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Simple Unprecedented Conversion of Phosphine Oxides and Sulfides to Phosphine Boranes using Sodium Borohydride

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A variety of phosphine oxides and sulfides can be efficiently converted directly to the corresponding phosphine boranes using oxalyl chloride followed by sodium borohydride. Optically active *P*-stereogenic phosphine oxides can be converted stereospecifically to phosphine boranes with inversion of configuration by treatment with Meerwein's salt followed by sodium borohydride.

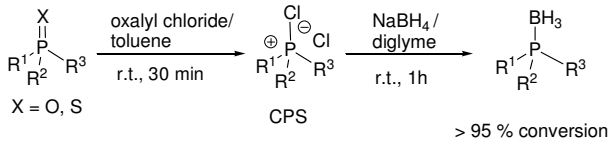
The reduction of phosphine chalcogenides has been a significant challenge in phosphorus chemistry for the past four decades.[1,2,3,4] The process is highly desirable because it provides access to the corresponding phosphines, which can be put to an extensive range of uses and also can be converted to other organophosphorus compounds. A very wide variety of all conceiveable reducing agents has been employed but none are problem-free.[1c] Although hydride reagents have attracted some recent attention,[2] at present silane reagents are the most commonly used, both in the laboratory and industrially.[4] A significant point in their favour is that, with care and with much process development, they can usually be made to stereospecifically reduce optically active phosphine oxides.[4d,5,6] Both silane and hydride reagents are commonly used in the presence of various modifiers: silanes are usually used with added tertiary amine,[4d,5] whereas hydrides may require initial treatment with strong alkylating agent[2f] and both have been used in the presence sacrificial phosphine.[2j,4f]

Despite this very large amount of research, it is still a reality of organophosphorus chemistry that reduction of a phosphine oxide will be the likely problem step in an organophosphorus synthetic sequence. The required silane or hydride reagents have relatively limited substrate compatibility and aggressive reaction conditions are often required leading to lowered yields. Among many, a striking example is provided by Gladiali and co-workers[7] who noted, in one of their diphosphane syntheses, that most of the product was lost in the final low-yielding (45-50%) reduction step. We ourselves have reported several cases where syntheses failed because the required reduction could not be placed at any point in the reaction sequence.[8] The avoidance of stereochemical control problems in oxide reductions was emphasised by Buono and co-workers as one of the advantages of their recent *P*-stereogenic phosphine borane synthesis.[9]

Once formed, the phosphines are relatively reactive (sometimes violently so) and are often converted to, and stored as, the corresponding phosphine boranes, from which they are easily deprotected, with stereocontrol, by a number of methods.[2c,d,10] The phosphine boranes are also interesting in their own right, with respect to both their metal complexation and polymer chemistry.[11,12] Herein, we report our discovery of an easy, convenient (one pot) and cheap method for the direct conversion, with or without stereocontrol, of phosphine oxide (or sulfide) to phosphine borane, by making use of readily available laboratory reagents. We believe that this is the first report of direct oxide to borane conversion.[12]

The first challenge in phosphine oxide reduction is the unreactivity of the phosphoryl system due to the high bond strength of the PO multiple bond.[13] With silane reagents this is overcome by formation of the strong SiO single bond[4d,g] whereas with hydride reagents,[2d] a strong alkylating agent can be used to form initially a pseudophosphonium species, which is then reduced by the hydride source. Sodium borohyride would be a first-choice hydride reagent because of its mild reactivity, ease of use and relatively low cost. But it requires a fairly reactive substrate and, indeed, is completely inert to phosphine oxide on its own.[2c] For some time, we have been studying chlorophosphonium salts (CPS)[14] because of their possible involvement in our dynamic resolution of *P*-stereogenic phosphines under asymmetric Appel conditions.[15,16] One of the methods we have found useful for CPS generation involves treatment of the corresponding phosphine oxide with oxalyl chloride.[17] Originally reported by Fukui and co-workers,[18] this method cleanly generates the corresponding chlorophosphonium chloride. It has been used recently to good effect both by Tanaka and co-workers[19] and notably by Denton and co-workers[20] in a catalytic version of the Appel conditions. One of our interests concerned the reactivity of the chlorophosphonium species towards hydride reduction[18b,19b,21] and we report now that addition of sodium borohydride acts as both hydride and borane source, giving phosphine borane directly (Scheme 1).

The methodology was applied to a variety of alkyl and aryl achiral and racemic phosphine oxides and sulfides, both tertiary and secondary, shown in Chart 1.† In each case, reaction with oxalyl chloride was followed by ^{31}P NMR and all the compounds showed rapid and clean conversion to a single species with a ^{31}P



Scheme 1. One-pot reduction of phosphine oxides using oxalyl chloride and $NaBH_4$

chemical shift, which, by analogy with the known triphenyl case[14] (64.4 ppm) we assign to the derived chlorophosphonium salt (CPS). The shifts are mostly in the ranges 57-65 ppm for triarylcases, 67-72 ppm for diarylmethyl cases rising to 90-100 ppm with greater alkyl substitution (ESI - Table A). Subsequent *in situ* treatment of the CPS with sodium borohydride in diglyme resulted in clean conversion to phosphine borane, all reactions at room temperature. Note also that the phosphine sulfides are converted *via* the same CPS.

