ORGANIC LETTERS

2008
Vol. 10, No. 5
977−980

Mild Synthesis of Organophosphorus Compounds: Reaction of Phosphorus-Containing Carbenoids with Organoboranes

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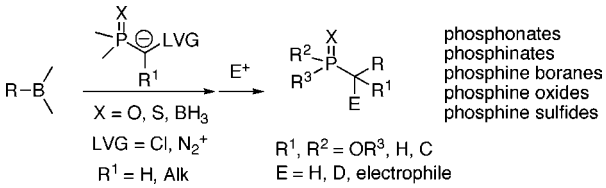
Received January 14, 2008

ABSTRACT



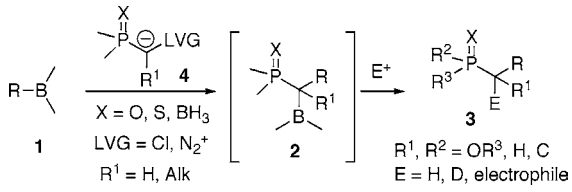
Organoboranes react with phosphorus-containing carbenoids to produce a variety of functionalized organophosphorus compounds under mild conditions. In some cases, selective migration of one group attached to boron can be observed. Phosphonite–borane complexes are introduced as novel synthons for the synthesis of phosphinic esters.

Organoboranes have often been homologated to various functional groups using carbenoids.[1] However, as far as we could determine, application of this general reactivity pattern has surprisingly not been implemented in organophosphorus chemistry. Herein we describe studies aiming at the functionalization of a C−B bond **1** into a C−C−P **3** motif using various organophosphorus carbenoids (Scheme 1).

Based on the extensive precedent for reaction of organoboranes with halocarbonyl anions and diazocarbonyl compounds, the feasibility of the analogous reaction of phosphorus-containing reagents appeared reasonable. One likely difference concerns the reactivity of the α-boron-substituted intermediate phosphorus species **2**. The synthetic strategy outlined below provides various organophosphorus compounds under mild conditions.

To test the possibility of the reaction depicted in Scheme 1, the reaction of dimethyl (diazomethyl)phosphonate (Seyferth/Gilbert reagent, **4a**)[2] with tributylborane was investigated. Treatment of **4a** with Bu_3B at room temperature in THF, resulted in the instantaneous evolution of N_2 and formation of **2a** which was hydrolyzed with water or D_2O

Scheme 1. Homologation of Phosphorus Carbenoids with Organoboranes

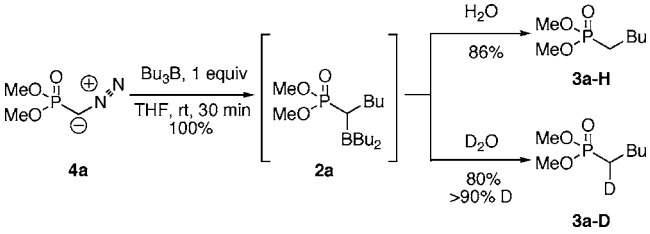


(1) Representative examples: (a) Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068. (b) Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006**, *8*, 773. (c) Goddard, J.-P.; Le Gall, T.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1455. (d) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294. (e) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (f) Larson, G. L.; Argüelles, R.; Rosario, O.; Sandoval, S. *J. Organomet. Chem.* **1980**, *198*, 15. (g) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230. (h) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936. (i) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 6891. (j) Hooz, J.; Morrison, G. F. *Can. J. Chem.* **1970**, *48*, 868. (k) Negishi, E.; Yoshida, T.; Silveira, A., Jr.; Chiou, B. L. *J. Org. Chem.* **1975**, *40*, 814. (l) Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 818. (m) Brown, H. C.; Rogic, M. M.; Rathke, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 6218. (n) Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 1911.

10.1021/ol800085u CCC: $40.75
Published on Web 02/06/2008

to produce dimethyl pentylphosphonate **3a** (protio **3a-H**, or deuterio **3a-D**) in 86% and 80% isolated yields, respectively (Scheme 2). In the latter case, deuterium incorporation was

Scheme 2. Reaction of Dimethyl (Diazomethyl)phosphonate with Tributylborane



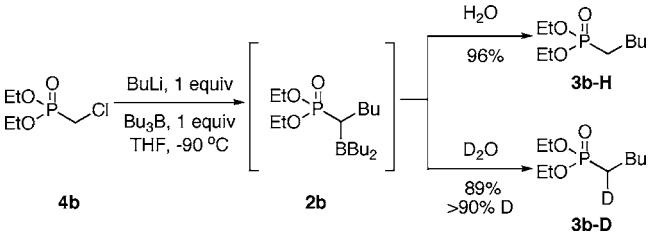
higher than 90% D. Encouraged by these two results, we then undertook a full investigation of the synthetic approach shown in Scheme 1.

