The lithiation and acyl transfer reactions of phosphine oxides, sulfides and boranes in the synthesis of cyclopropanes†‡

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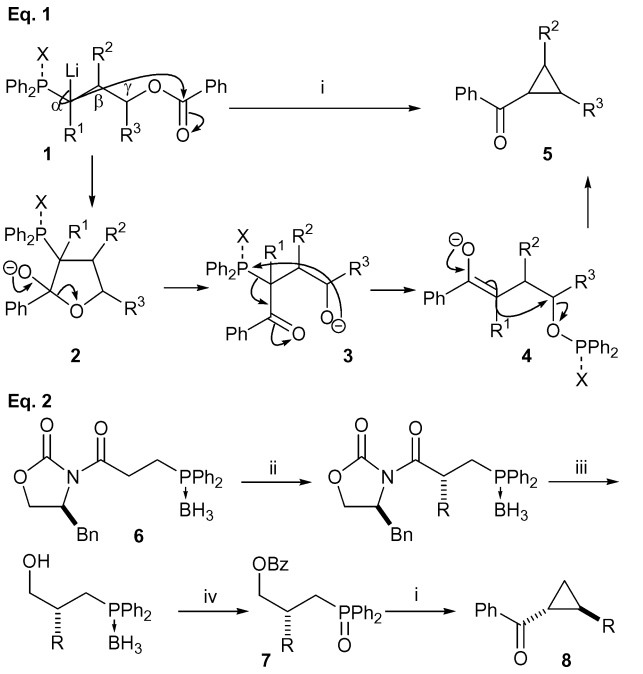
Phosphine oxides are lithiated much faster than phosphine sulfides and phosphine boranes. Phosphine sulfides are in turn lithiated much more readily than phosphine boranes. It was possible to trap a phosphine sulfide THF in one case which upon treatment with *t*-BuOK gave cyclopropane, showing that phosphine sulfides readily undergo both phosphinoyl transfer and cyclopropane ring closure just like their phosphine oxide counterparts. The obtained data show that phosphine oxides are easily lithiated and undergo phosphoryl transfer much more readily and faster than phosphine sulfides and phosphine boranes. The observations suggest that it would be possible to perform reactions involving phosphine oxides in the presence of phosphine boranes or phosphine sulfides, potentially allowing regioselective alkylation of phosphine oxides in the presence of phosphine boranes or phosphine sulfides.

We have previously reported the asymmetric diphenylphosphine oxide mediated cyclopropanation cascade reaction incorporating both acyl and phosphoryl transfers as key steps (Scheme 1, eqn (1), X = O) starting from α,γ-[1,2] and β,γ- and γ-substituted[3,4] diphenylphosphine oxides. More recently we reported the asymmetric cyclopropanation cascade reaction starting from β-substituted diphenylphosphine oxides **7** (Eq. 2) using an Evans oxazolidinone auxiliary to achieve asymmetric induction.[5] During the investigation of β-substituted cyclopropanation substrates we discovered that the diphenylphosphinoyl substituent was not compatible with the conditions used for the asymmetric alkylation (Step ii) resulting in loss of the auxiliary.[5] We successfully circumvented this problem by using diphenylphosphine borane **6** that could be converted to phosphine oxide **7** at a later stage (Step iv).

It was a natural extension of this work to investigate if phosphine boranes (**1**, X = BH_3, Scheme 1) could be converted to cyclopropanes **8** directly, eliminating the need for prior conversion to the phosphine oxide. Moreover, we decided to investigate the properties of diphenylphosphine sulfides (**1**, X = S) in this context. The key requirements for the cyclopropanation cascade reaction to occur are: i) the substrate is lithiated by a base (*e.g.* LDA), ii) the lithiated species **1** undergoes acyl transfer, **2**, iii) the phosphine derivative **3** is sufficiently electrophilic to be attacked by an internal oxygen nucleophile, and iv) enolate **4** can cyclise to give cyclopropane **5**.



Scheme 1 X = O, BH_3 or S. *Reagents and conditions*: i) LDA, THF, −78 to 0 °C; ii) LHMDS, THF, RX, −78 °C to room temp.; iii) $NaBH_4$, LiCl, EtOH; iv) a. DABCO, PhMe, 40 °C, b. H_2O_2, c. PhCOCl, Et_3N, DMAP, CH_2Cl_2.

Lithiated phosphine sulfides have been employed in reactions with aldehydes,[6] ketones[7] and carbonates,[8] suggesting that an intramolecular acyl transfer is plausible. Moreover, Imamoto has used LDA as the base in an intermolecular acyl transfer reaction between methyl diphenylphosphine borane **10** and ethyl benzoate.[9] Because phosphine boranes and sulfides are not expected to chelate lithium as well as phosphine oxides, this may be reflected in a lower or even a reverse diastereoselectivity in the formation of the 5-membered hemi-ketal **2**. With phosphine oxides the final cyclisation step is highly selective for the *trans*-cyclopropane product as this minimises unfavourable steric interactions in the

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† We dedicate this paper to Professor A. B. Holmes in recognition of Andy's distinguished contributions to organic chemistry and many years working together at Cambridge.

