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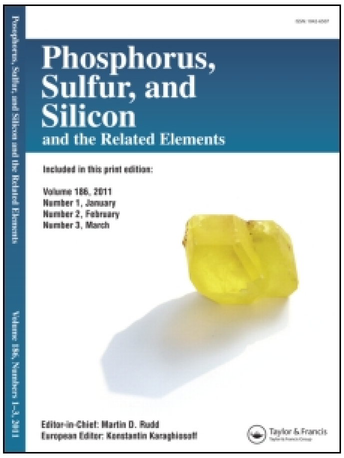

Phosphorus, Sulfur, and Silicon and the Related Elements

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To cite this Article Armstrong, David R. , Davies, Robert P. , Dunbar, Lorraine , Raithby, Paul R. , Snaith, Ronald and Wheatley, Andrew E. H.(1997) 'Lithjations of Phosphane Oxides', Phosphorus, Sulfur, and Silicon and the Related Elements, 124: 1, 51 — 62

To link to this Article: DOI: 10.1080/10426509708545610

URL: http://dx.doi.org/10.1080/10426509708545610

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Phosphorus, Sulfur, and Silicon, 1997, Vol. 124 & 125, pp. 51-62
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LITHIATIONS OF PHOSPHANE OXIDES

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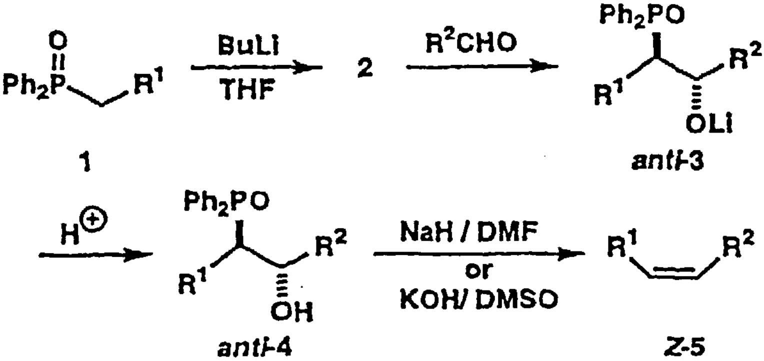
Two studies on lithiated phosphane oxides (Horner-Wittig reagents) are reported. In the first, attempted deprotonation of $Ph_2P(O)CH_3$ using the lithium amide $(Me_3Si)_2NLi$ leads merely to an adduct between the two species and suggests thereby an initiation step for many lithiation reactions. The mechanism and energetics of deprotonation have been studied further by *ab initio* MO calculations on the model system $H_2P(O)CH_3 + H_2NLi$. In a related study the phosphane oxide $Ph_2P(O)CH_2CHMeEt$ has been successfully lithiated in non-Lewis base media, affording a tetrameric $(LiO)_4$ cubane structure whose key feature is the presence of Li-C bonds.

Keywords: lithiations; phosphane oxides; X-ray structures

INTRODUCTION

The Wittig reaction, whereby aldehydes and ketones are converted to alkenes, was first described in 1953[1] and it remains a powerful tool for stereospecific carbon-carbon bond formation.[2] A key step in the reaction is generation of a phosphorus ylide by treatment of a phosphonium salt with a strong base. Modifications to the Wittig reaction have involved the introduction of phosphoryl-stabilised ylides, notably here ones derived from alkylphosphane oxides (the Horner-Wittig reaction).[3] A typical procedure is shown in Scheme 1. In this, an alkyl diphenylphosphane oxide **1**[4] is first lithiated in THF at -78°C to give **2**; the lithiating reagent used is commonly ^nBuLi, ^tBuLi or $^iPr_2NLi$(LDA). The lithium species is then reacted with aldehydes in a stereoselective manner to give, *via* **3**, largely *anti*-alcohols **4**. Purification and then stereospecific elimination of Ph_2PO^- leads finally to *Z*-alkenes **5**.



