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Chemistry of the Versatile (Hydroxymethyl)phosphinyl P(O)CH_2OH Functional Group

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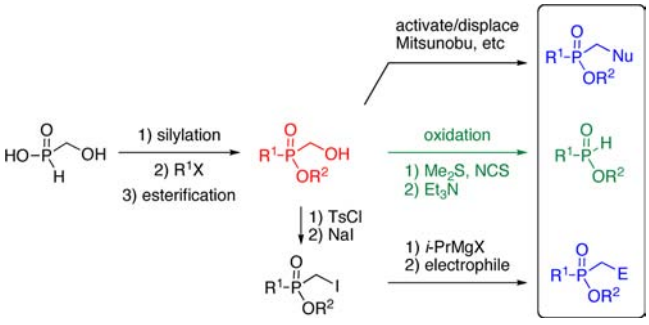
ABSTRACT



(Hydroxymethyl)phosphorus compounds are well-known and valuable compounds in general; however the use of (hydroxymethyl)phosphinates $R^1P(O)(OR^2)CH_2OH$ in particular has been much more limited. The potential of this functionality has not yet been fully realized because the mild unmasking of the hydroxymethyl group was not available. The mild *oxidative* conversion of $R^1P(O)(OR^2)CH_2OH$ into $R^1P(O)(OR^2)H$ using the Corey–Kim oxidation is described. Other reactions preserving the methylene carbon are also reported.

Compounds containing the P–CH_2OH motif have been employed in various applications.[1] For example, phosphines $R^1R^2P(CH_2OH)$ are useful synthetic intermediates and ligands.[1a−j] Similarly, their borane complexes $R^1R^2P(BH_3)CH_2OH$ have been elegantly employed in P-chiral synthesis.[1k−m] (Hydroxymethyl)phosphonates are common precursors for nucleophilic substitution,[1n,o] but the corresponding (hydroxymethyl)phosphinates $R^1P(O)(OR^2)$-CH_2OH **1** are less common, although they have been employed occasionally[1p,q] and their enzymatic kinetic resolution has been described.[1r,s] Interestingly, compounds **1** can also display significant biological activity.[2]

(1) For representative examples, see: (a) James, B. R.; Lorenzini, F. *Coord. Chem. Rev.* **2010**, *254*, 420. (b) Swor, C. D.; Hanson, K. R.; Zakharov, L. N.; Tyler, D. R. *Dalton Trans.* **2011**, *40*, 8604. (c) Hanton, M. J.; Tin, S.; Boardman, B. J.; Miller, P. *J. Mol. Catal. A: Chem.* **2011**, *346*, 70. (d) Griffiths, D. V.; Groombridge, H. J.; Salt, M. C. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 473. (e) Brown, G. M.; Elsegood, M. R. J.; Lake, A. J.; Sanchez-Ballester, N. M.; Smith, M. B.; Varley, T. S.; Blann, K. *Eur. J. Inorg. Chem.* **2007**, 1405. (f) Higham, L. J.; Whittlesey, M. K.; Wood, P. T. *Dalton Trans.* **2004**, 4202. (g) Raghuraman, K.; Pillarsetty, N.; Volkert, W. A.; Barnes, C.; Jurisson, S.; Katti, K. V. *J. Am. Chem. Soc.* **2002**, *124*, 7276. (h) Henderson, W.; Alley, S. R. *J. Organomet. Chem.* **2002**, *658*, 181. (i) Stark, G. A.; Riermeier, T. H.; Beller, M. *Synth. Commun.* **2000**, *30*, 1703. (j) Berning, D. E.; Katti, K. V.; Barnes, C. L.; Volkert, W. A. *J. Am. Chem. Soc.* **1999**, *121*, 1658. (k) Wiktelius, D.; Johansson, M. J.; Luthman, K.; Kann, N. *Org. Lett.* **2005**, *7*, 4991. (l) Shioji, K.; Kurauchi, Y.; Okuma, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 833. (m) Nagata, K.; Matsukawa, S.; Imamoto, T. *J. Org. Chem.* **2000**, *65*, 4185. (n) Folhr, A.; Aemissegger, A.; Hilvert, D. *J. Med. Chem.* **1999**, *42*, 2633. (o) Phillion, D. P.; Andrew, S. S. *Tetrahedron Lett.* **1986**, *27*, 1477. (p) Cristau, H.-J.; Hervé, A.; Virieux, D. *Tetrahedron* **2004**, *60*, 877. (q) Cristau, H.-J.; Hervé, A.; Loiseau, F.; Virieux, D. *Synthesis* **2003**, 2216. (r) Kielbasiński, P.; Albrycht, M.; Luczak, J.; Mikołajczyk, M. *Tetrahedron: Asymmetry* **2002**, *13*, 735. (s) Kielbasiński, P.; Omelanczuk, J.; Mikołajczyk, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3283. (t) Hall, R. G.; Riebli, P. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1557.

