JOC Article

Reactions of α-Boranophosphorus Compounds with Electrophiles: Alkylation, Acylation, and other Reactions

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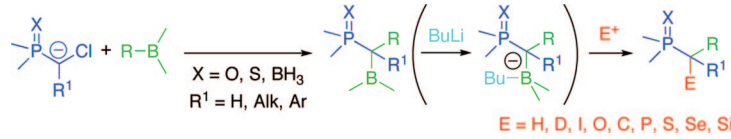
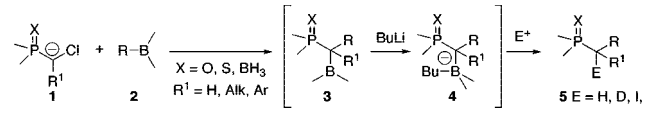


The homologation of phosphorus carbenoids with organoboranes leads to α-boranophosphorus compounds, which can be further functionalized through reactions with various electrophiles, either directly or after activation to the corresponding borate. A variety of substituted organophosphorus compounds can be obtained in one pot via reaction with many electrophiles. Complex structures are prepared in a single step using simple building blocks.

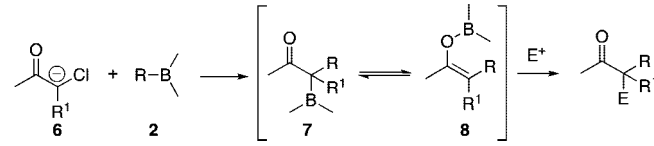
Introduction

Organophosphorus compounds, especially phosphonates, continue to be the object of significant scrutiny due to their importance in various applications, both as final products and as synthetic intermediates.[1] Simple methods readily delivering complex structures are particularly desirable and valuable. Recently, we disclosed a general approach based on the homologation of phosphorus carbenoids **1** with organoboranes **2** followed by electrophilic reactions with water (H_2O or D_2O), iodine, or phosphorus electrophiles to form compounds **5** in one pot (Scheme 1).[2,3] While the hydrolysis or iodinolysis of intermediates **3** occurred readily,[2] in the case of phosphorus electrophiles[3] activation of **3** to the corresponding borate **4** was necessary. Noteworthy was the fact that phosphorus carbenoids derived from phosphonates, thiophosphonates, phosphinates, boranophosphonites, and boranophosphines all reacted successfully to form intermediate **3**.[3] In addition, the selective transfer of one group in the organoborane could be achieved in some cases using 9-borabicyclononane (9-BBN) derivatives.[2] Based on these promising results, we have investigated the reactions of the α-boranophosphorus intermediates **3** and the corresponding borates **4** with a variety of other electrophiles, and we now report the scope and limitations of the method for the synthesis of a range of organophosphorus compounds.

SCHEME 1. Homologation of Phosphorus Carbenoids and Electrophilic Trapping



SCHEME 2. The Carbon Analogy: Formation of Enol Borinates from Carbonyl-Containing Carbenoids



Results and Discussion

Since a wide variety of α-boranophosphorus intermediates **3** could be prepared, the reactivity of these novel species could be probed. It is well-known that the analogous homologation of carbonyl-containing carbenoids **6** leads to α-boranocarbonyl intermediates **7** which tautomerize to the enol borinates **8** (Scheme 2).[4] These enol borinates are readily hydrolyzed or can further undergo various reactions, particularly aldol-type condensations. In the case of our phosphorus intermediates **3**, it was thus expected that reactivity would lie somewhere between that of the enol borinates **8** and unactivated boranes **2**. Indeed, unlike with boranes **2**, hydrolysis and iodinolysis of **3** readily take place.[2]

On the other hand, tautomerization of intermediate **3** into **9** (Scheme 3) might not occur readily even if silicon analogues

* Phone: (+1)-817-257-6201. Fax: (+1)-817-257-5851.

(1) (a) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000. (b) Savignac, P.; Iorga, B. *Modern Phosphonate Chemistry*; CRC Press: Boca Raton, 2003.

(2) Antczak, M. I.; Montchamp, J.-L. *Org. Lett.* **2008**, *10*, 977.

(3) Antczak, M. I.; Montchamp, J.-L. *Tetrahedron Lett.* **2008**, *49*, 5909.

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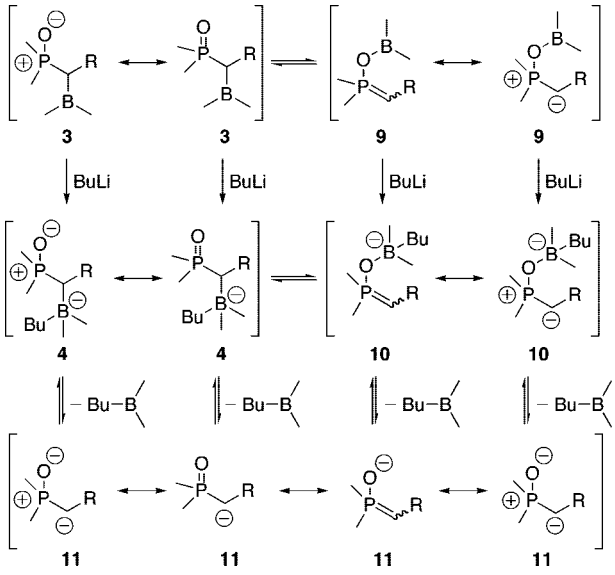
SCHEME 3. α-Boranophosphorus Intermediates



