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Chemoselective reduction of the phosphoryl bond of *O*-alkyl phosphinates and related compounds: an apparently impossible transformation†

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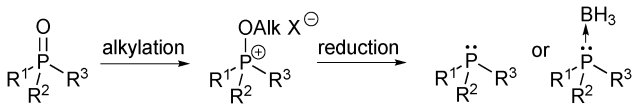
A method is reported for the phosphoryl bond cleavage of *O*-alkyl phosphinates, phosphinothioates and certain phosphonamidates to furnish the corresponding P(III) borane adducts. The two-step procedure relies upon initial activation of the phosphoryl bond with an alkyl triflate, followed by reduction of the resulting intermediate using lithium borohydride.

The development of a general method for the facile and chemoselective reduction of the phosphoryl bond has remained an issue in chemistry for many decades.[1] Traditional methods to affect this highly useful transformation have relied upon very reactive hydride sources, such as silanes[2] or hydrides,[3] which often preclude the presence of other susceptible functional groups in the substrate, and also have unpredictable stereochemical outcomes.[1a,b] Progress has accelerated in the intervening years,[4] and, recently, both ourselves[5–10] for hydrides and Beller and co-workers[11] for silanes have each contributed two methodologies such that the chemoselective reduction has been solved in certain instances. Now, the phosphoryl bond of tertiary and secondary phosphine oxides can be reduced, with good yield, in the presence of ketones, esters, olefins, nitriles and aldehydes.[8,11b]

However, there is another type of chemoselectivity that has seen much less progress. We refer to the reduction of phosphoryl species wherein the phosphorus is formally singly bonded to elements other than carbon or hydrogen. Previously, their reduction without concomitant loss of the P–heteroatom bond had been an intractable problem. We then reported[8] the first wide-scope methodology for the reduction of aminophosphine oxides (P(V) compounds with between one and three P–N bonds). The technique is based on reaction initially with oxalyl chloride, generating the corresponding chlorophosphonium chloride,[12] which is in turn easily reduced with borohydride to the corresponding phosphine borane.[8,13,14] Encouraged by this success, we wondered if we could go further and attempt the deoxygenation of phosphinates. This would achieve the apparently impossible task of breaking P=O in the presence of P–O. And to make the task even more challenging – there is a known effect whereby the more P–O bonds present in a P(V) species, the higher the bond dissociation energy of the associated phosphoryl bond.[15] The final products, some of which could be difficult to synthesise *via* solely P(III) starting materials, could find many uses, for instance as ligands in metal catalysed transformations.[16]

In our initial experiments, we found that neither *O*-alkyl nor *O*-aryl phosphinates reacted with oxalyl chloride to give a stable chlorophosphonium salt.[17] We therefore turned to our second methodology, which is *via* the reduction of alkoxy phosphonium species,[5–7] Scheme 1. The reduction can be done with LAH[5,7] or preferably L-selectride[9] to give the phosphines or with borohydride,[5–7,9] preferably lithium borohydride[10] to give the phosphine boranes.

To our knowledge there is only one report of phosphinate reduction by such a route, that of Rhomberg and Tavs in 1967,[18] who used Meerwein's salt[19] for the alkylation followed by reduction with magnesium in methanol, but obtained poor yields ($\leq$35%). Given our own previous success with Meerwein's salt,[6] we took that as our starting point but soon found that it was unsuitable. This is because the higher phosphoryl bond strength necessitates a much higher temperature for the alkylation. For example, *O*-ethyl diphenylphosphinate 1 reacts to give reasonable alkylation yields (>80%) only at 160 °C. Since these experiments had to be conducted in a sealed tube,[20] the diethyl ether by-product



Scheme 1 Reduction of phosphoryl species *via* alkoxyphosphonium intermediates.

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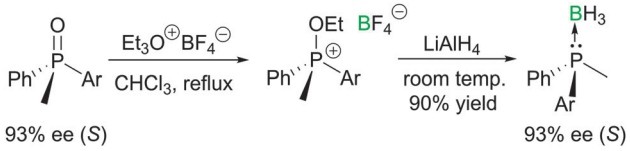
† Electronic supplementary information (ESI) available: Syntheses and characterisations of compounds **1–8**, their analogous boranes and other experimental details. See DOI: 10.1039/c5cc06389b



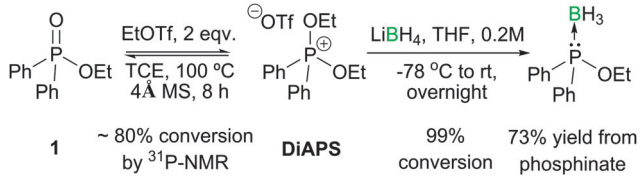
Scheme 2 Phosphine oxide reduction with Meerwein's salt/LAH giving phosphine borane directly (Ar: *o*-tolyl).