(2) (a) Vassiliou, S.; Kosikowska, P.; Grabowiecka, A.; Yiotakis, A.; Kafarski, P.; Berlicki, L. *J. Med. Chem.* **2010**, *53*, 5597. (b) Coudray, L.; Kantrowitz, E. R.; Montchamp, J.-L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 900. (c) Berlicki, L.; Obojska, A.; Forlani, G.; Kafarski, P. *J. Med. Chem.* **2005**, *48*, 6340. (d) Furet, P.; Caravatti, G.; Denholm, A. A.; Faessler, A.; Fretz, H.; Garcia-Echeverria, C.; Gay, B.; Irving, E.; Press, N. J.; Rahuel, J.; Schoepfer, J.; Walker, C. V. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2337. (e) Froestl, W.; Mickel, S. J.; Hall, R. G.; von Sprecher, G.; Diel, P. J.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297. (f) Magnin, D. R.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J. V.; Lawrence, R. M.; Chen, Y.; Sulsky, R. B.; Ciosek, C. P., Jr.; Harrity, T. W.; Jolibois, K. G.; Kunselman, L. K.; Rich, L. C.; Slusarchyk, D. A. *J. Med. Chem.* **1995**, *38*, 2569.

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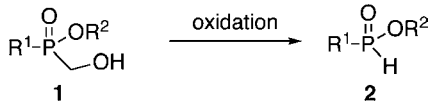
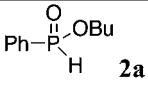
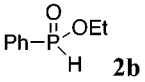
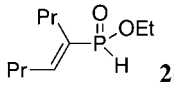
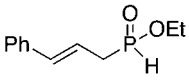
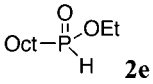
Table 1. Oxidative Conversion of (Hydroxymethyl)-phosphinates into *H*-Phosphinates



1 **2**

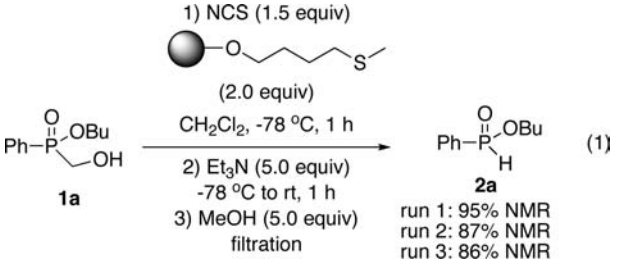
entry	1	conditions[a]	product	isolated (^{31}P-NMR) yield %
1a 1b	**1a**	A B	 **2a**	97 (100) 68 (83)
2	**1b**	A	 **2b**	95 (100)
3	**1c**	A	 **2c**	75 (80)
4	**1d**	A	 **2d**	92 (100)
5	**1e**	A	 **2e**	66 (82)

[a] Conditions A: Corey–Kim oxidation; (i) *N*-chlorosuccinimide (1.5 equiv), Me_2S (1.5 equiv), CH_2Cl_2, −78 °C, 10 min; (ii) $R^1P(O)(OR^2)CH_2OH$ (1 equiv), −78 °C, 1 h; (iii) Et_3N (5 equiv), −78 °C to rt, 1 h. Conditions B: Swern oxidation; (i) DMSO (3 equiv), oxalyl chloride (1.5 equiv), CH_2Cl_2, −78 °C; (ii) $R^1P(O)(OR^2)CH_2OH$ (1 equiv), −78 °C, 1 h; (iii) Et_3N (5 equiv), −78 °C to rt.