of **9** have been postulated.[5] Scheme 3 shows the possible structures, including resonance forms, for species derived from phosphonates or phosphine oxides. Resonance forms containing P(+)-O(−) are better representations than the P═O form even if the latter formalism is still most commonly employed. Activation of **3** and **9** with butyllithium would result in the organoborate intermediates, which could either react directly with electrophiles or lose the organoborane moiety forming reactive carbanions.[6] All attempts at spectroscopic detection of some of these species were unsuccessful, as was derivatization with trialkylsilyl trifluoromethanesulfonates.[7] No matter the actual species involved, it is clear that borates **4** and **10** and/or phosphorus anion **11** will be significantly more reactive than **3**, a fact previously illustrated with the successful reactions of **4** with phosphorus electrophiles.[3] Our latter work indicated that the reactivity of α-boranophosphorus compounds with electrophiles needed to be investigated, both directly and after in situ activation with BuLi. Since many transformations of organoboranes[8] and organoborates[6] are well-precedented, useful functionalizations from intermediates **3** and **4**, respectively, were expected and thus examined.

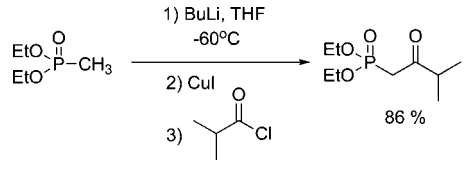
1. Carbon−Carbon Bond-Forming Reactions. Alkylation. Since carbon−carbon bond formation remains a major goal in organic synthesis, the reactivity of intermediates **3** was investigated with alkyl halides. However, perhaps not surprisingly, no alkylation took place directly. Fortunately, in situ activation with BuLi was sufficient to deliver good yields of alkylated products. The results are shown in Table 1. As expected, the butyl group from BuLi is not incorporated into the products. One group comes from the organoborane (in our case Bu_3B or *n*-heptyl$_3$B) and the other from the alkyl halide (MeI, BnBr, AllBr, OctI). Both phosphonate (entries 1 and 2) and boranephosphonite (entries 3 and 4) reacted satisfactorily. Additionally, even a simple alkyl iodide reacted smoothly to deliver the alkylated product (entry 4). Thus, alkylation to functional organophosphorus compounds can be achieved to deliver substituted organophosphorus species in a single pot.

Although not directly related to the sequence shown in Scheme 1, the direct nonhomologative alkylation of boranephosphonite complexes was briefly investigated (Table 2). Alkylation of phosphonate anions is well-known but in general not always efficient.[1b,9] Since boranophosphonites can be prepared through either homologation or alkylation of $(RO)_2P(BH_3)H$ as we previously reported,[9] it was of interest to examine their alkylation in order to compare with the present one-pot methodology. Interestingly, the chloromethylphosphonite borane complex was deprotonated efficiently with *n*-BuLi (entries 1 and 2), whereas octylphosphonite borane complex required *s*-BuLi instead (entries 3 and 4). In both cases, excellent yields of alkylated products were obtained. Entries 1 and 2 show products which can be employed as precursors to the homologation reaction described above.

Since we have already demonstrated the transformations of boranophosphonite complexes into either *H*-phosphinic esters or disubstituted phosphinic acids,[2,3,10] the formation of boranophosphonites through homologative or direct alkylations represents a powerful methodology to prepare phosphinic acids.

Unfortunately, attempts at the palladium- or nickel-catalyzed ($Pd(PPh_3)_4$, $PdCl_2$(dppf), $NiCl_2(PPh_3)_2$, $NiCl_2$(dppf)) Suzuki-type cross-coupling[8c,11] of intermediates **3** or **4** with aryl halides (PhI, PhBr) were unsuccessful under several conditions, even though the coupling of organoborates with aryl halides is well-precedented.[11] While more work would be necessary before dismissing this approach altogether, the hydrolysis of **3** or **4** was observed instead of the desired C−C bond formation. Another failed reaction was the radical addition of the α-boranophosphorus intermediate under free radical conditions.[12] Thus, one attempt at adding intermediate **3** to 1-octene under air gave only the hydrolyzed diethyl pentylphosphonate. This reaction was not investigated further.

Acylation. Next the acylation of intermediates **3** with acyl chlorides was investigated. The acylation of phosphonate anions has been reported by Savignac, but transmetalation to an organocopper species was necessary (eq 1).[13] The acylation of organoboron compounds has also been reported using palladium catalysis.[14]



(1)

(4) Representative examples: (a) Brown, H. C.; Rogic, M. M.; Rathke, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 6218. (b) Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 1911. (c) See also ref 14.

(5) De, B.; Corey, E. J. *Tetrahedron Lett.* **1990**, *31*, 4831.

(6) Negishi, E.; Idacavage, M. J. *Org. React.* **1985**, *33*, 1.

(7) ^{31}P NMR analysis of the crude reaction mixture (at room temperature) obtained from diethyl (chloromethyl)phosphonate and Bu_3B showed a very broad signal centered at 50 ppm (95%) and a sharp singlet at 55 ppm (5%). Hydrolysis of the mixture at this stage gives a sharp singlet at 34 ppm (100%) corresponding to diethyl pentylphosphonate. No attempt at variable-temperature NMR was made.

