COMMUNICATION

Exploitation of ylide steric bulk to alter cyclopropanation outcome during the reaction of 1,2-dioxines and stabilised phosphorus ylides

Thomas D. Avery, Ben W. Greatrex, Dennis K. Taylor * and Edward R. T. Tiekink

Department of Chemistry, The University of Adelaide, Australia, 5005.
E-mail: dennis.taylor@adelaide.edu.au

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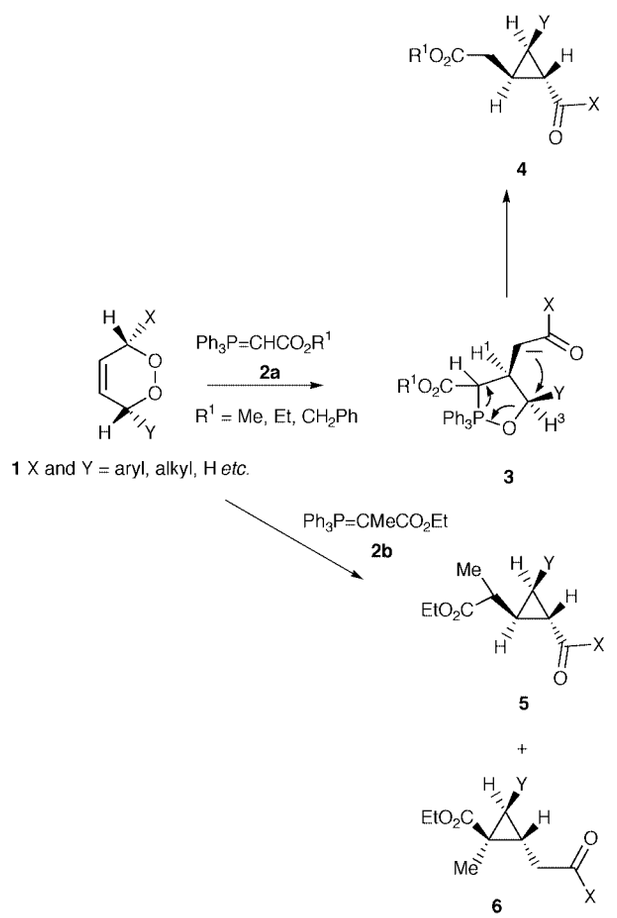
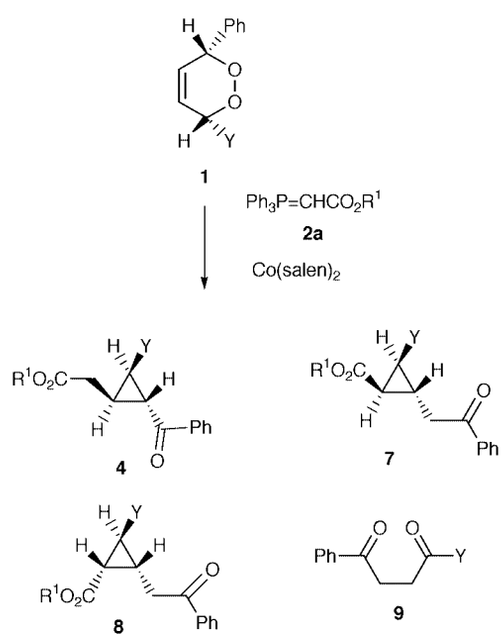
A new approach for the synthesis of diastereomerically pure cyclopropanes from 1,2-dioxines and sterically bulky stabilised phosphorus ylides is presented.

Organics containing the cyclopropane motif are of wide interest since many display novel biological activity, whilst others have been utilised as key intermediates in the synthesis of natural and non-natural products. Through a series of mechanistic studies we have elucidated a clear understanding of the complex relationship between 1,2-dioxines, and their isomeric *cis* and *trans* γ-hydroxy enones, *cis* and *trans* hemiacetals and β-ketoepoxides, and of how these precursors can be utilised to construct diastereomerically pure or enantiomerically pure diversely functionalised cyclopropanes.[1] We now 'expect' that the reaction of 1,2-dioxines **1** with stabilised phosphorus ylides containing an ester moiety **2a**, will afford diastereomerically pure cyclopropanes **4** in excellent yields through collapse of the intermediate 1,2λ^5-oxaphospholanes **3** (Scheme 1). Furthermore, we have demonstrated that the use of the bulkier di-substituted ylide **2b** allows for the incorporation of another stereogenic centre within the side chain of the cyclopropane **5**. However, during these investigations we also isolated (7%) another cyclopropane **6** which did not appear to originate from our proposed mechanism and we speculated that the steric bulk of the ylide may be the reason behind the formation of **6**. We now report on the exploitation of the steric bulk of the ester moiety of the stabilised ylides to completely alter the diastereomeric course of these cyclopropanation reactions.