However, one unexplored dimension is the conversion of (hydroxymethyl)phosphinates into the corresponding *H*-phosphinates $R^1P(O)(OR^2)H$ **2** so that the hydroxymethyl group becomes a P−H equivalent. Various methods have been developed for the synthesis of *H*-phosphinates,[3] several of which rely on a protecting group strategy.[4] To the best of our knowledge, however, cleavage of the protecting group is always conducted under either acidic or basic conditions.[4]

As part of our ongoing studies on the synthesis of phosphinic acids, we became interested in finding a new P−H equivalent, which could be unmasked under neutral conditions. We therefore investigated the *oxidative* cleavage of **1**. Based on the "Ciba-Geigy reagent"[4a,b,e] the formation of an aldehyde should lead to P−C bond cleavage. At the outset, because the desired *H*-phosphinate ester is easily oxidized, many methods were expected to result in overoxidation and were not considered (for example conditions using air or other stoichiometric oxidants in the presence of a metal catalyst or reagent, or TEMPO), even though the direct transformation of **1** into $R^1P(O)(OR^2)(OH)$ could be of interest in its own right. For example, chromate-based reagents gave low yields of *H*-phosphinate (20% with PCC, 28% with PDC, CH_2Cl_2, rt). Based on the above requirements, we quickly focused on sulfur-based oxidations such as Swern[5] and Corey–Kim[6] and then selected the latter as the method of choice.

Table 1 summarizes the results. Corey–Kim oxidation gave a cleaner reaction (entry 1a) than Swern oxidation (entry 1b) and consistently gave excellent results on various compounds. Although all the compounds in Table 1 were purified, in most cases the crude mixture is very clean and could be used directly in further reactions. Diethyl (hydroxymethyl)phosphonate also undergoes the reaction (76% ^{31}P NMR, 62% isolated), but (hydroxymethyl)-diphenylphosphine oxide is unsatisfactory (22% ^{31}P NMR). One advantage of the Corey–Kim oxidation is that the sulfide is regenerated at the end of the reaction. Because dimethyl sulfide is foul-smelling, the possibility of employing an oderless and reusable polymeric sulfide was investigated briefly (eq 1). Polystyrene supported 4-(methylthio)-1-butanol[7] gave excellent results in three successive runs where the polymer was simply filtered, washed, dried, and reused.

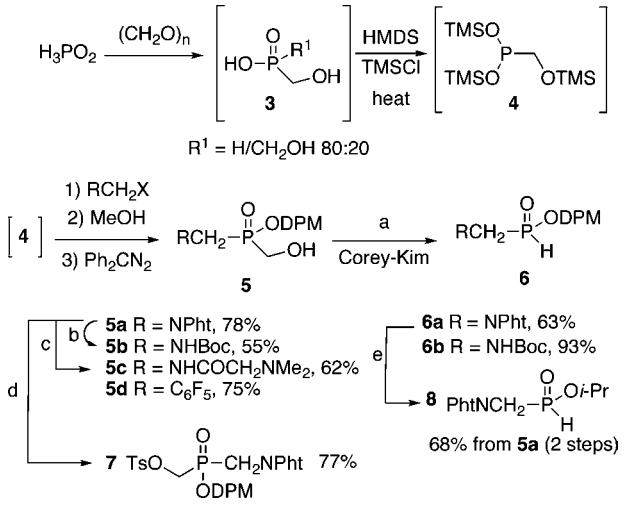


The oxidative cleavage methodology was then applied to the preparation of interesting *H*-phosphinates (Scheme 1). More than 35 years ago, Rosenthal described the Arbuzov reaction of bis(trimethylsilyl) [(trimethylsilyloxy) methyl]-phosphonite $(TMSO)_2PCH_2OTMS$ **4**,[8] a reagent prepared from the readily available (hydroxymethyl)-*H*-phosphinic acid **3**.[9]

In principle, silylated hypophosphorous acid (bis-(trimethylsilyloxy)phosphine, BTSP, $(TMSO)_2PH$) can be used directly, but there are problems with this reagent (pyrophoric, competitive disubstitution, stoichiometry)[3] which is well illustrated by Coward's work with $PhtNCH_2PO_2H_2$.[10] Combining Rosenthal's reagent with the present reaction should provide access to *H*-phosphinates not easily accessible otherwise. Scheme 1 shows a few examples of this strategy. The syntheses of

