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Stereoselective Acyl Transfer Reactions controlled by the Diphenylphosphinoyl Group: X-Ray Structures of Stable Crystalline Silylated Tetrahedral Intermediates

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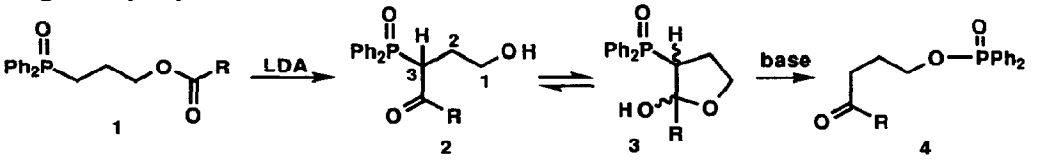
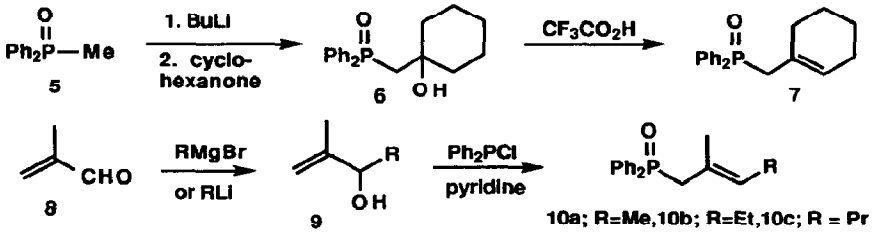
Abstract: Acyl transfer with LDA on benzoates of single diastereoisomers of 3-hydroxyalkyldiphenylphosphine oxides in the presence of trimethylsilyl chloride gives silylated tetrahedral intermediates in carbonyl displacement reactions with the stereochemically controlled creation of two new chiral centres. X-rays reveal the stereochemistry.

We have used the O to C acyl transfer reaction[1] of esters such as **1** in stereochemically controlled syntheses[2] of unsaturated alcohols[3] and cyclopropyl ketones[1] but the reaction is complicated by the appearance of the product as a mixture of the hydroxyketone **2** and two diastereoisomers of the hemiacetal **3**. If there are more chiral centres in the molecule, e.g. at C-1 and/or C-2 in **2**, it is often difficult to tell whether the hemiacetals belong to a single diastereoisomer of **2** or not. The reaction is capricious, sometimes giving low yields in inexperienced hands. This is not surprising as the hydrogen atom at C-3 in the product **2** is acidic enough to quench the lithium derivative of **1**: in a way it is more surprising that experienced operators routinely get more than 50% yield.[1-3] In addition, further acyl transfer, this time of the Ph_2PO group from C to O to give the phosphinate ester **4** often occurs under the conditions of the reaction.

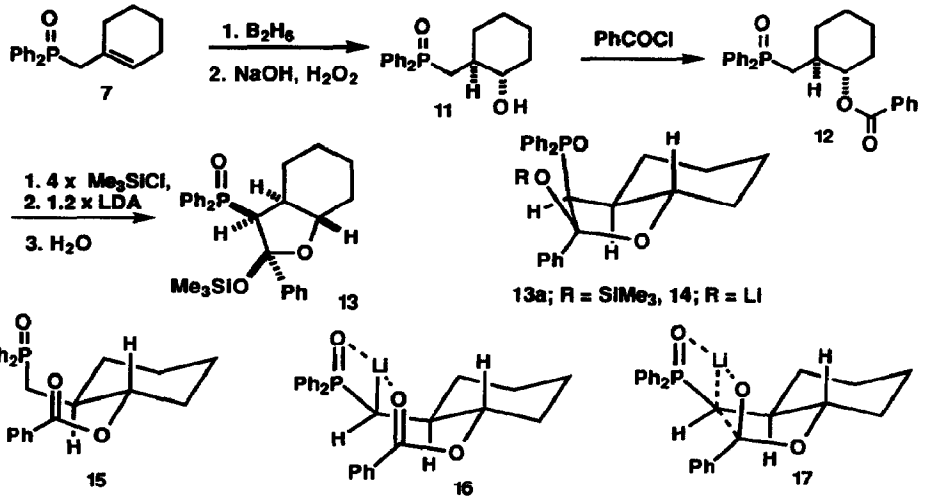


We have now studied acyl transfer on single diastereoisomers of alcohols produced by hydroboration either of cyclic allylic phosphine oxides, e.g. **7**, produced by dehydration of tertiary alcohols,[4] e.g. **6**, or of open chain allylic phosphine oxides **10** produced by the [2,3] Arbuzow rearrangement[5] from allylic alcohols **9**. Compounds **10** were produced as *E*:*Z* mixtures with good *E* selectivity (**10a**, 85:15; **10b**, 92:8; **10c**, 96:4) easily separable by crystallisation. We report a solution to all the above problems which provides a simple protocol for reliable acyl transfer, reveals the true mechanism of the reaction and shows that it is actually highly stereoselective.



