New synthetic methodology utilising 1,2-dioxines and stabilised phosphorus ylides: a highly diastereoselective cyclopropanation reaction

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A new method is described for the synthesis of diastereomerically pure cyclopropanes from substituted 1,2-dioxines 1a–c and stabilised phosphorus ylides 2a–e.

In 1994 the group of Adam and Treiber established for the first time that the peroxide bond of 1,2-dioxetanes is susceptible to nucleophilic 'attack' by simple diazoalkanes.[1] In this first report, 1,2-dioxetanes upon treatment with diazoalkanes afforded a mixture of products including 1,3-dioxolanes. More recently, the reactions between various methyl-substituted 1,2-dioxetanes and simple triphenylalkylidenephosphoranes were explored by the same group.[2] Initial nucleophilic 'attack' on the O–O linkage was proposed for the observed formation, at low temperature, of 2,2,2-triphenyl-1,4,2λ^5-dioxaphosphorinanes which, upon warming, ring-opened affording dipolar phosphonium alkoxides.

Herein we report that various 1,2-dioxines **1a**–**c** react under mild conditions with stabilised phosphorus ylides **2a**–**e** to afford novel diastereomerically pure cyclopropanes [reaction (1)]. To the best of our knowledge, the reactions of stabilised phosphorus ylides with 1,2-dioxines have not been reported until now. A typical reaction involved treatment of **1a**[3] with **2a** (1.1 equiv.) in an appropriate solvent (usually CH_2Cl_2) at ambient temperature. The major product formed was identified as the cyclopropane **3a** along with a trace of diketone **9a**[4]. Similar reactions afforded a variety of di- and tri-substituted cyclopropanes in excellent yields and are collated in Table 1. Compounds **1a** and **c** afforded essentially diastereomerically pure *trans*-cyclopropanes whilst **1b** afforded the *trans*-cyclopropane as the major diastereomer along with a minor amount of the *cis*-cyclopropane. Typically the isolated yields were within 10% of those quoted whilst the diastereomers were easily separated by column chromatography. The structure and relative stereochemistry of the cyclopropanes were unambiguously elucidated from a combination of ^{1}H, ^{13}C, DEPT, NOESY (^{1}H-COSY and HMQC with gradient coherence selection) NMR techniques.† X-Ray analysis‡ of **4a** (Fig. 1) unambiguously confirmed the general structural and stereochemical assignments elucidated by NMR spectroscopy.

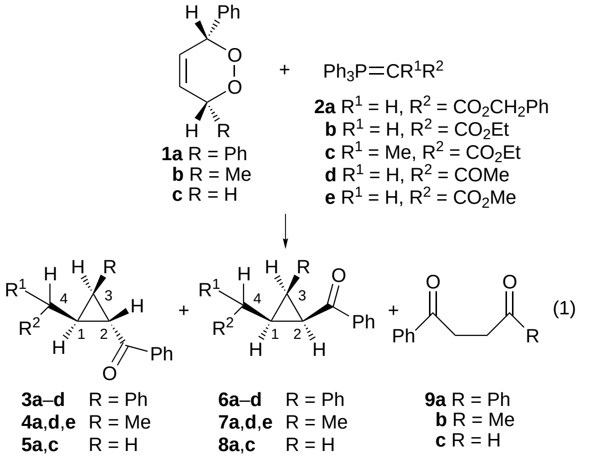


Table 1 Reaction of 1,2-dioxines **1a**–**c** with various stabilised phosphorus ylides **2a**–**e** at 25 °C[a]

1,2-Dioxine	Ylide	Yield of cyclopropane (%)		Yield of **9** (%)
1a	**2a**	**3a** (95)	**6a** (⩽2)	**9a** (3)
	2b	**3b** (96)	**6b** (⩽2)	**9a** (2)
	2c	**3c** (48)	**6c** (nd)	**9a** (52)
	2d	**3d** (nd)	**6d** (nd)	**9a** (100)
1b	**2a**	**4a** (84)	**7a** (15)	**9b** (⩽1)
	2d	**4d** (75)	**7d** (15)	**9b** (10)
	2e	**4e** (82)	**7e** (18)	**9b** (nd)
1c	**2a**	**5a** (100)	**8a** (nd)	**9c** (nd)
	2c	**5c** (80)	**8c** (nd)	**9c** (nd)[b]

[a] All reactions performed in CH_2Cl_2; yields were determined from the ^{1}H NMR spectra (600 MHz) of the crude reaction mixtures; nd denotes not detectable. [b] Another unidentified minor product present.

The effect of solvent and additives on the rate of reaction between **1a** and **2a** and the cyclopropane : diketone ratio **3a** : **9a** was evaluated. Our initial findings indicate that the overall rate of reaction increases only slightly with increasing solvent polarity. The small rate increase is inconsistent with a mechanism involving zwitterionic intermediates in the rate-determining step. The relative rate and product ratio was unaffected by the addition of TEMPO suggesting that free radicals are not involved. Additionally, the formation of 'free' carbenes can be excluded on the basis that addition of excess cyclohexene failed to compete in cyclopropane formation. This

