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Rearrangement of *S*-(2-Aminoethyl) Thiophosphates to *N*-(2-Mercaptoethyl)-phosphoramidates

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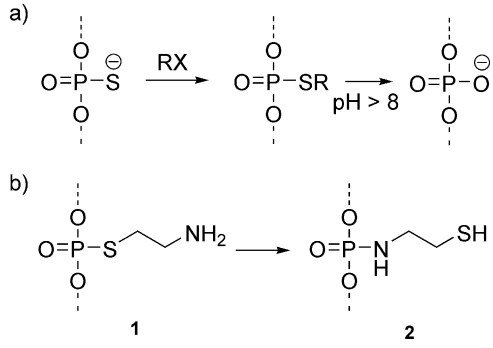
A novel rearrangement of *S*-(2-aminoethyl) thiophosphates to *N*-(2-mercaptoethyl)phosphoramidates was discovered and developed. The reaction proceeds smoothly at room temperature under basic conditions and the resulting thiol could subsequently be alkylated. The reaction mechanism is investigated by electron structure calculations using density functional theory at the B3LYP/6-31G(d) and B3LYP/6-311+G(d,p) levels. The calculations indicate that the reaction proceeds in a two step process when two explicit solvent molecules are included. In the presence of water the rearrangement reaction proceeds in competition with hydrolysis.

Introduction

Our interest in oligonucleotide conjugation has inspired us to explore new chemical transformations that potentially can be applied for DNA functionalization. Phosphorus chemistry offers a great opportunity to introduce site-specific modification at the backbone of oligodeoxynucleotides without interfering with the Watson–Crick hydrogen bonding. Thiophosphates are excellent and soft nucleophiles which have been extensively utilized for site-specific conjugation by aliphatic nucleophilic substitution[1] or by conjugate addition.[2] The main drawback of this approach is the sensitivity of thiophosphoric acid triesters towards hydrolysis (Scheme 1, a). We speculated that the lability of the P–S bond may be applied for introducing other functionalities at phosphorus by an intramolecular substitution reaction. Here our studies on the formation and rearrangement of *S*-(2-aminoethyl) thiophosphoric acid triesters **1** into the stable *N*-(2-mercaptoethyl)phosphoramidates **2** are presented (Scheme 1, b).



Scheme 1. a) Alkylation of a thiophosphate and subsequent hydrolysis. b) Proposed rearrangement reaction leading to a stable *N*-(2-mercaptoethyl)phosphoramidate **2**.

First, we have studied previously reported related substitution reactions at carbon. The rearrangement of *O*-ethyl *S*-(2-hydroxyethyl) thiocarbonate to *O*-ethyl *O*-(2-mercaptoethyl) carbonate which decomposes to give ethylene sulfide, ethanol and carbon dioxide has been described (Scheme 2, a).[3] It is proposed that the rearrangement proceeds via the 1,3-oxathiolane intermediate. The similar S,N rearrangement has been developed in protein synthesis and plays an important role in native chemical ligation[4,5] (see part b of Scheme 2).

The rearrangements of *S*-(3-hydroxyalkyl) and *S*-(2-hydroxyalkyl) thiophosphates to 3-mercaptoalkyl and 2-mercaptoalkyl phosphoric acid triesters have also been reported.[6–8] It was claimed that the rearrangement proceeds via five- or six-membered cyclic intermediates respectively, where a six-membered cyclic intermediate forms upon heating at 120–180 °C.[6] The five-membered cyclic intermediate is formed faster but its formation is followed by fast decomposition to generate phosphate and ethylene sulfide (Scheme 2, c).[8] The relation between the rearrangement rate and the structure of the thiophosphates has been systematically studied.[9–13] It turned out that the rearrangement differs depending on the R groups. The dialkyl triesters (R = alkyl) generally give the thiol products; the bulkier R is, the slower is the rearrangement.[8,9] Cyclic alkyl R groups further facilitate the rearrangement.[10] The diaryl triesters (R = Ar) often stop at the cyclic intermediate due to the steric hindrance and since phenols (or derivatives) are good leaving groups.[11,12] Rearrangements of dimeth-

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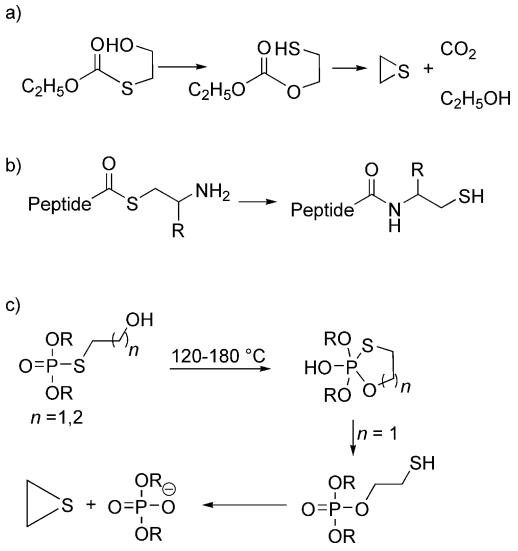