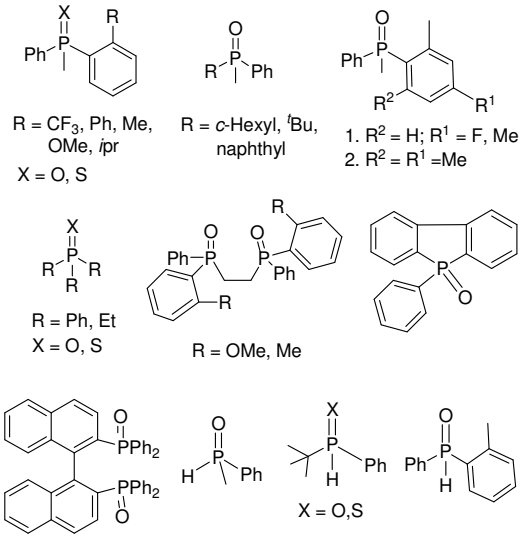
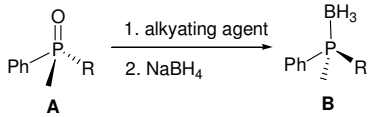


Chart 1. Oxides and sulfides converted according to Scheme 1

We also studied an enantiomerically enriched *P*-stereogenic case, (*S*)-methylphenyl*o*-tolylphosphine oxide (of 93% ee). Disappointingly, this gave racemic phosphine borane under a variety of reaction conditions.[22] It was our strong suspicion that this racemisation was induced by the presence of the chloride counter ion of the chlorophosphonium salt. Therefore we considered how we could generate a pseudophosphonium salt with a non-nucleophilic counter-ion, in order to stop any racemisation process. This caused us to re-consider alkylation of the PO bond,[23] in particular the work of Imamoto and co-workers.[2d] They had shown that stereospecific reduction could be effected by initial treatment at room temperature with methyl triflate, followed by LAH reduction at low temperature of the alkoxyphosphonium triflate that was formed. Since the sodium borohydride method had worked so well for us, we were encouraged to use it instead as the reductant and we were gratified to find that it worked in reasonable yield with the expected inversion and the same optical purity, both at low and ambient temperatures (Table 1, entries 1/2).

In searching for an alternative to methyl triflate, we settled on triethyloxonium tetrafluoroborate (Meerwein's salt), which had previously been used to convert phosphine oxides to alkoxyphosphonium salts.[24] We found that it could convert (*S*)-methylphenyl*o*-tolylphosphine oxide (of 93% ee) cleanly in DCM to the ethoxyphosphonium salt, as judged by ^{31}P NM R (δ 71.9 ppm). Subsequent treatment with sodium borohydride yielded, stereospecifically, the corresponding inverted phosphine borane, again in reasonable yield (entry 3). The methyl analogue behaved similarly (entry 4) as did several other enantioenriched phosphine oxides (entries 5-10).

Table 1. Stereospecific reduction/boronation[a] of optically active *P*-stereogenic phosphine oxides.



#	R	Alkyl.agent	Yield (%)[b]	% ee A (config)[c]	% ee B (config)[c]
1	*o*-tolyl[d,e]	MeOTf	62	93 (*S*)	93 (*S*)
2	*o*-tolyl[d]	MeOTf	73	93 (*S*)	93 (*S*)
3	*o*-tolyl	$[Et_3O]BF_4$	76	93 (*S*)	93 (*S*)
4	*o*-tolyl	$[Me_3O]BF_4$	71	93 (*S*)	93 (*S*)
5	*o*-anisyl	$[Et_3O]BF_4$	67	95 (*R*)	95 (*R*)
6	*o*-anisyl	$[Me_3O]BF_4$	71	95 (*R*)	95 (*R*)
7	*o*-biphenylyl	$[Et_3O]BF_4$	68	81 (*S*)	81 (*S*)
8	mesityl	$[Et_3O]BF_4$	67	44[f]	44[f,g]
9	*tert*-butyl	$[Et_3O]BF_4$	63	53 (*R*)	53 (*R*)
10	*tert*-butyl	$[Et_3O]BF_4$	68	46 (*S*)	46 (*S*)

[a] Unless otherwise specified the addition of alkylating agent (in DCM) and $NaBH_4$ (in diglyme) was carried at room temperature followed by refluxing; [b] isolated yield; [c] by CSP HPLC, configuration determined as described in SI; [d] in DME solvent [e] $NaBH_4$ was added at -78 °C; [f] configuration not assigned; [g] % ee measured by conversion to corresponding phosphine oxide.

In all of the experiments reported in Table 1, a small but noticeable amount of phosphine oxide with the same *ee* as the starting material was recovered after reduction was complete, accounting for the reduced yield of phosphine borane. This may result from hydrolysis of the alkoxyphosphonium salt by adventitious water, although it is surprising that this would occur with full retention of configuration. However the most significant point in this regard is that sodium borohydride, unlike LAH, does not react with this reformed phosphine oxide, so that there is no risk of its direct non-specific reduction, which sometimes leads to erosion of ee with LAH. We will report subsequently on the optimisation of this stereospecific reduction and on the mechanism of the borohydride reduction/boronation of the CPS for which both stepwise and concerted versions can be written.

In conclusion, we have found a convenient method for conversion of a wide range of tertiary and secondary, phosphine oxides and sulfides directly to phosphine borane in excellent yield. The method has significant advantages over the other common reduction methods (other hydrides and silanes): milder

conditions, easier to handle reagents and significantly expanded substrate scope. In addition, preliminary studies suggest that a similar methodology can be developed for stereospecific reduction of optically enriched *P*-stereogenic phosphine oxides. A significant advantage of the latter is that sodium borohydride will not reduce any of the oxide regenerated as side-product, which is not the case if, e.g. LAH is used. This holds out promise of being a mild and reliable stereospecific variant. We think therefore that together these two borohydride methods may prove to be the method of choice for this once recalcitrant reaction.

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† Electronic Supplementary Information (ESI) available: Full experimental procedure, and full characterization data for phosphine oxides, sulfides and boranes; ^{31}P NMR data for all CPS; NMR spectra and HPLC traces of phosphine boranes. See DOI: 10.1039/b000000x/

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