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Intramolecular Acylations of γ-Benzoyloxy Phosphine Oxides: Synthesis of Optically Active Cyclopropyl Ketones

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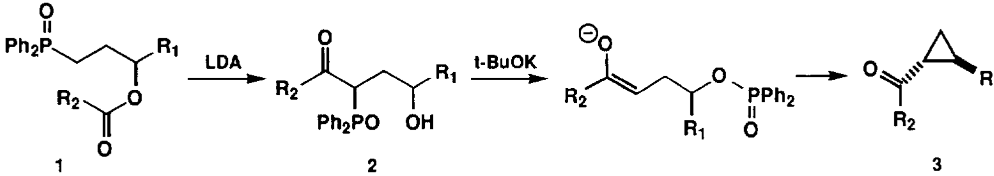
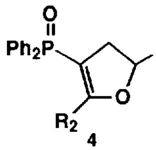
Abstract: Intramolecular acylation of γ-benzoyloxy phosphine oxides with LDA in the presence of Me_3SiCl gives silyl ethers with high stereoselectivity: treatment of these silyl ethers with t-BuOK gives optically active di- and trisubstituted cyclopropyl ketones in good yield.

We have previously described a synthesis of racemic cyclopropyl ketones *trans*-**3**. Intramolecular acylation of diphenylphosphinoyl esters **1** generated hydroxy ketones **2** which were cleanly converted into cyclopropyl ketones *trans*-**3** upon treatment with potassium *tert*-butoxide.[1] This route was far from ideal: hydroxy ketones **2** exist as a mixture of open chain and closed hemiketal forms and decompose in solution to dihydrofurans **4**. However, carrying out the acylation in the presence of an internal Me_3SiCl trap solved these problems since treatment of benzoate esters *anti*-**5** with Me_3SiCl and then LDA gave single diastereoisomers of silyl ethers **6**.[2]





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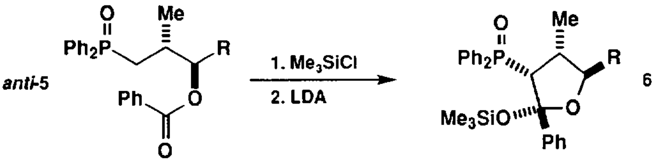
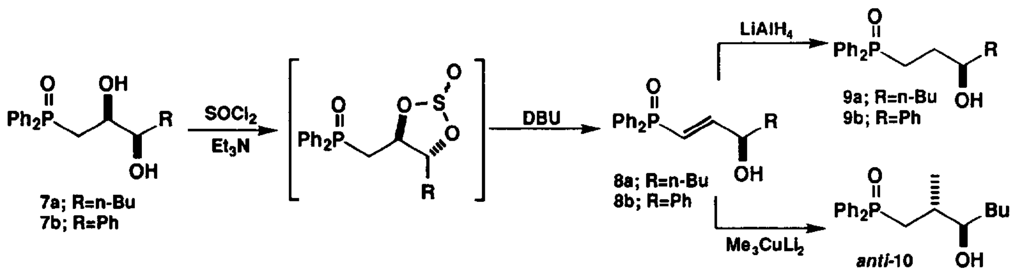


We now report syntheses of optically active silyl ethers and their direct conversion into optically active cyclopropyl ketones (with two or three ring substituents), an approach which combines the chemical stability of silyl ethers such as **6** with the synthetic utility of hydroxyketones such as **2**. Compounds containing cyclopropane rings show considerable promise as antiviral agents[3] and conformationally restricted analogues of natural amino acids.[4]

1,2 Diols **7a** (76% ee) and **7b** (86% ee), synthesised by Sharpless asymmetric dihydroxylation,[5] were converted into optically active hydroxy phosphine oxides **9** and **10** using a two step sequence. Vinyl phosphine oxides **8** were obtained by DBU elimination[6] of the cyclic sulfites[7] derived from 1,2 diols **7**. Addition of $LiAlH_4$ or Me_3CuLi_2 gave hydroxy phosphine oxides **9**[8] and **10**. Phosphine oxide **10** was produced with good *anti* selectivity[9] (82:18) as a mixture easily separable by HPLC.



