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Cleavage of P=O in the Presence of P–N: Aminophosphine Oxide Reduction with In Situ Boronation of the P^{III} Product

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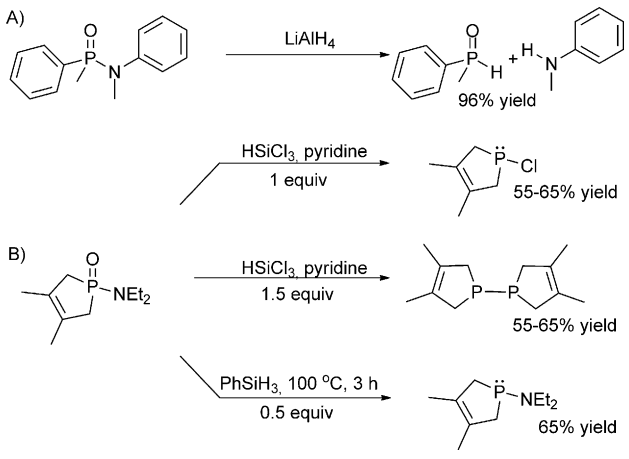
Abstract: In contrast to tertiary phosphine oxides, the deoxygenation of aminophosphine oxides is effectively impossible due to the need to break the immensely strong and inert P=O bond in the presence of a relatively weak and more reactive P–N bond. This long-standing problem in organophosphorus synthesis is solved by use of oxalyl chloride, which chemoselectively cleaves the P=O bond forming a chlorophosphonium salt, leaving the P–N bond(s) intact. Subsequent reduction of the chlorophosphonium salt with sodium borohydride forms the P^{III} aminophosphine borane adduct. This simple one-pot procedure was applied with good yields for a wide range of P–N-containing phosphoryl compounds. The borane product can be easily deprotected to produce the free P^{III} aminophosphine. Along with no observed P–N bond cleavage, the use of sodium borohydride also permits the presence of ester functional groups in the substrate. The availability of this methodology opens up previously unavailable synthetic options in organophosphorus chemistry, two of which are exemplified.

Keywords: aminophosphine oxide · chemoselectivity · in situ protection · main group elements · reduction

Introduction

The P=O bond is one of the strongest of those commonly encountered.[1] As such, the large amount of energy released during its formation can be of great benefit, acting as the driving force for many important transformations in organic chemistry; the Wittig, Appel, and Mitsunobu reactions being classic examples.[2] Conversely, this same bond strength leads to substantial difficulties in the deoxygenation of P=O-containing species; the conversion being highly desirable, permitting^ access to the, often very valuable, P^{III} analogue.[3,4] The challenge is twofold—how to avoid scission of other bonds to phosphorus and how to avoid reduction of other sensitive groups that may be present. Due to the inert nature of P–C bonds, options do exist for the reduction of most tertiary phosphine oxides,[5,6,7,8] which are successfully deoxygenated with both metal hydride[7] and silane reagents,[4d,8] in reasonable time and with good yields. However, the harsh conditions characteristic of these reagents renders them useless for deoxygenation of most other P=O-containing compounds such as phosphonates, phosphinates, phosphinamides, and phosphinamidates, which react with cleavage of the phosphorus–heteroatom (P–N and/or P–O) bond.[9,10] Similarly, phosphine oxides containing other reducible groups (e.g. esters, amides) are vulnerable to concomitant reduction, although excellent progress in this regard was achieved by Beller and co-workers.[8f,g]

For the case of aminophosphine oxides—those compounds containing at least one, direct phosphorus to nitrogen bond[11]—the difficulties are exemplified in Scheme 1.



Scheme 1. Previous attempts at aminophosphine oxide reduction.

As shown by Henson et al.,[9a] the P–N bond is generally cleaved on deoxygenation with $LiAlH_4$ (Scheme 1A), with only one reported exception for the case of a cyclic phosphineamide.[12] Reduction with silanes was studied by Quin and Szewczyk[10b] (Scheme 1B); using chlorosilane, they showed that, once again, loss of the P–N bond occurs but

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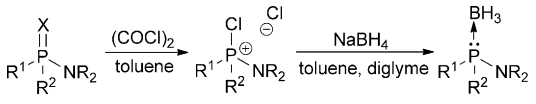
Table 1. Aminophosphine oxides reduced[a] with ^{31}P NMR data for substrates, CPS intermediates, and borane products.