presents a potential hazard and we were forced to switch to alkyl triflates as alkylating agents.[3b,6,21]

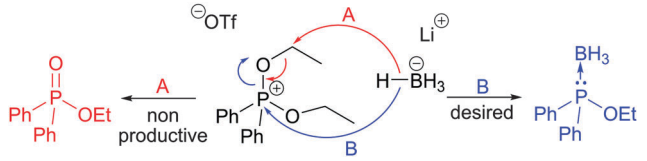
Digressing briefly, we did make one interesting observation in these preliminary studies with Meerwein's salt. When enantio-enriched tertiary phosphine oxide, (*S*)-methylphenyl(*o*-tolyl)-phosphine oxide (93% ee), was employed, the tetrafluoroborate salt could be formed by refluxing in chloroform for 2 hours with 1.2 equivalents of Meerwein's salt. The addition of LAH at room temperature then gave the corresponding phosphine borane, with 90% yield, Scheme 2. The reaction is completely stereo-specific, furnishing the product with inversion of configuration at phosphorus. Evidently, the excess LAH reduces the tetra-fluoroborate anion *in situ* furnishing borane, which then reacts with the initially formed phosphine.

Returning to the main topic, use of ethyl triflate as alkylating agent gave the desired dialkoxyphosphonium salt (DiAPS) with an identical conversion (80%) when reacted with ethyl diphenyl-phosphinate **1** in chloroform, again only at high temperature (160 °C). However, remarkably, it was found that switching to the higher boiling 1,1,2,2-tetrachloroethane (TCE, b.p. 147 °C) allowed the reaction temperature to be lowered to 100 °C or less with equivalent results,[22] Scheme 3. During these experiments a peculiar aspect of the alkylation reaction emerged, which is still not understood: the alkylation proceeds with higher conversion when activated 4 Å molecular sieves are present in the reaction. Rather a lot of sieves are necessary to maximise the effect, approximately 1 g of sieves per 100 mg of phosphorus species. It is clear that the sieves are not performing their common role of sequestering water, as all substrates and solutions were confirmed to be fully dry, by Karl Fischer titration, prior to running of the reaction, and water is not produced as a by-product.

It was found, as expected, that LAH is too harsh for the reduction of the *O*,*O*-dialkyl phosphonium species, cleaving both of the P–O bonds, and producing the secondary phosphine borane as the major product. On changing to our preferred lithium borohydride, a striking dependence on concentration was found. Thus, a 2 M solution in THF, did not produce any P(III) products, protected or otherwise, instead the starting P(V) phosphinate was



Scheme 3 Optimised conditions for the two-step deoxygenation of *O*-ethyl diphenylphosphinate **1** to phosphinite borane.



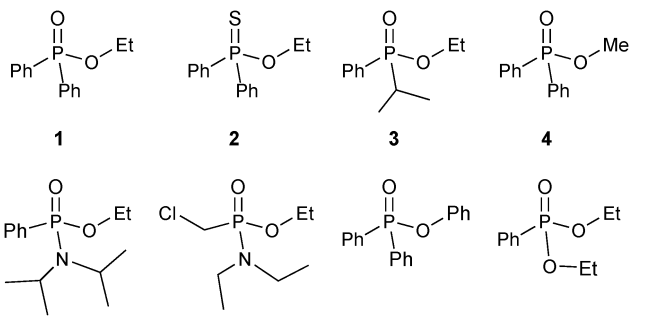
Scheme 4 Competing pathways in borohydride reduction of dialkoxy-phosphonium triflate.

fully regenerated. We have previously encountered this phenomenon in hydride reductions of pseudo phosphonium salts[6,7,9,10] It is explained by the alternative site of hydride attack[23] shown in Scheme 4 (path A). Fortunately, after some screening (see ESI†), we found that dilution of the hydride agent suffices to restore the desired product completely (Scheme 4, path B). Tetrahydrofuran was identified as the optimum solvent for the reduction step and dilution of the $LiBH_4$ from 2 M to 0.2 M increased the overall conversion to product from 0% (starting material fully regenerated) to 80% (>99% conversion from the intermediate, 73% isolated yield, for *O*-ethyl diphenylphosphinate).

Scheme 3 shows the optimised conditions for the two steps leading to desired P(III) borane product, starting from *O*-ethyl diphenylphosphinate **1**, showing that indeed a P=O bond can be removed while leaving a P–O intact.

We then subjected a number of related substrates to the methodology of Scheme 3, with the optimised results given in Table 1.

