a) Higson, A. P.; Sierzchala, A.; Brummel, H.; Zhao, Z. Y.; Caruthers, M. H. *Tetrahedron Lett.* **1998**, *39*, 3899. (b) Wada, T.; Shimizu, M.; Oka, N.; Saigo, K. *Tetrahedron Lett.* **2002**, *43*, 4137.
(11) Ravikumar, V. T.; Krotz, A. H.; Cole, D. L. *Tetrahedron Lett.* **1995**, *36*, 6587.
(12) Shimizu, M.; Tamura, K.; Wada, T.; Saigo, K. *Tetrahedron Lett.* **2004**, *45*, 371.
(13) (a) Golebiewska, J.; Rachwalak, M.; Jakubowski, T.; Romanowska, J.; Stawinski, J. *J. Org. Chem.* **2018**, *83*, 5496. (b) Golebiewska, J.; Stawinski, J. *J. Org. Chem.* **2020**, *85*, 4312.

(14) Within 15 min, the signal at δ_P = 59 ppm disappeared and was replaced with a broad resonance at ca. δ_P = 72 ppm (δ_B = –21 ppm), tentatively assigned to the corresponding chloroboranephosphonate (MS analysis). This was accompanied by a gradual conversion of diethyl H-phosphonate into its P-dimethoxytritylated derivative (signal at ca. δ_P = 27 ppm).

(15) At this stage of the investigations, no attempt was made to maximize the isolated yields of compounds **3** and **4**.

(16) For 1° or 2° amines, no reaction was observed with boranephosphonate diesters in the presence of DMTr-Cl, apparently due to the rapid conversion of the trityl reagent into inactive tritylamine derivatives. This is in contrast to the analogous reactions of 1° and 2° amines with boranephosphonates promoted by iodine, in which a rapid deboronation occurs leading ultimately to the formation of the corresponding phosphoramidate diesters (see also ref. 13 and references cited therein).

(17) (a) Lyle, R. L.; Boyce, C. B. *J. Org. Chem.* **1974**, *39*, 3708. (b) Redmore, D. *J. Org. Chem.* **1976**, *41*, 2148. (c) Kers, A.; Stawinski, J. *Tetrahedron Lett.* **1999**, *40*, 4263. (d) Kers, A.; Dembkowski, L.; Kraszewski, A.; Stawinski, J. *Heteroat. Chem.* **1999**, *10*, 492.

(18) Upon addition of 2,6-lutidine to the DMTr-Cl solution in DCM, the orange color due to the presence of the dimethoxytrityl cation changed to pale-yellow, indicating consumption of DMTr-Cl. For the reaction with pyridine, the color change from orange to yellow took place only after the addition of boranephosphonate **2a** to the reaction mixture.

(19) Stawinski, J.; Strömberg, R. *Di- and oligonucleotide Synthesis Using H-Phosphonate Chemistry*, In *Oligonucleotide Synthesis: Methods and Applications, Vol. 288*; Herdewijn, P., Ed.; Humana Press: Totowa, **2004**, 81–100.

(20) Strenkowska, M.; Wanat, P.; Ziemniak, M.; Jemielity, J.; Kowalska, J. *Org. Lett.* **2012**, *14*, 4782.