The solution is to carry out the acyl transfer *in the presence of* Me_3SiCl.[6] Treatment of the benzoate **12** with four equivalents of Me_3SiCl and then with 1.2 equivalents of LDA, all in THF, gave essentially a

single diastereoisomer of the crystalline silyl ether **13** in 83% yield. An X-ray crystal structure in combination with nOes on the ^1H NMR spectrum in solution revealed the stereochemistry of **13** and its conformation in solution **13a** in which both the Ph_2PO and $OSiMe_3$ groups are in a pseudo-axial orientation on the five-membered ring (the $SiMe_3$ group is not shown as it is directly towards the observer with the Si atom eclipsing the O atom). We had hoped for control[2] at the chiral centre next to the Ph_2PO group but were very surprised that we had trapped one epimer at the hemiacetal centre as well. Evidently the first product of the reaction is a single diastereoisomer of the lithium derivative **14** of the tetrahedral intermediate which is quickly trapped as its silyl ether.

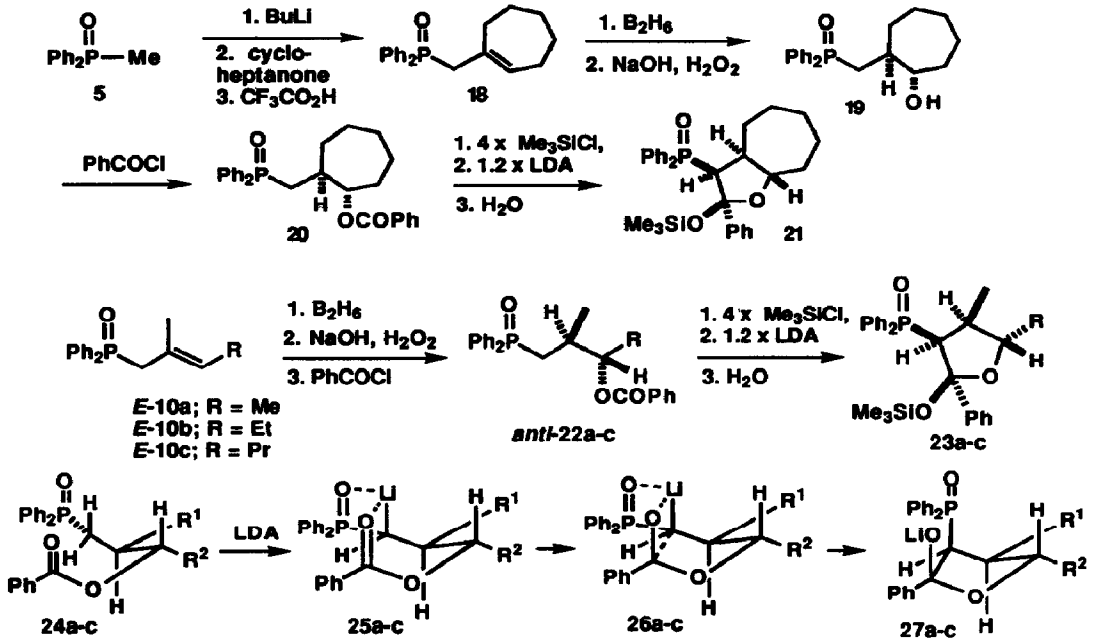


7 **11** **12** **13** **15** **16** **17**

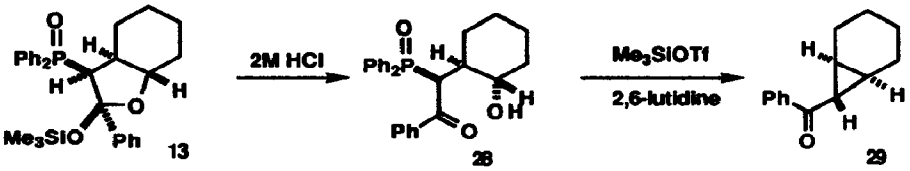
The stereochemical outcome can be explained if the ester **12** adopts the conformation **15** with the two large groups equatorial and the ester in its anomerically favoured *Z* conformation. At this point the Ph_2PO group can be anywhere in free space away from the rest of the molecule. It must now move into a pseudo equatorial position during lithiation to give a single diastereoisomer of **16** if both the P=O and C=O groups are needed to coordinate the Li atom. ^7Li NMR experiments on the structure of Ph_2POCH_2Li suggest the four-membered ring in **16** and calculations on the docking of CH_2O onto H_2POCH_2Li suggest the "ladder" structure for **17**.[7] The transition state for C-C bond formation **17** can then retain the shape of **16** and replacement of Li by C occurs with retention (90° between the old C-Li and new C-C bonds) to give the product **14** again without any important changes in the conformation of the molecule except the required 90° rotation of the C-P bond to put the Ph_2PO group in a pseudo axial position.