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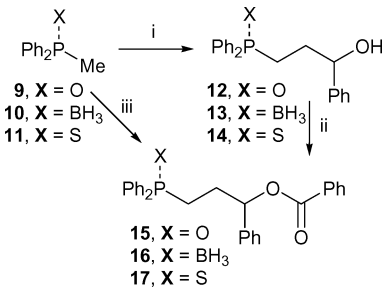
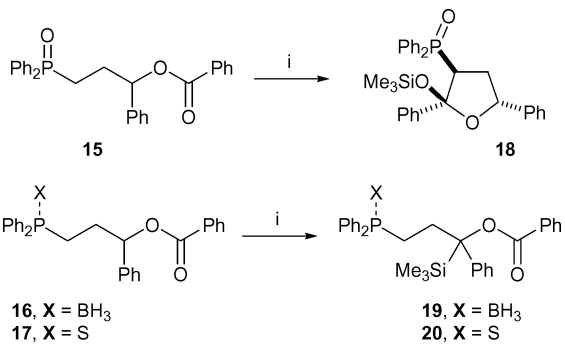
transition state. Hence, we expect to observe the same selectivity for the *trans*-cyclopropane product with the similarly bulky phosphine boranes and sulfides.

To best be able to monitor the reaction, we decided to study the acyl and phosphoryl transfers separately. To this end we would use Hutton's method of trapping the tetrahedral intermediate **2** (Scheme 1), as the corresponding trimethylsilyl ether.[10] For our initial investigation of the acyl transfer reaction we decided to use γ-substituted substrates **15** to **17** (Scheme 2). All three substrates were easily accessible by opening styrene oxide with lithiated phosphines **9** to **11** followed by benzoylation of alcohols **12** to **14** by a stepwise or a one-pot route.



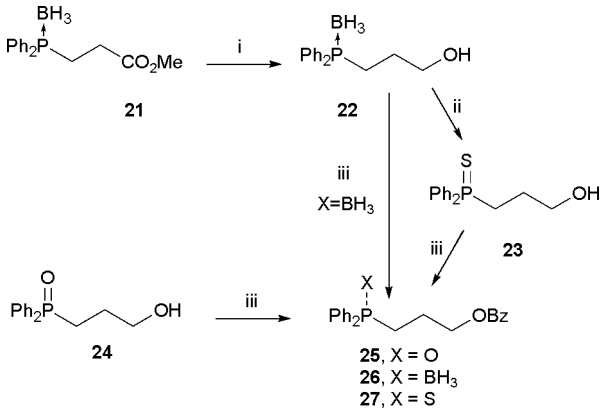
Scheme 2 Compounds **10** and **11** were prepared from diphenylmethylphosphine by mixing with BH_3·THF or elemental sulfur respectively. *Reagents and conditions*: i) *n*-BuLi, then styrene oxide, THF, 0 °C to room temp. **12**, 65%; **13**, 81%; **14**, 61%; ii) PhCOCl, DMAP, Et_3N, CH_2Cl_2. **15**, 86%; **16**, 71%; **17**, 92%; iii) a. *n*-BuLi, then styrene oxide, THF, 0 °C to room temp., b. PhCOCl. **15**, 91%; **16**, 81%; **17**, 64%.

Treatment of phosphine oxide **15** with LDA and chlorotrimethylsilane, under the conventional cyclopropanation conditions,[11] gave the expected THF product **18** in good yield (Scheme 3). However, using the same conditions both phosphine borane **16** and phosphine sulfide **17** failed to give any THF product. The *C*-silylated esters **19** and **20** were isolated as significant components in both cases. Moreover, small amounts of free alcohols **13** and **14** and the corresponding *O*-silylated compounds, were identified by ^{1}H NMR. This suggests that γ-deprotonation is competitive with α-deprotonation for compounds **16** and **17** and that phosphine boranes and sulfides are deprotonated much more slowly at the α-position when compared to phosphine oxides. In order to prevent γ-deprotonation we decided to remove the anion-stabilising phenyl γ-substituent and use a non-substituted carbon chain. Hence γ-benzoyloxy



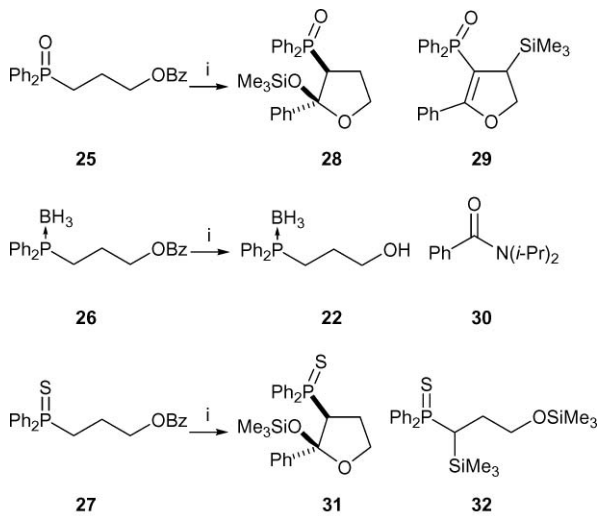
Scheme 3 *Reagents and conditions*: i) LDA, THF, TMSCl, –78 to 0 °C. **18**, 83%; **19**, 27%; **20**, 26%.