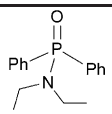
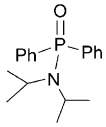
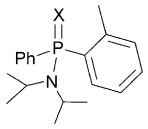
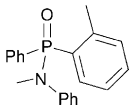
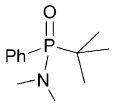
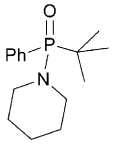
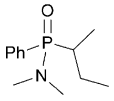
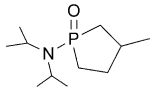
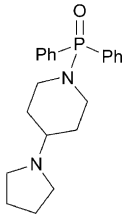
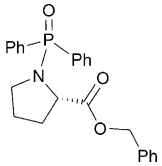
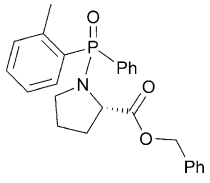
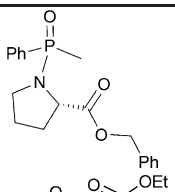
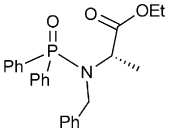
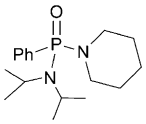
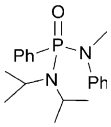
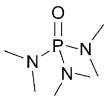
Entry	Substrate	Yield [%]	^{31}P NMR shifts (ppm) PX[b]	CPS[c]	PB[d]
1		86	30.4	70.8	67.5
2[e]		87	29.8	68.4	62.1
3[e]		86	X = O 34.1 X = S 61.1	69.8	64.2
4		84	32.3	64.5	68.1
5[e]		80	47.9	96.7	85.4
6[e]		83	44.8	91.9	83.0
7[f]		72	45.1 45.4	93.6	74.4
8[f]		90	68.3 67.8	105.2	79.8
9[g]		83	28.8	69.3	67.4
10		84	26.6	64.4	60.4
11[f]		88	30.3 30.5	66	59.6

Table 1. (Continued)

Entry	Substrate	Yield [%]	^{31}P NMR shifts (ppm) PX[b]	CPS[c]	PB[d]
12[f,h]		75	32.3 33.1	72.9	55.1
13		84	31.9	73.5	73.0
14[e]		85	26.2	58.4	85.1
15[e]		86	23.3	58.3	88.1
16[e]		82	24.2	53.9	103.4

[a] Procedure available in Experimental Section below or in the Supporting Information, isolated yields. [b] PX: phosphine oxide or sulfide. [c] CPS: shift assigned as chlorophosphonium salt, not isolated. [d] PB: phosphine borane, usually as broad quartets. [e] Initial conversion to CPS required heating to 70 °C. [f] Starting oxide was a mixture of two diastereomers. [g] Reduction product has second borane moiety bound to trialkyl amino group. [h] In the presence of Et_3N.

with formation of chlorophosphines or diphosphines, both of synthetic use in their own right.[13] More noteworthy was that, with phenylsilane, they did find cases, again mostly cyclic, of successful deoxygenation with retention of the P–N bond (Scheme 1B).[10b]

However the relatively moderate yields combined with the restricted scope, long reaction times, and the need for careful control of stoichiometry limit the usefulness of this method.

Results and Discussion

Herein, we present a new methodology for the reduction of aminophosphine oxides (Table 1). The reaction is a reliable, one-pot, high-yielding transformation; the final product being obtained as the aminophosphine borane adduct. The scope of the method is shown in Table 1, where it can be seen that it is applicable to both aryl and alkyl phosphinamides as well as examples of phosphonamide, phosphoramide, and thiophosphinamide.

