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Stannyl phosphaketene as a synthon for phosphorus analogues of β-lactams†

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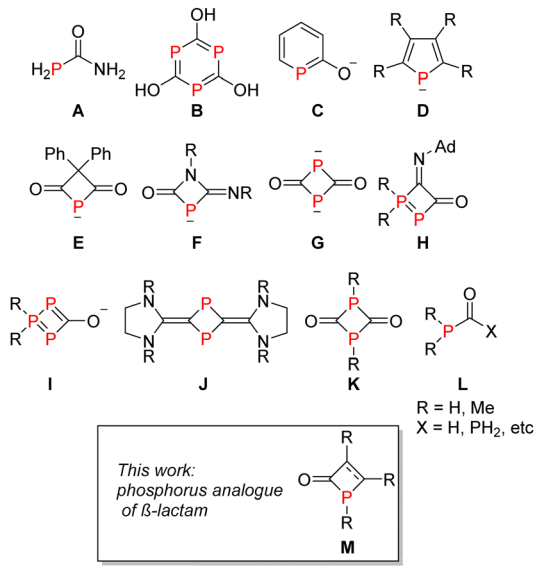
The reaction of the stannyl phosphaketene (Nacnac)SnPCO 1 (Nacnac = CH{(CMe)(2,6-^{i}Pr$_2$C$_6$H$_3$N)}$_2$) with B(C$_6$F$_5$)$_3$ produced the 1,4-addition product of (Nacnac)SnPCO(B(C$_6$F$_5$)$_3$). However, the corresponding reactions in the presence of dimethyl maleate, diisopropyl fumarate or diethyl-but-2-ynedioate gave [2+2] addition yielding four-membered phosphacycles, ((Nacnac)Sn(MeO$_2$C))CHPC(OB(C$_6$F$_5$)$_3$)-CH(CO$_2$Me), [(C$_6$F$_5$)$_3$B)PC(OSn)C(CO$_2$Me)CH(CO$_2$Me)]$_2$, (Nacnac)-Sn(^{i}PrO$_2$C)CC(OAl(C$_6$F$_5$)$_3$)P[CH(CO$_2{}^i$Pr)CH$_2$(CO$_2{}^i$Pr)]CH(CO$_2{}^i$Pr), and (Nacnac)SnP (EtO$_2$CCC(CO$_2$Et))CO(B(C$_6$F$_5$)$_3$), respectively. In contrast, the corresponding reaction of phenylacetylene gave the FLP-addition product (Nacnac)SnOC(P)C(Ph)CH(B(C$_6$F$_5$)$_3$). Collectively, this reactivity demonstrates that the stannyl phosphaketene 1 can act as a synthon for P-analogues of β-lactam derivatives.

As the first synthesis of an organic compound from inorganic reactants, Wöhler's synthesis of urea from ammonium cyanate (NH_4NCO) is considered to be a scientific milestone in modern organic chemistry.[1,2] In the past decade, the 2-phosphaethynolate anion (PCO^-) and its derivatives have been successfully applied as synthons to build heavier analogues of simple organic compounds, in which phosphorus replaces nitrogen.[3,4] For example, Goicoechea's group reported the synthesis of phosphinecarboxamide (Scheme 1, **A**), a phosphorus analogue of urea, exploiting the reaction of PCO^- with ammonium salts quantitatively.[5] The phosphorus analogue of isocyanic acid (HPCO) was synthesized by the same group employing a fatty acid to protonate NaPCO.[6] Grützmacher *et al.* synthesized the phosphorus analogue of cyanuric acid (**B**) by reacting PCO^- with B-chlorodiisopinocampheylborane and followed by alcoholysis,[7] whereas reacting PCO^- with alkyne gave the phosphorus analogue of pyridinolate (**C**) and pyrrolide (**D**).[8,9] Meanwhile, [2+2] cycloaddition reactions of PCO^- with diphenylketene and carbodiimide yielded the anionic four-membered heterocycles $P[C(O)]_2C(C_6H_5)_2^-$ (**E**) and $PC(O)(CNDipp)NDipp^-$ (**F**).[10] In addition, the dimerization of NaPCO in the presence of borane gave the phosphorus analogue of the 1,3-cyclobutanedione anion $P[C(O)]_2^{2-}$ (**G**).[11]



Scheme 1 Reported phosphorus analogues of the organic moiety.