(3) Review: Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388.
(4) For example: (a) Coudray, L.; Montchamp, J.-L. *Eur. J. Org. Chem.* **2009**, 4646. (b) Fougère, C.; Guénin, E.; Hardouin, J.; Lecouvey, M. *Eur. J. Org. Chem.* **2009**, 6048. (c) Belabassi, Y.; Antczak, M. I.; Tellez, J.; Montchamp, J.-L. *Tetrahedron* **2008**, *64*, 9181. (d) Abrunhosa-Thomas, I.; Sellers, C. E.; Montchamp, J.-L. *J. Org. Chem.* **2007**, *72*, 2851. (e) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385. (f) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9389.
(5) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (c) Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2407.
(6) (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. (b) Corey, E. J.; Kim, C. U. *Tetrahedron Lett.* **1974**, *15*, 287.
(7) Kerr, W. J.; Lindsay, D. M.; McLaughlin, M.; Pauson, P. L. *Chem. Commun.* **2000**, 1467. This is also available from Aldrich.
(8) Rosenthal, A. F.; Gringauz, A.; Vargas, L. A. *J. Chem. Soc., Chem. Commun.* **1976**, 384.
(9) For the preparation of **3**, see refs 1p and 2a.
(10) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502.

Scheme 1. A Strategy for the Synthesis of *H*-Phosphinates Based on the Hydroxymethyl Protecting Group[a]

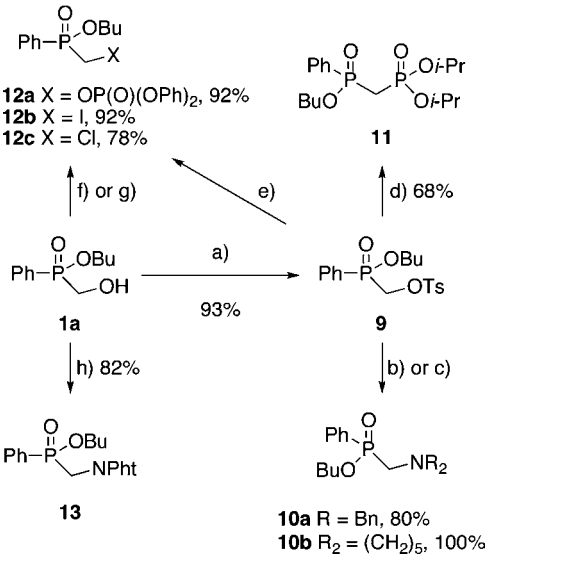


[a] See Supporting Information for detailed experimental procedures. DPM = diphenylmethyl, Ph_2CH. (a) (i) *N*-Chlorosuccinimide (1.5 equiv), Me_2S (1.5 equiv), CH_2Cl_2, −78 °C, 10 min; (ii) $R^1P(O)(OR^2)CH_2OH$ (1 equiv), −78 °C, 1 h; (iii) Et_3N (5 equiv), −78 °C to rt, 1 h. (b) (i) H_2NNH_2 (3 equiv), THF, rt, 16 h; (ii) Boc_2O (5 equiv), *i*-Pr_2NEt (5 equiv), THF, rt, 4 h. (c) (i) H_2NNH_2 (4 equiv), THF, rt, 16 h; (ii) Me_2NCH_2COOH (5 equiv), HOBt (5 equiv), EDC (5 equiv), CH_2Cl_2, rt, 2 h. (d) TsCl (2 equiv), *i*-Pr_2NEt (2.5 equiv), CH_2Cl_2, rt, 24 h. (e) *i*-PrOH (solvent), 4 Å MS, reflux, 3 h.

aminomethyl-*H*-phosphinates **6a** and **6b** and **8** were chosen because compounds of this type are very useful intermediates, often prepared through cumbersome sequences on limited scales.[11] Interestingly, compound **5a** is isolated as a solid, thus avoiding the need for chromatography. Direct oxidation of **5a** gave **6a**, but unfortunately pure **6a** could not be obtained because it is not very stable (purity ~85%). Therefore crude **6a** was treated with *i*-PrOH and transesterification to isopropyl ester **8** proceeded in good yield and purity (68% from **5a**). Intermediate **5a** was also converted into the Boc-protected **5b** which could then be oxidatively deprotected into **6b**. Conversion of **5a** into the *N,N*-dimethylglycine amide **5c** was uneventful. Deprotected **5c** is a known bacterial urease inhibitor.[2a] Finally tosylation of **5a** gave compound **7**.