Benzoylation of hydroxy phosphine oxides **9** and **10**, followed by intramolecular acylation using the LDA/Me3SiCl internal quench procedure gave good yields of silyl ethers **13** and **14** with excellent stereoselectivity (see Table). In particular, intramolecular acylation of benzoates **11** with only one chiral centre (γ to phosphorus) gave good yields of silyl ethers **13** as single diastereoisomers (entries 1 and 2), the sense of induction being determined by a 500 MHz NOESY analysis of silyl ether **13a**. We interpret these results in terms of the configurational instability of lithiated phosphine oxides:[10] lithiation of benzoates **11** is followed by equilibration to the lithium derivative whose true structure is **16**. Acylation then leads to the observed diastereoisomer.[2]

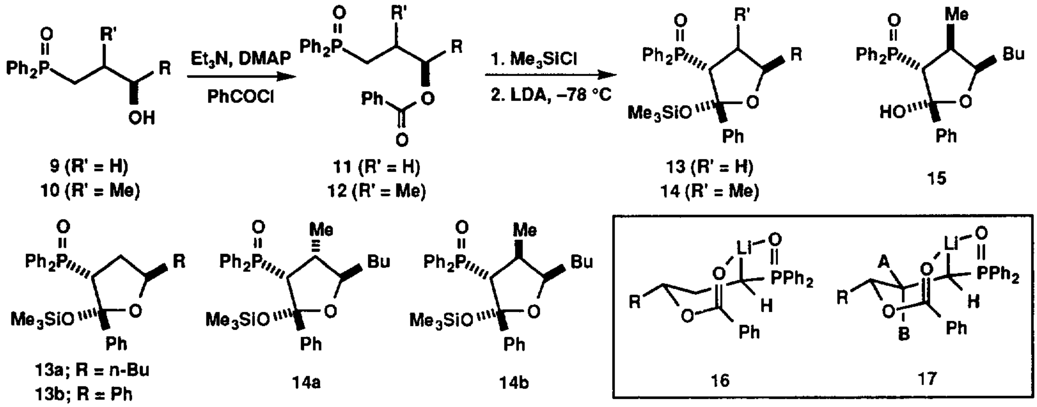


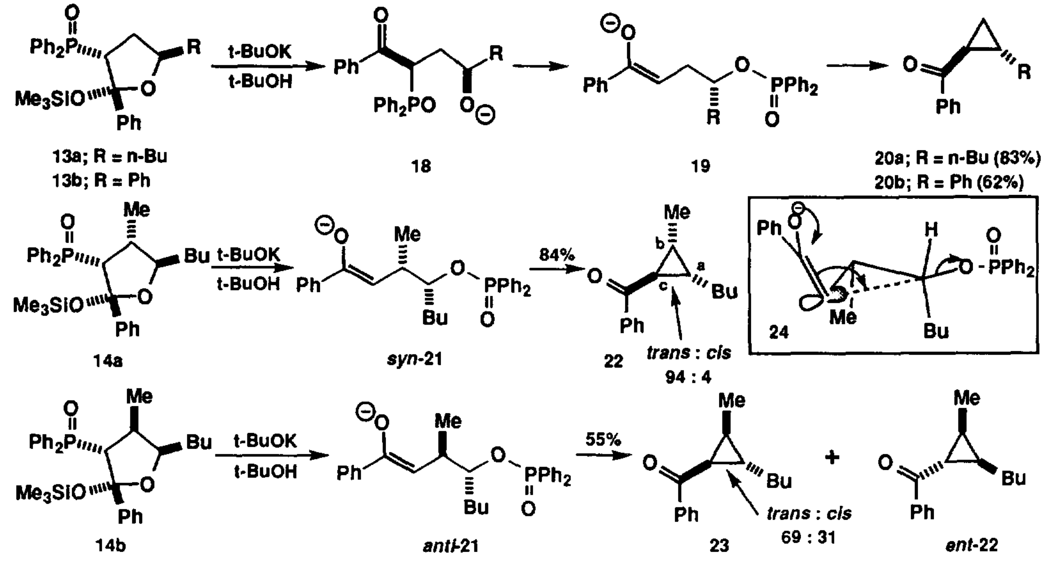
Table: Intramolecular acylation of benzoates **11** and **12**

Entry	Alcohol **9** or **10**			Benzoate **11** or **12**		Silyl ethers **13**-**14** or **15**		
		R	R'		Yield (%)		Yield (%)	dias.ratio
1	**9a**	n-Bu	H	**11a**	94	**13a**	55	>98:2
2	**9b**	Ph	H	**11b**	94	**13b**	88	>98:2
3	*anti*-**10**	n-Bu	Me	*anti*-**12**	86	**14a**	75	95:5
4	*syn*-**10**	n-Bu	Me	*syn*-**12**	85	**14b** **15**	64 20[a]	>98:2 87:13

[a] Decomposed to the dihydrofuran on standing.

The successful intramolecular acylation of benzoates *syn*- and *anti*-**10** also suggests that the chiral centre γ to phosphorus is controlling the stereoselectivity of the reaction: both *syn*- and *anti*-**10** generated silyl ethers **14** with the same relative stereochemistry between the chiral centres α and γ to phosphorus (entries 3-4).[11] Thus, in intermediate **17**, it is relatively unimportant whether the methyl group sits in the axial position **B** (benzoate *syn*-**12**) or in the equatorial position **A** (benzoate *anti*-**12**). This is, perhaps, not surprising since the axial position **B** does not suffer from 1,3 diaxial interactions.