Several groups have exploited the main-group phosphaketenes (EPCO, E = $(NR_2)_2P$, $(NR_2)_2Ge$, Ph_3Ge, Ph_3Si) to enable new synthetic strategies toward a wide range of novel phosphorus-containing heterocycles.[12–15] For example, Bertrand's group used the (phosphanyl)phosphaketenes as building blocks for a series of phosphorus heterocycles (**H** and **I**),[16] while Li and Grützmacher *et al.* reported an N-heterocyclic carbene stabilized dicarbondiphosphide, which could be

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reduced to give the derivative [(NHC)CPH]$_2$ (**J**).[17,18] Furthermore, Slootweg *et al.* reported the diphosphetanedione (**K**) originating from the cyclopropenylphosphaketene intermediate.[19] We have also employed the neutral PCO derivative Ph_3GePCO as the phosphorus source in the synthesis of *P*,*P*-dimethylformylphosphine, diphosphaureas and primary acylphosphine (**L**).[20–23]

More than half of all commercially available antibiotics in use are β-lactams.[24] For example, penicillin, penem, carbapenem, cephalosporin, cephamycin, monobactam, and their derivatives all feature 2-azetidionone cores.[25,26] Focusing attention on the phosphorus analogue of β-lactams, we note that such species scarcely appear in the literature. Ionkin *et al.* isolated the keto-form compound of 1,2-dihydrophosphate from the pyrolysis of its corresponding silyl enol-form.[27,28] Herein, we explore the reactivity of a stannyl phosphaketene and demonstrate that it acts as a synthon providing access to several rare examples of phosphorus analogues of β-lactam derivatives (Scheme 1, **M**).

The compound [(Nacnac)SnPCO] (Nacnac = CH{(CMe)(2,6-^{i}Pr$_2$C$_6$H$_3$N)}$_2$) **1** was readily prepared in 83% yield by the salt elimination reaction of the precursor [(Nacnac)SnCl][29] and NaPCO.[30] A similar preparation has been reported for the species [(HC{(CMe)(2-(Ph$_2$P)C$_6$H$_4$)}$_2$SnPCO].[31] Compound **1** exhibited a ^{31}P NMR resonance at −316.8 ppm, with a doublet at 189.4 ppm corresponding to the C signal of the P═C═O moiety. A crystallographic study (Fig. 1(a)) confirmed the formulation and revealed a simple end-on binding of the PCO fragment to Sn, with a Sn–P distance of 2.672(3) Å. The Sn–P, P–C and C–O distances of the PCO fragment are 2.672(3) Å, 1.597(6) Å, and 1.171(7) Å, respectively.

Compound **1** reacted with B(C$_6$F$_5$)$_3$ to give the product (Nacnac)SnPCO(B(C$_6$F$_5$)$_3$) **2**. A crystallographic study (Fig. 1) of **2** revealed the addition of the central gamma carbon of the Nacnac ligand and the B(C$_6$F$_5$)$_3$ across the CO fragment of the PCO unit affording tris-chelation to Sn. These new C–C and O–B bond lengths were found to be 1.578(2) Å and 1.510(3) Å. The Sn–P, P–C and C–O distances in the PCO fragment were found to be 2.6068(5) Å, 1.7063(18) Å, and 1.323(2) Å, respectively. A similar 1,4-addition product could be found for metal complexes incorporating Nacnac ligand.[32–37]

