

Preliminary communication

Experimental and molecular orbital calculational study of the stereoselective Horner–Wittig reaction with phosphine oxides: control of stereoselectivity by lithium

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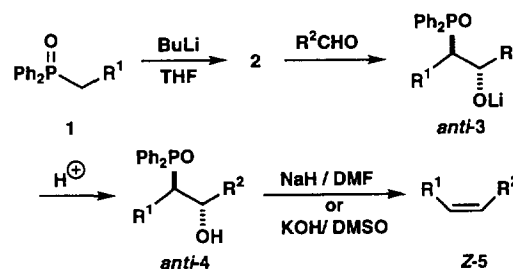
Abstract

Ab initio calculations have been used to determine the possible structure of lithium derivatives of phosphine oxides in THF: extension of these calculations to the docking of a carbonyl compound onto such a lithium derivative suggests an explanation for the anti selectivity of the Horner–Wittig reaction.

Keywords: Lithiated phosphine oxides; Ab initio calculations; Horner–Wittig reaction; Stereoselectivity

We have described [1,2] a version of the Horner–Wittig reaction in which lithium derivatives **2** of alkyl diphenylphosphine oxides **1** react with aldehydes in a stereoselective fashion to give predominantly anti alcohols **4** (Scheme 1). Purification by chromatography or crystallisation and stereospecific elimination of Ph_2PO^- with a sodium or potassium base completes a synthesis of *Z* alkenes **5**. In this paper, we provide an explanation for the observed anti selectivity: this is derived from some ab initio calculations on a model lithium derivative and on its reaction with $\text{CH}_2=\text{O}$, as well as from more extensive experience of the effects of different substituents R^1 and R^2 on the stereoselectivity of the reaction.

Three possible structures for lithiated phosphine oxides **2** are **6**, **7** and **8** (Scheme 2). Both structures **6** and **7** have an sp^3 hybridised carbon α to phosphorus, whilst structure **8** is sp^2 hybridised with no carbon–lithium contact whatsoever. Using X-ray crystallography and NMR methods, Denmark and coworkers [3] (for some ab initio calculations, see Ref. [4]) and Boche



Scheme 1.

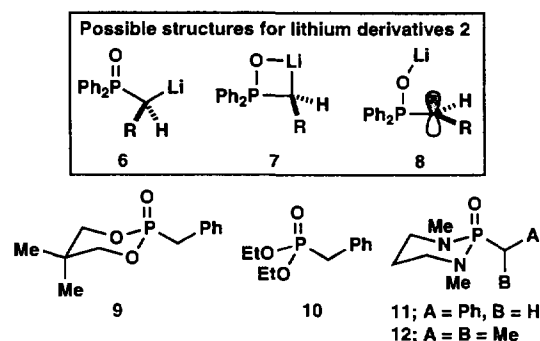
and coworkers [5] have shown that lithium derivatives of the closely related phosphonates **9** and **10** and phosphonamides **11** and **12** exist with sp^2 hybridised structures ² (equivalent to **8**). Unfortunately, we were unable to obtain crystals of lithiated phosphine oxides **2** of X-ray quality. Therefore, we decided to use ab initio calculations to predict their possible solution structures and to probe the mechanism and stereochemistry of their reactions with aldehydes.

Initial exploratory calculations were performed on $\text{H}_2\text{P}(\text{O})\text{Me}$ as a model system for phosphine oxides **1**

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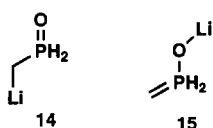
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² Lithiated **10**, **11** and **12** exist as dimers with a central $(\text{LiO})_2$ ring (see Refs. [3,4]67C:\JOM\6771\{5}).

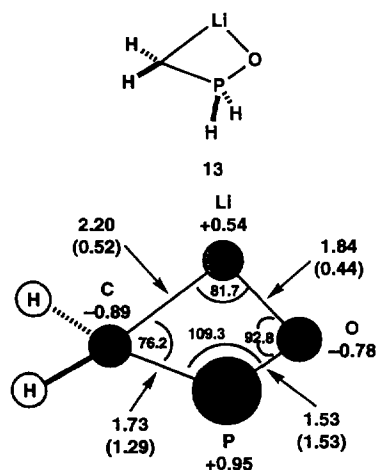
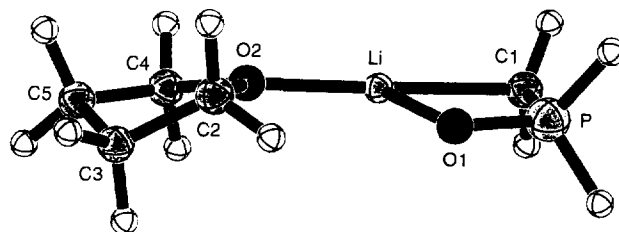