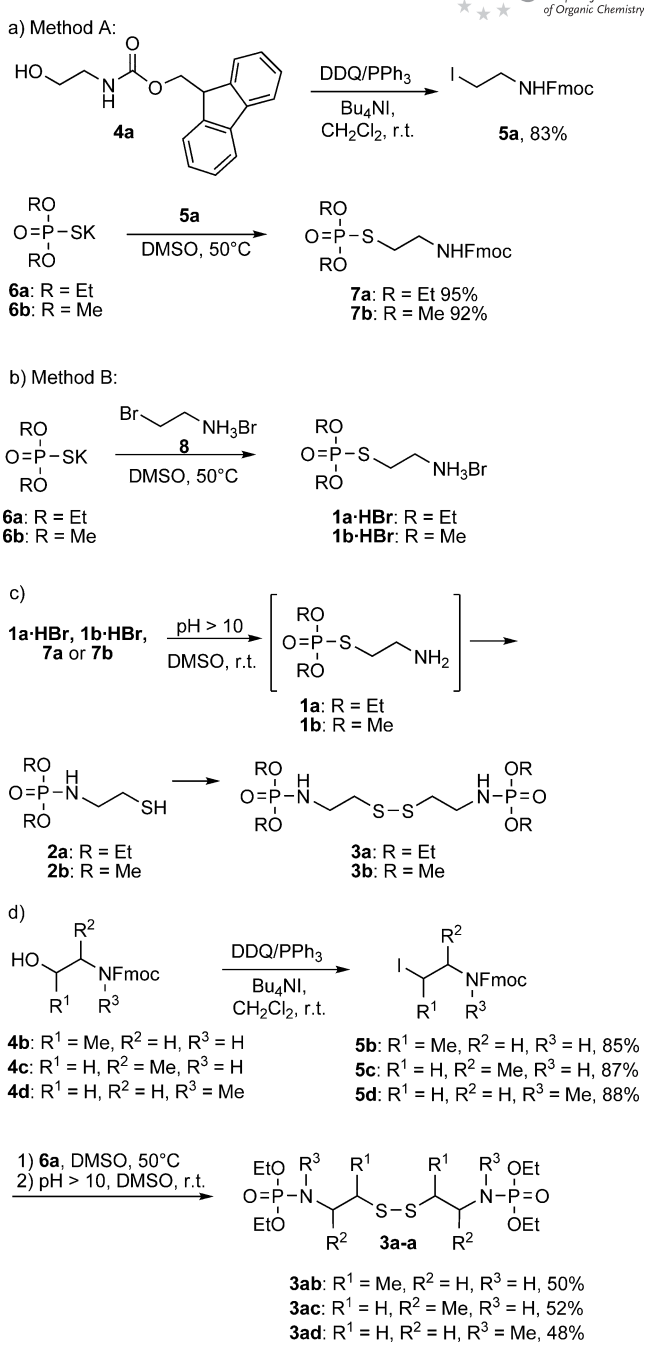
Scheme 2. a) Rearrangement of *O*-ethyl *S*-(2-hydroxyethyl) thiocarbonate. b) Native chemical ligation of protein. c) Rearrangement of *S*-(3-hydroxyalkyl) or *S*-(2-hydroxyalkyl) thiophosphates, R = alkyl or aryl group.

ylamido-*O*-phenyl-thiophosphoric acid have also been reported.[13]

Based on the reports described above we have investigated the rearrangement leading to the corresponding P–N analogs and in the following we demonstrate that in some cases the reaction shown in Scheme 1 (b) proceeds smoothly. Furthermore, density functional theory provided the theoretical calculations for the mechanism of the reaction.

Results and Discussion

The thiophosphates **6a** and **6b** were chosen for the formation of the central adducts *S*-2-aminoethyl thiophosphates **1a** and **1b**. It immediately turned out that **1** instantly undergoes rearrangement at room temperature. Hence, protected derivatives **1a·HBr**, **7a** and **1b·HBr**, **7b** of **1a** and **1b**, respectively, were prepared by two different methods in order to study the rearrangement. In Method A 2-(Fmoc-amino)ethanol (**4a**) was chosen as the starting material. Upon iodination using DDQ/PPh_3/Bu_4NI,[14] 2-(Fmoc-amino)ethyl iodide (**5a**) was formed in 83% yield. The methyl derivative **6b** was prepared by thioylation of dimethyl phosphite.[15] Alkylations of thiophosphates **6a** and **6b** with **5a** were performed at 50 °C for 3 h to obtain *O*,*O*′-diethyl *S*-[2-(Fmoc-amino)ethyl] thiophosphates **7a** and **7b** in almost quantitive conversions (Scheme 3, a). In Method B alkylation of thiophosphate (**6a**, **6b**) with 2-bromoethylamine hydrogen bromide (**8**) at 50 °C for 24 h gave **1a·HBr**, **1b·HBr** quantitively (Scheme 3, b) For both derivatives **1a·HBr** and **7a**, or **1b·HBr** and **7b**, base treatment will lead to the formation of **1a** and **1b** (Scheme 3, c).



Scheme 3. Development of the rearrangement. a) Preparation of Fmoc-protected starting materials. b) Preparation of starting materials protected as ammonium bromides. c) Demonstration of the rearrangement reaction. d) Preparation and rearrangements of three methylated derivatives.

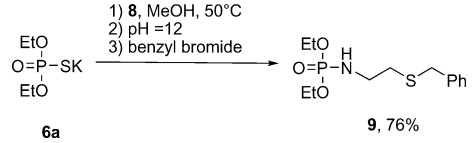
Rearrangement of **1a·HBr**, **1b·HBr** or **7a**, **7b** to *N*-(2-mercaptoethyl)phosphoramidates **2a** or **2b** was carried out by treating **1a·HBr**, **1b·HBr** or **7a**, **7b** with *t*BuOK in dry DMSO at room temperature. We have primarily used *t*BuOK as the base since it is non-nucleophilic and substitution at phosphorus is avoided. It was also demonstrated that DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) could be used as the base with similar success. ^{1}H NMR and ^{31}P NMR spectroscopic data were comparable to the data in

the literature,[16,17] confirming the structure of the expected product. The products **2a** and **2b** were formed in nearly quantitive conversions at room temperature at pH 12 in 10 min when **1a·HBr**, and **1b·HBr** were used, while **7a** and **7b** led to formation of side products. During work up, oxidation of the thiol adducts **2a**, **2b** to the disulfide **3a** and **3b** took place. Since the purification procedure is complicated because of facile oxidation of thiols to disulfides, only moderate and not optimized yields of compounds **3a** and **3b** were obtained (52 and 41%, respectively). However, capturing the thiol by an alkylating agent in situ led to significant higher yields (vide infra).

To demonstrate the use of the rearrangement for other detivatives methylated in three different positions, the three derivatives **4b**, **4c** and **4d** were prepared. Following iodination, the iodides, **5b**, **5c** and **5d** were treated with **6a** to produce the corresponding *S*-alkyl thiophosphates. In all three cases the base-induced rearrangement proceeded and disulfides **3ab**, **3ac** and **3ad** were obtained in yields of about 50% (Scheme 3, d).

