

Preliminary communication

Cyclobutanone as an electrophile for lithiated phosphine oxides:  
'internal quench' conditions

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Abstract

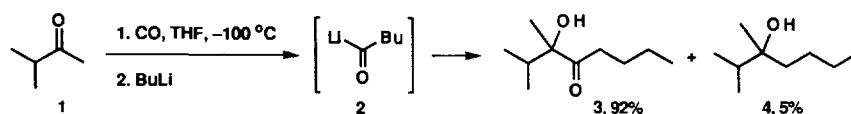
Cyclobutanone reacts more rapidly with lithiated phosphine oxides than with LDA and can be used under 'internal quench' conditions to investigate the stability and stereochemical integrity of some lithiated phosphine oxides. The results are used in diastereomerically controlled additions to other ketones.

Keywords: Phosphorus; Lithium; Silicon; Kinetic trap; Stereochemistry

1. Introduction

In 1974 Stork et al. [1] reported that capturing an LDA-derived kinetic lithium enolate rapidly with a reactive aldehyde (Stork made a most uncharacteristic mistake in this paper in calling benzaldehyde a *nucleophile*) prevented equilibration of the regioisomers of the enolate. In 1984 Corey and Gross [2] proposed an 'internal quench' in which the lithium enolate was formed with LDA in the presence of Me<sub>3</sub>SiCl as electrophile. The lifetime of the lithium enolate is very short under these conditions. This procedure has since been widely adopted for C–Li as well as O–Li compounds [3], and particularly by Cox and Simpkins [4] in asymmetric reactions with chiral versions of LDA. Lipshutz et al. [5] have recently shown that LDA does in fact react with Me<sub>3</sub>SiCl, but more slowly than the LDA forms lithium enolates.

By 1982 Seyferth and Weinstein [6] had already used an internal quench with Me<sub>3</sub>SiCl to trap RCOLi formed by RLi addition to carbon monoxide. Only when Me<sub>3</sub>SiCl was added before the BuLi was a good yield of RCO · SiMe<sub>3</sub> obtained. In 1983 Seyferth et al. [7] and Seebach and Weber [8] independently made a much more surprising observation: benzaldehyde could be used as an internal quench at –100 °C for RCOLi and for enolates derived from amino acids. Seyferth et al. [7] even used enolisable ketones successfully as trapping agents for organolithium compounds under internal quench conditions. Butyl lithium, CO and the ketone are all present in solution together, and yet good yields of adducts (3) from intermediate (2) and the carbonyl compound (1) are formed with only small amounts of the product (4) from BuLi acting as a nucleophile towards the ketone (1), and evidently without lithium enolate formation.



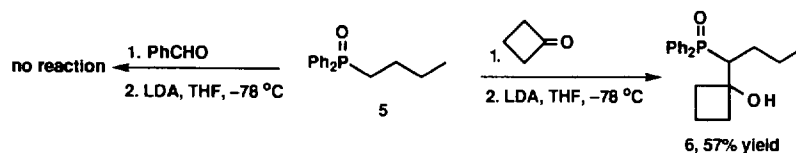
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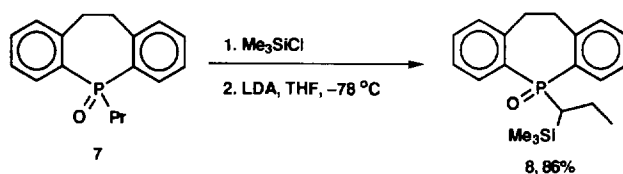
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## 2. A carbonyl compound as an electrophile for internal quench conditions

