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(3 + 2)-Cyclization Reactions of Unsaturated Phosphonites with Aldehydes and Thioketones

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This work is dedicated to Prof. Dr. Evamarie Hey-Hawkins on the occasion of her 66th birthday and in admiration of her contagious enthusiasm for phosphorus chemistry.

Abstract: By exploiting the unique reactivity of ethynyl-phosphonites we obtain novel P(V)-containing five-membered heterocycles via (3 + 2)-cyclization reactions with aldehydes or cycloaliphatic thioketones in satisfactory to excellent yields. Whereas reactions with thioketones to yield 1,3-thiaphospholes-3-oxides occur smoothly at room temperature with equimolar amounts of the starting materials in absence of any catalyst, the analogous conversions with aldehydes to generate 3-oxides of 1,3-oxaphospholes require addition of triethylamine as a base. We postulate a step-wise (3 + 2)-cyclization mechanism for the formation of the 1,3-thiaphosphole ring based on DFT quantum chemical calculations. With this study, we introduce new cyclization reactions originating from unsaturated phosphonites as central synthetic building blocks to yield previously inaccessible stable phosphorus-containing heterocycles with unexplored potential for the molecular sciences.

Introduction

P(III)-compounds carrying at least one alkoxy-substituent are well-known nucleophilic building blocks in organophosphorus chemistry, as they yield valuable products for organic synthesis, material science and medicinal chemistry in their reactions with electrophiles. Arguably the most prominent example is the Michaelis–Arbuzov reaction between phosphites, phosphonites or phosphinites and alkyl halides to generate phosphonates, phosphinates or phosphine oxides.[1] In transformations with carbonyl compounds, phosphites are frequently used in Abramov reactions for the synthesis of α-hydroxyphosphonates.[2] The Kabachnik–Fields reaction enables the formation of α-aminophosphonates by combining dialkyl phosphonates with amines and carbonyls.[3] Additionally, trialkyl phosphites have been used in reactions with enolizable cycloaliphatic thioketones and the 1:1 adducts were identified as sole products.[4]

Outside these examples with *C*-based electrophiles, alkoxy-substituted P(III)-compounds react smoothly with organic azides in Staudinger-type reactions to yield P(O)-NH-containing phosphor-, phosphon- or phosphinamidates[5] or with electrophilic disulfides to generate phosphorothioates.[6] Our group has taken advantage of the inherent chemoselectivity of Staudinger reactions[7] to install functional phosphor- and phosphonamidates on unprotected peptides and proteins and to obtain naturally occurring intrinsically labile pLys- or pCys peptides.[8]

In addition to these rather conventional *P*(III)-building blocks, unsaturated phosphonites **1** offer unique reactivity profiles due to the presence of both a nucleophilic P(III)-atom and an adjacent unsaturated C–C bond. Upon reaction of the phosphorus-atom, for example with an electrophile, the double- or triple-bond is transformed into an electrophile itself (Figure 1A). In previous works, we used this concept for modular bioconjugation strategies by reacting ethynyl-phosphonites via a chemoselective Staudinger-phosphonite reaction with an azide-containing molecule. The resulting electrophilic ethynyl-phosphonamidates can undergo selective thiol addition[9] for the formation of highly stable antibody-drug-conjugates

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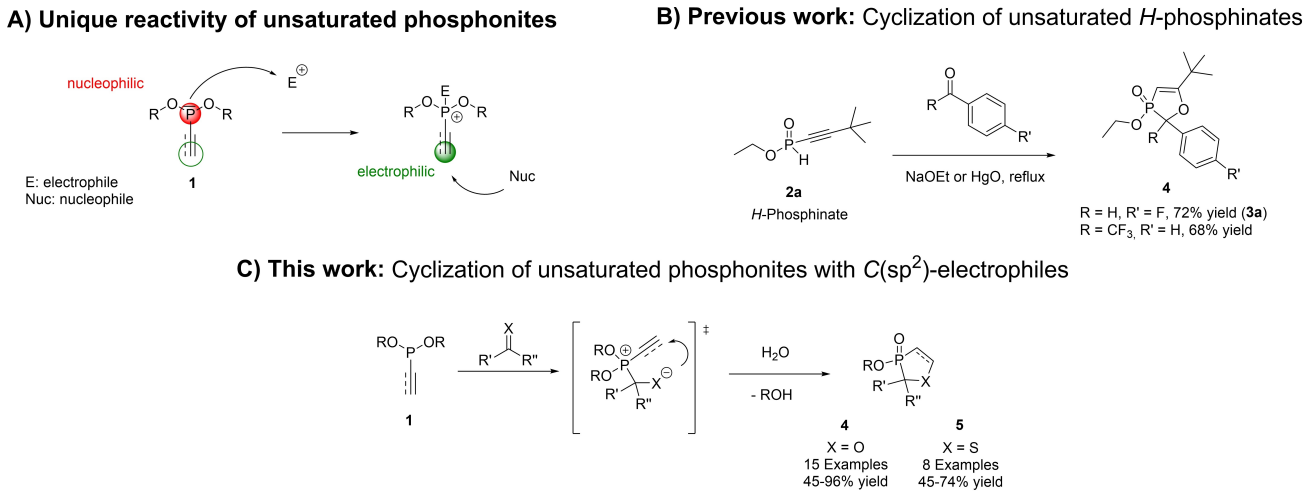


Figure 1. (A) Unique reactivity of unsaturated phosphonites **1** containing a nucleophilic phosphorus and a β-carbon with the potential of inducing electrophilicity. (B) Previous cyclisation reactions with unsaturated *H*-phosphinate **2 a** to form 1,3-oxaphosphole-3-oxides **4 a**.[14a,b] (C) General concept of this work to use unsaturated phosphonites **1** with aldehydes or thioketones for the formation of 1,3-oxaphosphole-3-oxides **4** or 1,3-thiaphosphole-3-oxides **5**.