SCHEME 1

In this paper we describe two related studies [5] which concern the first step of the Horner-Wittig synthesis, namely the lithiation of **1** to give **2**. Firstly, we show that $Ph_2P(O)CH_3$ [**1**, R^1 = H] is not in fact lithiated by the lithium amide $(Me_3Si)_2NLi$ but rather merely forms a complex with it. Such a finding has implications for how lithiations/deprotonations are initiated. In the second study we report on the successful lithiation (using ^nBuLi) of another phosphane oxide, $Ph_2P(O)CH_2CHMeEt$ [**1**, R^1 = CHMeEt], and on the solid-state structure of the isolated lithiated derivative.

RESULTS AND DISCUSSION

Reaction of $Ph_2P(O)CH_3$ with $(Me_3Si)_2NLi$

Treatment of $Ph_2P(O)CH_3$ with $(Me_3Si)_2NLi$ (1:1 equivs.) in hexane/toluene afforded a pale yellow solution from which cubic crystals could be isolated (70% yield) after refrigeration. ^1H, ^{13}C NMR spectroscopy showed that deprotonation of the phosphane oxide's methyl group had not occurred, but rather that the two "reactants" had simply combined to give the adduct $[(Me_3Si)_2NLi \cdot O{=}P(CH_3)Ph_2]_n$, **6**. X-ray crystallography showed **6** to be dimeric (n=2) in the solid state (Fig. 1).

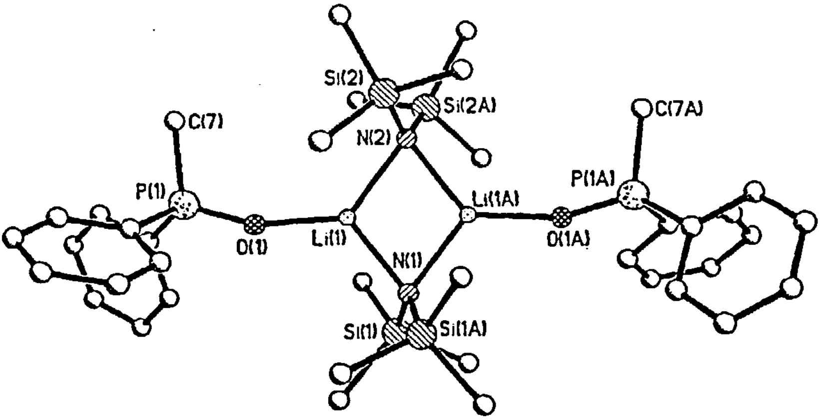


FIGURE 1 Solid-state structure of **6**.

The main structural features of **6** are the central N_2Li_2 ring (mean Li-N distance, 2.046Å) and the coordination of one intact phosphane oxide molecule to each lithium centre [Li-O, 1.878(7)Å]. The presence of these molecules is surprising, not least because **6** is isolated at room temperature and reagents such as ^nBuLi or LDA are, as noted above, known to lithiate $Ph_2P(O)CH_3$ at -78°C in THF (Scheme 1). The surprise is exacerbated by the result of heating a hexane/toluene solution of **6** at 80°C for four hours and then chilling to obtain crystals. These, **6'**, are simply a stereo-isomer of the first product, identical save that the phosphane oxide methyl groups, *cis* in **6** (Fig. 1), are now *trans* in **6'** (Fig. 2). Deprotonation has still been resisted.