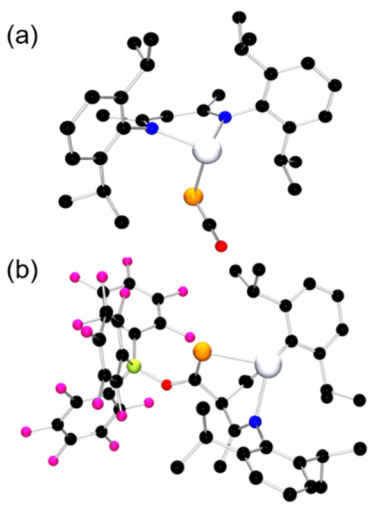
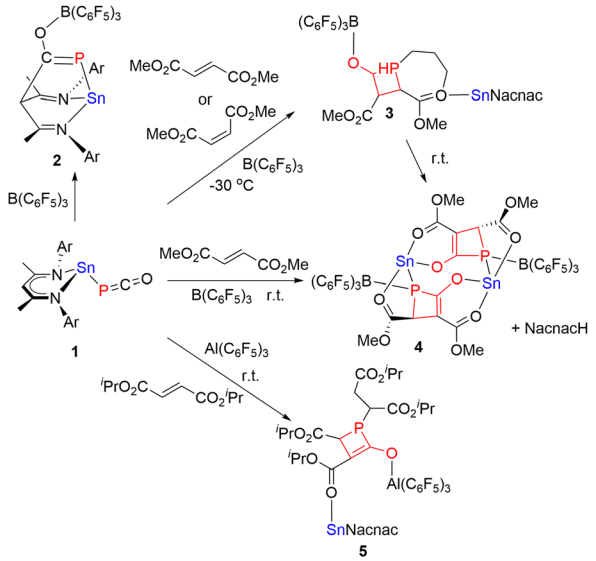


Fig. 1 POV-ray depiction of the molecular structures of (a) **1** and (b) **2**. Hydrogen atoms are omitted for clarity. C: black, N: blue, O: red, P: orange, B: yellow-green, F: pink, Sn: silver.



Scheme 2 Synthesis of **2**–**5**.

Compound **1** also reacted with B(C$_6$F$_5$)$_3$ and dimethyl maleate in a 1 : 1 : 1 ratio in toluene solution at −30 °C. This led to an immediate color change from yellow to brown (Scheme 2). The new product **3** showed a singlet at −193.9 ppm in the ^{31}P NMR spectrum and a ^{11}B NMR peak at −2.0 ppm consistent with the presence of a tetracoordinated boron atom. Colorless crystals of **3** were obtained after storing the reaction mixture at −30 °C overnight. X-ray crystallographic analysis of **3** (Fig. 2(a)) confirmed the formulation as ((Nacnac)Sn(MeO$_2$C))CHPC-(OB(C$_6$F$_5$)$_3$)CH(CO$_2$Me). Compound **3** contains a phosphetan-2-one ring coordinated to B(C$_6$F$_5$)$_3$ while an ester is coordinated to the cationic Sn center. The B–O bond length is 1.519(4) Å while the Sn–O bond length is 2.335(3) Å. The two C–P bond lengths (1.709(4) Å and 1.929(4) Å) in **3** indicate that a stronger P–C interaction in the PCO fragment is retained while the C–O distance (1.302(4) Å) in the phosphetan-2-one core reflects a C═O double bond. It is worth noting that when the *E*-isomer of dimethyl maleate, dimethyl fumarate was used as the substrate instead of its *Z*-isomer dimethyl maleate, only the same product **3** was isolated.

Performing this same reaction at ambient temperature showed that **3** is unstable as indicated by the appearance of a new singlet at 57.3 ppm in the ^{31}P NMR spectrum. The ^{11}B NMR spectrum also displayed a new broad peak at −15.2 ppm. Colorless crystals of **4** were isolated after work-up along with NacnacH. The molecular structure of **4** was formulated as [(C$_6$F$_5$)$_3$B)PC(OSn)C(CO$_2$Me)CH(CO$_2$Me)]$_2$ (Fig. 1(b)) consistent with the loss of the NacnacH, indicating the formal H atom migration from the phosphetan-2-one ring of **3** to the Nacnac