(8) (a) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975; Vol. 1. (b) Brown, H. C., Zaidlewicz, M. *Organic Synthesis via Boranes: Recent Developments*; Wiley: New York, 2001; Vol. 2. (c) Suzuki, A., Brown, H. C. *Organic Synthesis via Boranes: Suzuki Coupling*; Wiley: New York, 2003; Vol. 3.

(9) (a) Poindexter, M. K.; Katz, T. J. *Tetrahedron Lett.* **1988**, *29*, 1513. (b) Coutrot, P.; Savignac, P.; Mathey, F. *Synthesis* **1978**, 36. (c) Teulade, M. P.; Savignac, P.; Abouajouade, E.; Collignon, N. *J. Organomet. Chem.* **1986**, *312*, 283.

(10) Belabassi, Y.; Antczak, M. I.; Tellez, J.; Montchamp, J.-L. *Tetrahedron* **2008**, *64*, 9181.

TABLE 1. One-Pot Phosphorus Carbenoid/Alkylation Sequence via In Situ Activation with BuLi

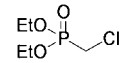
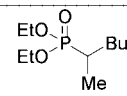
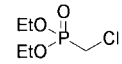
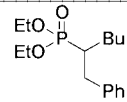
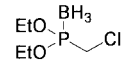
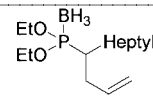
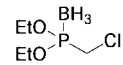
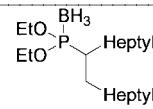
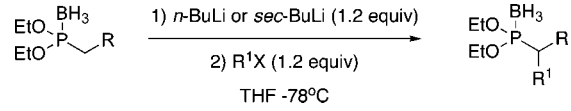
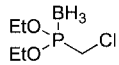
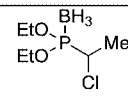
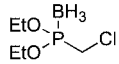
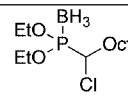
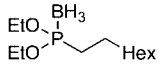
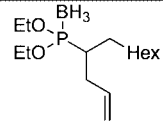
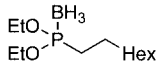
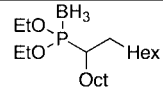
Entry	Starting material	Organoborane Reagent R_3B	Electrophile R^1X	Product	Isolated yield (%)
1		Bu_3B	Iodomethane		74
2		Bu_3B	Benzyl bromide		60
3		$(n\text{-Heptyl})_3B$	Allyl bromide		72
4		$(n\text{-Heptyl})_3B$	1-Iodooctane		76

TABLE 2. Alkylation of Boranophosphonites



Entry	Starting material	Electrophile R^1X	Product	Isolated yield (%)
1		Iodomethane		96[a]
2		1-Iodooctane		93[a]
3		Allyl bromide		77[b]
4		1-Iodooctane		76[b]

[a] *n*-BuLi was used. [b] *s*-BuLi was used.

In our case, as in the alkylation reaction, the formation of a borate intermediate via in situ addition of *n*-BuLi was necessary to achieve the desired acylation. Nonetheless, successful acylation was achieved in a variety of cases summarized in Table 3. Acylation with pivaloyl chloride takes place in good to excellent yields, using phosphonates, thiophosphonates, and boranophosphonites. Additionally, the formation of a quaternary carbon was observed in entry 2, while the selective migration of a benzyl group is illustrated in entry 6.

The reaction with benzoyl chloride was more complicated (Table 4) in part because of the competing formation of an enol benzoate. However and as expected, a substrate for which enolization is not possible, or the methanolysis of the reaction mixture during workup, provided the β-ketophosphonate in good yield (Table 5, entry 1 and 2, respectively).

Since β-ketophosphonates are well-known precursors to the Wadsworth−Horner−Emmons olefination, one example of a one-pot homologation/acylation/olefination process was investigated (eq 2). The trisubstituted alkene was obtained

(11) (a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (b) Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(12) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415.

(13) (a) Coutrot, P.; Savignac, P. *Synthesis* **1978**, 36. (b) Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649. (c) See also ref 1b, Chapter 7.

TABLE 3. Acylation of Organoborates 4 with Pivaloyl Chloride

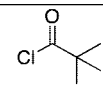
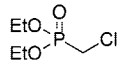
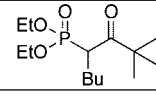
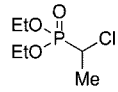
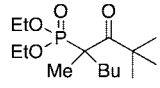
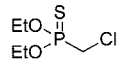
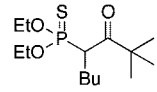
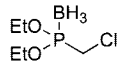
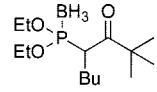
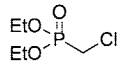
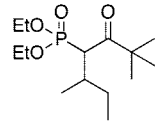
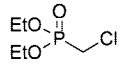
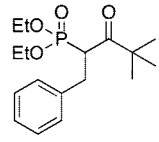
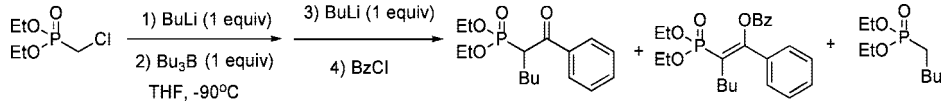
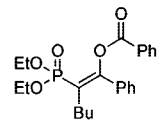
Entry	Starting material	Organoboron compound		Product	Isolated Yield (%)
1		Bu_3B	1.5 equiv		92
2		Bu_3B	1.5 equiv		78
3		Bu_3B	1.5 equiv		87
4		Bu_3B	1.5 equiv		65
5		$(sec\text{-}Bu)_3B$	1.5 equiv		86
6		B-benzyl-9-BBN	4.0 equiv		63