Having established the oxidative cleavage of (hydroxymethyl)phosphinates **1** as a viable synthetic methodology,

Scheme 2. Activation/Nucleophilic Displacement of (Hydroxymethyl)phosphinate **1a**[a]



[a] (a) TsCl (2 equiv), *i*-Pr_2NEt (2.5 equiv), CH_2Cl_2, rt, 24 h. (b) Bn_2NH (1.5 equiv), K_2CO_3 (3 equiv), CH_3CN, reflux, 48 h. (c) Piperidine (1.5 equiv), K_2CO_3 (2 equiv), CH_3CN, reflux, 16 h. (d) (*i*-PrO)$_2$P(O)H (1.5 equiv), NaH (2 equiv), CH_2Cl_2, rt, 20 h. (e) NaI (4 equiv), acetone, reflux, 24 h. (f) ClP(O)$(OPh)_2$ (1.5 equiv), $TiCl_4$ (2 mol %), Et_3N (1.5 equiv), CH_2Cl_2, rt, 6 h. (g) (i) $SOCl_2$ (1.5 equiv), pyridine (1.2 equiv), 50 °C, 20 h; (ii) BuOH. (h) Phthalimide (1.3 equiv), $PyPPh_2$ (1.3 equiv), DIAD (1.3 equiv), CH_2Cl_2, rt, 24 h.

we next turned our attention to reactions in which the methylene carbon is preserved. As mentioned earlier, this type of reaction although not unprecedented is surprisingly rare.[1p,q] Butyl (hydroxymethyl)phenyl phosphinate **1a** was chosen as a representative model compound.[12] The first type of reaction investigated was the activation–nucleophilic substitution sequence, which has been useful in the chemistry of phosphonates.[1n,o] Results are shown in Scheme 2. Tosylation to **9** was achieved in excellent yield under standard conditions. Displacement with a variety of nucleophiles proceeded in good to excellent yields. For example, the formation of **10a**–**b** with secondary amines takes place uneventfully.

Interestingly, reacting **9** with diisopropylphosphite under Michaelis–Becker conditions smoothly delivered (phosphinylmethyl)phosphonate **11**.[13] This type of compound is of interest for the preparation of biologically active pyrophosphate analogs. The (phosphinylmethyl)-phosphate motif is an emerging but underutilized mimic for pyrophosphate and phosphoryl transfer.[14] Precursor **12a** was easily synthesized from alcohol **1a**.[15]

(11) For example, see: (a) Yamagishi, T.; Mori, J.-i.; Haruki, T.; Yokomatsu, T. *Tetrahedron: Asymmetry* **2011**, *22*, 1358. (b) Yamagishi, T.; Ichikawa, H.; Haruki, T.; Yokomatsu, T. *Org. Lett.* **2008**, *10*, 4347. (c) Li, S.; Whitehead, J. K.; Hammer, R. P. *J. Org. Chem.* **2007**, *72*, 3116. (d) Yamagishi, T.; Haruki, T.; Yokomatsu, T. *Tetrahedron* **2006**, *62*, 9210. (e) Zhukov, Y. N.; Vavilova, N. A.; Osipova, T. I.; Khurs, E. N.; Dzhavakhiya, V. G.; Khomutov, R. M. *Mendeleev Commun.* **2004**, 93. (f) Cristau, H.-J.; Coulombeau., A.; Genevois-Borella, A.; Sanchez, F.; Pirat, J.-L. *J. Organomet. Chem.* **2002**, *643–644*, 381. (g) Buchardt, J.; Ferreras, M.; Krog-Jensen, C.; Delaisse, J.-M.; Foged, N. T.; Meldal, M. *Chem.—Eur. J.* **1999**, *5*, 2877. (h) Dorff, P. H.; Chiu, G.; Goldstein, S. W.; Morgan, B. P. *Tetrahedron Lett.* **1998**, *39*, 3375. (i) Verbruggen, C.; De Craecker, S.; Rajan, P.; Jiao, X.-Y.; Borloo, M.; Smith, K.; Fairlamb, A. H.; Haemers, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 253. (j) Grobelny, D. *Synth. Commun.* **1989**, *19*, 1177. (k) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G. *Tetrahedron* **1989**, *45*, 3787. (l) Natchev, I. A. *Liebigs Ann. Chem* **1988**, 861. (m) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845.

(12) PhP(O)(OBu)CH_2OH **1a** was prepared in one pot and 83% yield from commercially available phenyl-*H*-phosphinic acid through Dean–Stark esterification (*n*-BuOH, 5 equiv, toluene, 24 h) followed by reaction with paraformaldehyde (1 equiv, reflux, 24 h). See Supporting Information.

(13) For a related reaction, see: Hall, R. G.; Kane, P. D.; Bittiger, H.; Froestl, W. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 129.