The influence of pH on the reaction was studied by ^{31}P NMR in [D_6]DMSO at different pH values at room temperature. At pH 10, 15% rearrangement product was found; at pH 11, 60% rearrangement product was obtained, at pH 12, quantitive conversion was found. The pK_a of the protonated amine is 10.8, and the pH-dependency showed that the free amine undergoes rearrangement spontaneously. When the reaction of **1a·HBr** was performed in water (D_2O) 40% of the hydrolysis product diethyl phosphate was formed along with the expected product **2a** (**3a**).

To optimize the method for functionalization of thiophosphates and to avoid formation of the disulfide **3a** a one pot procedure involving the substitution with **8**, rearrangement and reaction of the thiol with an electrophile was developed (Scheme 4). Thiophosphate **6a** was subjected to reaction with **8** followed by increasing the pH to 12 to induce the rearrangement. After 10 min the thiol reactive electrophile benzyl bromide were added to the reaction mixture. The reaction was incubated at room temperature for 2 h, and 76% of the product **9** was isolated.



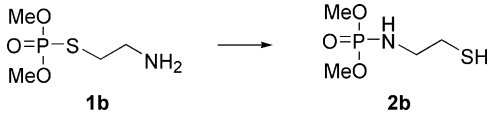
Scheme 4. One-pot functionalization of thiophosphates.

Whereas the rearrangement reaction of **1a** and methylated analogs proceed smoothly at room temperature we were very surprised to find that the 3 carbon analog diethyl *S*-(3-aminopropyl) thiophosphate was unwilling to undergo a similar rearrangement. This derivative gave no detectable amount of the rearrangement product as verified by the absence of the corresponding phosphoramidate signal in the ^{31}P NMR spectrum. If the reaction was heated only unidentified side products were observed.

Electron structure calculations were made to find a reaction mechanism for the rearrangement reaction of **1b** to **2b** and to estimate the involved activation energies.

The optimized gas-phase structures of the various species, as well as the transition states, were calculated by quantum chemical geometry optimizations using the software package Gaussian 03.[18] The chosen level of theory was the B3LYP implementation of the density functional theory (DFT). The calculations used the basis sets 6-31G(d) and 6-311+G(d,p), where the latter is expected to lead to the more accurate results. In a few cases the quality of the DFT estimates were checked by single point calculations using the more accurate coupled cluster technique, CCSD(T). The transition states (TS) were obtained using a synchronous transit-guided Quasi-Newton method[19] and explicit calculations (IRC) were performed to identify the species linked by the transition states. The thermodynamic properties of the species in water and DMSO solvents were estimated using the polarized continuum methods (PCM)[20,21] with single point calculations on the optimized structures from the DFT calculations. In this calculation the atomic radii were taken from the Universal Force Field (UFF).[22]

Three reaction paths for the rearrangement in Scheme 5 were investigated: In the first path (I) the reaction only involved reactant **1b** (Figure 1). In the second path (II) two explicit solvent water molecules were included (Figure 2) and in the third path, (III), the rearrangement has been investigated as a two-step reaction path via a cyclic intermediate (Figure 3) as suggested in the S,O rearrangement reactions.[6–8] The results for path (III) are also given when a single explicit water molecule are included in the calculations.



Scheme 5. Rearrangement of **1b** to **2b**.

Reaction path I in Figure 1 illustrates a concerted rearrangement reaction. The double headed arrows in TS_I indicate the dominant movement of atoms in the rearrangement mode. The attack of the nitrogen lone pair at phosphorus and the movement of hydrogen to sulfur proceed in synchronous motion with an increase in the P–S distance. The activation energy estimates for this rearrangement are in the range of 124 to 133 kJ/mol (Table 1) and ΔH_I are in the range of –25 to –29 kJ/mol in aqueous environment. We note that the CCSD(T) results are close to the B3LYP results.

The mechanism for the rearrangement in the presence of two explicit water molecules (Path II) is somewhat different as illustrated in Figure 2. It appears that the reaction proceeds through two transition states and an intervening intermediate.

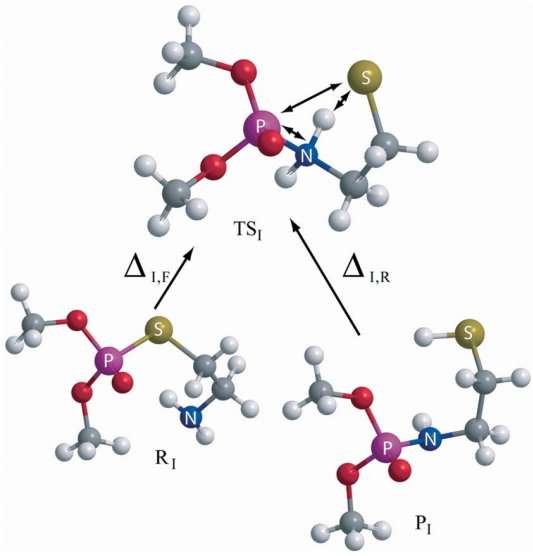


Figure 1. Reaction path (I) for the rearrangement reaction of **1b** to **2b**. The relative energies of the various states displayed are not to scale.

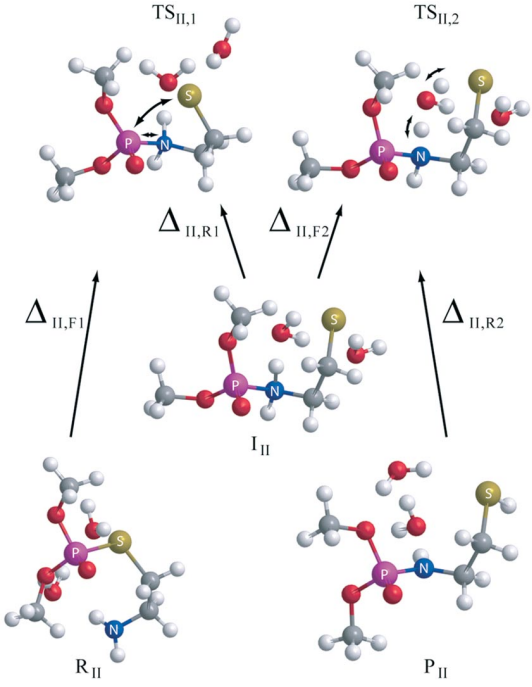


Figure 2. Reaction path II for the rearrangement of **1b** to **2b**. The relative energies of the various states displayed are not to scale.

