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Synthesis of 1,1-bis-phosphorus compounds from organoboranes

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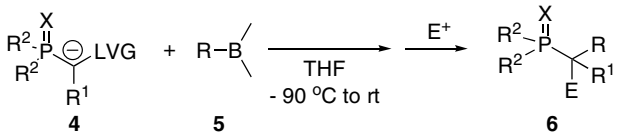
ABSTRACT

The facile synthesis of various P–C–P compounds is described, based on the reaction of phosphorus carbenoids with organoboranes, followed by reaction with phosphorus electrophiles. Using this approach, symmetrically and differentially substituted 1,1-bisphosphorus compounds can be obtained in good yields. A number of novel P–C–P motifs are described for the first time.

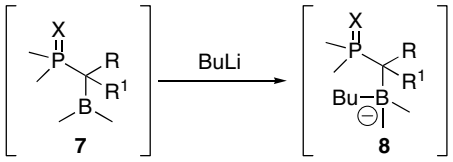
Organophosphorus compounds are important in a variety of applications, from medicines to pesticides, from ligands in catalysis to extractants and flame-retardants.[1] A special class of compounds contains the P–C–P motif, particularly 1,1-bisphosphonates **1**, which are hydrolytically stable analogs of inorganic pyrophosphate. These compounds have been used clinically for over 40 years because of their ability to bind strongly to the hydroxyapatite of the bone.[2] More recent studies have shown that the mode of action of bisphosphonates is more complex and that they can act at various biological sites (such as inhibition of isoprenoid biosynthesis),[3] although their impact on calcium metabolism remains the basis for their current medicinal use (a multi-billion dollar market for the treatment of osteoporosis). We previously reported an approach based on the radical reaction of sodium hypophosphite with terminal alkynes, to prepare novel 1,1-bis-*H*-phosphinates **2** which are precursors to **1**.[4] Another type of compound is the bidentate ligand 1,1-bis(diphenylphosphino)methane (dppm) **3** and related phosphines, used in catalysis.[5] Based on the importance of the 1,1-bis-phosphorus moiety, the preparation of P–C–P containing compounds prompted the present study.

We recently reported a novel approach to the preparation of organophosphorus compounds **6** based on the reaction of phosphorus carbenoids **4** with organoboranes **5** (Eq. 1).[6] This provided an access to phosphonates, phosphinates, phosphine–boranes, phosphine oxides, and phosphine sulfides. Because of the flexibility of the method, we investigated phosphorus electrophiles in order to prepare bis-phosphorus compounds, and the results are presented here:

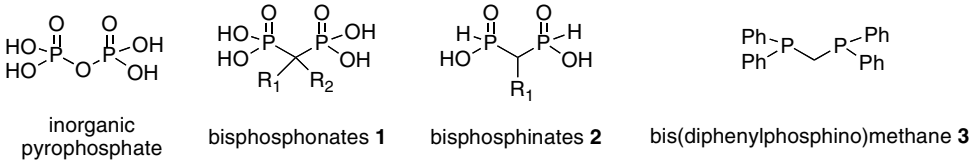


(1)

X = O, S, BH_3; LVG = Cl, N_2^+; R = Alk; R^1 = H, Alk;
R^2 = OEt, Ph; E = H, D, I



(2)