(ADCs).[10] In a similar manner, vinyl-phosphonites can be converted into cysteine reactive vinyl-phosphonamidates or used for selective peptide cyclisation.[11] In a reaction with electron deficient disulfides vinyl-phosphonites also form stable vinylphosphonothiolates as cysteine-selective electrophiles, which can be used for protein-protein conjugations.[12] Inspired by their unique reactivity, we now set out to investigate transformations of unsaturated phosphonites **1** with *C*(sp^2)-electrophiles. To the best of our knowledge only alkyne-substituted *H*-phosphinates **2** have been used as unsaturated P(III)-substrates in reactions with *C*(sp^2)-electrophiles, for instance, with imines to yield 1,3-azaphosphole-3-oxides.[13] Moreover, in only two specific examples with C=O-compounds, reactions with 4-fluorobenzaldehyde (**3 a**) or 2,2,2-trifluoroacetophenone resulted in the formation of 5-alkyl-substituted 1,3-oxaphosphole-3-oxides **4** with *H*-phosphinate **2 a** (Figure 1B).[14a,b] Presumably due to the low nucleophilic reactivity of *H*-phosphinates **2**, high temperatures and either the addition of alcoholates as strong nucleophilic bases or mercury-salts were required to ensure ring-closure resulting in a narrow substrate scope of the rarely described P-containing heterocycles **4**.[14,15]

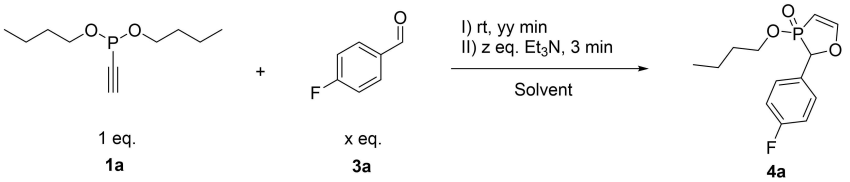
We hypothesized that unsaturated bisalkoxy-phosphonites **1** would provide a more general approach in such (3+2)-cyclization reactions. Thereby, we envisioned that the good nucleophilic properties of **1** enable the reaction with *C*(sp^2)-electrophiles, especially with rather unexplored aldehydes and thioketones, and subsequently induce electrophilicity at the terminal alkyne or alkene leading to efficient ring closure with the initially formed addition product (Figure 1C). Based on this proposal, we now describe a new high-yielding protocol, in which ethynyl-phosphonites **1** undergo reactions with various aldehydes or sterically demanding thioketones under mild conditions to 1,3-oxaphosphole-3-oxides **4** and previously unknown 1,3-thiaphosphole-3-oxides **5** in a simple process with a broad substrate scope (Figure 1C).

Results and Discussion

Ethynyl-phosphonites can be obtained in a two-step/one-pot protocol by reacting bis(diisopropylamino)chlorophosphine with an ethynyl-Grignard reagent, followed by addition of 1*H*-tetrazol and the corresponding alcohol.[10] During our investigation we focused on di(*n*-butyl)-ethynylphosphonite (**1 a**), since this ethynyl-phosphonite can be conveniently isolated by column chromatography in 70% yield and showed sufficient stability. The first attempts either in acetonitrile or in a water/acetonitrile mixture (3:1) to combine **1 a** with 4-fluorobenzaldehyde (**3 a**) as a reactive aldehyde did not lead to any conversion of the phosphonite (Table 1, entry 1&2); however, in one attempt we observed cyclisation after HPLC purification under basic conditions (20% yield), which prompted us to add triethylamine (Et_3N) as an external base. Further investigation confirmed that it was important to add the base after the aldehyde to the reaction mixture since the cyclisation did not occur when both reagents were added together. Upon screening different ratios and time intervals (Table 1, entries 3–10) we isolated the desired oxaphosphole-oxide **4 a** in an excellent yield of 92% with 5 equivalents aldehyde and base addition after 30 min at room temperature as a mixture of diastereomers in a 1:1 ratio using flash chromatography (Table 1, entry 8). Less equivalents and faster addition of the base (entries 3–7) as well as longer exposure (entry 9) led to decreased yields of 44–80%. Interestingly, aqueous conditions turned out to be essential to ensure product formation, since a reaction in acetonitrile with added base did not lead to product formation (entry 10).

Reactions of **1 a** with various aldehydes **3 a–j** yielded 1,3-oxaphosphole-3-oxides **4 a–j** in good to excellent yields (Table 2). We noted that various aromatic as well as aliphatic aldehydes were good substrates and to our delight, we observed compatibility with several functional groups, in particular the transformation of 4-formylbenzoate to **4 h** in 84%

Table 1. Screening conditions for the synthesis of 1,3-oxaphosphole-3-oxide **4a**.



1 eq. **1a** + x eq. **3a** → **4a**

Entry	Solvent	x eq. Aldehyde	Time of base addition	z eq. Et_3N	Isolated yield (%)
1	MeCN	1	-	0	0
2	MeCN : H_2O (3:1)	1	-	0	0[a]
3	MeCN : H_2O (3:1)	1	10 min	1	61
4	MeCN : H_2O (3:1)	1	20 min	1	56
5	MeCN : H_2O (3:1)	1	30 min	1	44
6	MeCN : H_2O (3:1)	5	10 min	5	70
7	MeCN : H_2O (3:1)	5	20 min	5	80
8	MeCN : H_2O (3:1)	5	30 min	5	92
9	MeCN : H_2O (3:1)	5	60 min	5	60
10	MeCN	5	20 min	5	0

[a] 20% after basic HPLC

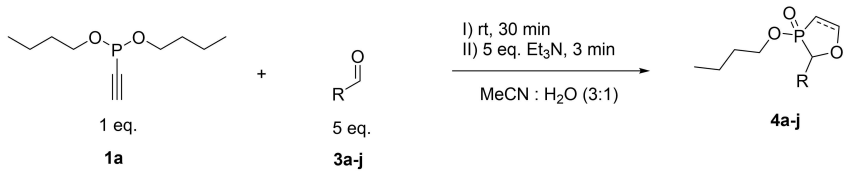
yield, which would be problematic with the harsh reaction conditions in the previously reported *H*-phosphinate protocol.[14a] For compound **4d**, two diastereomers could be separated via HPLC, all other compounds were isolated as diastereomeric mixtures in 1:1 ratios either by flash chromatography or HPLC purification. For compound **4g**, two of four diastereomers were obtained together. All isolated compounds were stable as CD_3CN-solutions at room temperature and ambient air for several months and showed no signs of decomposition. We also used acetone and 2,2,2-trifluoroacetophenone, in which the latter had been successfully used in the *H*-phosphinate protocol in the past (Figure 1B).[14b] In both cases, we did not observe any formation of the desired 1,3-oxaphosphole-3-oxides and no phosphonite conversion.