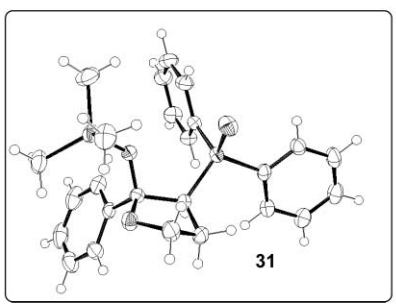
phosphines **25** to **27** were prepared (Scheme 4). Phosphine derivatives **25** and **26** were synthesised using conventional methods. Phosphine sulfide **27** was prepared in one-pot by a modification of Pellon's method[12] in the presence of elemental sulfur.



Scheme 4 *Reagents and conditions*: i) $LiBH_4$, ether, 0 °C, 99%; ii) DABCO, sulfur, toluene, 40 °C, 64%; iii) *n*-BuLi, THF, PhCOCl, 0 °C. **25**, 76%; **26**, 83%; **27**, 83%.

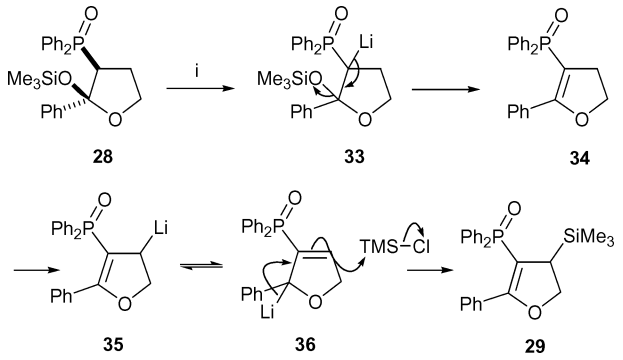
As expected, treatment of phosphine oxide **25** with LDA in the presence of chlorotrimethylsilane gave THF **28** (Scheme 5). However, a significant amount of dihydrofuran **29** was also isolated. Dihydrofuran **29** is probably the result of lithiation of the desired THF product **28**, followed by elimination to give





Scheme 5 *Reagents and conditions*: i) LDA, THF, TMSCl, –78 to 0 °C. **28**, 37%; **29**, 19%; **22**, 83%; **31**, 34%; **32**, 10%.

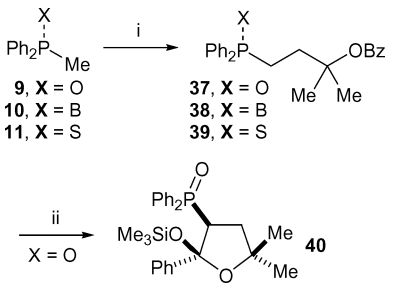
dihydrofuran **34**, followed by further deprotonation to give **35** and quenching with chlorotrimethylsilane (Scheme 6).



Scheme 6 *Reagents and conditions*: i) LDA, THF, TMSCl, −78 to 0 °C.

Phosphine borane **26** failed to give any THF product. The major products in this case were alcohol **22** and *N*,*N*-diisopropylbenzamide formed by nucleophilic cleavage of the carboxylic ester by LDA. The corresponding reaction with phosphine sulfide **27** did give the desired THF **31**, as well as the bis-silylated phosphine sulfide **32** and alcohol **23**. THF **31** was obtained as a single diastereoisomer and the stereochemistry was confirmed by X-ray crystallography (Scheme 5). Just as observed for phosphine oxides, the phosphorus-containing group lies *syn* to the silyl ether group, suggesting an interaction between the phosphine substituent and the *O*-coordinated lithium atom.[10]

Although γ-deprotonation is no longer a competing reaction, the absence of γ-substituents has made the carboxylic ester more susceptible to cleavage by LDA. The cleavage was only observed for phosphine borane **26** and phosphine sulfide **27**, presumably because lithiation at the α-position is much slower than for the corresponding phosphine oxide **25**, and the rate of ester cleavage becomes significant. We reasoned that double substitution at the γ-position (**37** to **39**, Scheme 7) would prevent γ-deprotonation and inhibit ester cleavage, encouraging the formation of THF products. The three cyclisation substrates were prepared by alkylating phosphines **9** to **11** with 2,2-dimethyloxirane followed by benzoylation in one pot. On treatment with LDA and chlorotrimethylsilane, phosphine oxide **37** underwent clean conversion to THF **40**. However, under the same conditions phosphine borane **38** gave only starting material. In the case of phosphine sulfide **39**, a trace of the desired THF was detected by ^{1}H NMR of the crude reaction mixture but the remainder was starting material. Evidently ester