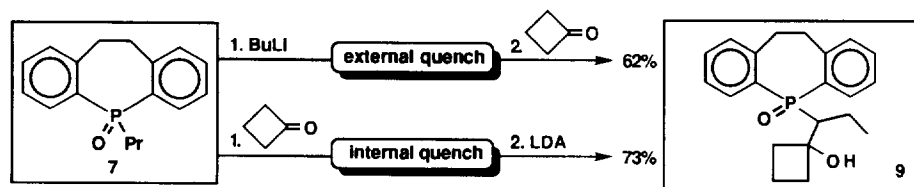
We report here our investigations into the behaviour of lithiated phosphine oxides using both  $\text{Me}_3\text{SiCl}$  and a new reagent for internal quench conditions, cyclobutanone. We wished to probe the structure and stereochemical integrity of lithiated phosphine oxides after the shortest possible lifetimes, and needed ideally a reactive achiral carbonyl compound as a model for the carbonyl electrophiles normally used [9]. Experiments on the simple phosphine oxide **5** showed that benzaldehyde was no good (0% yield of adduct), so we turned to cyclobutanone as a trapping agent. Our logic was that cyclobutanone would be a reactive electrophilic carbonyl compound because of ring strain and that enolisation would be inhibited for the same reason; the enolate would be even more strained. Cyclobutanone did indeed give the adduct (**6**) in reasonable yield. It is perhaps surprising that an enolisable ketone is successful while unenolisable and reactive benzaldehyde is not, but our arguments for cyclobutanone are evidently correct.



We first tried both internal quench procedures on the simple phosphepin (**7**). This was to prepare the way for an investigation [10] into the stability of lithium derivatives of chiral phosphepin oxides such as **10** and **12**. With  $\text{Me}_3\text{SiCl}$  as the trapping agent we obtained 86% of the C-silyl derivative (**8**). Lithiation occurs on the exocyclic alkyl chain and not at all on the benzylic positions in the backbone.



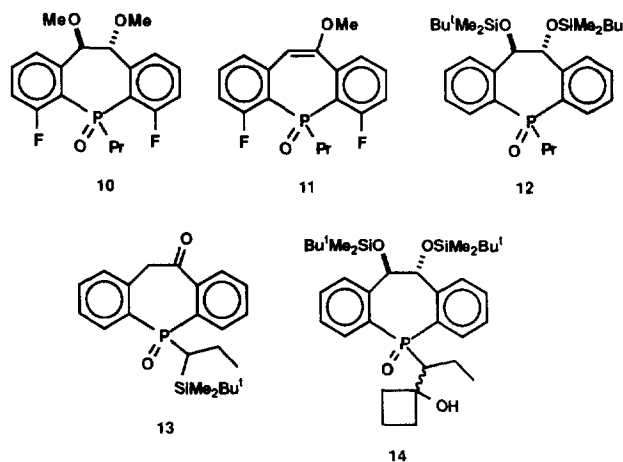
We then tried cyclobutanone as an external quench on the same phosphepin (**7**), using the procedure employed successfully [11] for many phosphine oxides and ketones (though not previously with cyclobutanone), and obtained the cyclobutanol (**9**) in a respectable yield. When we used the internal quench procedure, adding cyclobutanone first and LDA second, the yield was improved to 73%. Enolisation is evidently not a problem, though cyclobutanone alone does react with LDA to give the lithium enolate in the normal way [12]. The rest of this communication describes the application of the new cyclobutanone quench to a variety of problems in phosphine oxide chemistry.



## 3. Stability of lithium derivatives of chiral phosphepin oxides

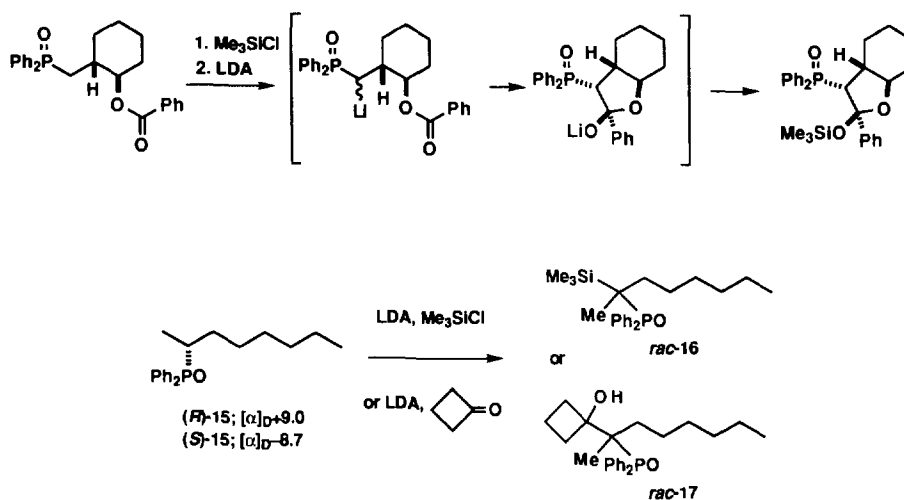
Because our attempts to prepare and react lithium derivatives of **10** and **12** with carbonyl compounds failed [but led instead to enol ether (**11**) and ketone (**13**)], we tried a cyclobutanone internal quench to minimise the time between