We began analysing the effect of steric bulk on cyclopropanation outcome with the diphenylmethyl (DPM) grouping. Thus, reaction of 1,2-dioxine **1** (Y = Ph) with ylide **2a** ($R^1 = Ph_2CH$) under the conditions specified within Table 1 (entry 1), resulted only in the formation of diastereomerically pure cyclopropane **4** (Scheme 2). Hence the DPM grouping fails to alter



Scheme 1



Scheme 2

the cyclopropanation outcome. A far more dramatic effect on cyclopropanation outcome was found during investigations utilising the *tert*-butyl ester stabilised ylide (entries 2–4, Table 1). Thus, reaction of 1,2-dioxine **1** (Y = Ph) with ylide **2a** ($R^1 = t$-Bu) at 25 °C resulted in the formation of three cyclopropyl isomers (entry 3). The first of these was simply the 'expected' *trans*-cyclopropane **4** resulting from collapse of the 1,2λ^5-oxaphospholane **3**, while the remaining two (**7** and **8**) represented a uniquely different cyclopropanation outcome. The structure and relative stereochemistry of these two new cyclopropanes were unambiguously elucidated from a combination of crystallography and ^{1}H, ^{13}C, gCOSY, gHSQC, and

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Table 1 Reaction of 1,2-dioxines **1** with various bulky ylides **2**[a]

Entry	Y	R^1	Solvent	Conc./M	Temp./°C	Cyclopropane (yield, %)	**9** (yield, %)
1	Ph	Ph_2CH	CH_2Cl_2	0.38	25	**4** (97) **7** (0) **8** (0)	3
2[b]	Ph	*t*-Bu	$CDCl_3$	0.08	−15	**4** (0) **7** (91) **8** (9)	0
3	Ph	*t*-Bu	CH_2Cl_2	0.40	25	**4** (19) **7** (70) **8** (8)	3
4	Ph	*t*-Bu	$CDCl_3$	0.08	60	**4** (33) **7** (52) **8** (6)	9
5[b]	Ph	1-Ad	$CDCl_3$	0.06	−15	**4** (12) **7** (67) **8** (20)	0
6	Ph	1-Ad	$CDCl_3$	0.06	25	**4** (30) **7** (61) **8** (9)	0
7	Ph	1-Ad	$CDCl_3$	0.15	25	**4** (58) **7** (35) **8** (5)	2
8	Ph	1-Ad	$CDCl_3$	0.06	60	**4** (42) **7** (45) **8** (6)	7
9	Ph	1-Ad	Toluene	0.06	100	**4** (75) **7** (5) **8** (0)	20
10[c]	H	*t*-Bu	CH_2Cl_2	0.12	−15	**4** (48) **7** (49) **8** (2)	0
11	H	*t*-Bu	CH_2Cl_2	0.54	25	**4** (77) **7** (22) **8** (1)	0
12	H	*t*-Bu	$CDCl_3$	0.12	60	**4** (81) **7** (14) **8** (5)	0
13	H	1-Ad	$CHCl_3$	0.1	25	**4** (19) **7** (64) **8** (17)	0
14	H	1-Ad	$CHCl_3$	0.06	60	**4** (79) **7** (18) **8** (3)	0

[a] 1-Ad refers to 1-adamantyl. Yields quoted refer to those determined from analysis of the crude mixtures by ^{1}H NMR (600 MHz). Isolated yields were within a few percent of the values given. General procedure for reactions performed at ambient and higher temperatures: the 1,2-dioxine **1** and ylide (1 equiv.) were combined in the appropriate solvent at the concentration specified and the mixture stirred under nitrogen for 3 days. The solvent was removed *in vacuo* and the residue subjected to flash chromatography (ethyl acetate–hexane, 1:4) to afford the observed products. [b] A catalytic amount (5 mol%) of Jacobson's catalyst was also added at −15 °C. The mixture was kept at this temperature for 2 days after which time it was allowed to warm to room temperature and was analysed. [c] Triethylamine (1 equiv.) added at −15 °C. The mixture was kept at this temperature for 3 days after which time it was allowed to warm to room temperature and was analysed.