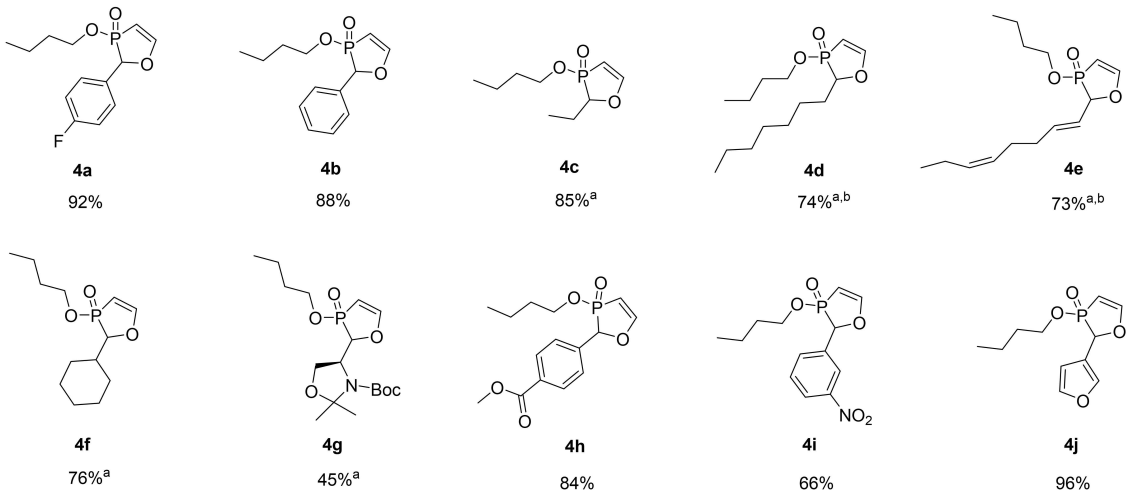
Next, we compared the reactivity of ethynyl-*H*-phosphinates and ethynyl-phosphonites in (3+2)-cyclization reactions with selected aldehydes. For this study, we obtained *n*-butyl ethynyl-*H*-phosphinate (**2b**) via acidic hydrolysis of **1a**[16] and monitored conversions with aldehydes **3** into 1,3-oxaphosphole-3-oxides **4** by ^{31}P NMR. In contrast to good to excellent conversions with ethynyl-phosphonite **1a** we observed significantly diminished outcomes with ethynyl-*H*-phosphinate **2b** when applying our previously optimized conditions (room temperature with subsequent addition of base). While aromatic aldehydes **3a** and **3b** still delivered good product conversions with 75% and 60%, we recorded drastically decreased values for the less reactive alkyl-aldehydes **3c**, **3f** and **3d** (32%, 14% and 8%, Figure 2A). Instead, we observed the formation of a different main product with a ^{31}P NMR-shift around 22 ppm in conversions of 27%, 54% and 51%. In an analogous reaction between **1a** and **3f** we only detected this compound in 8% conversion. We identified the main product for the reaction of **2b** with cyclohexancarbaldehyde (**3f**) as the non-cyclized *n*-butyl (cyclohexyl(hydroxy)methyl)(ethynyl)-phosphinate (**6**) (Figure 2B).

Performing the cyclization of ethynyl-*H*-phosphinate **2b** with 4-fluorobenzaldehyde (**3a**) under the previously reported conditions[14a] (acetonitrile reflux in presence of sodium ethoxide) did not result in the formation of **4a** but only in unidentified side products, which we attribute to the reaction of the unsubstituted alkyne with the strong base. These results demonstrate that the previously reported synthesis of heterocycles **4** according to Figure 1B[14a] is limited to *C*-substituted ethynyl-*H*-phosphinates and that ethynyl-phosphonites **1** are superior cyclization reagents with aldehydes. Furthermore, we transformed ethynyl-*H*-phosphinate **2b** into a silyl-ethynyl-phosphonite **1b** via silylation with *N*,*O*-bis(trimethylsilyl)acetamide (BSA), which led to an improved cyclization with 4-fluorobenzaldehyde (**3a**) with isolating **4a** in a yield of 85% (Figure 2C).

Additionally, we investigated the (3+2)-cyclization with other ethynyl-phosphinates. Following the protocol for the

Table 2. Synthesis of 1,3-oxaphosphole-3-oxides **4a–j** with di(*n*-butyl)ethynyl-phosphonite (**1a**) and various aldehydes **3a–j**. All compounds were isolated as diastereomeric mixtures in 1:1 ratios, determined by ^{31}P NMR.

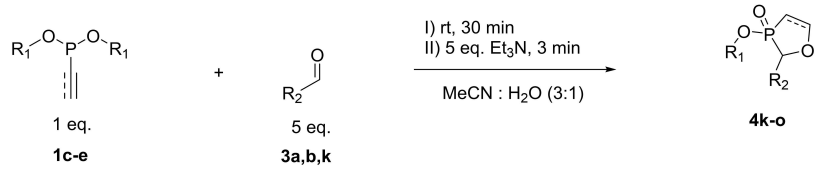


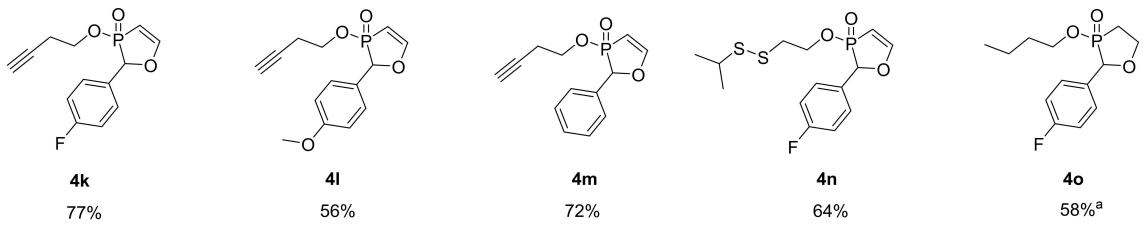


[a] Base-addition after 20 min. [b] MeCN:H_2O (9:1). [c] with crude phosphonite, THF/MeCN/H_2O.