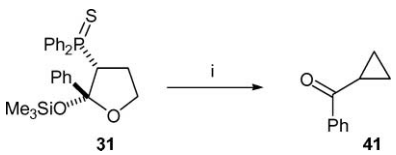


Scheme 7 *Reagents and conditions*: i) a. *n*-BuLi, then 2,2-dimethyloxirane, THF, 0 °C to room temp.; b. PhCOCl, DMAP, Et_3N, CH_2Cl_2. **37**, 76%; **38**, 75%; **39**, 84%; ii) LDA, THF, TMSCl, −78 to 0 °C, 55%.

cleavage and γ-deprotonation are hindered by the *gem*-dimethyl substituents but so too is α-deprotonation.

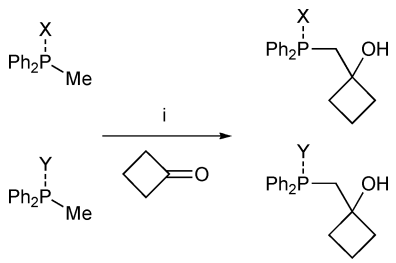
Whereas the above experiments demonstrate that acyl transfer is possible, if slow, for phosphine sulfides, phosphine boranes failed to yield any THF product. It appears that the success of the intermolecular acyl transfer reaction of phosphine boranes developed by Imamoto[9] is an anomaly. In the case of the substrate which most closely resembles our compounds, ethyl benzoate, the yield was rather low, possibly reflecting similar difficulties as are found for our substrates. That the reaction goes at all may be attributed to the proton being removed from a primary alkyl carbon so that the rate of deprotonation is competitive with nucleophilic attack of LDA on the electrophile; the substitution of an alkyl group for an α-hydrogen atom has been sufficient to inhibit metalation in less acidic phosphines.[13] It is telling that Imamoto obtains a better yield when dimethyl carbonate is used since the rate of attack of LDA on this electrophile will be reduced with respect to that on the ester while the rate of deprotonation remains constant.

Given that the unsubstituted phosphine sulfide **27** had undergone ring-closure to give THF **31**, a sample was treated with potassium *tert*-butoxide as with the corresponding phosphine oxides[11] to give cyclopropane **41** in good yield (Scheme 8). Phosphine sulfides might be useful in a more general synthesis of cyclopropanes where phosphine oxides are known to fail due to Lewis basicity.[5]



Scheme 8 *Reagents and conditions*: i) *t*-BuOK, *t*-BuOH, 35 °C, 77%.

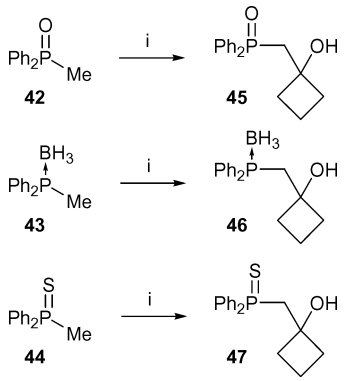
The relative rates of lithiation of phosphine oxide, boranes and sulfides were examined in more detail. Initially, we lithiated mixtures of two of the three phosphine derivatives with LDA in the presence of cyclobutanone as an internal trapping agent (Scheme 9).[14] Cyclobutanones enolise very slowly and we envisaged employing this method to study the relative rates of lithiation *via* the relative ratio of the addition products. By keeping the level of LDA sufficiently low, the reaction kinetics could be approximated to pseudo-first-order in base.



Scheme 9 X is not equal to Y. X or Y = O, BH_3, S. *Reagents and conditions*: i) LDA, THF, −78 to 0 °C.

Ratios of products would be monitored by NMR of crude reaction mixtures. To allow accurate determination of alkylation ratios, authentic samples of all three cyclobutanone addition products **45**

to **47** were required (Scheme 10). These were easily accessible *via* lithiation with LDA and alkylation with cyclobutanone.

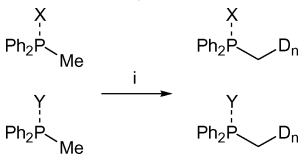


Scheme 10 *Reagents and conditions*: i) LDA, THF, then cyclobutanone, −78 °C. **45**, 67%; **46**, 37%; **47**, 66%.

Finally, mixtures of the three combinations of two of diphenylmethylphosphines **42** to **44** (X ≠ Y, Scheme 9) were prepared and treated with 0.1 equivalents of LDA in the presence of cyclobutanone. However, to our surprise only the phosphine oxide gave the expected addition product **45**. The sulfide and boranes adducts **46** and **47** were not formed, even in the reaction without the phosphine oxide. Seemingly, deprotonation of phosphine boranes and phosphine sulfides is slower than formation of the enolate of cyclobutanone.