lithiation and reaction with the carbonyl compound. Cyclobutanone, lithium tetramethylpiperidide and **12** led to our only observed carbonyl adduct (**14**), albeit in only 8% yield. Under these internal quench conditions the ketone (**13**) was still the major product, but at least with cyclobutanone some of the lithiated species could be trapped before its rearrangement (studies to produce improved chiral auxiliaries based on phosphepins are in progress).



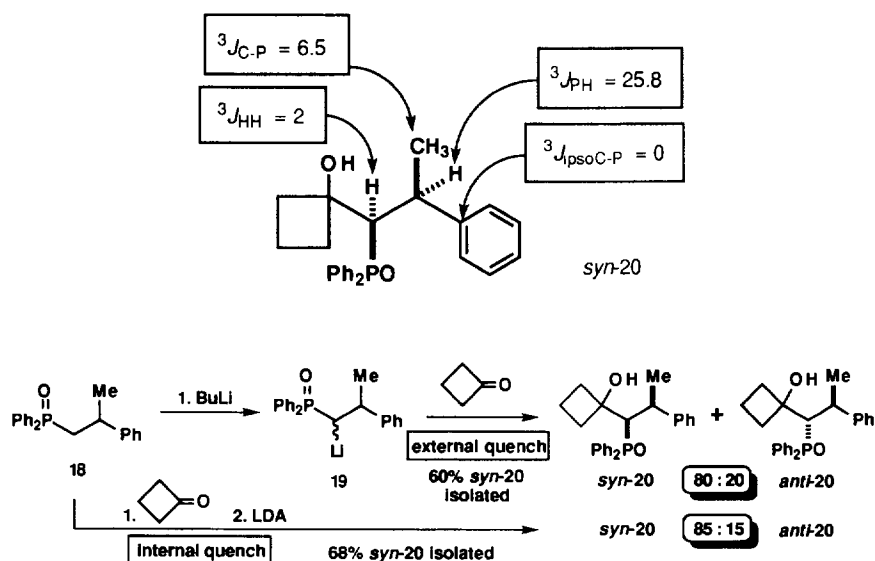
#### 4. Asymmetric reactions of open chain alkyl diphenylphosphine oxides

Internal quench experiments with cyclobutanone and  $\text{Me}_3\text{SiCl}$  on either enantiomer of the optically active phosphine oxide (**15**) gave only racemic adducts (**16**) and (**17**), which demonstrated that these lithium derivatives equilibrate rapidly even with very short lifetimes [13]. Armed with this knowledge, we have been able to develop some new asymmetric syntheses of cyclopropanes [14] using a secure remote stereogenic centre and allowing a developing centre next to phosphorus to equilibrate during an acyl transfer procedure involving acylation and silylation under internal quench conditions. Our stereoselective acyl transfers suggested that an intramolecular ester group could cooperate with  $\text{Me}_3\text{SiCl}$  as a double internal quench: the ester captures the C–Li while the  $\text{Me}_3\text{SiCl}$  captures the O–Li intermediate [9].