Scheme 2.

with the 6-31G basis set (plus a set of d orbitals on phosphorus [6]) at the SCF level by means of the GAMESS program [7]. Uncomplexed $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li}$ optimised to a planar four-membered ring structure **13** (Fig. 1) with lithium bonded to both the oxygen and carbon atoms (Li–O, 1.84; Li–C, 2.20 Å). Other possible structures, such as **14** and **15**, were not viable: structure **14** is 26.4 kcal mol⁻¹ less stable than **13**, whilst structure **15** moved to **13** on optimisation. Structure **13** clearly possesses features of the two structural extremes **14** and **15**, but it is still very polarised (charges: Li, +0.54; O, -0.78; C, -0.89; P, +0.95).



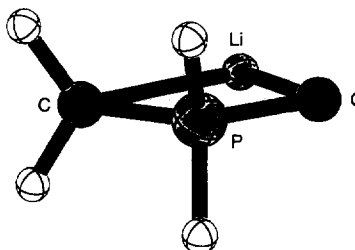
We then repeated the calculation on uncomplexed $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li}$ at the MP2 level [8] including the core electrons with the 6-31G* basis set. This was to ascertain what effect the inclusion of correlation energy

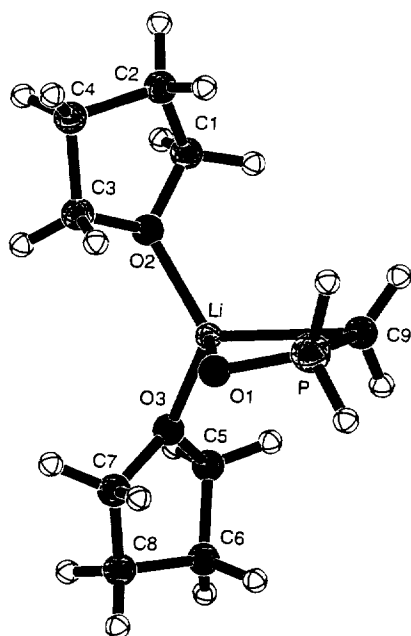
Fig. 1. Bond angles, atom charges, bond lengths and (bond indexes) in the calculated structure for uncomplexed $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li}$.Fig. 2. Mono-solvate $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li} \cdot \text{THF}$.

would have on our predicted structure. In fact, there was very little difference in the geometrical features (Li–O, 1.85; Li–C, 2.17; C–P, 1.73; P–O, 1.53 Å) and, as we shall see, the complexation energy at this higher level (26.9 kcal mol⁻¹ for one THF molecule and 19.3 kcal mol⁻¹ for $\text{CH}_2=\text{O}$) was essentially the same as that calculated at the lower level (see below). Therefore, the remainder of the calculations described in this paper have been performed with the 6-31G basis set (plus a set of d orbitals on phosphorus [6]) at the SCF level by means of the GAMESS program [7].

In the practical system (1 → 2) lithiation is carried out in THF; so, we optimised the mono-solvate $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li} \cdot \text{THF}$ to give, once again, the four-membered LiOPC ring structure (Fig. 2) which is expanded only slightly (Li–O 1.90; Li–C, 2.28 Å) from **13** while the charges are essentially the same (Li, +0.51; O, -0.78; C, -0.86; P, +0.94); there is a net transfer of only 0.05 e⁻ from THF to lithium. The complexation energy is a substantial 26.3 kcal mol⁻¹ and is reflected in a short Li–O(THF) bond (1.87 Å). This illustrates an important but little appreciated fact. Complexation of a lithiated organic molecule does very little to reduce the polarity of that molecule: the complex remains a highly polar (and reactive) species.

Introduction of a second molecule of THF gave similar results: di-solvate $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li} \cdot 2\text{THF}$ optimised to another four-membered ring structure (Fig. 3).

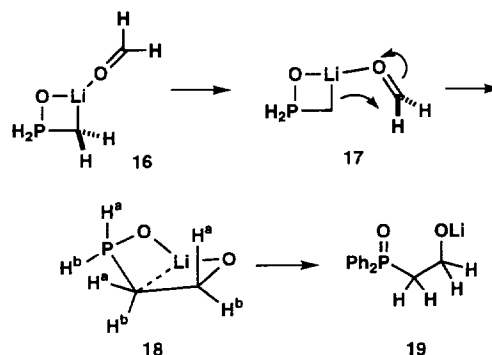


Fig. 3. Di-solvate $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li} \cdot 2\text{THF}$.