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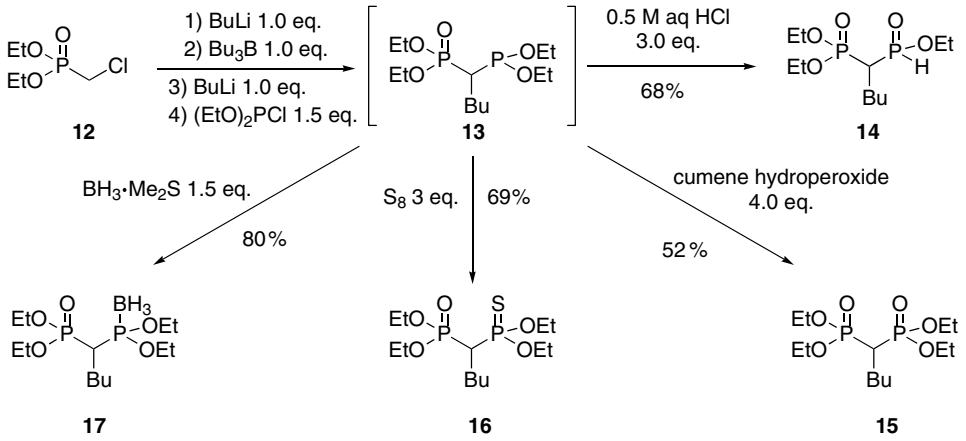
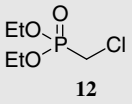
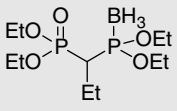
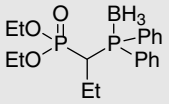
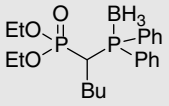
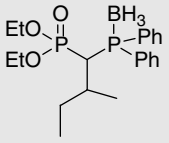
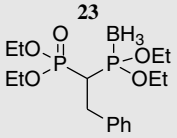
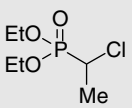
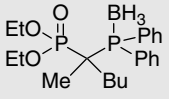
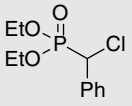
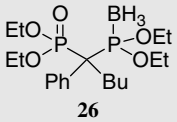
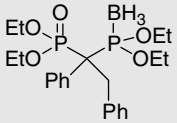


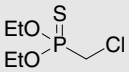
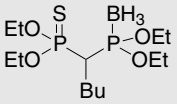
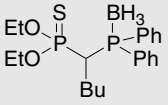
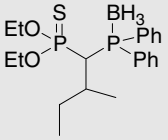
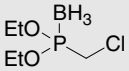
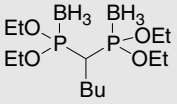
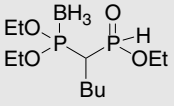
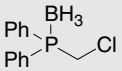
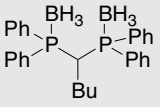
Scheme 1. Reactions of diethyl chloromethylphosphonate **12**.

Table 1
Reactions of phosphonate carbenoids

Entry	Starting material	Organoborane	Chlorophosphine	Product	Yield[a] (%)
1	 **12**	Et_3B	$(EtO)_2PCl$ **9** 1.5 equiv	 **20**	92
2	**12**	Et_3B	Ph_2PCl **11** 1.5 equiv	 **21**	62
3	**12**	Bu_3B	Ph_2PCl **11** 1.5 equiv	 **22**	89
4	**12**	$(sec\text{-}Bu)_3B$	Ph_2PCl **11** 1.5 equiv	 **23**	69
5	**12**	Benzyl-9-BBN	$(EtO)_2PCl$ **9** 4.0 equiv	 **24**	73
6	 **18**	Bu_3B	Ph_2PCl **11** 1.5 equiv	 **25**	76
7	 **19**	Bu_3B	$(EtO)_2PCl$ **9** 1.5 equiv	 **26**	54
8	**19**	Benzyl-9-BBN	$(EtO)_2PCl$ **9** 4.0 equiv	 **27**	64

[a] Isolated yields. See the Supplementary data file for experimental details.