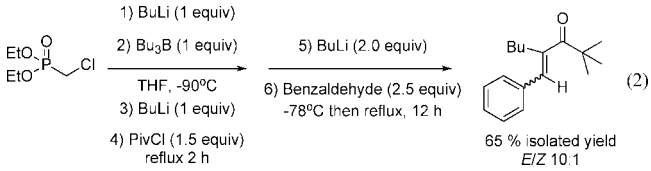
TABLE 4. Acylation of Organoborates 4 with Benzoyl Chloride



Entry	Number of equivalents Benzoyl chloride			
1	1.5 equiv	34 %[a] 28 %[b]	33 %[a] 30 %[b]	33 %[a] 18 %[b]
2	1.0 equiv	4 %[a]	44 %[a]	52 %[a]
3	4.0 equiv	70 %[a] 62 %[b]	30 %[a]	0 %[a]

[a] ^{31}P NMR yield. [b] Isolated yield.

as a 10:1 *E*/*Z* isomeric ratio in this particular case. The stereochemical assignment was conducted by 1D-NOE experiments, which showed NOEs between the vinylic hydrogen and the *t*-butyl group, as well as the allylic methylene and the phenyl group. The reaction illustrates a one-pot sequence of transformations leading to an unsaturated ketone in good yield. Because the process involves multiple components (organophosphorus carbenoid precursor, organoborane, acid halide, and carbonyl compound), an application to combinatorial synthesis can be readily envisioned.



2. Other Reactions of α-Boranophosphorus Intermediates 3 or 4 with Electrophiles. Based on the successful electrophilic trapping of intermediates **3** or **4**, other reactions were investigated (Table 6).

Aldol-like Condensations (Table 6, Entries 1−3). Based on the enol borinate **8** precedent,[15] C−C bond formation through aldol-like condensation was examined next. In this case, direct addition to benzaldehyde took place without prior activation as the borate ion. However, no diastereoselectivity was observed in the condensation process, unlike what has been observed with enolborinates. The tetrahedral nature of the phosphorus atom is no doubt the origin of this difference. On the other hand, acetone was completely unreactive. Because *β*-hydroxyphosphonates have been converted into olefins using fluoride ion,[16] these intermediates synthesized could also provide an approach to phosphorus-free olefins. Similar to the aldol-like condensation, dimethyl(methylene)ammonium iodide salt reacted successfully, and without addition of BuLi (entry 3).[17] Thus, *β*-aminophosphonates appear to be easily accessible.

Michael Addition (Table 6, Entry 4). Conjugate addition was examined next. Unlike the aldol condensation, the α-boranophosphorus intermediate does not react with 2-cyclohexenone directly. Fortunately, conversion to the borate followed by the addition of the unsaturated ketone in the presence of TMSCl resulted in the desired conjugate addition.

Halogenation (Table 6, Entry 5). As previously reported,[2] the iodination of intermediates **3** takes place readily, with selective cleavage of the carbon−boron bond next to the phosphorus atom. This reaction takes place directly through addition of iodine, in the absence of an external base. α-Iodophosphorus are quite scarce in the literature, and typically, sulfonates derived from the more readily available α-hydroxy compounds are preferred to create a leaving group at this position. Thus, the present method offers a rather unique opportunity at preserving a reactive bond once homologation has taken place. Since substitution of the iodide can be conducted, various other substituted compounds can conceivably be synthesized in two separate steps.

Chlorination and bromination were also tested briefly. However, none of these attempts resulted in anything positive. This might be surprising since enol borinates can be brominated with *N*-bromosuccinimide,[18] but since iodides are probably more desirable, these reactions were not investigated further. Because α-fluorophosphonates[19] have been considered as potential pharmacophores, we decided to investigate fluorination instead. Unfortunately, in spite of the many reagents and conditions investigated (Selectfluor, 1-fluoropyridinium triflate, *N*-benzenesulfonimide, 1-fluoropyridinium tetrafluoroborate, DAST, and xenon difluoride) with or without prior formation of an organoborate, none of the attempts yielded the desired product in any significant amount, if at all. In general, α-monofluorophosphonates are prepared in the literature from the corresponding α-hydroxyphosphonate using DAST. Thus, because α-hydroxyphosphorus compounds appear to be very important intermediates, the conversion of **3** and/or **4** was then investigated.

Hydroxylation (Table 6, Entry 6). The conversion of a carbon−boron bond into the corresponding alcohol, the cornerstone of the famous hydroboration−oxidation sequence, is one of the most well-known and useful transformation of organoboranes. Additionally, because α-hydroxyphosphonates are proven intermediates for the preparation of many compounds, this transformation appeared particularly important. Treatment of intermediate **3** using classic oxidation conditions (H_2O_2/NaOH, or the milder H_2O_2/AcONa) only gave the corresponding hydrolysis in high yield. This might be surprising since the oxidation of an α-boranophosphonate has been reported.[20] In our hands, aqueous conditions appear incompatible with the conversion of **3** into anything other than the protonated or deuterated compounds (we have not investigated tritiation, although this would be expected to be a valuable route to radiolabeled phosphorus compounds), nonaqueous oxidants were then examined. Treatment with PCC resulted in the formation of the corresponding alcohol in moderate yield (quantitative by ^{31}P NMR analysis). In standard organoborane oxidations with PCC, a ketone is normally obtained from overoxidation of the intermediate alcohol. It should be noted that simple α-hydroxyphosphonates are more easily and cheaply prepared from an aldehyde (or ketone) and an *H*-phosphonate.