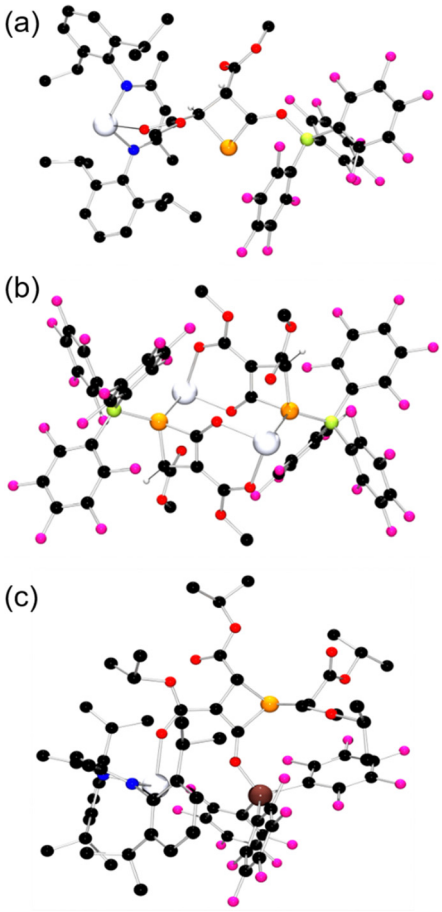
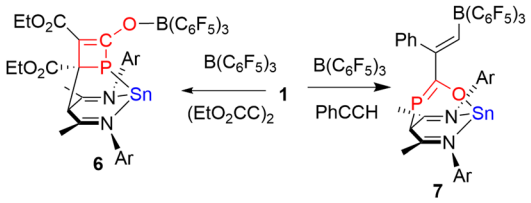


Fig. 2 POV-ray depiction of the molecular structures of (a) **3**, (b) **4** and (c) **5**. Hydrogen atoms are omitted for clarity. C: black, N: blue, O: red, P: orange, B: yellow-green, F: pink, Sn: silver.

ligand. The structural data reveal that both P and O atoms of the phosphetan-2-one are linked to the Sn^{2+} atom to afford a head-to-tail dimer with Sn–P and Sn–O distances of 2.8105(6) Å, 2.1422(16) Å, 2.2847(16) Å and 2.5004(16) Å. $B(C_6F_5)_3$ is bound to P generating tetracoordinated P centers with a B–P bond distance of 2.069(3) Å. The two C–P bond lengths of **3** (1.844(2) and 1.888(2) Å) are more symmetric than those in **2**, while the C–P–C angle found in **4** was 75.17(10)° in the phosphetan-2-one ring. It is interesting that **3** slowly converted to **4** when dissolving in CH_2Cl_2 at ambient temperature, indicating that **3** is an intermediate in the formation of **4**. The molecular structures of **3** and **4** are rare examples of the phosphorus-containing analogue of β-lactams stabilized by Lewis acids. In addition to **4**, the side product NacnacH was also isolated and was confirmed by its ^{1}H NMR spectrum.

The analogous reactions of **1**, with $Al(C_6F_5)_3$ and diisopropyl fumarate (1 : 1 : 2) proceeded in a toluene solution at ambient temperature. A new singlet around 44.5 ppm in the ^{31}P NMR spectrum indicated the formation of tricoordinated phosphine, while a new set of peaks at −120.9, −153.4 and −160.8 ppm in the ^{19}F NMR spectrum was consistent with a tetracoordinated Al center in the product. However, the reaction is not clean and



Scheme 3 Synthesis of **6** and **7**.

several side products were obtained from the ^{19}F NMR spectrum, which is likely due to the similar energy barrier between different H-migration reactions. Yellow crystals of **5** were obtained after storing the reaction mixture at −30 °C for 2 days, demonstrated the molecular structure of **5** to be (Nacnac)-Sn(^{i}PrO$_2$C)CC(OAl(C_6F_5)$_3$)P[CH($CO_2{}^i$Pr)CH$_2$($CO_2{}^i$Pr)]CH($CO_2{}^i$Pr) featuring a four-membered ring of phosphetan-2-one similar to the ones in **3** and **4**. The three C–P bond lengths in **5** (1.865(55) Å, 1.874(5) Å and 1.888(5) Å) are very close to each other.