synthesis of **1a** (see Supporting Information), di(but-3-yn-1-yl) ethynylphosphonite (**1c**) and bis(2-(isopropyldisulfaneyl)ethyl) ethynylphosphonite (**1d**) could be isolated and were successfully employed in reactions with aromatic aldehydes **3a**,**b**,**k**, resulting in the isolation of 1,3-oxaphospholane-3-oxides **4k–o** in moderate to good yields of 56–77%. We also tested if the aldehyde cycloaddition proceeds with vinyl-phosphonites. For this, di(*n*-butyl)-vinylphosphonite (**1e**) was synthesized according to the protocol for the synthesis of **1a** (see Supporting Information); however, in contrast to **1a,c,d** the vinyl-phosphonite **1e** proved to be less stable in the presence of air and could not be isolated via column chromatography. Therefore, the reaction was performed with crude di(*n*-butyl)-vinylphosphonite (**1e**), which allowed the isolation of 1,3-oxaphospholane-3-oxide **4o** in 58% yield (Table 3).

Table 3. Synthesis of 1,3-oxaphosphole-3-oxides **4k–o** starting from different unsaturated phosphonites **1c-e** and the aldehydes **3a**,**b**,**k**.





[a] with crude phosphonite, THF/MeCN/H_2O.

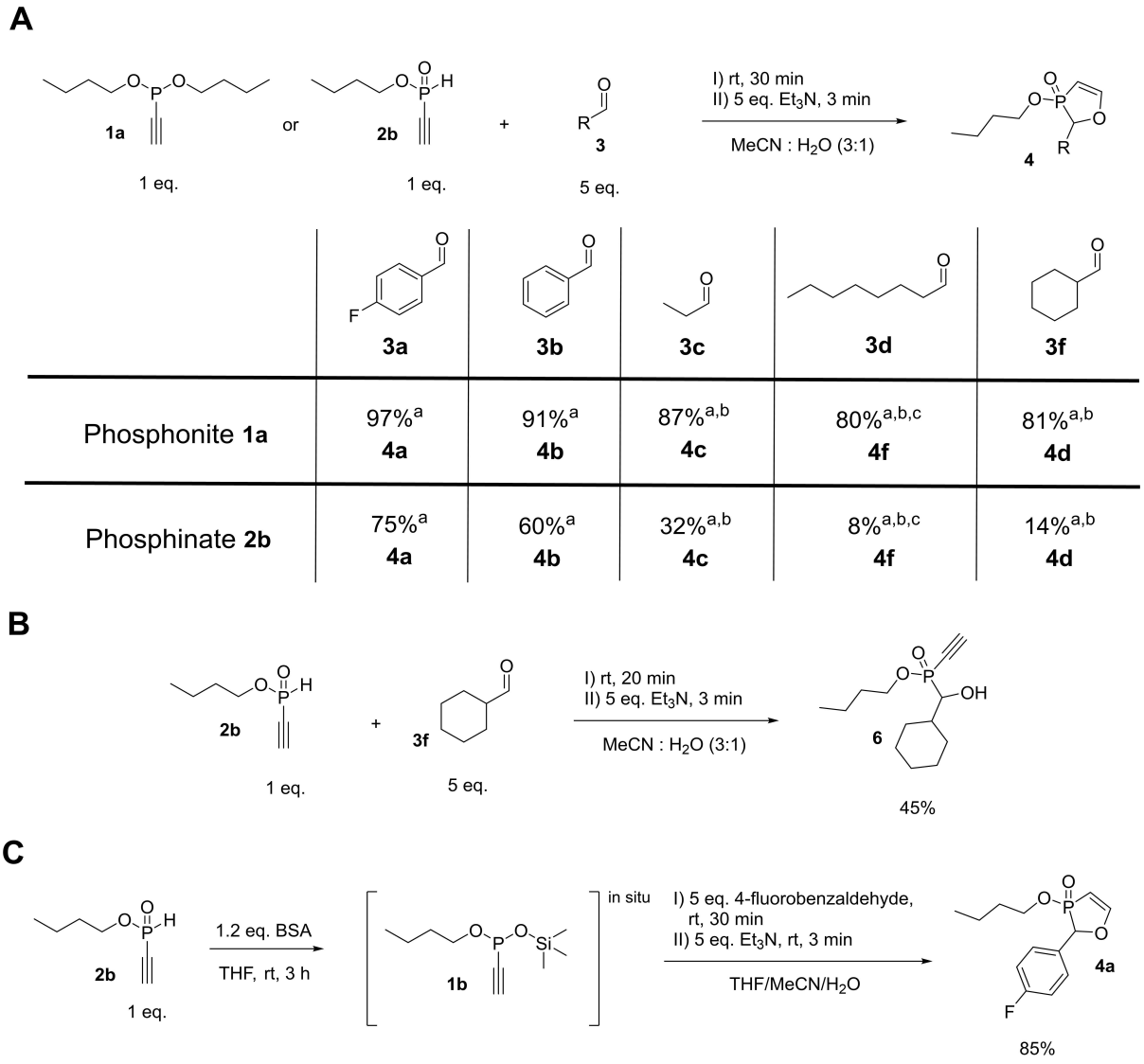


Figure 2. (A) Comparison of the formation of oxaphosphole-3-oxides **4** employing either *n*-butyl ethynyl-*H*-phosphinate (**2 b**) or di(*n*-butyl)-ethynylphosphonite (**1 a**) as the precursor. [a] Conversion determined with ^{31}P NMR. [b] Base-addition after 20 min. [c] MeCN:H_2O (9 : 1). (B) Isolation of *n*-butyl (cyclohexyl(hydroxy)methyl)(ethynyl)phosphinate **6** as the main product for the reaction of *n*-butyl ethynyl-*H*-phosphinate (**2 b**) with cyclohexancarbaldehyde (**3 f**). (C) Improved cyclization of ethynyl-*H*-phosphinate **2 b** with 4-fluorobenzaldehyde (**3 a**) via silylation with BSA, which leads to an in situ generated silyl-ethynyl-phosphonite **1 b**.