Next, an alternative method of measuring the relative rates of lithiation, by treating the three combinations of phosphines **42** to **44** with *n*-butyllithium followed by a MeOD quench, was tested (Table 1). If equilibration of the lithiated derivatives were fast, the absence of an internal quench would mean that the method could not be used to measure relative deprotonation rates. Still, it would provide valuable information on ratios at equilibrium. In order to assess which ratio was being measured by the method, two different experiments were carried out. In one experiment the mixture was quenched with MeOD at −78 °C after 30 min and in the other, the lithiated species were allowed to equilibrate at 0 °C for 18 h followed by quenching with MeOD. The ratios of the derivatives were identical (Table 1), implying either that the kinetic and thermodynamic ratios are identical or that thermodynamic equilibration is rapid.

Table 1 *Reagents and conditions*: i) a. *n*-BuLi, THF. b. MeOD. $n = 1–3$



Starting mixture		Amount of each compound deuterated (%)[a]		
X	Y	**42**	**43**	**44**
42	**43**	45 (93)	<1 (<1)	—
42	**44**	95 (>99)	—	<1 (<1)
43	**44**	—	<1 (<1)	88 (78)

[a] Initial numbers refer to experiment with quenching at −78 °C after 30 min. Numbers in brackets refer to ratios obtained in equilibration experiment (0 °C for 18 h) before deuteration. Determined by ^{1}H NMR.

As before, the level of phosphine oxide product was considerably higher than those of both the phosphine borane and the phosphine sulfide. The experiment also clearly showed that phosphine sulfides are more acidic than phosphine boranes, mirroring the acyl transfer experiments above (Scheme 5).

The success in the formation of acyl transfer products from the series of benzoylated phosphine derivatives is reflected in the lithiation competition experiments, *i.e.* phosphine oxides lithiate faster than the sulfides, which in turn lithiate faster than the boranes. This experimental trend in rates of lithiation was also investigated by DFT calculations at the B3LYP/6-31G(d) level[15–20] using PC-GAMESS.[21] Initially, two sets of reaction pathways were calculated. One set of structures involves a lithium amide base, and the other an alkyl lithium, to represent the two sets of experiments.

The lithium-amide-containing calculations were based on the X-ray crystal structure of the stable complex[22] **48** (Fig. 1). This structure, derived from lithium bis(trimethylsilyl)amide (LHMDS) and diphenylmethylphosphine oxide, does not react to give a lithiated phosphine oxide. LHMDS does not lithiate simple phosphine oxides at synthetically useful rates. Lithium dialkylamides are more reactive however, and in the calculations $LiNMe_2$ is used as a model for LDA, and dimethyl ether as a model for THF.[23] In addition, trimethylphosphine derivatives **49–51** (Scheme 11) are used to represent diphenylmethylphosphine derivatives **42–44** (Scheme 10). Both kinetic measurements and calculations indicate that LDA can react as a monomer[23,24] or a dimer,[25,26] often with coordination of the substrate to one of the lithium atoms through a Lewis-basic atom such as oxygen. Structure energy minimisations were performed for phosphine oxide **49**, sulfide **50** and borane **51**. Lithiation transition structures **55–57** were then found (with one imaginary vibration), based on the structure of complex **48** but including only one phosphine and a dimethyl ether as a THF substitute. Ground states (**52–54** and **58–60**) on either side of the lithiation transition state were found by initial IRC calculation and minimisation. Pre-lithiation structures **52–54** are similar to complex **48**, whereas post-lithiation structures **58–60** involve carbon–lithium bonds, as observed in the X-ray structures of lithiated phosphine oxides.[27]