The dominant motion in the rearrangement mode in the first transition state, $TS_{II,1}$, is an asymmetric stretch of the P–S and P–N bonds. $TS_{II,1}$ is linked to an intermediate, I_{II}.

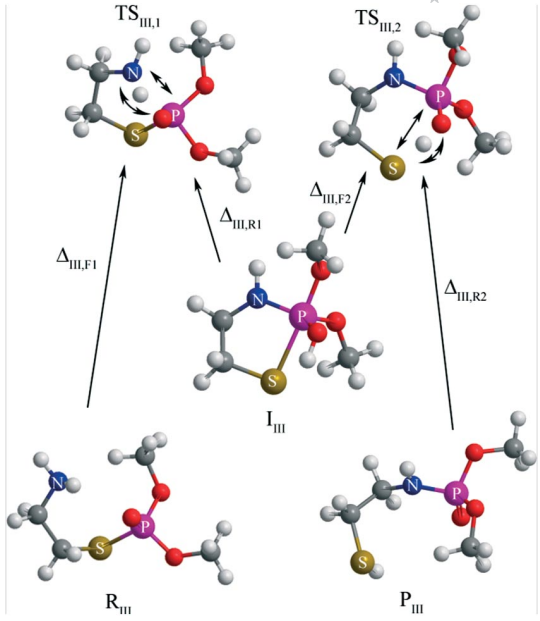


Figure 3. Reaction path III for the rearrangement of **1b** to **2b**. The relative energies of the various states displayed are not to scale.

Table 1. Energy differences for reaction path I illustrated in Figure 1 calculated at various levels of quantum mechanical approximations. The data are obtained using the PCM theory to simulate the aqueous and DMSO environment with the latter results in brackets.

Level of calculation	$\Delta_{I,F}$ [kJ/mol]	$\Delta_{I,R}$ [kJ/mol]	ΔH_I [kJ/mol]
B3LYP/6-31G(d)	124.8 (126.5)	149.9 (150.7)	–25.1 (–24.2)
B3LYP/6-311+G(d,p)	133.1 (134.8)	159.1 (160.1)	–26.0 (–25.1)
CCSD(T)/6-31G(d) //B3LYP/6-31G(d)	125.1 (127.0)	153.8 (154.7)	–28.7 (–27.7)

In I_{II} the P–S bond length is longer than the corresponding one in the reactant complex R_{II} and, likewise, the P–N bond length is longer than the one in the product complex P_{II}. Another feature of I_{II} is that a hydrogen atom has not yet been transferred from nitrogen to sulfur, and as a result, they are positively and negatively charged, respectively. In the second transition state, $TS_{II,2}$, the transfer of the hydrogen from N to S is mediated in a domino-effect type of motion (Grotthuss effect)[23] involving a water molecule. We note that only one of the two explicit water molecules participates in the rearrangement mode in $TS_{II,2}$. The other one is non-participating, suggesting that additional explicit water molecules will also be non-participating. In Table 2 we list the various estimates for the activation energies involved in path II.

Table 2. Energy differences for reaction path II illustrated in Figure 2 calculated at various levels of quantum mechanical approximations. The data are obtained using the PCM theory to simulate the aqueous environment.

Level of calculation	$\Delta_{II,F1}$ [kJ/mol]	$\Delta_{II,R1}$ [kJ/mol]	$\Delta_{II,F2}$ [kJ/mol]	$\Delta I_{II,R2}$ [kJ/mol]	ΔH_{II} [kJ/mol]
B3LYP/6-31G(d)	90.9	55.1	8.6	68.0	–23.6
B3LYP/6-311+G(d,p)	83.1	27.7	11.1	105.1	–38.5

Table 3. Energy differences for reaction path III illustrated in Figure 3 calculated at various levels of quantum mechanical approximations. The data are obtained using the PCM theory to simulate the aqueous and DMSO environment with the latter results in brackets.

Level of calculation	$\Delta_{III,F1}$ [kJ/mol]	$\Delta_{III,R1}$ [kJ/mol]	$\Delta_{III,F2}$ [kJ/mol]	$\Delta_{III,R2}$ [kJ/mol]	ΔH_{III} [kJ/mol]
B3LYP/6-31G(d)	154.3 (153.9)	68.4 (68.2)	5.17 (4.98)	108.5 (107.6)	–17.4 (–17.0)
B3LYP/6-311+G(d,p)	158.9 (158.3)	77.2 (77.6)	5.89 (6.71)	108.8 (108.2)	–21.2 (–20.8)

It appears from a comparison of the results listed in Tables 1 and 2 that the inclusion of two water molecules in the rearrangement reaction reduces the activation energy by about 50 kJ/mol and changes the energy gain going from reactant to product from ΔH_I = –26.0 kJ/mol to ΔH_{II} = –38.5 kJ/mol at the B3LYP/6-311+G(d,p) level in aqueous environment.

The experimental results show that the rearrangement reaction will proceed smoothly even though no water is added to the solution (pure DMSO). This probably indicates that the proton transfer could proceed through the primary amine group on another reactant complex which has not yet taken part in the reaction. This has not been investigated theoretically.

The reaction in which one of the methoxy groups at phosphorus in **1b** is replaced by intramolecular substitution with the amine forming a cyclic product was also investigated. For the reaction with and without explicit water molecules the reaction paths are similar having an activation energy of about 172 kJ/mol at the B3LYP/6-311+G(d,p) level. The ΔH for the cyclization reaction is approximately zero. The cyclic product for reactions of **1a** was not observed experimentally.

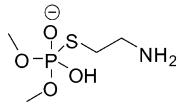
A reaction path for the rearrangement of **1b** to **2b** involving a cyclic intermediate similar to what was suggested for the analogous S,O rearrangement (see Scheme 1, b).[6–8] has also been investigated. The reaction path is illustrated in Figure 3.