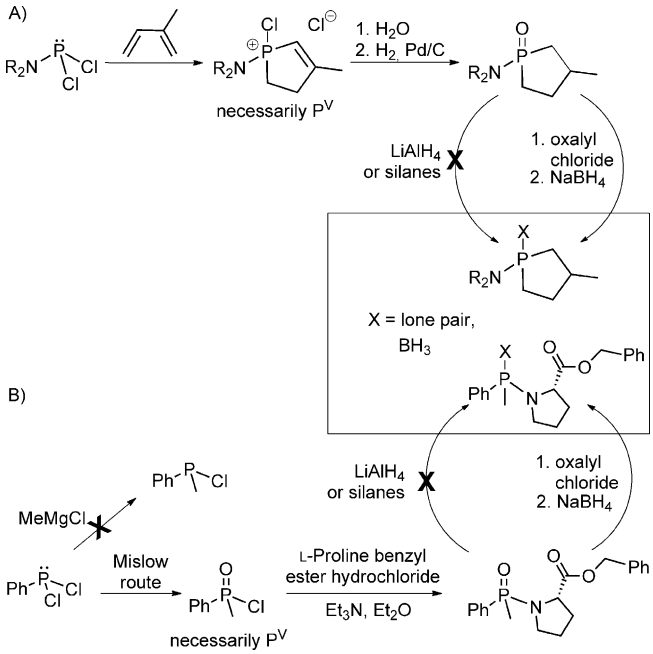
The success of the method depends on the generation in situ of an intermediate chlorophosphonium salt (CPS), which is then subsequently reduced/boronated with sodium borohydride. The conversion of tertiary phosphine oxide to

chlorophosphonium salt with oxalyl chloride was first described by Masaki and Fukui[14] some time ago and the transformation has been used to good effect by several groups.[4g,6,7h] We ourselves recently published a related reduction of secondary and tertiary phosphine oxides and sulfides.[15] However its use for phosphorus amides had never previously been considered. It occurred to us that, if it would work, the way would then be open to have chloride act as the leaving group while allowing nitrogen to remain, and we were gratified to find that the whole conversion can indeed be performed irrespective of the number of P–N bonds present, and that each bond is fully retained in the product. The irreversible formation of the chlorophosphonium salt[16] (CO_2 and CO by-products) allows it to act as a convenient intermediate, effectively breaking the thermodynamic profile of the reaction down from one very large step into two more energetically feasible steps. The specificity of the oxalyl chloride reaction combined with the lowering of energy required at any one time permits the observed chemoselectivity, and retention of the susceptible P–N bond. Also significant is that other reducible groups can be present such as esters (Table 1, entries 10–13).

The reaction procedure is relatively straightforward. For certain examples, particularly those featuring small substituents on the phosphorus center, reaction with oxalyl chloride occurs almost immediately, with obvious evolution of the gaseous by-products. In contrast, bulky and strongly electron-donating groups close to the site of reaction significantly reduce the rate of reactions; these compounds typically require heating for complete conversion to the chlorophosphonium salt. The chlorophosphonium salt can be observed and monitored by NMR spectroscopy, but is relatively unstable and so once formed should be promptly reduced/boronated by the addition of sodium borohydride in diglyme (2.1 equivalents).

It is also favorable that the final product is the phosphine borane adduct as these have long-been used for convenient handling and storage, owing to enhanced oxygen and moisture stability. The borane can be easily displaced, with stereocontrol, by a number of methods,[17] demonstrated for entries 6 and 11 (Table 1) using 1,4-diazabicyclo[2.2.2]octane (DABCO; 5 equiv, 80 °C) yielding the free aminophosphine with 100 % conversion (see the Supporting Information for procedure and characterization). In aminophosphines it is to be expected[18] that the phosphorus rather than the nitrogen is boronated and this was confirmed by X-ray crystallography in selected cases (Table 1, entries 9, 10, and 14). It is also notable that, where there is a free amino group, this was also boronated giving a bis-borane adduct (Table 1, entry 9), presumably due to the use of two equivalents of sodium borohydride.

As well as being a powerful general method for aminophosphine oxide reduction, this new reaction also lifts a significant limitation in organophosphorus synthesis methodology: until now it was not possible to construct a P^{III} aminophosphine by a route that involved attachment of the nitrogen substituent to a P^V center. Since many important organophosphorus methods necessarily generate P^V centers, this was a major restriction. Its lifting is illustrated by two of the examples in Table 1 (entries 8 and 12). McCormack cycloaddition[19] (Scheme 2 A) is a most useful method for forming



Scheme 2. Examples (highlighted) of aminophosphines and their related boranes difficult to synthesize by other means.