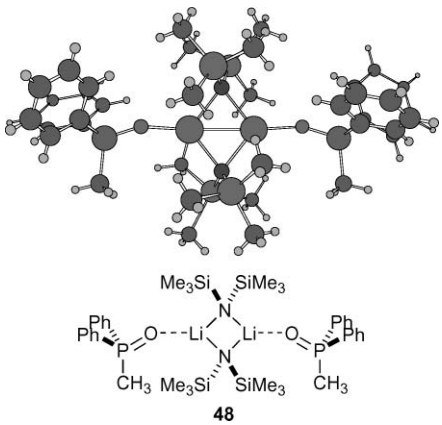
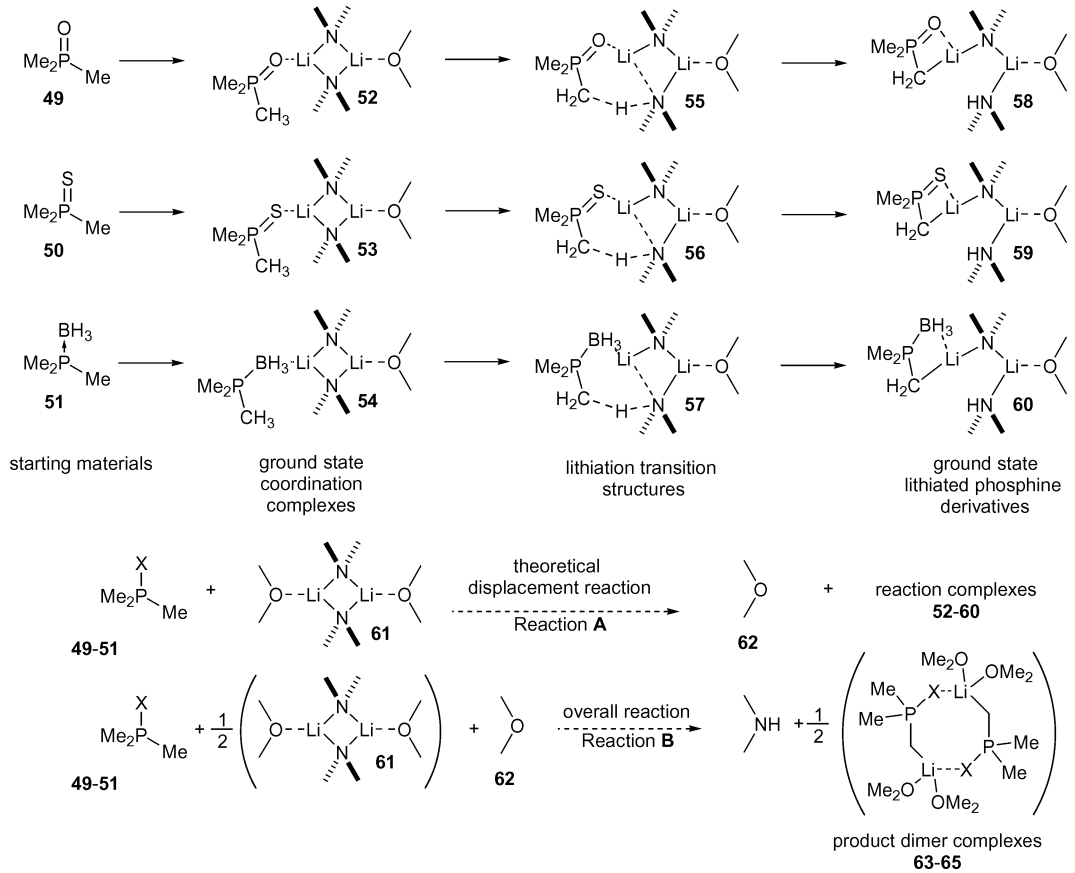


Fig. 1

The energies of these starting materials and complexes can be compared relative to dimethyl ether **62** and its complex **61** (Scheme 11). For each phosphine reaction complex (both ground states and transition state), theoretical reaction energies were



Scheme 11

calculated for the displacement of dimethyl ether **62** from complex **61**. Overall, this process results in a relative energy scale so that each reaction complex **52–60** can be compared to its own starting material **49–51**. Table 2 shows the relative energies (after ZPE correction) for the initial complexes, the lithiation transition states, and the product complexes. Zero-point energies are calculated using unscaled vibrational frequencies.

The results show that the phosphine oxide pre-lithiation complex **52** is more stable (by 41 kJ mol^{-1}) than the related sulfide **53**, which in turn is more stable (by 5 kJ mol^{-1}) than the borane **54**. This relative stability is reflected in the transition state energies (**55** is more stable than **56**, which is more stable than **57**), and the products **58–60**. While the initial lithiations to give complexes **58–60** are rather endothermic, these structures can rearrange to give the less unfavourable lithiated dimers **63–65** and regenerate half of a lithium amide dimer **61** and dimethyl amine. The oxide dimer is a thermodynamically favoured product, but the sulfide and borane dimers are slightly unfavoured. In reality these lithiations do happen as demonstrated above (*e.g.* Scheme 10) and by others,[6–9] but it may be that the most stable of the many possible product solution aggregates and solvates have not been modelled. The reaction of the boranes and sulfides are however sluggish in comparison with the oxides, even though the reactions are predicted to occur by comparing the pK_a of a secondary amine (*ca.* 44 in DMSO)[28] with that of a phosphine oxide (*ca.* 31 in DMSO) or sulfide (*ca.* 30 in DMSO).[29]

The transition state energies (relative to uncomplexed starting materials) are consistent with the experimentally observed