The dominant motion in the first transition state, $TS_{III,1}$, in reaction path III is the transfer of one of the protons from the amine to the double bonded oxygen on phosphorus. Simultaneously the shortening of the P–N distance thereby forming the cyclic intermediate I_{III} is seen. In the second transition state, $TS_{III,2}$, which connects the cyclic intermediate to the rearrangement product, the dominant motion is lengthening of the P–S bond simultaneously with the transfer of the hydrogen from the hydroxy group on phosphorus to the negatively charged sulfur atom. The major difference between reaction path III in Figure 3 and reaction path I in Figure 1 is that the hydrogen atom does not transfer directly to the sulfur atom but rather moves to the double bonded oxygen forming a hydroxy group and thereby a cyclic intermediate. In Table 3 we list the various estimates for the activation energies pertaining to path III.

It appears from Tables 1, 2, and 3 that the activation energy for reaction path III is higher than those for reaction path I and II.

Inclusion of a single explicit water molecule in the rearrangement of **1b** to **2b** leads to an activation energy of 129.3 kJ/mol for path III. This is slightly less than the activation energy found for path I but still much higher than the one found for path II (83.1 kJ/mol).

The hydrolysis performed with hydroxide, results in a two-step reaction path via intermediate **10** where the P–S bond and the P–OH bond are longer than those in the reactant and the product complex, respectively. The activation energy for formation of the intermediate from the reactant is 33.4 kJ/mol in aqueous solution and the activation energy from the intermediate to the product is 22.5 kJ/mol. The total energy gain in the reaction is –194.7 kJ/mol. The activation energy of water hydrolysis has been calculated to about 206.6 kJ/mol at B3LYP/6-311+G(d,p) in aqueous solution.



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Although, it was found that the activation energy barrier for the hydrolysis with hydroxide [33.4 kJ/mol at the B3LYP/6-311+G(d,p) level] is significantly lower than the rearrangement reaction in the presence of two explicit water molecules [83.1 kJ/mol at the B3LYP/6-311+G(d,p) level], the experimentally observed distribution of the rearrangement and hydrolysis products at pH 12 in D_2O were found to be 60:40. The explanation is that we are comparing an intramolecular reaction with a bimolecular reaction. Furthermore it is obvious that the distribution of products is strongly pH-dependent. The favored pH represents a balance where the amine should be non-protonated and the concentration of hydroxide as low as possible.

Conclusions

A new rearrangement of *S*-(2-aminoethyl) thiophosphate to *N*-(2-mercaptoalkyl)phosphoramidate has been developed. The reaction proceeds smoothly at room temperature at pH 12. Theoretical calculations strongly suggest that the mechanism of the rearrangement involves two steps combining the reactant to the product via a zwitterionic intermediate (path II). Water catalyses the proton transfer. The resulting thiols **2a** and **2b** tend to form the corresponding disulfides during purification, but it was demonstrated that the thiol can be trapped by alkylation with benzyl bromide in an overall yield of 76% for the alkylation, rearrangement and alkylation steps. Further application of the novel reaction for labeling of DNA with the site-specificly generated thiol functionality is in progress.

Experimental Section

General Methods: Commercially available starting materials were used without further purification. Solvents were dried according to standard procedures. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). The liquid-state ^{1}H and ^{13}C and ^{31}P NMR spectra were recorded at 400, 100 and 100 MHz, respectively, on a Varian Mercury (9.4 T) spectrometer using $CDCl_3$ as the solvent unless otherwise stated. The chemical shifts are reported in ppm with $CHCl_3$ (δ = 7.26 ppm) as the reference for ^{1}H, with H_3PO_4 (δ = 0 ppm) as the reference for ^{31}P, and relative to the central $CDCl_3$ resonance (δ = 77.3 ppm) in the ^{13}C NMR spectra. Yields refer to isolated and spectroscopically homogeneous materials. High resolution mass spectra were obtained on an LC-TOF spectrometer (Micromass).

Alcohol 4b: To a stirred solution of Fmoc-Cl (0.35 g, 1.4 mmol) in Et_2O (5 mL) in ice bath, a solution of (±)-2-amino-1-propanol (0.11 mL, 1.4 mmol) in Et_2O (5 mL) was slowly added. After 20 min, the ice bath was removed and the reaction was continued at room temperature. After 2 h, the white precipitate was removed by filtration, and the filtrate was washed with water and dried with $MgSO_4$. Column chromatography of the crude mixture on silica gel using *n*-pentane/ethyl acetate (9:1) as eluent gave **4b** as white powder (0.3860 g, 1.30 mmol) in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 7.2 Hz, 2 H), 7.52 (d, J = 7.2 Hz, 2 H), 7.33 (t, J = 7.2 Hz, 2 H), 7.25 (t, J = 7.2 Hz, 2 H), 5.11 (br., 1 H), 4.36 (d, J = 6.8 Hz, 2 H), 4.14 (t, J = 6.4 Hz, 1 H), 3.84 (m, 1 H), 3.26 (m, 1 H), 2.99 (m, 1 H), 1.11 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 144.0, 141.4, 127.9, 127.3, 125.3, 120.1, 67.51, 67.03, 48.28, 47.32, 20.69 ppm. MS: calcd. 320.1263 $[M + Na]^+$, found 320.1271 $[M + Na]^+$.

Alcohol 4c: To a stirred solution of Fmoc-Cl (0.35 g, 1.4 mmol) in Et_2O (5 mL) in ice bath, a solution of (±)-1-amino-2-propanol (0.12 mL, 1.4 mmol) in Et_2O (5 mL) was slowly added. After 20 min, the ice bath was removed and the reaction was continued at room temperature. After 2 h, the white precipitate was removed by filtration, and the filtrate was washed with water and dried with $MgSO_4$. Column chromatography of the crude mixture on silica gel using *n*-pentane/ethyl acetate (9:1) as eluent gave **4c** as white powder (0.3891 g, 1.31 mmol) in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, J = 7.2 Hz, 2 H), 7.43 (d, J = 7.8 Hz, 2 H), 7.20 (t, J = 7.2 Hz, 2 H), 7.12 (t, J = 7.8 Hz, 2 H), 4.19 (d, J = 6.8 Hz, 2 H), 4.00 (t, J = 6.4 Hz, 1 H), 3.59 (m, 1 H), 3.34 (m, 2 H), 0.99 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 143.8, 141.2, 127.6, 126.9, 124.9, 119.8, 66.45, 65.39, 48.37, 47.01, 16.76 ppm. MS: calcd. 320.1263 $[M + Na]^+$, found 320.1261 $[M + Na]^+$.