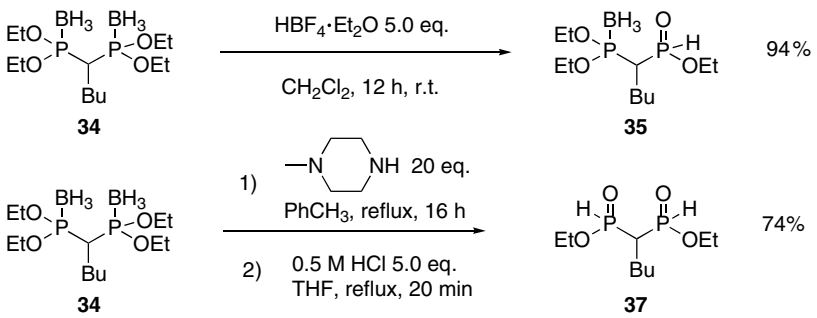
Table 2
Reactions of other phosphorus carbenoids

Entry	Starting material	Organoborane	Chlorophosphine	Product	Yield[a] (%)
1	 **28**	Bu_3B	$(EtO)_2PCl$ **9** 1.5 equiv	 **31**	69
2	**28**	Bu_3B	Ph_2PCl **11** 1.5 equiv	 **32**	89
3	**28**	$(sec\text{-}Bu)_3B$	Ph_2PCl **11** 1.5 equiv	 **33**	62
4	 **29**	Bu_3B	$(EtO)_2PCl$ **9** 1.5 equiv	 **34**	82
5	**29**	Bu_3B	$(EtO)_2PCl$ **9** 1.5 equiv	 **35**	82[b]
6	 **30**	Bu_3B	Ph_2PCl **11** 1.5 equiv	 **36**	77

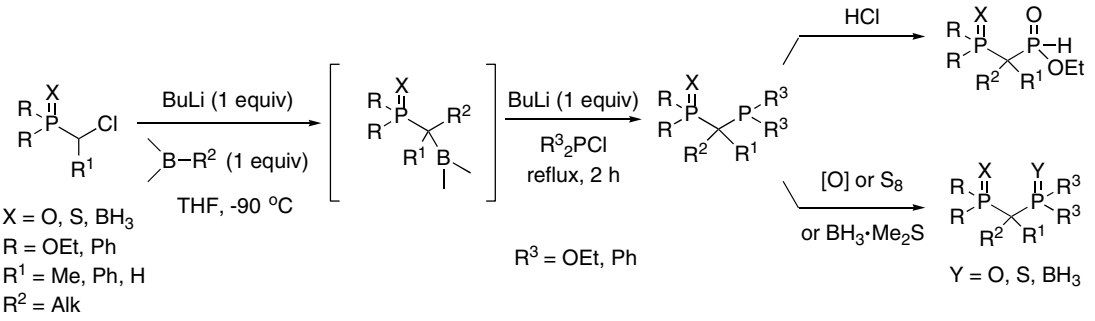
[a] Isolated yields. See the Supplementary data file for experimental details.
[b] Obtained after hydrolysis of the intermediate phosphonite with aqueous HCl.

Unlike the direct hydrolysis or iodinolysis of the α-boranophosphorus intermediate,[6] direct treatment with diethyl chlorophosphite $(EtO)_2PCl$ **9**, diethylchlorophosphate $(EtO)_2P(O)Cl$ **10**, or chlorodiphenylphosphine Ph_2PCl **11**, did not result in the desired P–C bond formation. However, activation of the intermediate **7** as the borate complex **8** (Eq. 2) allowed reaction with the P(III) electrophiles, but not with the less reactive P(V) **10**. Reactions involving the transfer of a group in organoboranes, such as the Matteson–Pasto rearrangement, have been known for a long time.[7] Initially, we focused on diethyl chloromethylphosphonate $(EtO)_2P(O)CH_2Cl$ **12** as the carbenoid precursor to delineate the scope of the reaction. Since $(EtO)_2P(O)Cl$ **10**, did not react, the direct synthesis of bisphosphonates was not possible. However, this does not constitute a major impediment since bisphosphonates can be synthesized easily using literature procedures, such as alkylation of commercially available methylenebisphosphonates.[8] Indeed, other P–C–P functionalities are significantly more interesting since methods for their syntheses either do not exist, or are limited to a handful of compounds.[9]

Reaction of **12** with *n*-butyl lithium at low temperature (−90 °C) forms the corresponding carbenoid **4** which then reacts with various organoboranes as we previously reported.[6] Addition of another equivalent of BuLi to the resulting intermediate **7** formed borate **8**, which then reacted with diethyl chlorophosphite



Scheme 2. Decomplexation of phosphonite-boranes.