During our studies, we observed that the cyclization reaction with aldehydes requires water, as the product heterocycles **4** are not formed under anhydrous conditions (Table 1, entry 10). Consequently, we assumed that water is involved in the mechanism and hypothesized that after ring closure the *P=O*-bond could be formed via two different pathways: either involving nucleophilic attack of water on the phosphorus-atom or via an Arbuzov-like reaction with water attacking a carbon in α-position to the P–O-alkoxy substituent. We performed an experiment with O^{18}-labelled water, which revealed a strong preference of the direct nucleophilic attack of water on the phosphorus-atom as we almost exclusively observed the O^{18}-labelled compound **4 a–1** over the non-labelled **4 a–2** in a ratio of 95 : 5 (Figure 3, Figure S1).

Cyclization of ethynyl-phosphonites with thioketones

Encouraged by those results, we next focused on the cyclization of ethynyl-phosphonites with thioketones. Thioketones are good electrophiles and in general more reactive when compared to ketones. For instance, a thioxosteroid reacts chemoselectively at the C=S bond with a hydrazine,[17] which can be rationalized by an increase of electrophilicity of the C=S vs. the C=O supported by quantum-chemical calculations.[18] Additionally, ketones usually undergo reactions with nucleophiles yielding the products of the 'carbophilic' attack, whereas thioketones are known to react in both 'carbo'- and 'thiophilic' mode to form a new C–Nu or S–Nu bond, respectively. For

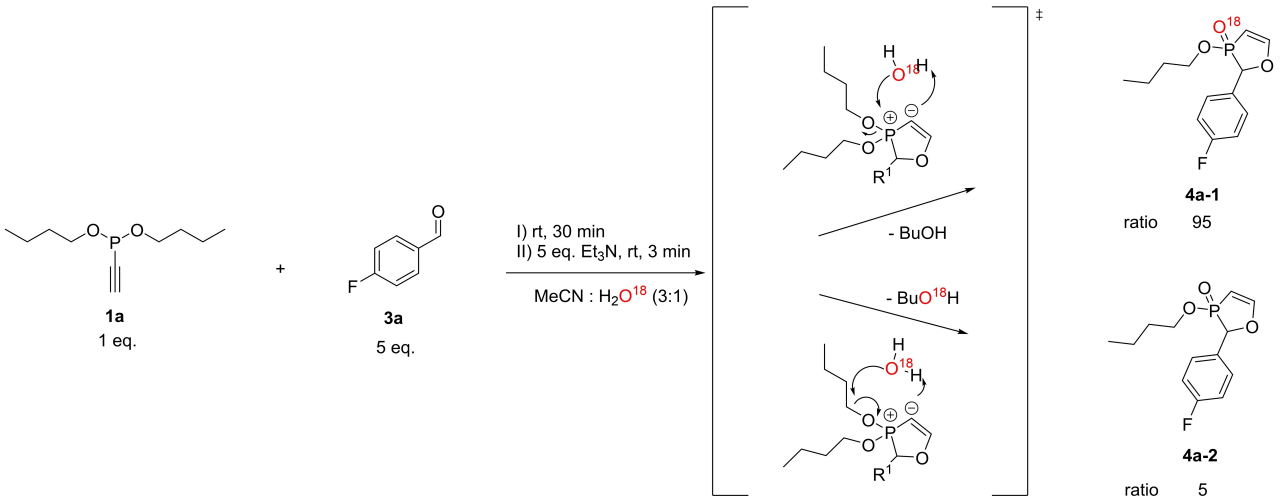


Figure 3. Mechanistic proposal for the formation of the *P*=*O*-bond and the influence of water in the reaction mixture. The reaction of ethynylphosphonite **1 a** with 4-fluorobenzaldehyde (**3 a**) was performed in MeCN: H_2O^{18}(3:1). 3 min after Et_3N addition an LC–MS-analysis (Figure S1) of the reaction-mixture was performed and masses corresponding to both the O^{18}-labelled heterocycle **4 a-1** and the non-labelled *P*-*O*-heterocycle **4 a-2** were observed in a ratio of 95:5.

example, adamantanethione (**7 a**) reacts with Grignard reagents giving thiols or sulfides, depending on the solvent used in the reaction.[19] On the other hand, phenyllithium was reported to transform thiobenzophenone (Ph_2C=S) in benzene-etheral solution following the thiophilic mode, exclusively.[20]

For reactions with P(III)-reagents, it was previously reported that cyclohexanethione ($C_5H_{10}C$=S) can be converted with phosphites to form α-thio-substituted phosphonate derivatives via initial carbophilic attack of the *P*-nucleophile. Notably, no alternative thiophilic attack was reported and no reaction was observed with sterically demanding thioketones, for example, thiocamphor (**7 b**).[4] We initiated our experiments by reacting **1 a** with one equivalent adamantanethione (**7 a**) as a well-known representative of cycloaliphatic thioketones **7** at room temperature in anhydrous tetrahydrofuran (THF) without addition of a catalyst. After 3 h, the characteristic orange color of **7 a** vanished. After solvent removal, we analyzed the crude reaction mixture by ^{1}H- and ^{31}P NMR. These observations pointed towards the formation of the 1,3-thiaphosphole 3-oxide derivative **5 a**, since the signals corresponded to those described for 1,3-oxaphosphole-3-oxides **4** (see Supporting Information). Thin layer chromatography (TLC) of the crude reaction mixture revealed only one major product of medium polarity (R_f = ca. 0.5; SiO_2/CH_2Cl_2: MeOH (98:2)). We isolated this product with preparative TLC plates coated with silica and crystalized it from hexane/CH_2Cl_2 as colorless needles with narrow melting point 96–98 °C. Further HR-MS and ^{13}C NMR-measurements (see Supporting Information) as well as X-ray analysis (Figure 4) unambiguously confirmed the formation of 1,3-thiaphosphole 3-oxide derivative **5 a**.

