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 wide variety of all conceivable 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 favor is that, with care and with much process development, they can usually be made to stereospecifically reduce optically active phosphine oxides.$^{4,5,6}$ Both silane and hydride reagents are commonly used in the presence of various modifiers: silanes are usually used with added tertiary amine,$^{4,5}$ whereas hydrides may require initial treatment with strong alkylating agent$^{20}$ and both have been used in the presence sacrificial phosphine.$^{2,4,14}$

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 Gladi 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.$^{2,6,10}$ 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$^{4,5}$ whereas with hydride reagents,$^{2,4}$ a strong alkylating agent can be used to form initially a pseudophosphonium species, which is then reduced by the hydride source. Sodium borohydride 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.$^{22}$ 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$^{18,19b,21}$ 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.$^{1}$ 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 phosphate oxides using oxalyl chloride and NaBH₄

\[
\begin{array}{c}
\text{Oxid} \quad \text{alkylation with NaBH₄ in diglyme, r.t., 30 min} \\
\text{CPS} \\
\end{array}
\]

Scheme 1. Oxides and sulfides converted according to Scheme 1

Chart 1. Oxides and sulfides converted according to Scheme 1

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

Table 1. Stereospecific reduction/boration\(^a\) of optically active \(P\)-stereogenic phosphate oxides.

<table>
<thead>
<tr>
<th>#</th>
<th>R</th>
<th>Alkyl agent</th>
<th>Yield</th>
<th>% ee A</th>
<th>% ee B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>o-tolyl(^{1,2})</td>
<td>MeOTf</td>
<td>62</td>
<td>93 (S)</td>
<td>93 (S)</td>
</tr>
<tr>
<td>2</td>
<td>o-tolyl(^3)</td>
<td>MeOTf</td>
<td>73</td>
<td>93 (S)</td>
<td>93 (S)</td>
</tr>
<tr>
<td>3</td>
<td>o-tolyl</td>
<td>[Et₂O]BF₄</td>
<td>76</td>
<td>93 (S)</td>
<td>93 (S)</td>
</tr>
<tr>
<td>4</td>
<td>o-tolyl</td>
<td>[Et₂O]BF₄</td>
<td>71</td>
<td>93 (S)</td>
<td>93 (S)</td>
</tr>
<tr>
<td>5</td>
<td>o-anisyl</td>
<td>[Et₂O]BF₄</td>
<td>67</td>
<td>95 (R)</td>
<td>95 (R)</td>
</tr>
<tr>
<td>6</td>
<td>o-anisyl</td>
<td>[Me₂O]BF₄</td>
<td>71</td>
<td>95 (R)</td>
<td>95 (R)</td>
</tr>
<tr>
<td>7</td>
<td>o-biphenyl</td>
<td>[Et₂O]BF₄</td>
<td>68</td>
<td>81 (S)</td>
<td>81 (S)</td>
</tr>
<tr>
<td>8</td>
<td>mesityl</td>
<td>[Et₂O]BF₄</td>
<td>67</td>
<td>44(^f)</td>
<td>44(^f)</td>
</tr>
<tr>
<td>9</td>
<td>tert-butyl</td>
<td>[Et₂O]BF₄</td>
<td>63</td>
<td>53 (R)</td>
<td>53 (R)</td>
</tr>
<tr>
<td>10</td>
<td>tert-butyl</td>
<td>[Et₂O]BF₄</td>
<td>68</td>
<td>46 (S)</td>
<td>46 (S)</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise specified the addition of alkylating agent (in DCM) and NaBH₄ (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; \(^e\) NaBH₄ was added at -78 °C; \(^f\) configuration not assigned; \(^g\) ee measured by conversion to corresponding phosphate oxide.

In conclusion, we have found a convenient method for conversion of a wide range of tertiary and secondary, phosphate 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
funding this chemistry under Grant RFP/08/CHE1251. We are therefore that together these two borohydride methods may prove to be the method of choice for this once recalcitrant reaction.

We thank sincerely Science Foundation Ireland (SFI) for this journal is © The Royal Society of Chemistry [year].

† Electronic Supplementary Information (ESI) available: Full experimental procedure, and full characterization data for phosphine oxides, sulfides and boranes. DGG also thanks University College Dublin to be the method of choice for this once recalcitrant reaction. There it is not the case if, e.g. LAH is used. This holds out promise therefore that together these two borohydride methods may prove to be the method of choice for this once recalcitrant reaction.

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10 Another recent report of hydride reduction of phosphonate salts with viable leaching groups; K. M. Pietrusiewicz, K. Dzuba, M. Lubanska, 18th International Conference on Phosphorus Chemistry, Wroclaw, Poland, July 11–15, 2010 Abstract No S.01.08.


We will report shortly on our studies of this involvement.

We also found that these species could be generated with sulfuryl chloride, methanesulfonfonyl chloride or thionyl chloride but oxalyl chloride was more convenient on a laboratory scale. (See ESI). See ESI for details of reactions of enantiomerically enriched phosphate oxides with sodium borohydride after treatment with oxalyl chloride, sulfuryl chloride, thionyl chloride or methane sulfonyl chloride with different temperature and solvent systems. J. Am. Chem. Soc. 2007, 129, 9566.


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