While the synthesis of **4a** is relatively straightforward, a large body of literature is available on the preparation and reactivity of diethyl (chloromethyl)phosphonate **4b**.[3] We thus turned our attention to this phosphonate carbenoid precursor. Functionalized phosphonates have importance in multiple fields, particularly as intermediates in the synthesis of biologically active compounds.[4] Initially, Bu_3B was selected as a model reagent to investigate the reactivity of the presumed intermediate. Deprotonation of **4b** and reaction with Bu_3B at −90 °C gave excellent results upon simple hydrolysis (Scheme 3).[5] Diethyl pentylphosphonate **3b-H** was obtained in 96% isolated yield, and deuterated **3b-D** was obtained in 89% (>90% D).

In the next stage, we studied other carbenoid precursors with Bu_3B, and these results are shown in Table 1.

A variety of precursors[6] reacted successfully with Bu_3B (Table 1). Yields are good to acceptable, and the lower yield is observed only when a second migration is involved (entry 3). In this case, a second equivalent of BuLi must be added prior to hydrolysis to promote the second migration. It should

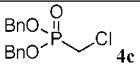
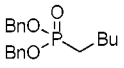
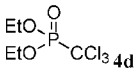
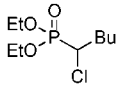
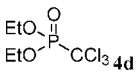
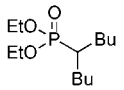
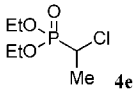
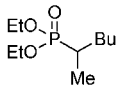
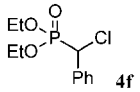
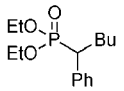
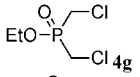
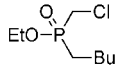
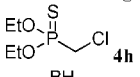
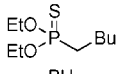
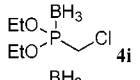
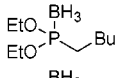
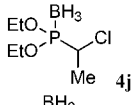
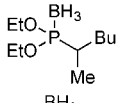
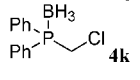
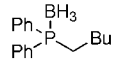
Scheme 3. Reaction of Diethyl (Chloromethyl)phosphonate with Tributylborane



be noted that the second butyl group in the product is then as likely to originate from the added butyllithium (33% chance) as from the initial Bu_3B (Scheme 4). This might have been true with any combination of BuLi/Bu_3B. However, entry 10 shows that the butyl group came from the organoborane, and additional results below indicate that the BuLi used to generate the carbenoid is not incorporated into the product.

It is important to note that the direct alkylation of phosphonate anions is often inefficient, so that secondary phosphonates are not readily available.[7] Similarly, the classic Arbuzov reaction rarely works well to produce secondary phosphonates.[8]

Table 1. Reactions of Carbenoid Precursors with Bu_3B, Then H_2O[a]

entry	starting material **4**	product **3**	isolated yield (%)
1	 **4c**		85
2	 **4d**		70
3	 **4d**		52[b]
4	 **4e**		63
5	 **4f**		60
6	 **4g**		78
7	 **4h**		90
8	 **4i**		92
9	 **4j**		86
10	 **4k**		62[c]

[a] Same conditions as in Scheme 3. Details can be found in the Supporting Information. [b] An additional 1 equiv of BuLi was added prior to hydrolysis. [c] *s*-BuLi was used in place of *n*-BuLi.

(2) (a) Seyferth, D.; Marmor, R. S. *Tetrahedron Lett.* **1970**, 2493. (b) Brown, D. G.; Vethuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.

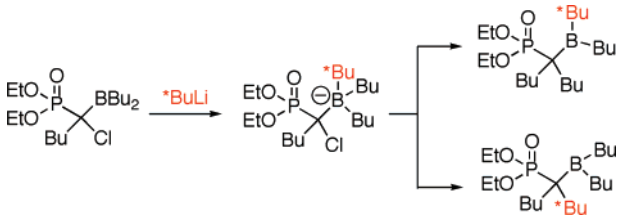
(3) Waschbüsch, R.; Carran, J.; Marinetti, A.; Savignac, P. *Chem. Rev.* **1997**, *97*, 3401.

(4) (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.

(5) **Typical Experimental Procedure.** A flame-dried, 50 mL flask was purged with nitrogen and charged with diethyl (chloromethyl)phosphonate **4b** (4.0 mmol, 746 mg, 1.0 equiv) and dry THF (20 mL). The solution was cooled below −90 °C (liquid nitrogen/ethanol bath), and *n*-butyllitium (1.6 M solution in hexane, 2.5 mL, 4.0 mmol, 1.0 equiv) was added slowly by syringe followed by Bu_3B (1.0 M solution in diethyl ether, 4.0 mL, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to room temperature and was quenched by addition of water. The resulting biphasic mixture was stirred at reflux for 2 h. After being cooled to room temperature, the layers were separated, the aqueous phase was extracted with EtOAc (3×), the combined organic layers were dried with $MgSO_4$, and solvents were removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/hexane 1:1, v/v) yielded diethyl pentylphosphonate **3b-H** (3.84 mmol, 800 mg, 96%). Additional details can be found in the Supporting Information.