Next, we applied the base-free reaction conditions to a reaction of **1 a** with thiocamphor (**7 b**), which delivered a 1:1 mixture of two inseparable isomeric products **5 b** and **5 b'**, isolated after chromatographic purification in 47% yield. We observed very similar chemical shift for the HC=CH unit in both

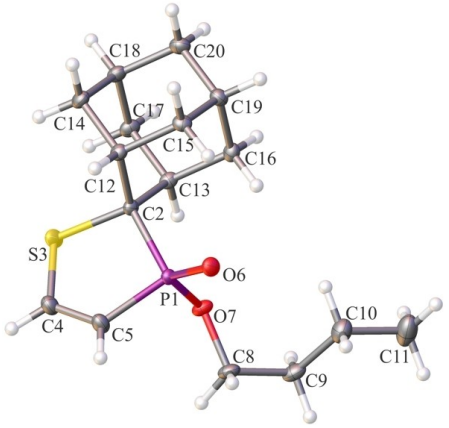
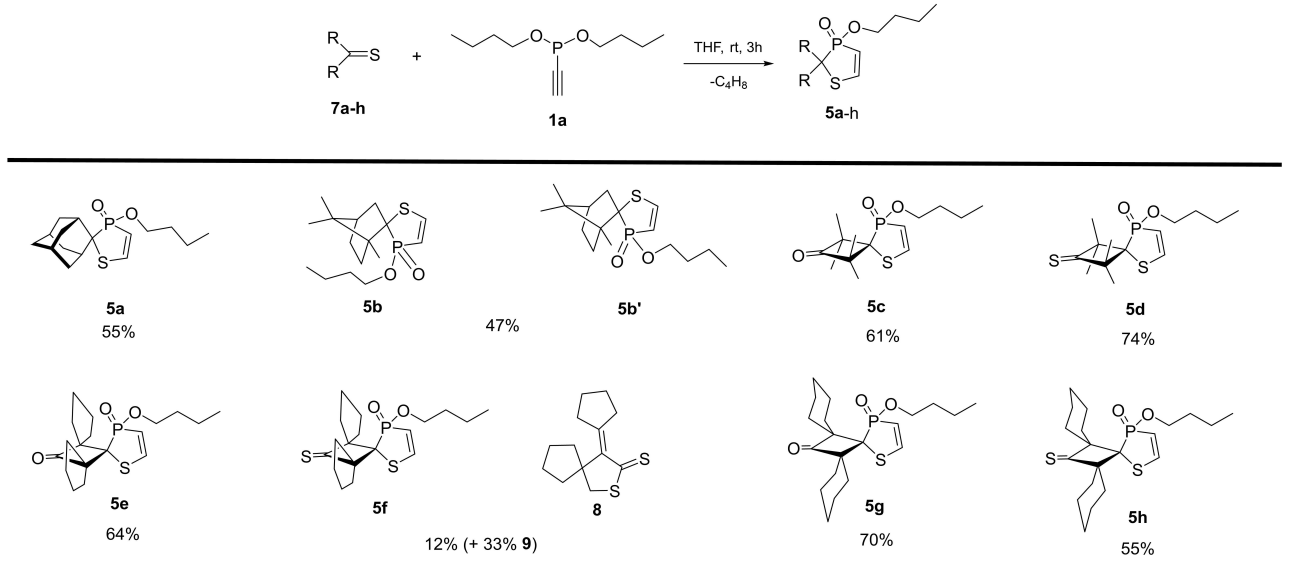


Figure 4. ORTEP structure of 1,3-thiaphosphole-3-oxide **5 a**; 50% probability.

^{1}H- and ^{13}C NMR spectra suggesting that they correspond to structurally similar endo-cycloadducts which differ by orientation of the P=O bond (Table 4). Similar stereoisomers were reported for cycloadducts of **7 b** with 1,3-dipoles, for example, with fluorinated nitrile imines.[21] It is worth noting that **7 b** does not react with trialkyl phosphites,[4] which demonstrates that **1 a** is a more reactive nucleophile than trialkyl phosphites in these reactions. Furthermore, we tested different aromatic thioketones, such as thiobenzophenone and thiofluorenone in a transformation with **1 a** (Scheme S1).

Although we observed that the characteristic blue color of thiobenzophenone vanished upon addition of the unsaturated phosphonite **1 a**, we were unable to isolate the desired heterocyclic compound and mostly obtained benzophenone in 70% yield. In addition, thiofluorenone also did not result into the formation of a spiro-fluorene derivative of compound-type **3**. In this case thiofluorenone was rapidly converted into the known bisfluorenylidene, which was previously reported to

Table 4. Reaction of cycloaliphatic thioketones **7a–h** with phosphonite **1a** leading to corresponding 1,3-thiaphosphole 3-oxides **5a–h**.



form upon treatment of thiofluorenone with tributylphosphine.[22] At this point, we are unable to provide a convincing explanation of the failed reactions; nevertheless, it is worth emphasizing that aromatic thioketones like thiobenzophenone and thiofluorenone are known to show diverse reaction mechanisms including radical pathways with different nucleophiles and air oxygen; which in some instances could be the reason for the S→O exchange. For example, these differences were reported for reactions of thiobenzophenone with BuLi[20] as well as for reaction of another aromatic thioketone (thioxanthione) with methoxyallenyl anion.[23] Encouraged by the excellent results for the reaction of cycloaliphatic thioketones with ethynyl-phosphonite **1a**, we evaluated the chemoselectivity of this transformation in the presence of ketones. Ethynyl-phosphonite (**1a**) was combined with adamantanethione (**7a**) and adamantanone in anhydrous THF at room temperature. After 3 h, LC–MS and ^{31}P NMR analysis of the reaction mixture revealed that only **7a** reacted, since solely 1,3-thiaphosphole-3-oxide **5a** was observed in 97% conversion (Figure S2). Next, we focused on compounds carrying both a thioketone as well as ketone functionality. 3-Thioxo-2,2,4,4-tetrametyhylcyclobutanone (**7c**) as well as the monothiones **7e** and **7g** were smoothly converted into the corresponding 1,3-thiaphosphole 3-oxides **5c**, **5e** and **5g** with equimolar amounts of **1a** in good yields of 61–70%. In all cases, the ^{13}C NMR-spectrum showed characteristic signals for the unconverted C=O bond. Analogously, dithiones **7d** and **7h** showed the reaction of a single thioketone unit when one equivalent of **1a** was used and delivered the heterocycles **5d** and **5h** in yields of 74% and 55%, respectively. Reaction of **1a** with the rather unstable dithione **7f** was less efficient and the expected 1:1 cycloadduct was isolated in 12% yield only. Instead, we mainly isolated dithiolactone **8** in 33% yield, which was also observed as an isomerization product in an earlier work under completely different conditions.[24]