Related reactions with alkynes were also probed. The reaction of **1**, $B(C_6F_5)_3$ and diethyl-but-2-ynedioate in a ratio of 1 : 1 : 1 afforded light yellow crystals of **6** that were isolated in 57% yield (Scheme 3). The ^{31}P and ^{11}B NMR spectra of **6** displayed singlets at 34.1 and −1.7 ppm, respectively. The molecular structure of **6** was confirmed as (Nacnac)SnP(EtO$_2$C CC(CO$_2$Et))CO($B(C_6F_5)_3$) *via* a single-crystal X-ray diffraction analysis (Fig. 3). In this case, it appears that subsequent to a [2+2] addition to the PCO fragment, the *beta*-carbon of Nacnac and the borane have effected a frustrated Lewis pair (FLP)-type addition to the phosphacycle, affording the phosphetan-2-one ring in **6**. This fragment is analogous to that in the previously reported germanium analogue.[38]

The corresponding reaction of **1**, $B(C_6F_5)_3$ and phenylacetylene in toluene, gave a new species **7** which was evidenced by the observation of a new singlet at 109.6 ppm in the ^{31}P NMR

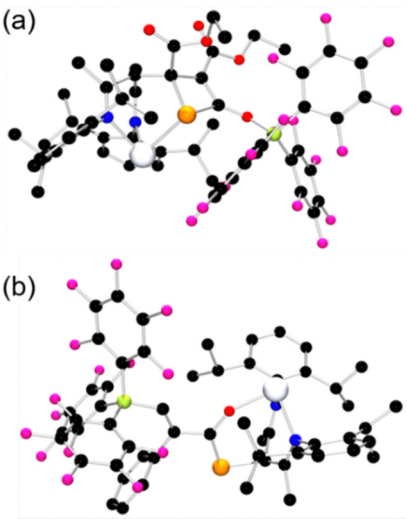


Fig. 3 POV-ray depiction of the molecular structures of (a) **6** and (b) **7**. Hydrogen atoms are omitted for clarity. C: black, N: blue, O: red, P: orange, B: yellow-green, F: pink, Sn: silver.

spectrum. A single-crystal XRD study of **7** confirmed the formulation as (Nacnac)SnOC(P)C(Ph)CH(B(C_6F_5)$_3$) (Fig. 3). In this case, the unactivated alkyne does not undergo [2+2] cyclization, rather only the FLP-addition of B(C_6F_5)$_3$ and the basic C of the PCO fragment to the alkyne is seen. This latter reactivity is directly analogous to FLP additions to alkynes.[39,40] Interestingly the formation of **7** stands in contrast to the corresponding reaction of the germanium analogue, which gave a Ge/B FLP addition to the phenylacetylene.[38]

In summary, herein we have described the use of group 13 Lewis acids B(C_6F_5)$_3$ and Al(C_6F_5)$_3$ in promoting the [2+2] addition of the stannyl phosphaketene (NacnacSnPCO) with alkenes and alkynes en route to the phosphacycles **2-7**. The isolation of **3-5** represents rare examples of phosphorus analogues of β-lactam. Specifically, further H-transfer of **3** led to the formation of derivative product **4** and ligand-eliminated product **5**. In contrast to alkene, when alkyne substrates were used, intramolecular 1,4-additions to the γ-C of the Nacnac ligand were obtained. The corresponding product **6** with a phosphetan-2-one structure could also be classified as a phosphorus analogue of the β-lactam derivative. The potential of the above novel phosphacycles to exhibit antimicrobial activity is part of our ongoing efforts.

Experimental data has been provided as ESI.†

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Conflicts of interest

There are no conflicts to declare.

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