Amination. Although the direct amination of organoboranes is well-known,[4] attempts at converting **3** using these reagents (organic azides, chloroamine, hydroxylamine-*O*-sulfonic acid, or *O*-(mesitylsulfonyl)hydroxylamine) failed to give the desired amino-substituted product. Similarly, prior activation to the borate **4** followed by electrophilic amination[21] reagents was not satisfactory. Much like the fluorination mentioned above, a significant amount of effort was devoted to this direct transformation since α-aminophosphonates (and phosphinates) are valuable compounds, which often display biological activities.[22] Thus, we were unable to find a direct, one-pot method to derivatize the C−B bond into a C−N bond. Nonetheless, the transformation has some precedent from other intermediates, such as the α-hydroxyphosphonates.

(14) Acylation of organoboron compounds using palladium catalysis: (a) Urawa, Y.; Ogura, K. *Tetrahedron Lett.* **2003**, *44*, 271. (b) Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057. (c) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109.

(15) Enol borinates and aldol: (a) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387. (b) Gennari, C. *Pure Appl. Chem.* **1997**, *69*, 507. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (d) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (e) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 2716. (f) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1992**, *57*, 3767. (g) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147. (h) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 7162. (i) Mukaiyama, T.; Inomata, K.; Muraki, M. *Am. Chem. Soc.* **1973**, *95*, 967.

(16) Kawashima, T.; Ishii, T.; Inamoto, N.; Tokitoh, N.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 209. Olefin geometry is controlled by a stereospecific *syn* elimination.

(17) For the Mannich-type reaction of enol borinates, see: (a) Nolen, E. G.; Aliocco, A.; Broody, M.; Zuppa, A. *Tetrahedron Lett.* **1991**, *32*, 73. (b) Nolen, E. G.; Aliocco, A.; Vitarius, J.; McSorley, K. *J. Chem. Soc. Chem. Commun.* **1990**, 1532.

(18) Hooz, J.; Morrison, G. F. *J. Can. Chem.* **1972**, *50*, 2387.

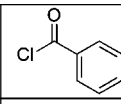
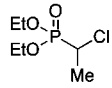
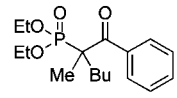
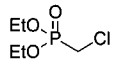
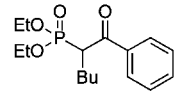
(19) (a) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868. (b) See also ref 1b, Chapter 3. For electrophilic fluorination, see: (c) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431.

(20) Agnel, G.; Negishi, E.-i. *J. Am. Chem. Soc.* **1991**, *113*, 7424.

(21) Electrophilic amination reviews: (a) Erdik, E. *Tetrahedron* **2004**, *60*, 8747. (b) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947.

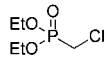
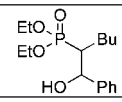
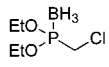
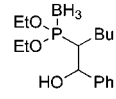
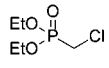
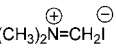
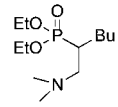
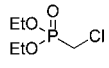
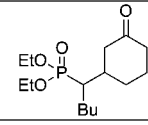
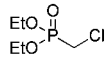
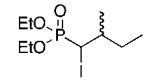
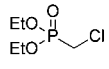
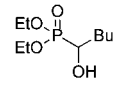
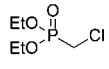
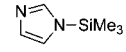
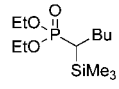
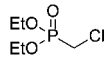
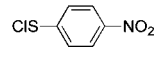
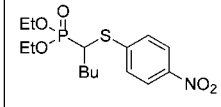
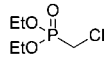
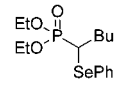
(22) (a) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids*; John Wiley & Sons, Inc.: New York, 2000. (b) Ma, J.-A. *Chem. Soc. Rev.* **2006**, *35*, 630. (c) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899. (d) Collinsova, M.; Jiracek, J. *Curr. Med. Chem.* **2000**, *7*, 629. (e) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237.

TABLE 5. Acylation of Organoborates 4 with Benzoyl Chloride

Entry	Starting material	Organoboron compound		Product	Isolated Yield (%)
1		Bu_3B	1.5 equiv		66
2[a]		Bu_3B	4.0 equiv		78

[a] The reaction mixture was treated with MeONa (4 equiv) before workup.