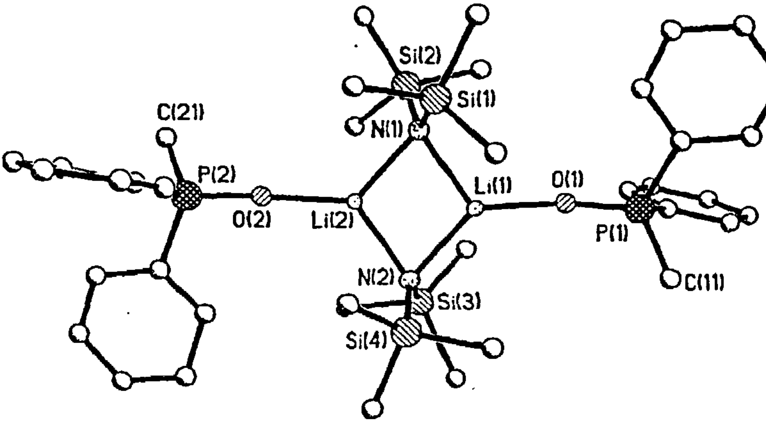


FIGURE 2 Solid-state structure of **6'**.

The isolation of **6/6'** has possible implications for the mechanisms of deprotonation reactions using metal-containing bases. It has been speculated upon that the likely initiation step will involve coordination of the organic precursor (when this contains suitable functionalities) to the metal centre of the base.[6] Prior to **6/6'**, the only solid-state structure relevant to such a proposed initiation step was the complex between $(Me_3Si)_2NLi$ and the (seemingly) enolisable ester $Me_2CHO(^tBu)C{=}O$.[7] There, the failure to deprotonate was attributed to the unfavourable position of the enol H atom in that, were it to be abstracted, it would not prove possible to delocalise the ensuing negative charge into the adjacent carbonyl π-orbitals. In the case of **6/6'** inspection of Fig. 1 and/or Fig.2 suggests a rather simpler, steric explanation for the blocking of deprotonation. Thus it is seen that the bulky Me_3Si groups shield the $N^{\delta-}$ amide centres and prevent close approach of these centres to the phosphane oxide methyl groups. This inhibition is illustrated further by a space-filling model of **6** (Fig. 3) and is quantified by the large Li-O-P (*ca* 160°) and O-P-C(H_3) [*ca* 115°] angles found in both **6** and **6'**.

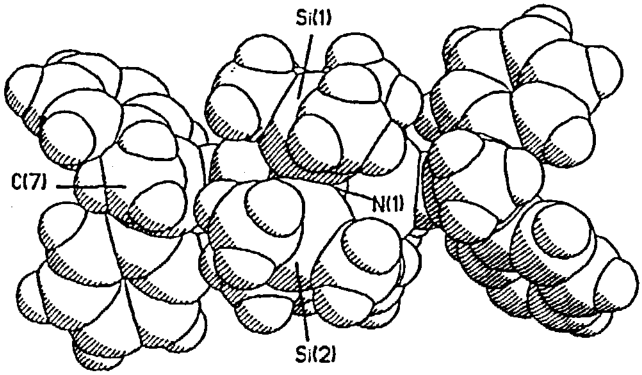


FIGURE 3 Space-filling model of **6**..

In order to probe further the mechanism of alkylphosphane oxide deprotonation and to gain insight into the energetics involved, we have examined the model system $H_2P(O)CH_3 + H_2NLi$ by *ab initio* MO calculations. These were carried out using the 6-31G basis set (plus, where relevant, a set of d orbitals on phosphorus[8]) by means of the program GAMESS.[9] All species were optimised freely, without imposed geometric constraints. Mirroring the (albeit dimeric) experimental adducts **6** and **6'**, it is found that formation of an initial (monomeric) complex between the two reactants is highly favoured; this complex $H_2P(CH_3)O{\cdot}LiNH_2$ [Fig.4(a)] is 32.3 kcal mol^{-1} more stable than the separate components, lending weight to the supposition that reactant complex formation may be a first step towards such deprotonation reactions. In this complex the C-H bond of the phosphane oxide is well separated from the NH_2 unit of the lithium amide [(C)H...N(H_2), 2.368Å] and there is no significant