Table 1 Substrates subjected to two-step reduction according to Scheme 3 and their optimised conditions



	Alkylation conditions[a]				
Substrate	Time[b] (h)	Temp. (°C)	Equiv. ROTf	DiAPS conv.[c] (%)	Borane yield[d] (%)
1	8	100	2	80	73
2	8	100	2	80	72[e]
3	6	100	2	100	80
4[f]	16	75	2	86	60
5[g]	2	80	1.66	87	50
6[g]	23	80	1.66	58	32
7		Various		<10	0
8		Various		<10	0

[a] With ethyl triflate unless noted otherwise, all substrates dried thoroughly prior to use. [b] Time periods are strict, with deviation in either direction lowering conversion. [c] By ^{31}P-NMR spectroscopy. [d] Isolated yield, balance is returned starting material unless noted otherwise. [e] Balance is rearranged starting material. [f] Methyl triflate used, necessitating a lower reaction temperature. [g] Reduction performed in IPA/THF (4:1).

The thiophosphoryl analogue *O*-ethyl diphenylphosphinothioate **2**,[24] on alkylation, has different potential leaving groups, –OEt and –SEt, present in the intermediate. In the event, the reaction proceeds with exclusive loss of the thiolate moiety, forming *O*-ethyl diphenylphosphinite borane as the product. Unsurprisingly, given the difference in bond energies, the returned P(v) material (20%) is the rearranged compound, with P=O and P–SEt bonds, analogous to a thiono–thiolo rearrangement.[25]

The alkylaryl analogue *O*-ethyl phenyl(isopropyl)phosphinate (**3**) behaved well in the reaction and was convenient in that it could be fully alkylated, likely due to the stabilising effect of the more electron-donating P-alkyl group on the positively charged DiAPS intermediate. This allowed us to probe the mechanism of alkylation, especially whether it is reversible. To do so, a solution of *O*,*O*-diethyl phenyl(isopropyl)phosphonium triflate was formed and confirmed to be the sole phosphorus species present in solution by ^{31}P-NMR spectroscopy. Then, two equivalents of methyl triflate were added and this mixture was heated to 75 °C for 15 hours. Analysis of the resulting mixture showed the *O*,*O*-diethyl phosphonium species as previously observed, but now accompanied by the *O*,*O*-dimethyl and mixed *O*-methyl, *O*-ethyl salts, showing that indeed the reaction between a phosphinate and alkyl triflate is in dynamic equilibrium.

Variation of the ester group was explored with *O*-methyl species **4**. In this case, methyl triflate (b.p. 97–99 °C) was used to ensure formation of a symmetric triflate salt. A similar alkylation yield was obtained but a lower yield of the *O*-methyl diphenylphosphinite borane was obtained (60%). Once again, we explain this on the availability of the two different reaction pathways of reduction (Scheme 4). The lower steric requirement about the alkoxy α-carbon in the case of a methyl group makes substitution at that position more competitive with that at the phosphorus centre, relative to the P–OEt examples, causing a greater proportion of starting material to be reformed.

Next we sought to expand the scope to phosphonamidates: analogous P(v) compounds featuring a P–N bond, as well as the P–O bond (substrates **5** and **6**). Under the same conditions as for phosphinate alkylation, these compounds were found to undergo significant decomposition *via* cleavage of the P–N bond. However, by lowering both the reaction temperature for the first step, to 80 °C, and the excess of ethyl triflate, to 1.66, more favourable conversions to the intermediate could be obtained. The subsequent treatment with lithium borohydride (0.2 M in THF) once again fully returned the starting phosphonamidate. However a solvent screen showed that a mixture of IPA/THF (4 : 1, overall concentration of reductant: 0.4 M) gave reasonable yields of 50% and 32% for the derived boranes of 5 and 6 respectively. Again, the mass balance mostly consisted of returned starting material. This also can be explained on the basis of Scheme 4, in this case a consequence of the participation of the nitrogen lone pair of electrons in the P–N bonding.[26] This would reduce the positive charge on phosphorus in the intermediate, making it less electrophilic, thereby discouraging pathway B.

Finally extension to phosphonate **8** was unsuccessful, being hindered by low conversion in the alkylation step. The same issue arose with phenyl ester **7**, echoing its unreactivity with oxalyl chloride.[17] It is likely that the bond energies for the phosphoryl systems of these two species are too high to be adequately activated by alkylation under these conditions.[15]

In conclusion, a method for the phosphoryl deoxygenation of *O*-alkyl phosphinates, phosphinothioates and certain phosphonamidates has been described. The method relies upon activation of the strong phosphoryl bond prior to introduction of the reductant, as well as the creation of a symmetric phosphonium salt intermediate, to enable overall P=O bond cleavage using lithium borohydride. The use of such mild conditions should also allow the technique to be extended to substrates featuring other susceptible functional groups.

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