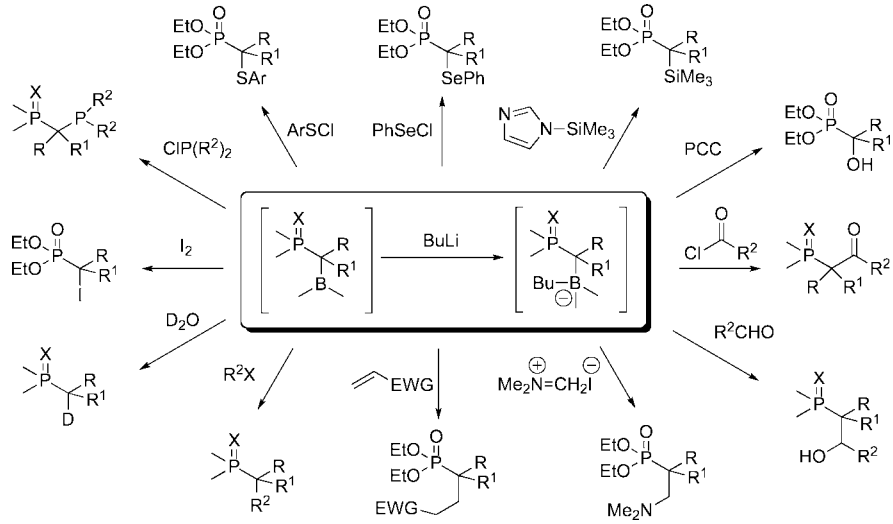
TABLE 6. Other Electrophilic Reactions

Entry	Starting material	Organoboron compound	Electrophile	Product	Isolated Yield (%)
1		Bu_3B	PhCHO		70 (dr: 50/50)[b]
2		Bu_3B	PhCHO		78 (dr: 50/50)[b]
3		Bu_3B			78
4[a]		Bu_3B	2-cyclohexenone + TMSCl		60 (dr: 80:20)[b,c]
5		*sec*-Bu_3B	I_2		72 (dr: 50/50)[b]
6		Bu_3B	PCC		50
7[a]		Bu_3B			71
8		Bu_3B			65
9		Bu_3B	PhSeCl		82

[a] *n*-BuLi (1 equiv) was added prior to the electrophile. [b] Diastereomeric ratio. [c] Unassigned.

Silylation (Table 6, Entry 7). As mentioned previously, attempts at trapping any species akin to **9** or **10** through silylation were not successful. On the other hand, the reaction of **4** (activation to the borate was required) with *N*-

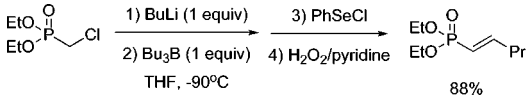
SCHEME 4. Reactions Summary



trimethylsilylimidazole[23] resulted in the clean formation of the corresponding organosilicon compound. α-(Trimethylsilyl)phosphonates are well-known reagents for the Peterson olefination.

Sulfur and Selenium (Table 6, Entries 8 and 9). Finally, the direct conversion of **3** and **4** into sulfur- and selenium-containing compounds was examined. The preparation of sulfur- and selenium-substituted phosphonates is well-known in the literature.[24] Typically, these require the formation of a simple thiomethyl- or selenenylmethylphosphonate (often through Arbuzov reaction of the halomethylchalcogenide) followed by deprotonation and alkylation. Diethyl chloromethylphosphonate was homologated in the usual manner with Bu_3B. The resulting intermediate **3** directly reacted successfully with commercially available *p*-nitrophenylsulfenyl chloride to form the corresponding thioether in 65% yield. The use of PhSSPh did not lead to any C−S bond formation.

A similar reaction with phenylselenenyl chloride resulted in complete conversion (by ^{31}P NMR monitoring) into the corresponding selenide with an 82% isolated yield. Since selenides are easily eliminated via oxidation to the corresponding olefins, a one-pot process was developed for homologation/selenenylation/oxidation into the corresponding unsaturated phosphonate in outstanding overall yield for this single-pot, four-step process (eq 3).



(3)

Conclusion

In conclusion, the reactivity toward a wide range of electrophiles of α-boranophosphorus intermediates formed during the homologation of phosphorus-substituted carbenoids with organoboranes was investigated (Scheme 4). The direct alkylation methodology provides a most powerful entry into substituted organophosphorus compounds in a single step. Other useful transformations such as acylation or chalcogen formation were demonstrated, even if some other attempted reactions (cross-coupling, radical addition, fluorination) have failed. While many combinations of phosphorus reagent, organoborane, and electrophile have yet to be investigated, the present work represents a useful guideline for possible synthetic applications. Because of the sheer number of combinations which can be envisioned, further developments might be possible. Nonetheless, the homologation/electrophilic trapping sequence described herein represents a general and flexible one-pot approach toward many substituted organophosphorus reagents and often offers a useful alternative to literature synthetic methodologies. At this time, our laboratory is focusing on the use of chiral auxiliaries.

Experimental Section

Preparation of the Starting Materials. The starting materials used in this study were prepared using our previously described methodologies.[2,3] Details are provided in the Supporting Information.

General Procedure for the Transformation P−C−B Complex into P−C−C via Alkylation (Table 1). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl (chloromethyl)phosphonate, or diethoxy(chloromethyl)phosphine borane (2.50 mmol, 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 by syringe followed by organoboranes (2.50 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled to −78 °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 electrophile (3.75 mmol, 1.5 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After the mixture was cooled to rt, THF was removed in vacuo, the residue was diluted with EtOAc (20 mL) and washed with water (30 mL). The aqueous phase was then extracted with EtOAc (2 × 30 mL), the combined organic fractions were dried with $MgSO_4$, and the solvent was removed in vacuo. The purification of the crude product by flash chromatography on silica gel yielded the described compound.