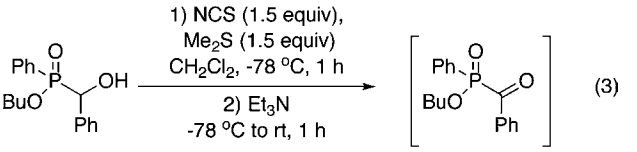
(14) (a) Guranowski, A.; Starzynska, E.; Pietrowska-Borek, M.; Rejman, D.; Blackburn, G. M. *FEBS J.* **2009**, *276*, 1546. (b) Nguyen, L. M.; Niesor, E.; Bentzen, C. L. *J. Med. Chem.* **1987**, *30*, 1426.

(Halomethyl)phosphinates **12b** and **12c** were synthesized either from **9** under Finkelstein conditions or directly from **1a** using thionyl chloride. The latter reaction required treatment with *n*-BuOH in order to reconvert the chlorophosphinate intermediate formed under the conditions. Finally, Mitsunobu reaction produced phthalimide **13**. Diphenyl-2-pyridylphosphine was used in order to facilitate the removal of the phosphine oxide byproduct from the desired compound. Surprisingly few examples of the Mitsunobu reaction of (hydroxymethyl)phosphinates have been reported.[16]

We recently reported the functionalization of organophosphorus carbenoids with organoboranes.[17] Unfortunately, treatment of (chloromethyl)phosphinate **12c** under our published conditions with *s*-BuLi and Bu_3B was not successful, nor were the reactions of **9** and **12b**. On the other hand, the conversion of diethyl (iodomethyl)-phosphonate to the corresponding Grignard reagent via metal−halogen exchange is known.[18] Therefore, the corresponding reaction was attempted on **12b**. The result is shown in eq 2. Further work will be required to fully develop/optimize this type of reaction.

(2)

Finally, the Corey−Kim oxidation of PhP(O)(OBu)CH-(OH)Ph **15** was conducted. The corresponding acyl phosphinate **16** was obtained cleanly and in quantitative yield (eq 3). This functionality is rare and not stable to chromatographic purification: deacylation to the *H*-phosphinate took place to produce PhP(O)(OBu)H **2a** in 69% isolated yield. Like their acylphosphonate counterparts, acylphosphinates have been synthesized from the Arbuzov reaction between a phosphonite and an acid chloride.[19] Exploiting the mild synthesis of acylphosphinates might be another promising area of research to explore reactivity without intermediate purification.



(3)

In conclusion, this work provides a new dimension in the chemistry of (hydroxymethyl)phosphinates for organophosphorus synthesis, either through functionalization preserving the methylene carbon or, even more importantly, through oxidative cleavage to unmask the *H*-phosphinate moiety. (Hydroxymethyl)phosphinates are versatile intermediates, which should prove useful both in the synthesis of complex organophosphorus compounds and, possibly, as pharmacophores in biologically active molecules. The sila-Arbuzov with **3**/esterification/oxidation sequence represents a novel and versatile approach to the synthesis of *H*-phosphinate esters. Further applications, and especially the development of this reaction for the asymmetric synthesis of P-chiral compounds, will be reported in due course.

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Supporting Information Available. Detailed experimental procedure, spectral data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(15) Jones, S.; Selitsianos, D. *Org. Lett.* **2002**, *4*, 3671.
(16) (a) Coudray, L.; Pennebaker, A. F.; Montchamp, J.-L. *Bioorg. Med. Chem.* **2009**, *17*, 7680. (b) Nawrot, B.; Michalak, O.; De Clercq, E.; Stec, W. J. *Antiviral Chem. Chemother.* **2004**, *15*, 319. (c) Gajda, T. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *85*, 59. (d) Maier, L.; Spörri, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *70*, 49.
(17) (a) Antczak, M. I.; Montchamp, J.-L. *J. Org. Chem.* **2009**, *74*, 3758. (b) Antczak, M. I.; Montchamp, J.-L. *Tetrahedron Lett.* **2008**, *49*, 5909. (c) Antczak, M. I.; Montchamp, J.-L. *Org. Lett.* **2008**, *10*, 977.
(18) Coutrot, P.; Youssefi-Tabrizi, M.; Grison, C. *J. Organomet. Chem.* **1986**, *316*, 13.
(19) (a) Samanta, S.; Perera, S.; Zhao, C.-G. *J. Org. Chem.* **2010**, *75*, 1101. (b) Walker, D. M.; McDonald, J. F.; Franz, J. E.; Logusch, E. W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 659.