The LiOPC ring is enlarged even further (Li–O 1.96; Li–C, 2.45 Å), the two Li–O(THF) bonds are, as expected, longer (1.94 Å) and the complexation energy of the second molecule of THF is $14.0 \text{ kcal mol}^{-1}$. In other words, the total complexation energy going from the unsolvated complex $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li}$ to the di-solvated complex $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li} \cdot 2\text{THF}$ is 40 kcal mol^{-1} . These *ab initio* calculations suggest that structure **7** (probably with one or two complexed THF molecules [9]) is a possible solution structure for lithiated phosphine oxides **2**.³ Recent work on lithiated phosphazenes [12] and phosphonates [13] also suggests similar four-membered ring structures for these intermediates.

Next, we turned our attention to exploring the reaction between uncomplexed $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li}$ **13** and $\text{CH}_2=\text{O}$ (Scheme 3). Initially, complexation between the carbonyl oxygen and lithium occurs to give a ‘loose’ complex **16** in which the plane of the H–C–H unit of the aldehyde is coplanar with the plane of the LiOPC ring. The complexation energy is $19.2 \text{ kcal mol}^{-1}$ and the aldehyde is barely perturbed: it retains the π -bond (C=O 1.214 Å, bond index 2.07) and can rotate freely ($0.08 \text{ kcal mol}^{-1}$ required) about its bond to lithium. Initial complexes with C–C bonds were not viable: under optimisation they gave **16**.

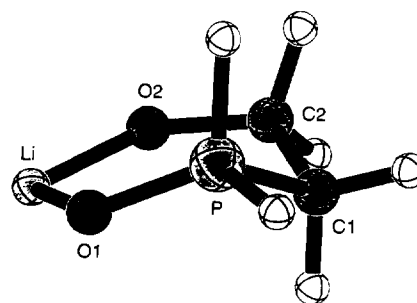
The aldehyde in **16** is then primed for C–C bond formation **17** whilst retaining the Li–O interaction:



Scheme 3.

charges in **16** are now CHO, -0.54 ; CHO, $+0.23$; PC, -0.87 . A free optimisation (planarity neither assumed nor fixed) gave the folded intermediate complex **18** (Fig. 4) which was found to be $33.3 \text{ kcal mol}^{-1}$ lower in energy than **16**. The key changes in bond lengths and bond indexes as the new C–C bond forms (**16** → **18**) are summarised in Table 1. They are all to be expected during the conversion of **16** to **19**. In intermediate **18** there is an ‘axial’ and ‘equatorial’ arrangement of P–H and C–H bonds, although these are perhaps better described as ‘inside’ (H^a) or ‘outside’ (H^b) the folded [2.2.0] hexane structure. The effect of adding a THF solvent molecule to the results depicted in Scheme 3 was also investigated. (The complexation of $\text{CH}_2=\text{O}$ to the mono-solvate $\text{H}_2\text{P}(\text{O})\text{CH}_2\text{Li} \cdot \text{THF}$ is $14.4 \text{ kcal mol}^{-1}$ and the four-membered LiOPC ring becomes so distorted that the Li–C bond length increases to 3.95 Å (with a concomitant shortening of the P–C bond (1.68 Å) and the Li–O(P) bond (1.76 Å)). In this case, the Li–C bond has broken and the organolithium is truly primed for reaction. The main effect of an additional coordinating THF solvent molecule on intermediate **18** was to increase the Li–O(P) bond length to 2.04 Å. This suggests that this will be the bond to break in the next stage of the reaction. Coordination of a THF solvent molecule to intermediates **16** and **18** did not alter the relative energies of these species.)

We believe that the anti selectivity observed in the real version of the reaction can be rationalised using the

Fig. 4. Calculated structure for **18**.

³ Theoretical calculations suggested a similar four-membered LiOSC ring structure for lithiated sulphones, but X-ray crystallography subsequently demonstrated that this was not the case (see Refs. [10,11]).