Diethyl 1-methylpentylphosphonate (Table 1, entry 1):[25] Yield 74%; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.04 − 4.16 (m, 4 H),

(23) Other reagents (TMSCl, TIPSCl, TBSOTf, TIPSOTf) did not give satisfactory results. For the silylation of enol borinates to silyl enol ethers with *N*-trimethylsilylimidazole, see: Hooz, J.; Oudenes, J. *Tetrahedron Lett.* **1983**, *24*, 5695. For the preparation of α-trimethylsilyl phosphonate, see ref 1b, Chapter 2.

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1.36−1.79 (m, 7 H) 1.30 (t, J = 7 Hz, 6 H), 1.17 (dd, J_{HH} = 7 Hz, J_{HP} = 18 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.6 (t, J_{POC} = 6 Hz), 30.9 (d, J_{PC} = 140 Hz), 29.8, 29.6, 22.7, 16.7 (d, J_{POCC} = 6 Hz), 14.2, 13.3 (d, J_{PCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.7.

General Procedure for the Alkylation of Boranophosphonites (Table 2). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethoxy-(chloromethyl)phosphine-borane (4.0 mmol, 736 mg, 1.0 equiv) and dry THF (20 mL). The solution was cooled to − 78 °C, and *n*-butyllithium (3.0 mL, 1.6 M solution in hexane, 4.8 mmol, 1.2 equiv) was added slowly via syringe. The reaction mixture was stirred at − 78 °C for 5 min, and then electrophile (4.8 mmol, 1.2 equiv) was added. The reaction was warmed slowly to rt and was quenched by addition of H_2O (15 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo. The purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:99, v/v) yielded the described compounds.

Diethoxy(1-chloroethyl)phosphine borane (Table 2, entry 1):[2] Yield 96%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.10−4.24 (m, 4 H), 3.93 (q, J = 7 Hz, 1 H), 1.66 (d, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 6 H), 0.50 (qd, J_{BH} = 94 Hz, J_{PBH} = 16 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.6, 37.5 (d, J_{PC} = 58 Hz), 18.3, 16.5; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 141.4 (q, J_{PB} = 75 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ −44.4 (dq, J_{BP} = 75 Hz, J_{BH} = 94 Hz); HRMS calcd for $C_6H_{21}BClNO_2P$ ($[M + NH_4]^+$) 216.1092, found 216.1089.

General Procedure for the Transformation of P−C−B Complex into P−C−C via Acylation (Tables 3−5). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen and charged with diethyl (chloromethyl)phosphonate, diethyl (1-chloroethyl)phosphonate, diethyl (chloromethyl)phosphonothioate, or diethoxy(chloromethyl)phosphine borane (2.50 mmol, 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 by syringe followed by organoboranes (2.50 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled to −78 °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 pivaloyl chloride (see Table 3 for number of equivaletns). The resulting mixture was heated at reflux for 2 h under nitrogen. After the mixture was cooled to rt, THF was removed in vacuo, and the residue was diluted with EtOAc (20 mL) and washed with water (20 mL). The aqueous phase was then extracted with EtOAc (2 × 30 mL), the combined organic fractions were dried with $MgSO_4$, and the solvent was removed in vacuo. The purification of the crude product by flash chromatography on silica gel yielded the described compound.

Diethyl 1-(2,2-dimethylpropionyl)pentylphosphonate (Table 3, entry 1): Yield 92%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.05 − 4.21 (m, 4 H), 3.64 (dm, J_{PH} = 21 Hz, 1 H), 1.78 − 2.00 (m, 2 H), 1.24 − 1.36 (m, 4 H), 1.33 (t, J = 7 Hz, 6 H), 1.20 (s, 9 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 212.5 (d, J = 6 Hz), 62.7 (t, J_{POC} = 7 Hz), 46.5 (d, J_{PC} = 130 Hz), 45.5, 31.1 (d, J_{PCCC} = 13 Hz), 29.2 (d, J_{PCC} = 6 Hz), 26.8, 22.8, 16.6 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.9; HRMS calcd for $C_{14}H_{29}O_4P$ 292.1803, found 292.1802.

General Procedure for the Transformation of P−C−B Complex into P−C−C via Aldol Reaction. A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen and charged with diethyl (chloromethyl)phosphonate, or diethoxy(chloromethyl)phosphine borane (2.50 mmol, 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 by syringe followed by Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt, and benzaldehyde (292 mg, 2.75 mmol, 280 μL, 1.1 equiv) was added. The resulting mixture was heated at reflux for 2 h under nitrogen. After the mixture was cooled to rt, THF was removed in vacuo, the residue was diluted with EtOAc (20 mL) and washed with water (20 mL). The aqueous phase was then extracted with EtOAc (2 × 30 mL), the combined organic fractions were dried with $MgSO_4$, and the solvent was removed in vacuo. The purification of the crude product by flash chromatography on silica gel yielded the described compounds.