Alcohol 4d: To a stirred solution of Fmoc-Cl (0.776 g, 3.0 mmol) in Et_2O (15 mL) in ice bath, a solution of 2-(methylamino)ethanol (0.24 mL, 3.0 mmol) in Et_2O (15 mL) was slowly added. After 20 min, the ice bath was removed and the reaction was continued at room temperature. After 2 h, the white precipitate was removed by filtration, and the filtrate was washed with water and dried with $MgSO_4$. Column chromatography of the crude mixture on silica gel using *n*-pentane/ethyl acetate (9:1) as eluent gave **4d** as white powder (0.77 g, 2.6 mmol) in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 7.2 Hz, 2 H), 7.53 (d, J = 6.4 Hz, 2 H), 7.34 (t, J = 7.8 Hz, 2 H), 7.26 (t, J = 7.2 Hz, 2 H), 4.54 (br., 1 H), 4.37 (d, J = 6.8 Hz, 2 H), 4.18 (t, J = 6.4 Hz, 1 H), 3.70 (m, 1 H), 3.39 (m, 2 H), 3.11 (m, 1 H), 2.88 (d, J = 17.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 156.4, 143.9, 141.3, 127.7, 127.1, 125.0, 124.9, 120.0, 67.53, 67.27, 60.53, 60.33, 51.61, 50.96, 47.24, 35.68, 35.20 ppm. MS: calcd. 320.1263 $[M + Na]^+$, found 320.1287 $[M + Na]^+$.

2-Fmoc-Amino Ethyl Iodide 5a: To a flame-dried flask containing a mixture of DDQ (0.5448 g, 2.4 mmol) and PPh_3 (0.6288 g, 2.4 mmol) in dry CH_2Cl_2 (30 mL), $(n\text{Bu})_4\text{NI}$ (0.8865 g, 2.4 mmol) was added at room temperature. 2-(Fmoc-amino)ethanol (**4a**) (0.5660 g, 2.0 mmol) was then added to the solution. The yellow color of the solution immediately changed to deep red. After 20 min, the solvent was evaporated. Column chromatography of the crude mixture on silica gel using *n*-pentane/ethyl acetate (9:1) as eluent gave **5a** as white powder (0.54 g, 1.66 mmol) in 83% yield; m.p. 148–150 °C, ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.87 (d, J = 7.2 Hz, 2 H), 7.64 (d, J = 7.2 Hz, 2 H), 7.39 (t, J = 7.2 Hz, 2 H), 7.31 (t, J = 7.2 Hz, 2 H), 5.12 (br. 1 H), 4.31 (d, J = 7.2 Hz, 2 H), 4.20 (t, J = 6.8 Hz, 1 H), 3.29 (q, J = 7.0 Hz, 2 H), 3.17 (t, J = 6.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 156.6, 144.5, 141.4, 128.3, 127.8, 125.8, 120.8, 66.11, 47.42, 43.60, 6.92 ppm. MS: calcd. 416.0123 $[M + Na]^+$, found 416.0100 $[M + Na]^+$.

Iodides 5b, 5c and 5d: To a flame-dried flask containing a mixture of DDQ (0.2724 g, 1.2 mmol) and PPh_3 (0.3144 g, 1.2 mmol) in dry CH_2Cl_2 (15 mL), $(n\text{Bu})_4\text{NI}$ (0.4433 g, 1.2 mmol) was added at room temperature. **4b** (or **4c** or **4d**) (0.2970 g, 1.0 mmol) was then added to the solution. The yellow color of the solution immediately changed to deep red. After 20 min, the solvent was evaporated. Column chromatography of the crude mixture on silica gel using *n*-pentane/ethyl acetate (9:1) as eluent gave the product.

5b (using 4b): White powder (0.345 g, 0.85 mmol) in 85% yield; m.p. 118–120 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.6 Hz, 2 H), 7.68 (d, J = 7.2 Hz, 2 H), 7.40 (t, J = 7.2 Hz, 2 H), 7.31 (t, J = 7.2 Hz, 2 H), 4.32 (d, J = 7.2 Hz, 2 H), 4.19 (dt, J^1 = 6.8, J^2 = 23 Hz, 1 H), 3.36 (m, 2 H), 3.15 (m, 1 H), 1.76 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 144.0, 141.5, 128.0, 127.3, 125.3, 120.2, 67.07, 50.99, 47.40, 28.48, 25.65 ppm. MS: calcd. 430.0280 $[M + Na]^+$, found 430.0287 $[M + Na]^+$.

5c (using 4c): White powder (0.354 g, 0.87 mmol) in 87% yield; m.p. 147–149 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.6 Hz, 2 H), 7.69 (d, J = 7.2 Hz, 2 H), 7.40 (t, J = 7.2 Hz, 2 H), 7.33 (t, J = 7.6 Hz, 2 H), 4.33 (d, J = 7.2 Hz, 2 H), 4.26 (m, 2 H), 3.53 (m, 1 H), 3.31 (m, 1 H), 3.24 (m, 1 H), 1.13 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 144.1, 141.6, 128.0, 127.4, 125.4, 120.3, 67.09, 47.53, 46.73, 21.54, 16.96 ppm. MS: calcd. 430.0280 $[M + Na]^+$, found 430.0291 $[M + Na]^+$.

5d (using 4d): White powder (0.358 g, 0.88 mmol) in 88% yield; m.p. 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 7.8 Hz, 2 H), 7.50 (dd, J^1 = 7.2, J^2 = 15.6 Hz, 2 H), 7.41 (t, J = 7.8 Hz, 2 H), 7.34 (t, J = 7.8 Hz, 2 H), 4.54 (d, J = 6.4 Hz, 2 H), 4.43 (d, J = 6.8 Hz, 2 H), 4.24 (m, 1 H), 3.64 (t, J = 7.8 Hz, 1 H), 3.35 (J = 7.8 Hz, 1 H), 3.25 (J = 6.8 Hz, 1 H), 2.94 (d, J = 32 Hz, 3 H), 2.81 (t, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 155.8, 144.0, 141.5, 127.9, 127.3, 125.2, 124.8, 120.4, 120.2, 67.65, 67.24, 51.98, 51.64, 47.43, 35.26, 35.01, 1.55, 0.90 ppm. MS: calcd. 430.0280 $[M + Na]^+$, found 430.0290 $[M + Na]^+$.