P-containing five-membered rings. However, the methodology always yields a P^V species, initially a chlorophosphonium salt, which, upon hydrolysis, becomes a phosphine oxide, therefore the aminophosphine product of entry 8 in Table 1 could previously have been made only with great difficulty. Another example concerns the phenylmethyl substitution motif, which is very difficult to construct in the P^{III} series due to uncontrollable multiple substitutions. For instance the aminophosphine with a ester-protected amino acid substituent in Scheme 2B (entry 12 in Table 1) cannot be made by sequential addition of the groups to a P^{III} precursor without either significant contamination of double addition products, if methyl Grignard is added first, or attack at the carbonyl if the organometallic is added second. The phenylmethyl motif is normally accessed from methylphenylphosphinic chloride, produced by the sequence of steps developed by Mislow and co-workers.[20] However, previously, this could not be used for aminophosphines because reduction would have removed the amino group. Again, this restriction is now lifted and this method can be applied for any non-bulky aminophosphines. Furthermore, one of the main advantages of being able to work with P^V compounds, the increased stability, early on in the synthesis, with subsequent reduction to a P^{III} product, if desired, is now a possibility for a myriad of novel compounds. Finally, since the amino substituent can act as a dummy group for other heteroatom substituents,[21] the synthesis of phosphorous, phosphonous,

and phosphinous acid derivatives is now, in principle, much easier.

Conclusion

In summary, we present an unprecedented high-yielding aminophosphine oxide deoxygenation, with no phosphorus–nitrogen bond cleavage. Furthermore the product is the protected borane adduct, allowing easy manipulation. The methodology breaks the transformation down into two steps, first breaking the very strong phosphoryl bond, replacing the oxygen with the better leaving group, chloride. This facilitates subsequent reduction with safe and cheap sodium borohydride, allowing the presence of, for example, ester functional groups. We believe that this new methodology opens up completely new synthetic strategies in organophosphorus chemistry because nitrogen (and oxygen by proxy) substituents can now be attached to P^V centers and be retained on conversion to P^{III}.

Experimental Section

General procedure for deoxygenation of aminophosphine oxides and sulfides: To a stirred solution of aminophosphine oxide or sulfide (1.0 mmol) in toluene (2 mL) was added oxalyl chloride (1.0 mmol) dissolved in toluene (2 mL) dropwise at room temperature under a nitrogen atmosphere. The formation of chlorophosphonium salt (CPS) at this point was normally evident by vigorous gas evolution and was confirmed by ^{31}P NMR spectroscopy of the reaction mixture. In some cases noted in the Supporting Information, where the gas evolution was less pronounced, the mixture had to be heated to 70 °C (approximate boiling point of oxalyl chloride) for one hour to effect complete conversion to CPS. Alternatively in those cases, the reaction could be left at room temperature overnight. After formation of CPS (typically 30 min), sodium borohydride (2.1 mmol) dissolved in diglyme (ca. 3 mL) was added dropwise to the reaction mixture and heated to 70 °C for one hour, after which ^{31}P NMR spectroscopy shows full completion of CPS to phosphine borane (as indicated by characteristic quartet splitting). The reaction mixture was washed with deionized water (2×5 mL) and the isolated organic layer was dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the toluene was removed in vacuo to give a colorless solution, which was eluted through a silica plug first with cyclohexane to remove the high boiling diglyme then with 50:50 cyclohexane/ethyl acetate to isolate the aminophosphine borane product. Solvent removal in vacuo yielded the pure aminophosphine borane.

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Synthetic Methods

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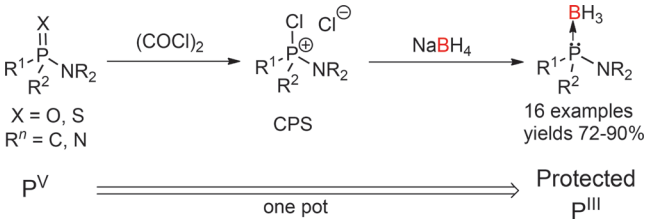
Cleavage of P=O in the Presence of P–N: Aminophosphine Oxide Reduction with In Situ Boronation of the P^{III} Product



To sever and protect: Aminophosphine oxides, with between one and three direct P–N bonds, can be reduced to the corresponding aminophosphine borane adduct in a one-pot reduction/boronation reaction, with high yield. This new transformation is achieved by initial conversion to the chlorophosphonium salt (CPS), using oxalyl chloride, followed by reduction, with sodium borohydride. Along with no observed P–N bond cleavage these mild conditions also allow the use of substrates featuring ester functional groups.