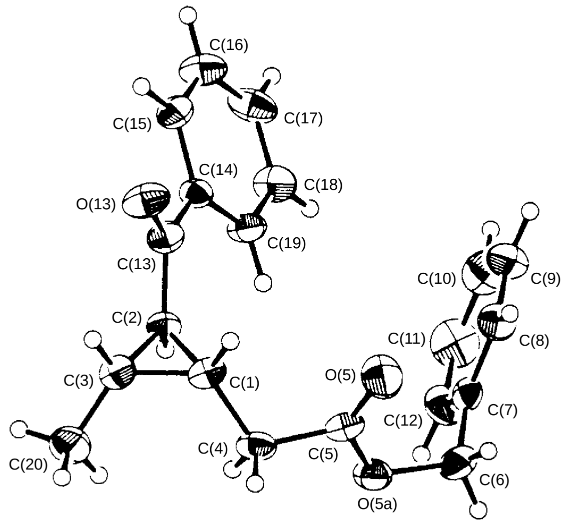


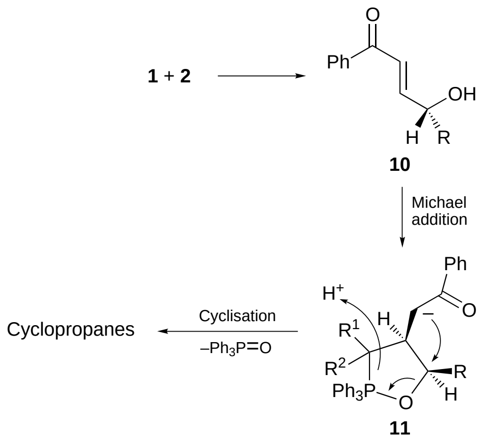
Fig. 1 Molecular structure of **4a** showing the crystallographic numbering scheme employed: O(5)–C(5)–C(4)–C(1) 34(1)°, C(5)–O(5a)–C(6)–C(7) −82.6(8)°, C(2)–C(13)–C(14)–C(15) 159.5(7)°

conclusion was further supported by the observation that only a trace of the carbene dimer ($<1\%$) could be detected by ^{1}H NMR analysis of the crude reaction mixtures. Finally, performing the reaction at 80 °C simply lead to an increased rate without a change in product outcome or ratio.

The reaction of equimolar amounts of **1a** and **2a** in C_6D_6 was monitored by ^{31}P NMR spectroscopy. At no time could any 'free' triphenylphosphine or zwitterionic intermediates be detected. Careful ^{1}H NMR analysis of the crude mixture after cessation of the reaction revealed the presence of **3a**, **9a**, Ph_3PO and unreacted **2a**. All **1a** had been consumed affording **3a** and **9a** in a 77 : 22 ratio. The remaining 1% constituted the *cis*-cyclopropane. Formation of Ph_3PO (75%) parallels the yield of the cyclopropane as expected. Most important was the observation that 22% unreacted **2a** remained and parallels **9a** formation (22%). This observation suggests that formation of **9a** is catalytic in ylide. Indeed, analysis of all crude reaction mixtures by ^{31}P and ^{1}H NMR spectroscopies showed the same trend. Blank reactions showed that formation of **9a–c** was not promoted by Ph_3PO. We have evidence that the rearrangement **1a** → **9a** is not promoted by 'free' Ph_3P liberated during the ylide reaction, *e.g.* addition of excess Ph_3P to the reaction mixture containing **1a** and **2a** failed to dramatically change product outcome. Based on these initial findings we suggest that formation of **9a** in the reaction of **1a** with **2a** is promoted by the ylide acting as a weak base[5] in a catalytic manner. Base catalysed rearrangement (Kornblum–De La Mare decomposition) of cyclic peroxides has been reported previously and is initiated by removal of a proton from the carbon adjacent to the O–O linkage.[6] Finally, the observation that the more sterically hindered **2c** affords less cyclopropane **3c** when compared to that for **2b** in identical solvents suggests that there is a steric component to the two competing processes.

A significant mechanistic finding was the observation of the *trans*-alcohol **10** intermediate during ^{1}H NMR monitoring of these reactions. Indeed, we were able to isolate a quantity of **10** from the reaction mixture and demonstrate that it lead to the observed cyclopropanes and no 1,2-diketone upon addition of ylid. Although the reaction manifold is complicated by many factors, Scheme 1 depicts a general mechanistic overview. Interaction of **1** and **2** leads in a rate-limiting step to the formation of the key intermediate **10**. Michael addition of the ylide to **10**, followed by cyclisation, proton transfer and extrusion of triphenylphosphine oxide from **11** affords the observed cyclopropanes. In competition with this process is the known cyclisation[6] of (*Z*)-**10** *via* the hemi-acetal and rearrangement leading to formation of **9**.

Synthetically, this novel reaction has several advantages over existing methods[7] for cyclopropane formation involving phosphorus ylides, as functionalised cyclopropanes are formed in a highly diastereoselective manner in excellent yields. We are currently evaluating the reactions of various 1,2-dioxines, alkyl hydroperoxides and disulfides with a variety of stabilised and non-stabilised ylides (phosphorus, sulfur *etc.*) and full mechanistic details will be presented in due course.



Scheme 1

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Notes and References

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† All new compounds have been fully characterised by elemental analysis, spectroscopy and mass spectrometry.

‡ *Crystal data*: $C_{20}H_{20}O_3$, triclinic, space group $P\bar{1}$ with a = 7.952(3), b = 18.417(4), c = 5.680(2) Å, α = 90.51(2), β = 92.28(3), γ = 85.25(3)°, U = 828.4(4) Å^3, Z = 2, D_c = 1.236 g cm^{-3} and μ = 0.82 cm^{-1}. Single-crystal X-ray diffraction data were collected at 293 K on a Rigaku AFC6R diffractometer (Mo-Kα radiation) with $\theta/2\omega$ scans, $3 < \theta < 27.5°$. The structure was solved with SIR92 and refined with the TEXSAN Structure Analysis Package (Molecular Structure Corporation, 1985) of crystallographic programs. A total of 937 reflections with $I \geqslant 3.0\sigma(I)$ were used in the refinement which converged with R = 0.063 and R_w = 0.050 $\{1/[\sigma^2(F) + 0.006F^2]\}$. CCDC 182/708.

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