Table 2

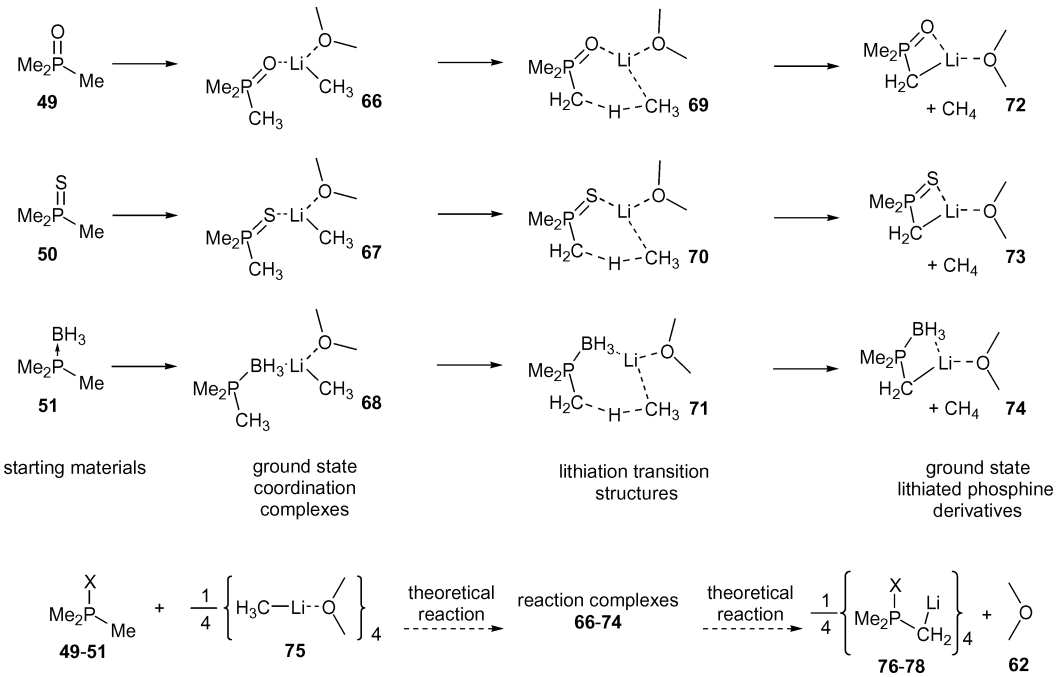
	Initial complex ground states		Lithiation transition states		Lithiated product ground states		Lithiated product dimers	
X	Structure	Relative energy[a] / kJ mol^{-1}	Structure	Relative energy[a] / kJ mol^{-1}	Structure	Relative energy[a] / kJ mol^{-1}	Structure	Relative energy[b] / kJ mol^{-1}
O	**52**	–24.7	**55**	+35.8	**58**	+19.4	**63**	–32.6
S	**53**	+16.7	**56**	+74.4	**59**	+41.4	**64**	+11.1
BH_3	**54**	+22.2	**57**	+88.6	**60**	+57.7	**65**	+22.7

[a] Energies (after ZPE correction) are calculated for the reaction **A** in Scheme 11 to make each complex (and dimethyl ether **62**) from the respective starting material (**49–51**) and complex **61**. [b] Energies (after ZPE correction) are calculated for the reaction **B** in Scheme 11 to make half of each complex (**63–65**) (and dimethyl amine) from the respective starting material (**49–51**), half of dimer complex **61** and an additional free dimethyl ether **62**.

Table 3

X	Initial complex ground states		Lithiation transition states		Lithiated product ground states		Lithiated product tetramers	
	Structure	Relative energy[a] / kJ mol^{-1}	Structure	Relative energy[a] / kJ mol^{-1}	Structure	Relative energy[a] / kJ mol^{-1}	Structure	Relative energy[a] / kJ mol^{-1}
O	**66**	+2.1	**69**	+48.0	**72**	−56.8[b]	**76**	−115.9[c]
S	**67**	+38.5	**70**	+81.5	**73**	−41.2[b]	**77**	−55.8[c]
BH_3	**68**	+49.6	**71**	+99.0	**74**	−19.5[b]	**78**	−25.4[c]

[a] Energies (after ZPE correction) are calculated for the reaction in Scheme 12 to make each complex from the respective starting material (**49–51**) and a quarter of complex **75**. [b] Energy of methane is included. [c] Energies of methane and dimethyl ether **62** are included.



Scheme 12

lithiation of phosphine oxides being much faster than for the related sulfides and boranes. However, if the transition states are compared to the respective pre-lithiation complexes the activation energies do not follow the previous pattern, and the phosphine oxide should lithiate slower than the sulfide (**52** to **55** +61 kJ mol^{-1}, **53** to **56** +58 kJ mol^{-1}, **54** to **57** +67 kJ mol^{-1}). These comparisons imply that the total activation energy from uncomplexed phosphine derivative (**49–51**) must be considered when rationalising the observed rates. In turn this implies that the complexes **53** and **54** are not heavily populated (even if complex **52** is heavily populated) and that the majority of the phosphine derivatives **50** and **51** are uncomplexed in the bulk of the reaction.