Increasing the amount of ethynyl-phosphonite **1a** to two equivalents did not lead to the conversion of the second thioketone unit. This finding was unexpected, since **7d** is known to yield 1:2 cycloadducts (as mixtures of syn- and anti-stereoisomers) in 1,3-dipolar cycloadditions with diazomethane[25] and nitryl imines.[21] Moreover, **7d** undergoes a hetero-Diels–Alder reaction with nitrosostyrene (1:2 ratio of substrates) leading to the formation of the six-membered bis-cycloadduct employing both C=S unites.[26] However, when an azoalkene was used as a heterodiene under analogous conditions, no formation of the expected bis-cycloadduct was observed and the 1:1 cycloadduct was the only product.[27] We attribute the failed conversion to the steric hindrance in the initially formed 1:1 spiro-cycloadduct, which prevents the nucleophilic attack of the second molecule of **1a** onto the unconverted C=S bond in dithiones **7f** and **7h**. In addition, change of the conformation of the four-membered ring after rehybridization of spiro-C(3) atom ($Csp^2 \rightarrow Csp^3$) can also play a role in substantial diminishing of its reactivity. In analogy to **3a**, molecular structures of 1,3-thiaphosphole-3-oxides **3e** and **3h** were also confirmed by single-crystal X-ray analysis (Figure S27).

Computational analysis

Finally, we performed computational, quantumchemical analysis to determine a mechanistic picture for the transformation of ethynyl-phosphonites. As a representative model system, we chose the reaction between phosphonite **1a** and 2,2,4,4-tetramethylcyclobutylthioketone (**7k**) and performed DFT calculations (wb97xd/6-311+G(d) level of theory employing the PCM solvation model).[28] Unfortunately, all attempted calculation of **1a** with aldehydes were unsuccessful.

Our calculations revealed that the reaction of **1a** and **7k** follows a stepwise pathway. We determined three transition

states **TS1**, **TS2** and **TS3** as well as two intermediates **9k** and **10k** (Figure 5). In the initial stage, the interactions between **1a** and **7k** lead to the formation of the first transition state **TS1**. This is associated with an enthalpy increase to about 11 kcal/mol (Figure 5A) and an entropy reduction due to the highly organized structure of **TS1** results in the reduction of entropy. Consequently, we estimate the Gibbs free energy of the activation to be 25 kcal/mol. Notably, within **TS1**, one new heteronuclear σ-bond, that is, P(3)–C(4) (2.345 Å), is formed associated with non-synchronical reorganization of the electron density (Figure S28). **TS1** can be considered as a polar structure in light of the high global electron density transfer (GEDT) value, which is calculated to be 28e. The intrinsic reaction coordinate (IRC) calculations suggested the starting configuration transformed via **TS1** to another energy minimum that can be considered as the first intermediate (**9k**) of the reaction. Intermediate **9k** exhibits a zwitterionic nature, which is again confirmed by GEDT analysis. Its conversion proceeds via a second transition state **TS2**. Within this process, the new σ-bond C(1)-S(5) (2.809 Å), leading to the closure of five-membered ring, is formed (Figure S28), which proceeds by a similar rate constant as the first stage of the analyzed reaction. The kinetically limiting reaction step is the elimination of but-1-ene and formation of P-ylide **10k** (Figure 5A). This intermediate is converted into the final product **5k** via a pseudocyclic, six-membered transition state **TS3**. Within this TS, two σ-bonds, that is, O–C: 1.928 Å and C–H: 1.267 Å, are broken and simultaneously a new C–H bond is formed (1.545 Å) (Figure S28). It is worth noting that similar elimination mechanisms under anhydrous conditions were observed for the synthesis of carboxylic acids from alkyl carboxylates[29] and for the reaction of diethyl ethynylphosphonite with in situ generated nitrile imines, which led to formation of the P=O functionality in P-oxides of [1,2,4]-diazaphosphonines.[30] The IRC calculations suggested a transition state **TS3** between the intermediate **10k** on one side and the products (**5k** + but-1-ene) on the other side. Formally, the entire reaction pathway can be considered as a fully irreversible process (Figure 5).

Taken together, we envision three-stage mechanism for the reaction of ethynyl-phosphonites with thioketones as illustrated in Figure 5: (i) Addition of the P(III)-compound to the electrophilic thioketone and the formation of a zwitterionic intermediate, (ii) single-step ring closure and (iii) a pseudocyclic but-1-ene elimination accompanied by formation of 1,3-thiaphospole ring. As a result, ethynyl-phosphonites like **1a** undergo a formal oxidation and are converted into a P(V)-containing 1,3-thiophosphole 3-oxide **3**.

A

Transition	ΔH	ΔG	ΔS
1a + 7k → TS1	11.13	26.10	-50.21
1a + 7k → 9k	-3.62	10.34	-46.82
9k → TS2	14.30	17.45	-10.58
9k → 10k	-5.06	-3.15	-6.40
10k → TS3	30.28	31.97	-5.67
10k→ 5k + but-1-ene	-33.43	-44.26	36.31

B

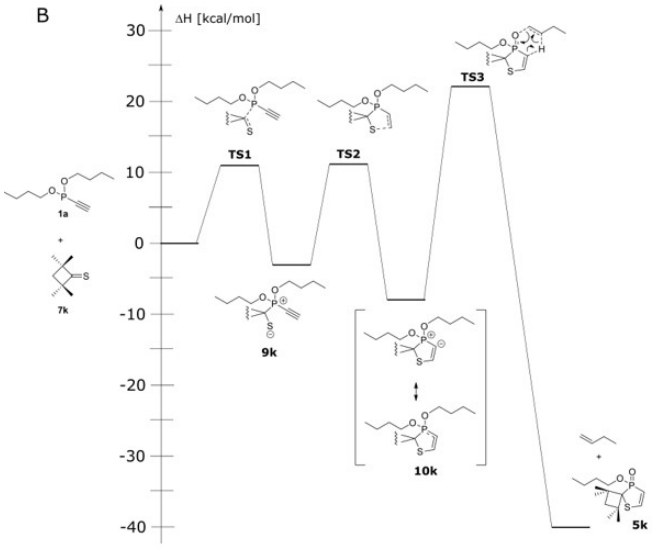


Figure 5. (A) Kinetic and thermodynamic parameters of the reaction between phosphonite **1a** and thioketone **7k** in THF (wb97xd/6-311 + G-(d)(PCM) calculations; ΔH and ΔG values are giving in kcal/mol; ΔS values are giving in cal/mol·K). (B) Enthalpy profile of the reaction between phosphonite **1a** and thioketone **7k** in THF solution, according to wb97xd/6-311 + G(d)(PCM) calculations.