C...Li interaction (distance, 3.383Å). Transition to the saddle point for proton transfer [Fig. 4(b)] involves an increase in energy of only 8.7 kcal mol^{-1}. In this transitional state, one methyl proton is midway between the C and N centres (1.376Å from both) and a Li-C interaction is more apparent (distance, 3.190Å). Such a change is brought about mainly by a decrease in the O-Li-N angle from 131.0° in the initial complex to 118.2° in the saddle point. This equates to the classical view of deprotonation, namely attack by an anionic species (here, H_2N^-) on a C-H bond; however, such a view oversimplifies the reaction mechanism by ignoring the initial complexation of the two reagents. The reaction is completed by proton transfer to give an ammonia complex of the lithiated phosphane oxide [Fig.4(c)]. This product is 16.5 kcal mol^{-1} more stable than the saddle point and so 7.8 kcal mol^{-1} more stable than the initial complex. Overall, the enthalpy of reaction from $H_2P(O)CH_3$ and H_2NLi to $H_2P(CH_2)OLi{\cdot}NH_3$ is 40.1 kcal mol^{-1}, 23.8 kcal mol^{-1} of which is the complexation energy of the NH_3 to the lithiated phosphane oxide.

The above calculational results suggest two reasons for the failure to observe deprotonation in the experimental system **6,6'**. The first, noted earlier, is the prevention of close approach of the $N^{\delta-}$ centre of $(Me_3Si)_2NLi$ to the CH_3. In the model system such approach, i.e., movement to the saddle point, requires merely 8.7 kcal mol^{-1}. This activation energy will be considerably higher when the groups on P and on N are other than H. The second possible reason concerns the fact that in the model system complexation of the product by the co-produced NH_3 contributes a significant amount to the overall reaction enthalpy. In the experimental system, deprotonation would afford $(Me_3Si)_2NH$, a large and poor complexant. Thus the failure of $(Me_3Si)_2NLi$ to lithiate $Ph_2P(O)CH_3$ could, in part, reflect a suppressed complexation energy.