Table 1

Calculated changes in bond length and bond index as new C–C bond is formed (16 → 18)

Bond	'Loose' complex 16		Intermediate complex 18		Changes
	Bond length (Å)	Bond index	Bond length (Å)	Bond index	
C–C	3.990	0	1.559	1.01	new C–C bond is formed
C–O	1.214	2.07	1.388	1.16	C=O lengthens and weakens
Li–C	2.281	0.47	3.212	0.03	Li–C bond is broken
P–C	1.714	1.32	1.804	1.03	P–C loses double bond character
P–O	1.527	1.54	1.508	1.63	strengthens slightly
Li–O(C)	1.890	0.36	1.706	0.60	strengthens considerably
Li–O(P)	1.882	0.42	1.869	0.39	weakens slightly

results obtained from the *ab initio* calculations. Our preferred interpretation is exemplified by the sequence **20** → **21** → *anti*-**4** (Scheme 4). As the new C–C bond is formed, **20**, the substituents R¹ and R² will prefer the less sterically demanding outside positions in the intermediate complex **21**. The aldehyde substituent R² prefers the outside position, both because it occupies the outside position and to avoid severe 1,3-diaxial interactions with one of the phenyl rings of the diphenylphosphinoyl group. The substituents R¹ and R² then appear on the same side of the intermediate lithium alkoxide **3** as it is first formed and this leads to *anti*-**4**.

This new mechanistic description of the Horner–Wittig addition reaction has now been used to interpret the stereoselectivities observed with different substituents in both the phosphine oxide (R¹) and aldehyde (R²) side chains. The experimental facts about the reaction may be summarised as follows.

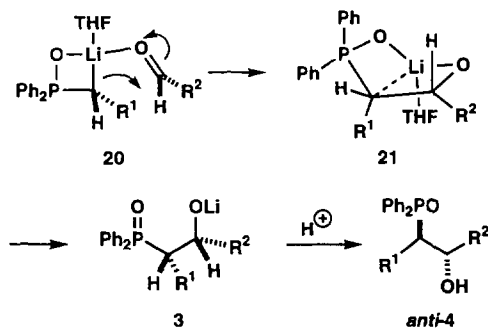
(1) Lithium is necessary, since other metals (e.g. sodium and potassium) lead to direct formation of the alkene; THF is the best solvent since there are solubility problems in Et₂O and the stereoselectivity is lost in hydrocarbon solvents [1].

(2) Reduced stereoselectivity is observed if the phosphine oxide side chain (R¹) contains heteroatom substituents (RO or R₂N) which are capable of coordinating to the lithium in the lithiated phosphine oxides **2**. Examples include methyl and silyl ethers, lithium alkoxides, ketals, lithiated amines and amides at various positions along the side chain [14]. Chelating groups in

the R¹ side chain could bond to the lithium atom during bond formation **20**. This chelation across the bottom face of **21** could make R² move into the inside position to avoid the R¹ side chain.

(3) Chelating groups on the aldehyde side chain (R²) do not, in general, lead to reduced stereoselectivity. Presumably, the chelating group in R² is too far away from the lithium atom during bond formation **20** to have an effect.

(4) Branching in the phosphine oxide side chain (R¹) leads to severely reduced stereoselectivity. A more thorough investigation of this effect is presented in Table 2 and can be rationalised by considering intermediate **21**. If R¹ is large, especially branched at the first carbon atom, the *gauche* interactions between it and P–Ph on the one side and R² on the other may erode the stereoselectivity as R¹ would prefer to end up in the inside position in **21**. An alternative explanation can also account for the reduced stereoselectivity: if R¹ is large then it may prefer to remain in the outside position; however, the *gauche* interactions between it and R² may lead to R² occupying the inside position in **21**. (5) Independently, Kaufmann and Schwartze [15] have reported that replacing the phenyl rings in the diphenylphosphinoyl group Ph₂PO with larger (Ar = *o*-tolyl) or chelating (Ar = *o*-anisyl) substituents on the phosphinoyl group Ar₂PO lead to increased *anti* selectivity in the formation of **4**. Both of these results can be rationalised using intermediate **21**: a chelating *o*-MeOC₆H₄ group on the phosphorus atom might com-



Scheme 4.

Table 2

Diastereoselectivity in the Horner–Wittig reaction as a function of steric hindrance

Aldehyde R ²	Ratio <i>anti</i> : <i>syn</i> in product alcohol 4 (yield, %)		
	R ¹ = Me	R ¹ = ⁱ Pr	R ¹ = cyclohexyl
Ph	85:15 (94) ^a	67:33 (79)	80:20 (80)
2-MeOC ₆ H ₄	81:19 (91)	—	65:35 (91)
4-MeOC ₆ H ₄	87:13 (92)	68:32 (87)	75:25 (99)
Et	—	50:50 (89)	46:54 (91)
Me	75:25 (93)	—	50:50 (87)

^a R¹ = ⁿPr in this case.

pete with P=O as a coordinating group for Li, whilst larger aryl groups on phosphorus will in any case increase the preference of R², and to a lesser extent R¹, for the outside position.