It was obviously essential to discover whether this remarkable stereochemical result was a consequence of the equatorial position of both substituents on the six-membered ring in **15** so we carried out four further acyl transfers: on the seven-membered ring compound **20** and on the open chain compounds *anti*-**22a**, **22b** and **22c** made by hydroboration of the corresponding allylic phosphine oxides **18** and *E*-**10a-c**. Under the same conditions all esters **20** and *anti*-**22a-c** gave single diastereoisomers of the silyl ethers **21** and **23a-c**, the two new chiral centres in all four having the same relative configurations as those in **13**. An X-ray crystal structure of **23a** and nOe experiments on **21** and **23a-c** confirmed the stereochemistry. Presumably the conformation of the esters **20** and *anti*-**22**, the structure of the key intermediates and the structure of the transition states in these reactions must resemble **15**, **16** and **17** sufficiently for the same stereochemical

result. We therefore suggest that the detailed mechanism of these reactions is as shown for **24** to **27** and that the true product of an acyl transfer without Me_3SiCl is the lithium derivative of the hemiacetal **27**. This may equilibrate to the open chain lithium alkoxide or during work-up to the hydroxyketone **2** and so lose stereochemical integrity at the hemiacetal centre and at the centre next to phosphorus by enolisation.



Products **13**, **21** and **23** are trapped tetrahedral intermediates in carbonyl substitution reactions. It is of course nothing unusual to find stable hemiacetals, whether silylated or not, nor to trap tetrahedral intermediates in nucleophilic substitution at the carbonyl group by a heteroatom (O or N) nucleophile,[8] but it is very unusual to trap such an intermediate when a carbon nucleophile displaces an oxygen leaving group. In such reactions the product is normally the hydroxy ketone[9] and the nearest analogy to these reactions is probably the stable intermediates $R^1R^2C(OLi)_2$ in the displacement[10] of OH from a carboxylic acid by RLi. Hemiacetals have been trapped by silylation during the reduction of esters with DIBAL, and with good stereoselectivity during the addition of $ClCH_2Li$ to esters of 2-haloacids.[12]



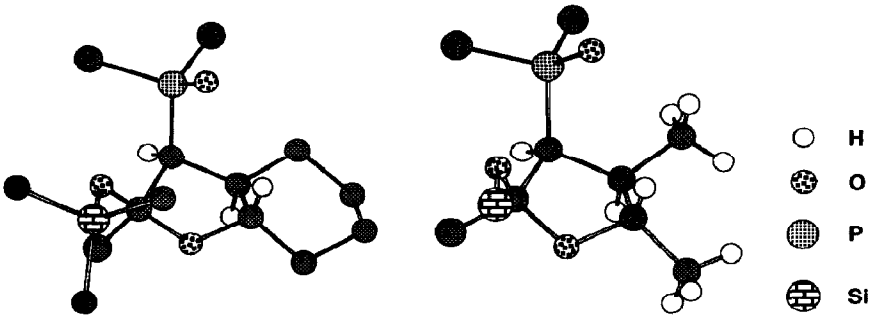
The Me_3Si group can easily be removed from any of the silyl ethers with acid (2M HCl) to give the hydroxyketones, e.g. **28** without epimerisation. Desilylation with fluoride epimerises the centre next to the Ph_2PO group. Attempts to *replace* the Me_3Si, or any other silyl group, onto compounds such as **28** by a variety of reagents were unsuccessful, the commonest result being the formation of phosphinate esters or, with Me_3SiOTf and 2,6-lutidine, the cyclopropyl ketones, e.g. **29** (89% yield). These are then very unusual

reactions: it is possible to trap the tetrahedral intermediate when O is displaced by C, but impossible in the commoner situation where OH adds to a carbonyl group. Single diastereoisomers of hydroxyketones, e.g. **28**, are precursors to *E*-homoallylic alcohols by stereochemically controlled reduction and Horner-Wittig elimination.[1-3]

Alkene	Alcohol	Yield (%) from hydroboration	Ester	Yield (%)	Acyl transfer product	Yield (%)	Stereo-selectivity
7	**11**	77	**12**	90	**13**	87	100:0
18	**19**	86	**20**	94	**21**	83	100:0
***E*-10a**		79	***anti*-22a**	99	**23a**	68	100:0
***E*-10b**		82	***anti*-22b**	89	**23b**	64	94:6[a]
***E*-10c**		84	***anti*-22c**	81	**23c**	65	100:0

[a]The stereochemistry of the minor diastereoisomer is unknown.

Figures: X-ray structures of **13** and **23a**. Phenyl rings of the Ph_2PO and PhCO groups are reduced to single carbon atoms in both compounds and the methyl groups of the Me_3Si group in **23a** are omitted for clarity.



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