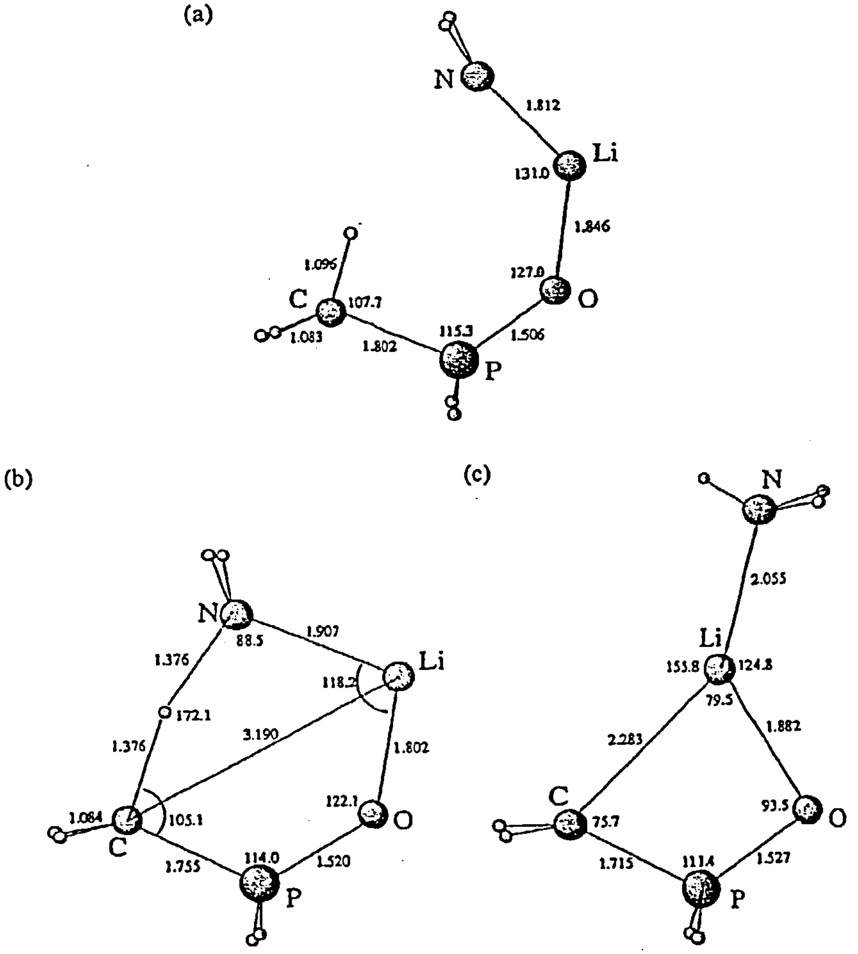


FIGURE 4 *Ab initio* optimised geometries (bond lengths in Å, angles in °) of (a) initial complex $H_2P(CH_3)O{\cdot}LiNH_2$, (b) saddle point for proton transfer, and (c) the final complex $H_2P(CH_2)OLi{\cdot}NH_3$.

Successful Lithiation of a Phosphane Oxide

Having failed (retrospectively, for good reasons) to lithiate

$Ph_2P(O)CH_3$ using $(Me_3Si)_2NLi$, we turned our attention to other phosphane oxides and to other lithiating reagents (notably ^nBuLi, which is known to effect such lithiations; Scheme 1). In fact, rather few solid-state structures of lithiated phosphane oxides and related species are known. Not one contains lithium to carbon bonding. For example, lithiations in THF of the precursors shown below (Fig. 5) afford dimeric complexes having central $(LiX)_2$ rings (X = O or S) with two THF ligands solvating each lithium centre and with near-planar (sp^2) carbanionic carbon centres which are well-displaced from the lithium centres (C...Li distances of 3.7Å or more).[10]

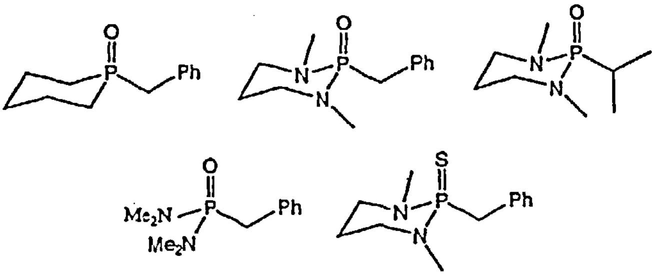


FIGURE 5 Phosphane oxide and related molecules which have been lithiated in THF to give solid-state dimers without Li...C contacts

In THF solutions of these lithiated species, NMR spectroscopic studies have shown that sp^2 carbanionic centres are retained. In marked contrast, however, similar solution studies on a series of lithiated alkylthiophosphoramides showed the presence of sp^3 hybridised carbanionic centres and Li-C contracts.[11] Clearly, the presence or otherwise of Li-C bonding will depend on a combination of the nature of the substituents on the phosphorus (especially the $-CHR^1R^2$ unit which is to be lithiated) and of the nature and number of Lewis base molecules which attach to the lithium centre. This is borne out in part by *ab initio* MO calculations (6-31G basis set plus a set of d orbitals on P) on $H_2P(O)CH_2Li$ and on its complexes $H_2P(O)CH_2Li{\cdot}xTHF$ (x = 1 or 2).[12] The uncomplexed species optimises as a four-membered ring with both Li-O (1.84Å) and Li-C (2.20Å) contacts. Attachment of one THF molecule affords a complexation energy of 26.3 kcal mol^{-1} [*cf* Fig. 4(c)]. The ring is retained although it expands in size; in particular the Li-O distance lengthens to 1.90Å and the Li-C one to 2.28Å. Complexation by a second THF molecule (complexation energy 14.0 kcal mol^{-1}) causes further expansion of the ring. The Li-O distance becomes 1.96Å, but the lengthening is more marked for the Li-C contact, now 2.45Å. Such a distance represents a rather weak Li-C bond. One can thus appreciate why such a bond might be absent altogether in experimental systems when the substituents on phosphorus and on the carbanionic carbon are other than H atoms.