In summary, the ab initio calculations described in this paper have shed new light on the possible structure of lithiated phosphine oxides in THF and on the factors that are responsible for highly stereoselective Horner–Wittig addition reactions. Details of the formation of the lithium derivative have started to emerge from the crystal structure [16] of the Ph₂P(Me)O · LiN(SiMe₃)₂ complex, which may be regarded as a model for the deprotonation reaction observed with *n*-butyllithium, and which shows a definite O–Li bond.

Acknowledgements

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References

- [1] A.D. Buss and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, (1985) 2307.
- [2] (a) A.D. Buss, N. Greeves, R. Mason and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, (1987) 2569. (b) J. Clayden and S. Warren, *Angew. Chem. Int. Ed. Engl.*, 35 (1996) 241.
- [3] (a) S.E. Denmark and R.L. Dorow, *J. Am. Chem. Soc.*, 112 (1990) 864. (b) S.E. Denmark, P.C. Miller and S.R. Wilson, *J. Am. Chem. Soc.*, 113 (1991) 1468.
- [4] C.J. Cramer, S.E. Denmark, P.C. Miller, R.L. Dorow, K.A. Swiss and S.R. Wilson, *J. Am. Chem. Soc.*, 116 (1994) 2437. C.J. Cramer and S.E. Denmark, *J. Org. Chem.*, 55 (1990) 1806.
- [5] W. Zarges, M. Marsch, K. Hams, F. Hailer, G. Frenking, and G. Boche, *Chem. Ber.*, 124 (1991) 861.
- [6] (a) W.J. Hehre, R. Ditchfield and J.A. Pople, *J. Chem. Phys.*, 56 (1972) 2257. (b) P.C. Hariharan and J.A. Pople, *Theor. Chim. Acta*, 28 (1973) 213. (c) J.D. Dill and J.A. Pople, *J. Chem. Phys.*, 62 (1975) 2921.
- [7] (a) M. Dupuis, D. Spangler and J.J. Wendoloski, *GAMESS NRCC Software Catalogue, Program No. 2GOI*, Vol. 1, 1980. (b) M.F. Guest, J. Kendrick and S.A. Pope, *GAMESS Documentation*, Daresbury Laboratory, Warrington, UK, 1983. (c) M.F. Guest, P. Fantucci, R.J. Harrison, J. Kendrick, J.H. van Lenthe, K. Schoeffel and P. Sherwood, *GAMESS-UK Daresbury*, CFS Ltd., 1993.
- [8] C. Moller and M.S. Plesset, *Phys. Rev.*, 46 (1934) 618.
- [9] (a) D. Seebach, *Angew. Chem. Int. Ed. Engl.*, 27 (1988) 1624. (b) R.E. Mulvey, *Chem. Soc. Rev.*, 20 (1991) 167. (c) K. Gregory, P. von R. Schleyer and R. Snaith, *Adv. Inorg. Chem.*, 37 (1991) 47.
- [10] S. Wolfe, L.A. La John and D.F. Weaver, *Tetrahedron Lett.*, 25 (1984) 2863.
- [11] G. Boche, *Angew. Chem. Int. Ed. Engl.*, 28 (1989) 277.
- [12] F. López-Ortiz, E. Peláez-Arango, B. Tejerina, E. Pérez-Carreño and S. García-Granda, *J. Am. Chem. Soc.*, 117 (1995) 9972.
- [13] R. Koch and E. Anders, *J. Org. Chem.*, 60 (1995) 5861.
- [14] (a) C. Earnshaw, C.J. Wallis and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, (1979) 3099. (b) P.M. Ayrey, M.A. Bolton, A.D. Buss, N. Greeves, D. Levin, P. Wallace and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, (1992) 3407. (c) C.A. Cornish and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, (1985) 1585. (d) D. Cavalla, W.B. Cruse and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, (1987) 1883.
- [15] T. Kaufmann and P. Schwartze, *Chem. Ber.*, 119 (1986) 2150.
- [16] D.R. Armstrong, M.G. Davidson, R.P. Davies, H.J. Mitchell, R.M. Oakley, P.R. Raithby, R. Snaith and S. Warren, *Angew. Chem. Int. Ed. Engl.*, 35 (1996) 1942.