Treatment of silyl ethers **13a-b** and **14a-b** with potassium *tert*-butoxide in *tert*-butanol initiated a remarkable cascade of events which led to the formation of cyclopropyl ketones **20a-b, 22** and **23**. We propose that desilylation was followed by ring opening to generate alkoxy ketones **18** which rearranged by phosphinoyl transfer to enolates **19**. Cyclisation of these enolates led to the formation of the cyclopropyl ketones. In the synthesis of cyclopropyl ketone **22**, each chiral centre is controlled by a different factor: centre (a) is controlled by the inversion of a displacement reaction (**21**→**22**), centre (b) is already present in benzoate *anti*-**12** and centre (c) is controlled by which face of the enolate reacts.



In particular, reaction of silyl ethers **13a-b** with potassium *tert*-butoxide in *tert*-butanol generated cyclopropyl ketones **20a** (*trans*:*cis* >95:5) and **20b** (*trans*:*cis* >95:5).[12] The cyclisation of enolates **19** is stereoselective because the substituents prefer to be *trans* in the transition state. On standing in acidic solution ($CDCl_3$) **20b** gave a thermodynamic 67:33 *trans*:*cis* ratio. No equilibration occurred in basic solution and all other ratios quoted in this letter are kinetically controlled.

Our route is particularly well suited to the synthesis of optically active cyclopropyl ketones with a chiral centre at each corner of the three-membered ring: compound **22** was obtained as a 94:6 mixture of diastereoisomers in 84% yield. This is a result of the highly stereoselective cyclisation of enolate *syn*-**21** in which both alkyl groups are *trans* to the forming phenyl ketone (figure **24**). This favourable cyclisation is not available to enolate *anti*-**21**, and therefore reaction of silyl ether **14b** gave a 61:27:11 mixture of cyclopropyl ketones *trans*-**23**, *cis*-**23** and *ent*-**22** in a poor 55% yield. Presumably, a S_N1 mechanism is competitive with stereospecific S_N2 inversion.

Optically active di- and trisubstituted cyclopropyl esters and amides are most usually synthesised by the metal-catalysed addition of carbene equivalents to alkenes in the presence of chiral ligands[13], but the diastereoselectivities are poor unless very bulky diazoacetates are used[14] or the reaction is intramolecular.[15] Several asymmetric syntheses of cyclopropanes using homochiral nucleophiles as chiral auxiliaries are known. In particular, Johnson[16] has synthesised ketone **20b** by adding the anion of a chiral sulfoximine to an unsaturated ketone and Hanessian[17] has synthesised tri- and tetrasubstituted cyclopropyl carbonyl compounds by adding the anion of a *trans*-chloroallyl phosphonamide to unsaturated ketones, esters and amides.

Our route combines the advantages of these two approaches: our cyclisation precursors are synthesised by a catalytic asymmetric method, the Sharpless dihydroxylation reaction, and the intermediacy of anionic intermediates in the ring-closure enables our reactions to be highly diastereoselective in favourable cases. The method is particularly useful for the synthesis of di- and trisubstituted cyclopropyl ketones with one or two alkyl groups *trans* to the acyl substituent.

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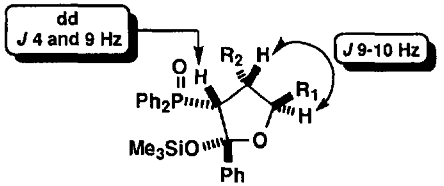
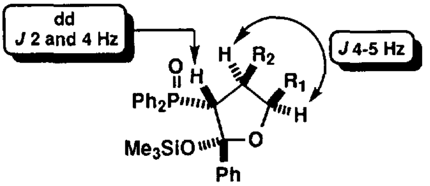
9. The *anti* selectivity of these additions was established by 500 MHz NMR analysis of silyl ether **14** (R = Ph; R' = Me) and by coupling constant correlations (Footnote 11).
10. We have recently demonstrated that lithiated phosphine oxides are not configurationally stable in THF at –78 °C: O'Brien, P.; Warren, S. *Tetrahedron Lett.*, **1995**, *36*, 8473-8476.
11. For silyl ethers **13** and **14**, we have noticed the following trends in proton NMR coupling constants:





12. Typical $^3J_{HH}$ coupling constant values for adjacent protons in cyclopropyl rings: $^3J_{HH}$(trans)=4-9.5 Hz and $^3J_{HH}$(cis)=7-13 Hz: Williams, D.H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*, McGraw-Hill, London, 5th edition, **1995**, page 164.
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