Given the above findings we lithiated the phosphane oxide $Ph_2P(O)CH_2CHMeEt$ which has flat (Ph) groups and a sterically rather undemanding alkyl substituent. In order to further encourage the formation of a species with Li-C bonds and hence sp^3 carbanionic centres, the lithiation was carried out in non-Lewis base media. Hence ^nBuLi was added to a toluene solution of the phosphane oxide (1:1 equivs.) at -78°C. A yellow solution formed, from which a yellow solid precipitated at near room temperature. The solid was dissolved by addition of HMPA and warming, cooling then affording crystals of $[Ph_2P(O)CHLiCHMeEt]_n$, 7. This is tetrameric in the solid state. Most importantly, each unit of the tetramer contains a lithium-carbon bond and hence an sp^3, pyramidalised carbanionic centre (Fig. 6).

The structure of 7 is the first for an uncomplexed lithiated phosphane oxide or related species (phosphonamides etc; see Fig. 5).

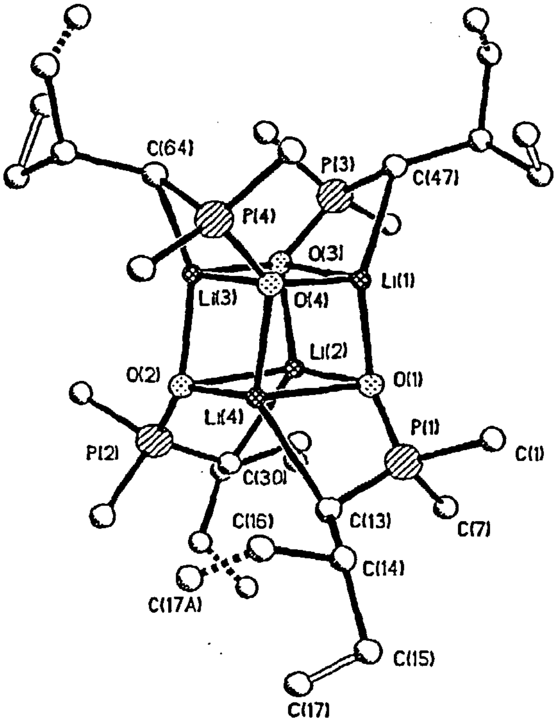


FIGURE 6 Solid-state structure of 7.

Its core consists of an Li_4O_4 cube formed by the stacking of two dimeric rings [Li(3)O(3)Li(1)O(4) and Li (2)O(2)Li(4)O(1)]. The carbanionic centre of each monomer unit contacts a lithium centre to give a four-membered O-P-C-Li chelate ring. Within these rings the Li-O distances average 2.27Å and the Li-C ones average 2.23Å, comparable with Li-C bonding distances within lithium alkyl structures, e.g., in $(^tBuLi)_4$, average 2.25Å.[13] It can also be noted that each unit contains two stereogenic centres, one present in the precursor and one generated by lithiation. Two of the new stereogenic centres [P<u>C</u>HRLi] in the tetramer are <u>R</u> (C13 and C30) and two are

S (C47 and C64). Unfortunately, however, it is impossible to decide which diastereoisomers are present because of disorder among the methyl and ethyl groups.

The Li-C contacts within **7** seem remarkably resilient. It has already been noted that **7** can be crystallised in the presence of HMPA, without incorporation of this powerful complexant (which would likely have led to displacement of C from Li). Further, the ^{13}C NMR spectrum of a solution of **7** in THF implies retention of C-Li bonds and so of sp^3 carbanionic centres. Thus the -*C*HLiCHMeEt resonance is found at δ36.78, hardly changed from that at δ36.92 for the -CH_2CHMeEt resonance in the precursor phosphane oxide. Such findings suggest that it may well be profitable to examine the stereochemical courses of Horner-Wittig reactions (Scheme 1) using toluene as the solvent or using pre-isolated (from toluene) lithiated phosphane oxides which are then dissolved in THF prior to addition of the carbonyl compound.

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