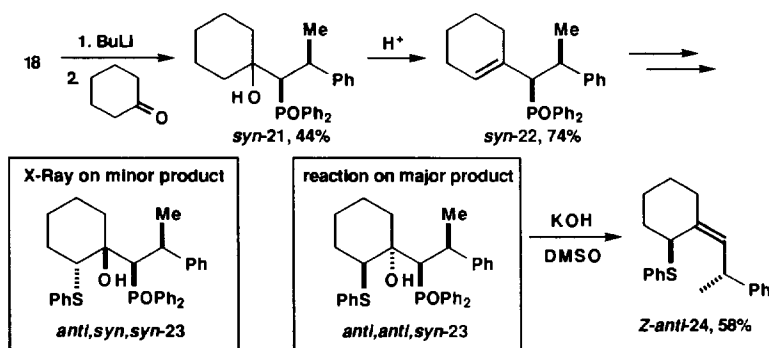


### 5. Diastereoselectivity in reactions of lithiated phosphine oxides with ketones

Given that lithium derivatives of simple phosphine oxides equilibrate rapidly on the timescale of their addition to cyclobutanone, it seemed likely that diastereoselectivity might be achieved in addition of a chiral phosphine oxide to a ketone, as only the more reactive of the two diastereoisomers of the lithium derivative (e.g. **19**) might react. We tested this idea with racemic phosphine oxide (**18**) under both internal and external quench conditions. Both gave good yields and *syn* stereoselectivity: the internal quench was, if anything, better. The stereochemistry of *syn*-**20** was assigned spectroscopically, key coupling constants (Hz) are shown on the diagram below. The coupling constant between the two marked hydrogens (2 Hz) is a typically small value for a *syn* compound. Attempted reaction of **18** with cyclohexanone under internal quench conditions gave only an 18% yield of **21**.



With the cyclobutanone model as our guide, we added the lithium derivative of the phosphine oxide **18** to cyclohexanone to give *syn*-**21** with good stereoselectivity (above 95:5) but in poor yield (44%). We had previously described [15] this compound as *anti*-**21**, but have now converted it into the allylic phosphine oxide *syn*-**22** and hence by epoxidation and addition of PhSLi/PhSH [16] to *anti,anti,syn*-**23**. The minor product from the epoxidation was converted by addition of PhSLi/PhSH into *anti,syn,syn*-**23**, whose configuration was determined by X-ray (the X-ray crystal structure of *anti,syn,syn*-**23** was kindly determined by Dr. P.R. Raithby). Since both epoxides are made from the same allylic phosphine oxide **22** and both epoxidation and opening of the epoxide with PhSLi are stereospecific, the major isomer must be *anti,anti,syn*-**23**, and the *syn* relationship in both **21** and **22** is proved. Stereospecific Horner–Wittig elimination on the major isomer *anti,anti,syn*-**23** finally gave the allylic sulfide (**24**) with two 1,4-related stereogenic centres flanking a *Z*-alkene. The configuration of the cyclobutanone adduct (**20**) was determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR correlation with *syn*-**21**.



## 6. Summary

Cyclobutanone can be used as an electrophile under internal quench conditions with lithiated phosphine oxides. Though  $\text{Me}_3\text{SiCl}$  is the most general and useful of the reagents used to trap organolithium species after short lifetimes, cyclobutanone succeeds where other carbonyl compounds fail (whether enolisable, such as cyclohexanone, or unenolisable, such as benzaldehyde), and provides a good model for the behaviour of other ketones with the same organolithium species. The internal quench procedure gives results from the shortest possible lifetime of the organolithium species in the presence of a carbonyl compound. This is an important consideration as carbonyl compounds interact with lithiated phosphine oxides by first forming an Li–O bond, an interaction not possible for  $\text{Me}_3\text{SiCl}$ , so this new internal quench procedure provides a more realistic model for the reactions actually used than does the more general  $\text{Me}_3\text{SiCl}$  quench [17].

## 7. Typical procedure: illustrated for the conversion of the phosphepin 7 to the adduct 9

Cyclobutanone (20  $\mu\text{l}$ ) was added to a solution of the phosphine oxide (50 mg, 0.185 mmol) in THF (1.5 ml). The solution was cooled to  $-78^\circ\text{C}$  and a slight excess of LDA (0.194 mmol) added. The typical red colour of the lithium derivative is not seen. After 5 min MeOH (50  $\mu\text{l}$ ) was added and the solution was allowed to warm to room temperature. Aqueous  $\text{NH}_4\text{Cl}$  (0.5 ml) was added, the THF was removed under low pressure and the residue extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 ml). Column chromatography on silica eluting with 1:1 EtOAc/hexane gave the adduct (46 mg, 73%).

## Acknowledgements

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