Conclusions

In summary, we developed new (3 + 2)-cyclization protocols for the synthesis of previously inaccessible P(V)-heterocycles. Key to success was the use of unsaturated phosphonites like ethynyl- or vinyl-phosphonites as substrates in reactions with aldehydes or thioketones as C(sp^2)-electrophiles. We observed smooth reactions at room temperature leading to the fast formation of 1,3-oxa- and 1,3-thiaphosphole-3-oxides in good to very good yields. Whereas reactions with aldehydes require the addition of an external base and the presence of residual amounts of water, we found that the corresponding reactions with thioketones occur under anhydrous conditions with equimolar amounts of starting materials at room temperature without the addition of an external base.

Our protocol offers straightforward access to 1,3-oxo- and 1,3-thiaphosphole derivatives that in contrast to extensively studied 1,3-thiazoles[31] constitute lesser known classes of five-membered P-containing-heterocycles.[32]

Previously, methods to access 1,3-thiaphospholes were very limited[33] and moreover, preparation of their 3-oxides had not been reported. In addition, this study once more demonstrates that thioketones are prone electrophiles and react more efficiently with P(III)-compounds than their oxo-analogues. Taken together, we open new prospects for the engineering of unprecedented P-containing heterocycles with biological activity[34] as well as their further functionalization in cycloaddition reactions, which are currently ongoing in our laboratory.

Experimental Section

General procedure for the synthesis of unsaturated phosphonites: Unsaturated phosphonites were synthesized according to a modified literature procedure.[10] Bis(diisopropylamino)chlorophosphine (1.0 equiv.) was dissolved in anhydrous THF using ultrasonic irradiation, the solution was cooled to 0 °C and a vinyl- or ethynylmagnesium bromide solution (0.5 M in THF, 1.3 equiv.) was added dropwise. The cooling source was removed and the yellowish brown solution was stirred for 30 min. The corresponding alcohol (2.5 equiv.) was mixed with an 1*H*-tetrazole solution (0.45 M in MeCN, 2.5 equiv.) and the solution was added to the reaction mixture, the resulting light brown suspension was stirred overnight at room temperature under argon atmosphere. Afterwards either the crude phosphonite was used for further reactions or the reaction mixture was filtered via centrifugation and the filtrate was purified with silica gel column chromatography (*n*-hexane:EtOAc, 4:1).

General procedure for the synthesis of 1,3-oxaphosphole-3-oxides with unsaturated phosphonites and aromatic aldehydes: Unsaturated phosphonite (1) (0.1 mmol, 1.00 equiv.) was dissolved in 1.50 mL CH_3CN and the aldehyde (0.5 mmol, 5.00 equiv.) was added. Then 0.50 mL H_2O was added and the solution was stirred for 30 min at room temperature followed by addition of 69.30 µL Et_3N (0.5 mmol, 5.00 equiv.), afterwards the solution was stirred for 3 more minutes. The reaction mixture was then diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$ and the resulting crude product was purified either by silica flash chromatography (n-hexane:EtOAC, 1:4→0:1, 0.5% Et_3N) or by basic preparative reversed phase HPLC (MeCN:$H_2$0, 20:80→99:1 in 40 min, 0.15% NH_3).

General procedure for the synthesis of 1,3-oxaphosphole-3-oxides with unsaturated phosphonites and aliphatic aldehydes: Unsaturated phosphonite (0.1 mmol, 1.00 equiv.) was dissolved in 1.50 mL CH_3CN and the aldehyde (0.5 mmol, 5.00 equiv.) was added. Then 0.50 mL H_2O was added and the solution was stirred for 20 min at room temperature followed by addition of 69.30 µL Et_3N (0.5 mmol, 5.00 equiv.), afterwards the solution was stirred for 30 more minutes. The reaction mixture was then diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$ and the resulting crude product was purified either by silica flash chromatography (n-hexane:EtOAC, 1:4→0:1, 0.5% Et_3N) or by basic preparative reversed phase HPLC (MeCN:$H_2$0, 20:80→99:1 in 40 min, 0.15% NH_3).

General procedure for the synthesis of 1,3-thiaphosphole-3-oxides with ethynyl-phosphonite and cycloaliphatic thioketones: A solution of di(n-butyl)ethynylphosphonite **1a** (61 mg, 0.3 mmol) in 0.6 mL anhydrous tetrahydrofuran (THF) was stirred at room temperature in a round bottom flask (5 mL) and the corresponding thioketone (0.3 mmol) was added. Stirring was continued for 3 h, during this time the characteristic red color of thioketones vanished. The solvent was evaporated under reduced pressure and the residue was analyzed by ^{1}H NMR. Crude products were separated by PLC; solid products were additionally purified by recrystallization from hexane with small amount of dichloromethane (slow evaporation at room temperature). Calculated yields refer to products isolated after chromatographic purification.

Procedure for the mechanistic investigation of 1,3-oxaphosphole-3-oxide formation with H_2O^{18}: Di(n-butyl)ethynylphosphonite **1a** (0.05 mmol, 1.00 equiv.) was dissolved in 0.75 mL anhydrous CH3CN and 4-fluorobenzaldehyde (**3a**) (0.25 mmol, 5.00 equiv.) was added. Then 0.25 mL H_2O^{18} was added and the solution was stirred for 30 min at room temperature followed by addition of 34.65 µL Et_3N (0.25 mmol, 5.00 equiv.), afterwards the solution was stirred for 3 more min. and an LC–MS analysis of the reaction mixture was done and masses for both the ^{18}O-labelled heterocycle **4a–1** and the non-labelled *P-O*-heterocycle **4a–2** were observed in a ratio of 95:5.

Characterization of all isolated compounds can be found in the Supporting Information.

Deposition Number(s) 2129514 (for **5a**), 2129513 (for **5e**) and 2129515 (for **5h**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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