***O*,*O*′-Dimethyl Thiophosphate, Sodium Salt 6b:** To a stirred solution of diethyl phosphite (0.44 g, 4 mmol) in CH_2Cl_2 (60 mL), phenylacetyl disulfide (3.63 g, 12 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (3.3 mL) was added. The reaction mixture turned to purple in 10 min. After 1 h, the reaction mixture was extracted with 0.01 M NaOH aqueous solution and washed with diethyl ether. The aqueous phase was dried to get **6b** as white powder (0.58 g, 3.5 mmol) in 89% yield; m.p. 195–197 °C, ^{1}H NMR (400 MHz, CD_3OD): δ = 3.61 (d, J = 12.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz,

CD_3OD): δ = 53.12, 53.06 ppm. ^{31}P NMR (100 MHz, CD_3OD): δ = 59.1 ppm. MS: calcd. 186.9571 $[M + Na]^+$, found 187.0077 $[M + Na]^+$.

***O,O′*-Diethyl *S*-[2-(Fmoc-amino)ethyl] Thiophosphate (7a):** To a stirred solution of **6a** (0.2080 g, 1.1 mmol) in DMSO (1 mL), was added **5a** (0.3930 g, 1.0 mmol). The reaction mixture was stirred at 50 °C for 3 h. The reaction mixture was extracted 3 times with diethyl ether and washed with brine and water. The combined extracts were evaporated to dryness to get **7a** as brown oil (0.41 g, 0.95 mmol) in 95% yield. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 7.84 (d, J = 8.0 Hz, 2 H), 7.66 (d, J = 7.2 Hz, 2 H), 7.37 (t, J = 7.6 Hz, 2 H), 7.28 (t, J = 7.2 Hz, 2 H), 5.86 (br., 1 H), 4.29 (d, J = 6.8 Hz, 2 H), 4.18 (t, J = 6.4 Hz, 1 H), 4.02 (m, 4 H), 3.22 (t, J = 7.0 Hz, 2 H), 2.82 (m, 2 H), 1.21 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 156.7, 144.5, 141.4, 128.3, 127.7, 125.8, 120.8, 66.1, 63.91, 63.86, 47.35, 41.47, 30.44, 16.58, 16.51 ppm. ^{31}P NMR (100 MHz, $[D_6]$DMSO): δ = 26.4 ppm. MS: calcd. 458.1166 $[M + Na]^+$, found 458.1177 $[M + Na]^+$, 474.0923 $[M + K]^+$.

***O,O′*-Dimethyl *S*-[2-(Fmoc-amino)ethyl] Thiophosphate (7b):** To a stirred solution of **6b** (0.180 g, 1.1 mmol) in DMSO (1 mL), was added **5a** (0.3930 g, 1.0 mmol). The reaction mixture was stirred at 50 °C for 3 h. The reaction mixture was extracted 3 times with diethyl ether and washed with brine and water. The combined extracts were evaporated to dryness to get **7b** as brown oil (0.38 g, 0.92 mmol) in 92% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.0 Hz, 2 H), 7.59 (d, J = 7.8 Hz, 2 H), 7.40 (t, J = 7.8 Hz, 2 H), 7.31 (t, J = 7.6 Hz, 2 H), 5.43 (br., 1 H), 4.41 (d, J = 7.2 Hz, 2 H), 4.22 (t, J = 6.8 Hz, 2 H), 3.79 (d, J = 12.4 Hz, 6 H), 3.50 (t, J = 5.6 Hz, 2 H), 2.99 (dt, J^1 = 5.6, J^2 = 17.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 144.0, 141.5, 127.9, 127.2, 120.1, 66.95, 54.27, 54.21, 47.37, 41.92, 30.67 ppm. ^{31}P NMR (100 MHz, $CDCl_3$): δ = 29.0 ppm. MS: calcd. 408.1035 $[M + H]^+$, found 408.1098 $[M + H]^+$.

***O,O′*-Diethyl *S*-(2-Aminoethyl) Thiophosphate Hydrogen Bromide (1a·HBr):** To a stirred solution of **6a** (0.104 g, 0.5 mmol) in $[D_6]$-DMSO (1.0 mL), was added **8** (0.104 g, 0.5 mmol) at 50 °C. ^{31}P NMR showed the reaction is completed in 12 h in quantitive conversion. After removal of KBr by filtration, **1a·HBr** was used without further purification. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 8.22 (br., 3 H), 4.03 (m, 4 H), 3.00 (m, 4 H), 1.20 (t, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.05, 63.99, 42.55, 42.51, 34.11, 34.08, 16.28, 16.21 ppm. ^{31}P NMR (100 MHz, $[D_6]$-DMSO): δ = 26.4 ppm. MS: calcd. 214.0667 $[M–Br]^+$, found 214.0678 $[M–Br]^+$.

***O,O′*-Dimethyl *S*-(2-Aminoethyl) Thiophosphate Hydrogen Bromide (1b·HBr):** To a stirred solution of **6b** (0.082 g, 0.5 mmol) in $[D_6]$-DMSO (1.0 mL), was added **8** (0.104 g, 0.5 mmol) at 50 °C. ^{31}P NMR showed the reaction is completed in 12 h with quantitive conversion. After removal of KBr by filtration, **1b·HBr** was used without further purification. ^1H NMR (400 MHz, CD_3OD): δ = 3.81 (d, J = 12.8 Hz, 6 H), 3.26 (t, J = 7.2 Hz, 2 H), 2.95 (dt, J^1 = 7.2, J^2 = 15.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 54.73, 54.66, 42.44, 28.12, 28.09 ppm. ^{31}P NMR (100 MHz, CD_3OD): δ = 32.5 ppm. MS: calcd. 186.0354 $[M – Br]^+$, found 186.0378 $[M – Br]^+$.