A similar set of calculations was performed to model the lithiations with butyllithium (Scheme 12). In this case CH_3–Li and trimethylphosphine derivatives were used as substitutes. Unlike for other lithiation systems using alkyllithiums and where experiment and calculation often point to the reaction of alkyllithium monomers[30–34] or dimers,[35] little is known about the stoichiometry of pre-reaction complexes of phosphine oxides and alkyllithiums. For simplicity a one-to-one model complex was chosen, with a single chelating solvent molecule. The energies of the complexes **66–71** are, as above, derived from the theoretical reaction of each starting material (**49–51**) with dimethyl ether–methyllithium tetramer[36] complex **75**. The energy of the by-product methane is included in the energies shown for complexes **72–74** (Table 3). As above the lithiated phosphine derivatives can aggregate to give for example tetramers[27] **76–78**, but in this case the increased basicity of methyllithium is quite enough to ensure complete lithiation without this additional driving force. The solvated dimers **63–65** are more stable, per phosphorus, than the tetramers **76–78** and two unsolvated ethers **62**, and these solvated dimers can of course be the reaction product with either base.

For complexes **66–74** the calculated energies show the same trends as those involving the lithium amide dimers above. The phosphine oxide forms the most stable complex with the alkyllithium, and the energetically favourable interaction results in the lithiation transition states and product energies also being more stable. In each case the sulfide is less stable and the borane the least stable. Again it is interesting to note that the activation energy from pre-lithiation complex to transition state is lower for the sulfide than the oxide (**66** to **69** +46 kJ mol^{-1}, **67** to **70** +43 kJ mol^{-1}, **68** to **71** +50 kJ mol^{-1}). This reduced rearrangement energy may result

Table 4

X	Uncoordinated ground states: Structure	Uncoordinated ground states: Relative energy[a] / kJ mol^{-1}	Coordinated ground states: Structure	Coordinated ground states: Relative energy[a] / kJ mol^{-1}
O	**79**	0	**82**	−120.6
S	**80**	−4.5	**83**	−104.6
BH_3	**81**	+1.4	**84**	−82.7

[a] Energies are all relative to the energy of formation of complex **79** from oxide **49**.

from a reduced build-up of strain in the transition state of the sulfide due to a longer P–S bond length, but it is known that the thio-carbonyl compounds can be more acidic than their oxygen counterparts.[37]

A final set of calculations highlights how significant the coordination of lithium in the three types of phosphines changes the overall stability of the alkyllithium products (Fig. 2). In each case the energy (relative to the respective starting material **49–51**) of the simple unsolvated alkyllithium was calculated for two conformations. The two conformations are ground-state structures involving either close contact of the lithium to the oxygen, sulfur or borane, or no close contact in an *anti*-arrangement around the phosphorus–carbon bond. Table 4 shows that the energies of lithiation to give the uncoordinated compounds **79–81** are similar. However once the C–P bond is rotated and the lithium coordinates to the oxygen, sulfur or borane (**82–84**), the oxide is significantly more stable than the sulfide, which is in turn more stable than the borane. These results are similar to those calculated above, and again emphasise the large contribution that the oxygen–lithium interaction makes to the chemistry of phosphine oxides.[5]

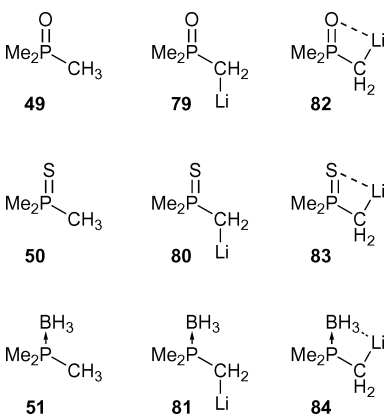


Fig. 2

In conclusion, we have demonstrated that phosphine oxides are lithiated much faster than phosphine sulfides and phosphine boranes, and that phosphine oxides are significantly more useful in the synthesis of cyclopropanes. Phosphine sulfides are in turn lithiated much more readily than phosphine boranes, but we only achieved the synthesis of one phosphine sulfide derived cyclopropane. This result does however show that phosphine sulfides readily undergo phosphinoyl transfer and that diphenylthiophosphinate is an efficient leaving group in a cyclopropane ring closure. Evidently a reliable synthesis of cyclopropanes, using current Warren group methodology with different phosphine derivatives, requires preparation *via* the phosphine oxide and interconversion of derivatives as a necessary step. These observations do suggest that it would be possible to perform reactions involving phosphine oxides in the presence of a phosphine borane or a phosphine sulfide. This could potentially find applications in regioselective alkylation of phosphine oxides in the presence of phosphine boranes or phosphine sulfides, for example in the Horner–Wittig olefination,[38] the phosphine oxide mediated cyclopropanation cascade reaction[11,39] or the synthesis of non-symmetric chiral bis-phosphine ligands for metal catalysis.[40]

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