Diethyl (1-hydroxyphenylmethylpentyl)phosphonate (Table 4, entry 1): Yield 70%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23−7.40 (m, 5 H), 4.76−5.87 (m, 1 H), 3.82−4.22 (m, 4 H), 2.07−2.19 (m, 1 H), 1.14−1.52 (m, 6 H), 1.36 (t, J = 7 Hz, 3 H), 1.23 (t, J = 7 Hz, 3 H), 0.75 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.3 (d, J = 13 Hz), 128.5, 128.3, 127.9, 127.0, 126.1, 73.7 (d, J_{PCC} = 4 Hz), 71.4 (d, J_{PCC} = 4 Hz), 62.2 (d, J_{POC} = 7 Hz), 72.1 (d, J_{POC} = 7 Hz), 44.6 (d, J_{PC} = 134 Hz), 44.3 (d, J_{PC} = 134 Hz), 31.0 (d, J_{PCCC} = 6 Hz), 30.1 (d, J_{PCCC} = 6 Hz), 26.4 (d, J_{PCC} = 4 Hz), 22.6, 16.7 (d, J_{POCC} = 6 Hz), 16.5 (d, J_{POCC} = 6 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 34.32 and 34.29; HRMS calcd for $C_{16}H_{27}O_4P$ 314.1647, found 314.1639.

Diethyl 1-Phenylselenylpentylphosphonate (Table 6, Entry 9).[26] A flame-dried, 100 mL, three-necked, round-bottomed flask was purged with nitrogen and charged with diethyl (chloromethyl)phosphonate (465 mg, 2.5 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below −90 °C (liquid nitrogen/ethanol bath), and *n*-butyllithium (2.5 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by Bu_3B (2.5 mmol, 2.5 mL, 1.0 M solution in Et_2O, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled to −78 °C (dry ice/acetone bath), and a red-brown solution of phenylselenyl chloride (2.87 mmol, 505 mg, 1.15 equiv) in 5 mL of dry THF was added slowly. The addition of each drop was accompanied by the instantaneous discharge of color. After addition was complete, the resulting yellow reaction mixture was allowed to warm to rt and then was heated at reflux for 2 h under nitrogen. After the mixture was cooled to rt, solvent was removed in vacuo, and the residue was diluted with EtOAc (20 mL) and washed with water (30 mL). The aqueous phase was then extracted with EtOAc (2 × 30 mL), the combined organic fractions were dried with $MgSO_4$, and the solvent was removed in vacuo. The purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 4:6, v/v) gave diethyl 1-phenylselenylpentylphosphonate (746 mg, 2.05 mmol, 82%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64−7.57 (m, 2 H), 7.26−7.29 (m, 3 H), 4.08−4.23 (m, 4 H), 3.00 (tt, J = 10 Hz, J = 4 Hz, 1 H), 1.45−2.05 (m, 6 H), 1.31 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 0.87 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 134.6, 129.6 (d, J = 3 Hz), 63.2 (d, J_{POC} = 7 Hz), 62.7 (d, J_{POC} = 7 Hz), 39.0 (d, J_{PC} = 149 Hz), 30.1 (d, J_{PCCC} = 11 Hz), 30.0, 22.3, 16.6 (d, J_{POCC} = 6 Hz), 16.5 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 28.1; HRMS calcd for $C_{15}H_{25}O_4PSe$ 364.0707, found 364.0704.

Diethyl (Z)-1-Pentenylphosphonate (eq 3).[27] A flame-dried, 100 mL, three-necked, round-bottomed flask was purged with nitrogen and charged with diethyl (chloromethyl)phosphonate (933 mg, 5.0 mmol, 1.0 equiv) and dry THF (20 mL). The solution was cooled below −90 °C (liquid nitrogen/ethanol bath), and *n*-butyllithium (5.0 mmol, 2.5 M solution in hexane, 2.0 mL, 1.0 equiv) was added slowly by syringe followed by Bu_3B (5.0 mmol, 5.0 mL, 1.0 M solution in Et_2O, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled to

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−78 °C (dry ice/acetone bath), and a red-brown solution of phenylselenyl chloride (5.75 mmol, 1.10 g, 1.15 equiv) in 5 mL of dry THF was added slowly. The addition of each drop was accompanied by the instantaneous discharge of color. After addition was complete, the resulting yellow reaction mixture was allowed to warm to rt and then was heated at reflux for 2 h under nitrogen. ^{31}P NMR analysis indicated the formation of α-selenophosphonate, which was converted into diethyl (*Z*)-1-pentenylphosphonate by the addition of pyridine (2.37 mg, 30 mmol, 2.40 mL, 6.0 equiv) at −78 °C (dry ice/acetone bath) followed by 30% H_2O_2 (30 mmol, 6.0 equiv) and H_2O (1:1 by volume) at 0 °C. After warming to rt, the organic layer was separated and aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic fractions were dried with $MgSO_4$, and the solvent was removed in vacuo. The purification of the crude product by flash chromatography on silica gel (EtOAc/Hexanes 1:1, v/v) gave the diethyl (*Z*)-1-pentenylphosphonate (906 mg, 4.40 mmol, 88%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.80 (ddt, J = 53 Hz, J = 13 Hz, J = 7 Hz, 1 H), 5.52 (tt, J = 19 Hz, J = 13 Hz, J = 2 Hz, 1 H), 4.03−4.17 (m, 4 H), 2.18−2.26 (m, 2 H), 1.45 (q, J = 7 Hz, 2 H), 1.34 (t, J = 7 Hz, 6 H), 0.95 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 20.0.

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Supporting Information Available: Spectral data and additional experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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