***O,O′*-Diethyl *N*-(2-Mercaptoethyl)phosphoramidate (2a) and Disulfide 3a:** To a stirred solution of **1a·HBr** (0.15 g, 0.5 mmol) in $[D_6]$-DMSO (0.5 mL), was added KO*t*Bu (0.112 g, 1.0 mmol) at room temperature. ^1H NMR and ^{31}P NMR showed the reaction is completed in 10 min and **2a** was obtained with quantitative conversion. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 3.84 (m, 4 H), 2.98 (m, 1 H), 2.57 (q, J = 7.0 Hz, 2 H), 2.32 (t, J = 6.8 Hz, 2 H), 1.94 (t, J = 7.0 Hz, 1 H), 1.15 (t, J = 7.0 Hz, 6 H) ppm. ^{31}P NMR (100 MHz, $[D_6]$DMSO): δ = 9.57 ppm.

The reaction mixture was extracted 3 times with diethyl ether and washed with brine and water. The combined organic phase was evaporated to dryness. Column chromatography of the crude mixture on silica gel using *n*-pentane/ethyl acetate (3:1) to CH_2Cl_2/MeOH (9:1) as eluent gave **3a** (0.055 g, 0.13 mmol) as brown oil in 52% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.96 (m, 8 H), 3.12 (dt, J^1 = 7.2, J^2 = 11.2 Hz, 4 H), 2.68 (t, J = 6.8 Hz, 4 H), 1.20 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.54, 62.48, 40.50, 40.46, 30.47, 16.45, 16.39 ppm. ^{31}P NMR (100 MHz, $CDCl_3$): δ = 9.47 ppm. MS: calcd. 447.0919 $[M + Na]^+$, found 447.0895 $[M + Na]^+$, 458.1198 $[M + K]^+$.

Disulfides 3ab, 3ac and 3ad: To a stirred solution of **6a** (0.104 g, 0.5 mmol) in $[D_6]$DMSO (1 mL), was added **5b** (or **5c** or **5d**) (0.204 g, 0.5 mmol). The reaction mixture was stirred at 50 °C for 3 h. ^{31}P NMR (δ = 26.7 ppm) showed the reaction is completed in quantitive conversion. After reaction mixture was cooled down to room temperature, KO*t*Bu (0.112 g, 1.0 mmol) was added. After 20 min, the reaction was extracted 3 times with diethyl ether and washed with brine and water. The combined organic phase was evaporated to dryness. Column chromatography of the crude mixture on silica gel using *n*-pentane/ethyl acetate (3:1) to CH_2Cl_2/MeOH (9:1) as eluent gave the product.

3ab (using 5b): Brown oil (0.057 g, 0.12 mmol) in 50% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.11 (m, 8 H), 3.20 (m, 2 H), 3.05 (m, 2 H), 2.47 (m, 2 H), 1.47 (d, J = 6.4 Hz, 6 H), 1.31 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.13, 63.09, 47.61, 43.12, 30.80, 16.42, 16.36 ppm. ^{31}P NMR (100 MHz, $CDCl_3$): δ = 9.77 ppm. MS: calcd. 475.1231 $[M + Na]^+$, found 475.1235 $[M + Na]^+$.

3ac (using 5c): Brown oil (0.059 g, 0.13 mmol) in 52% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.00 (m, 8 H), 3.36 (m, 2 H), 2.97 (m, 2 H), 2.60 (m, 2 H), 1.26 (m, 12 H), 1.16 (d, J = 7.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.66, 62.63, 47.69, 30.57, 22.39, 16.54, 16.48 ppm. ^{31}P NMR (100 MHz, $CDCl_3$): δ = 9.90 ppm. MS: calcd. 491.0971 $[M + K]^+$, found 491.1008 $[M + K]^+$.

3ad (using 5d): Brown oil (0.055 g, 0.12 mmol) in 48% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.03 (m, 8 H), 3.21 (m, 4 H), 2.68 (d, J = 9.2 Hz, 6 H), 2.63 (t, J = 6.8 Hz, 4 H), 1.30 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.49, 62.45, 48.89, 48.77, 47.51, 32.54, 32.42, 16.41, 16.34 ppm. ^{31}P NMR (100 MHz, $CDCl_3$): δ = 9.59 ppm. MS: calcd. 447.0919 $[M + Na]^+$, found 491.0971 $[M + K]^+$, 491.0998 $[M + K]^+$.

Disulfide 3b: To a stirred solution of **1b·HBr** (0.13 g, 0.5 mmol) in methanol (1.0 mL), was added KO*t*Bu (0.112 g, 1.0 mmol) at room temperature. After 20 min, the solvent was evaporated. Column chromatography of the crude mixture on silica gel using CH_2Cl_2/methanol (95:5) as eluent gave **3b** as brown oil (0.077 g, 0.21 mmol) in 41% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (d, J = 11.2 Hz, 12 H), 3.25 (m, 4 H), 2.78 (t, J = 6.4 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.45, 53.39, 39.99, 39.96, 29.83 ppm. ^{31}P NMR (100 MHz, $CDCl_3$): δ = 10.7 ppm. MS: calcd. 391.0293 $[M + Na]^+$, found 391.0286 $[M + Na]^+$.

***N*-[2-(Benzylthio)ethyl]phosphoramidate (9):** To a stirred solution of **6a** (0.104 g, 0.5 mmol) in methanol (1.0 mL), was added **8** (0.104 g, 0.5 mmol) at 50 °C. After 20 h, the reaction mixture was cooled down and KO*t*Bu (0.112 g, 1.0 mmol) was added at room temperature. After 10 min, benzyl bromide (0.17 g, 1.0 mmol) was added. After 2 h, the solvent was evaporated. Column chromatography of the crude mixture on silica gel using CH_2Cl_2/methanol (95:5) as

eluent gave **9** as brown oil (0.115 g, 0.38 mmol) in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (m, 5 H), 4.15 (s, 2 H), 4.05 (m, 4 H), 3.06 (m, 2 H), 2.44 (t, J = 8.0 Hz, 2 H), 1.30 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 129.1, 128.6, 127.8, 62.72, 62.61, 50.10, 45.26, 45.22, 29.37, 29.33, 16.47, 16.40 ppm. ^{31}P NMR (100 MHz, $CDCl_3$): δ = 9.98 ppm. MS: calcd. 304.1136 $[M + H]^+$, found 304.1179 $[M + H]^+$, 327.0620 $[M + Na]^+$.

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