Scheme 3. Overall summary of P–C–P synthesis.

9 in good yield. The resulting intermediate could be either hydrolyzed, treated with an oxidant, sulfur, or BH_3 (Scheme 1).[10] Based on these positive results, a full investigation was conducted.

Table 1 summarizes the results with phosphonate carbenoids using borane complexation of the intermediate P(III) compound. The phosphonate–phosphonite-borane complexes were obtained in moderate to good yields. Compound **12** afforded various substitution patterns (Table 1, entries 1–5). Entry 5 shows the successful selective transfer of a 9-BBN substituted borane.[6] As expected, substituted phosphonates **18** and **19** gave the corresponding dialkylated products in useful yields (entries 6–9).

Based on these results, other carbenoid precursors were examined (Table 2). Phosphonothioate **28**,[6] phosphonite-borane **29**,[6] and phosphine–borane **30**[6] could all be employed successfully. As with phosphonate **12**, hydrolysis of the intermediate produced the *H*-phosphinate product (Table 2, entry 5), and interestingly in this case, simple acid hydrolysis resulted in the cleavage of only one phosphonite-borane group.

While P–C–$P(OEt)_2$ species can be cleaved directly with concentrated HCl (**14** Scheme 1, and **35** Table 2, entry 5), borane complexes can also be cleaved using different conditions (Scheme 2). While treatment of **34** with HBF_4, cleaves only one group (as with HCl) to form **35**, complete decomplexation to **37** is also possible using an amine base followed by hydrolysis of the intermediate bisphosphonite. 1,1-Bis-*H*-phosphinate esters similar to **37** have been previously synthesized using our radical hydrophosphinylation followed by esterification,[4] but the present approach provides added flexibility in the type of accessible phosphorus functionalities.

Scheme 3 summarizes the present methodology. A wide variety of known (bisphosphonate, bisphosphine–borane complexes)[9] as well as novel bisphosphorus functionalities can be synthesized in one-pot from readily available reagents.

In conclusion, a wide variety of P–C–P compounds can be obtained using our methodology. Because pyrophosphate analogs are common motifs in biologically important compounds, and because bisphosphines are useful ligands, the present work should be useful for the preparation of a variety of P–C–P functionalities. The advantage of our reaction is that the direct alkylation approach is only well precedented with methylenebisphosphonates. Because a P(III) intermediate is involved herein, several different organophosphorus functionalities can be prepared from a single intermediate. Therefore, the reaction lends itself to combinatorial approaches. Implementation of this methodology to the preparation of biologically relevant pyrophosphate analogs will be investigated in future studies.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.144.

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10. Representative experimental procedure Scheme 1, compound **17** (for additional details, see Supplementary data): A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl (chloromethyl)phosphonate **12** (2.50 mmol, 465 mg, 1.0 equiv) and dry THF (10 mL). The solution was cooled below −90 °C (liquid nitrogen/ethanol bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly via syringe, followed by tributylborane (2.50 mmol, 1.0 M in Et_2O, 2.5 ml, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to −70 °C (dry ice/acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by diethyl chlorophosphite **9** (3.75 mmol, 0.54 mL, 1.5 equiv). The resulting mixture was then heated at reflux for 2 h under nitrogen. After cooling to rt, $BH_3{\cdot}Me_2S$ (3.80 mmol, 2.0 M in THF, 1.90 mL, 1.5 equiv) was added and stirring was continued for 15 min. The solvent was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2×), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 4:6, v/v) yielded **17** (684 mg, 2.00 mmol, 80%).