(6) Detailed procedures for the preparation of the reagents **4** can be found in the Supporting Information.

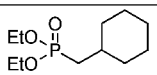
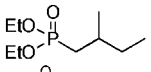
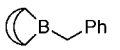
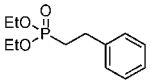
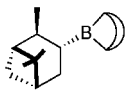
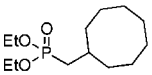
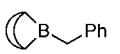
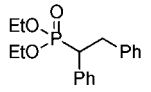
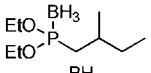
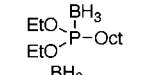
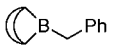
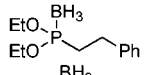
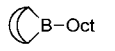
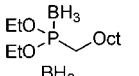
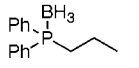
Scheme 4. Butyl Group Scrambling in Table 1, Entry 3



Aside from phosphonate derivatives (entries 1−5), phosphinate (entry 6), phosphonothioate (entry 7), boranophosphonates (entries 8 and 9), and phosphine−borane complex (entry 10) could also be prepared (Table 1). The latter compounds have obvious potential in the synthesis of ligands for transition-metal-catalyzed reactions. Our approach therefore seemed promising and potentially important as a general route to produce various organophosphorus compounds.

The next question was to determine the reactivity of other organoboron compounds, as well as the migratory selectivity with nonsymmetrical organoboranes (Table 2). As shown

Table 2. Reactions with Other Organoboranes[a]

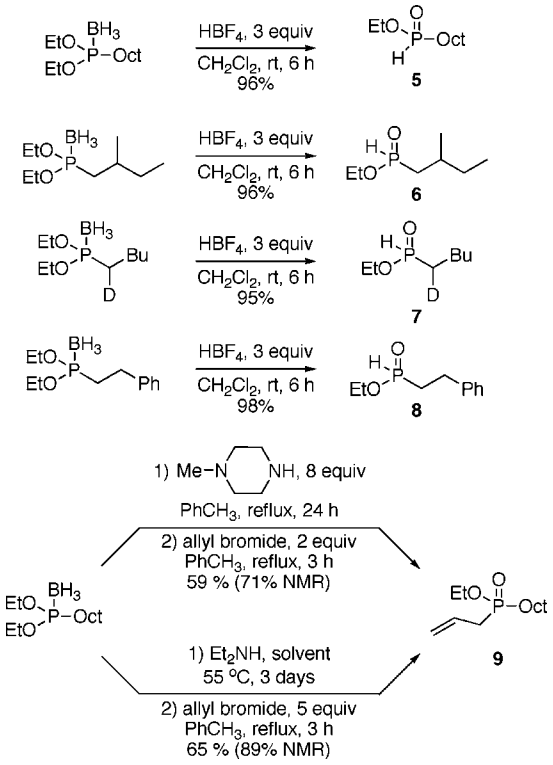
entry	starting material **4**	organoboron compound **1**	product **3**	isolated yield (%)
1	**4b**	Cy_3B		83
2	**4b**	$(sec\text{-}Bu)_3B$		86
3	**4b**			69
4	**4b**			83
5	**4f**			59
6	**4i**	$(sec\text{-}Bu)_3B$		82
7	**4i**	$(n\text{-Heptyl})_3B$		73
8	**4i**			71
9	**4i**			62
10	**4k**	Et_3B		85

[a] Products were isolated after hydrolysis by column chromatography (see the Supporting Information for details).

in Table 2, a variety of organoboranes could be employed. Selective transfer of benzyl and octyl groups was observed (entries 3, 5, 8, and 9). However, the cyclooctyl group migrated selectively in the case of Alpine borane (entry 4).

The successful reactions with phosphonite−borane **4i** provided a variety of novel phosphonite−borane complexes ("boranophosphonates") **3**.[9] We were particularly interested in these intermediates as precursors to H-phosphinate esters. Conversion of these complexes to phosphinate derivatives could be achieved easily (Scheme 5). Cleavage to ethyl

Scheme 5. Conversion of Phosphonite−Boranes into Phosphinate Esters



H-phosphinate esters **5**−**8** was readily accomplished with tetrafluoroboric acid. Under these conditions, no further hydrolysis of the ester group was observed. Interestingly, decomplexation to the phosphonite derivative could be conducted with amines, and subsequent treatment with allyl bromide, in "one-pot", led to an Arbuzov reaction with formation of a disubstituted phosphinate **9**. Although more work must be done to develop and optimize this tandem decomplexation−Arbuzov reaction, these results are promising for the preparation of complex phosphinic acid derivatives.

Organoboranes have become routine and ubiquitous reagents in organic synthesis. One important reason for this success is the wide variety of functional groups that can be obtained by transforming a carbon−boron bond.[10]

Thus, intermediates **2** could potentially be functionalized beyond simple hydrolysis/deuterolysis using other electro-

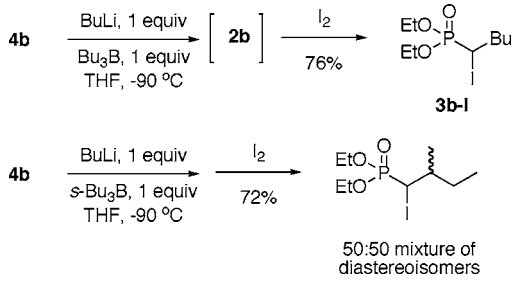
(7) (a) Poindexter, M. K.; Katz, T. J. *Tetrahedron Lett.* **1988**, *29*, 1513. (b) Coutrot, P.; Savignac, P.; Mathey, F. *Synthesis* **1978**, 36. (c) Teulade, M. P.; Savignac, P.; Abouajouade, E.; Collignon, N. *J. Organomet. Chem.* **1986**, *312*, 283. See also ref 4b.

(8) (a) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415. (b) Engel, R.; Cohen, J. I. *Synthesis of Carbon−Phosphorus Bonds*, 2nd ed.; CRC Press: Boca Raton, 2003.

(9) For a review on phosphine−borane complexes, see: Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *178*−*180*, 665.

philes. The reactivity of **2** remains to be fully investigated at this time, but here we report the successful iodination of these intermediates to provide highly functional α-iodo phosphonates (Scheme 6). It is interesting to note that one

Scheme 6. Synthesis of α-Iodophosphonates



C−B bond reacts selectively, as would be expected from a boron enolate character in **2**.[11] These iodophosphonates might also be precursors to valuable compounds[12] such as α-aminophosphonates and related compounds. Direct amination of **2** is also a possibility that will be investigated as a route to α-aminophosphonates.

In conclusion, we have demonstrated a novel synthesis of organophosphorus compounds using organoboron reagents. In some cases, selective transfer of one group attached to the boron atom has been achieved. Reagent **4i** was introduced as a novel precursor of H-phosphinate derivatives. Further elaboration of the reactive intermediates **2** using various electrophiles will be reported in due course. Implementation of an asymmetric version using chiral phosphorus and/or chiral boron reagents will also be the focus of future investigations.

Acknowledgment. We thank the Robert A. Welch Foundation (Grant No. P-1666) and the National Institute of General Medical Sciences/NIH (1R01 GM067610) for the financial support of this research. We also thank the reviewers for helpful suggestions.

Supporting Information Available: Representative experimental procedures, preparation of reagents **4**, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800085U

(10) (a) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975; Vol. 1. (b) Brown, H. C.; Zaidlewicz, M. *Organic Syntheses via Boranes: Recent Developments*; Wiley: New York, 2001; Vol. 2. (c) Suzuki, A.; Brown, H. C. *Organic Syntheses via Boranes: Suzuki Coupling*; Wiley: New York, 2003; Vol. 3. (d) Negishi, E.; Idacavage, M. J. *Org. React.* **1985**, *33*, 1. (e) Weill-Raynal, J. *Synthesis* **1976**, 633.

(11) For references on the conversion of C-B into C-I, see: (a) Montchamp, J.-L.; Migaud, M. E.; Frost, J. W. *J. Org. Chem.* **1993**, *58*, 7679. (b) Brown, H. C.; Rathke, M. W.; Rogic, M. M.; De Lue, N. R. *Tetrahedron* **1988**, *44*, 2751. (c) Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1980**, *45*, 3578.

(12) For references on the use of secondary α-iodophosphonates, see: (a) Balczewski, P.; Szadowiak, A.; Bodzioch, A.; Bialas, T.; Wieczorek, W. M.; Szyrej, M. *J. Organomet. Chem.* **2007**, *692*, 997. (b) Balczewski, P.; Szadowiak, A.; Bialas, T. *Heteroatom Chem.* **2006**, *17*, 22. (c) Miryan, N. I.; Isaev, S. D.; Kovaleva, S. A.; Petukh, N. V.; Dvornikova, E. V.; Kardakova, E. V.; Yurchenko, A. G. *Russ. J. Org. Chem.* **1999**, *35*, 857. (d) Russell, G. A.; Shi, B. Z.; Jiang, W.; Hu, S.; Kim, B. H.; Baik, W. *J. Am. Chem. Soc.* **1995**, *117*, 3952.