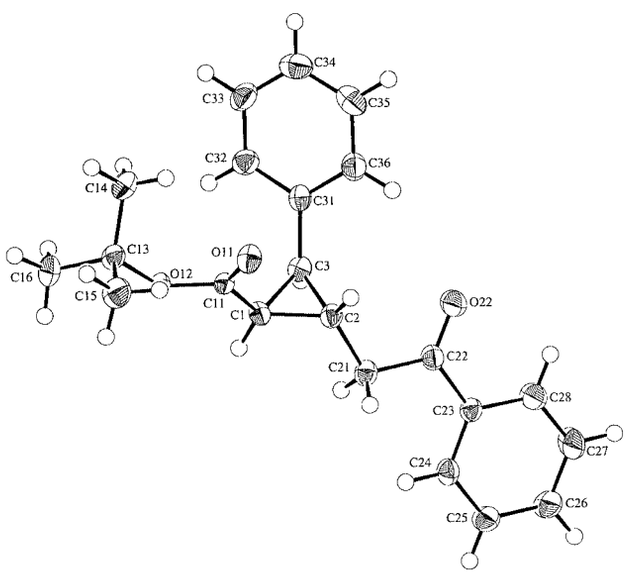

Fig. 1 Molecular structure of **7** (Y = Ph, R^1 = *t*-Bu) showing the crystallographic numbering scheme employed: O(11)–C(11)–C(1)–C(2) 1.1(4)°, O(22)–C(22)–C(21)–C(2) 1.1(3)° and C(32)–C(31)–C(3)–C(1) −69.2(3)°.

gHMBC NMR techniques.† Fig. 1 represents the molecular structure of **7** (Y = Ph, R^1 = *t*-Bu).‡,[2]

To rule out the possibility that the minor cyclopropane **8** was formed first under the reaction conditions, and then isomerised to **7**, we treated isolated cyclopropane **8** with excess ylide under identical reaction conditions (with triphenylphosphine oxide present) and found no isomerisation. We next analysed the effect of temperature on reaction outcome. Performing the identical reaction at 60 °C resulted in an increase in yield of the 'normal' *trans*-cyclopropane **4** at the expense of cyclopropanes (**7** and **8**) (entry 4). A slight increase in the yield of 1,4-diketone **6** was also noticed and is expected at elevated temperatures through a competing Kornblum–De La Mare rearrangement.[3] We have previously reported the use of $Co(salen)_2$ (salen = 2,2′-[ethane-1,2-diylbis(nitrilomethylidyne)]dibenzenethiolato) or Jacobson's catalyst to dramatically accelerate these cyclopropanation reactions.[1] These catalysts rapidly induce rearrangement of the 1,2-dioxines to their corresponding *cis* γ-hydroxy enones which are the key intermediates required for cyclopropanation.[4] Hence we next performed the identical reaction at −15 °C in the presence of a catalytic amount (5 mol%) of Jacobson's catalyst (entry 2). At this temperature none of the 'normal' *trans*-cyclopropane isomer **4** was detected whilst the yield of **7** had increased to 91%.

In order to further evaluate the effect of ylide steric bulk on cyclopropanation outcome we investigated the use of the 1-adamantyl ester which has a slightly smaller cone angle than the *tert*-butyl moiety (entries 5–9). Utilisation of this ylide **2a** (R^1 = 1-Ad) resulted in a decrease in yield of (**7** and **8**) with a concomitant increase in the yield of the 'normal' *trans* isomer **4** (compare entries 6 and 3). Performing the reaction at elevated temperature once again favoured the formation of the 'normal' *trans*-cyclopropane **4** (entries 8 and 9) while lower temperatures were found to favour the formation of **7** and **8** (entry 5). An important observation was that simply increasing the overall reaction concentration favours the formation of the 'normal' *trans*-cyclopropane over **7** and **8** (compare entries 6 and 7). In addition, we have previously noticed that the sterics and electronics of the substituent Y within the 1,2-dioxines **1** have little effect on cyclopropanation outcome and as such we anticipated that this new route to diastereomerically pure cyclopropanes of type **7** would be applicable to a wide range of substituents.[1] This assumption was verified with the use of 1,2-dioxine **1** (Y = H) which afforded the di-substituted cyclopropanes **4** and **7** in good yields at elevated and sub-ambient temperatures respectively (entries 10–14). Once again, the use of sterically bulky ester ylides under concentrated conditions favours the formation of the 'normal' *trans* isomer **4** while dilute conditions favour the formation of **7** and **8**.

Finally, monitoring the reaction between 1,2-dioxine (**1**, Y = Ph) with the *tert*-butyl ester ylide (entry 3) by ^{31}P NMR at 20 °C revealed the initial formation of two phosphorus containing intermediates corresponding to signals at 23.99 and 24.29 ppm.§ These two intermediates which were in a relative ratio of *ca.* 9:1, respectively, then decayed over 12 hours to afford the observed cyclopropanes **7**, **8** and TPPO. These chemical shifts are inconsistent with a neutral pentavalent oxaphospholane ring of type **3** and are more appropriately assigned as being due to charged species.[5] The exact nature of these intermediates is yet to be fully established.

We conclude that the steric bulk of the ester moiety of stabilised phosphorus ylides has a dramatic effect on cyclopropanation outcome observed during the reaction between 1,2-dioxines and stabilised ester ylides. Whereas previously, utilisation of sterically 'non-bulky' ylides (*e.g.* Me, Et, Bn) afforded the 'normal' *trans* diastereomerically pure cyclopropanes **4** in excellent yields at ambient temperature, we now find that sterically bulky ylides (*e.g.* *t*-Bu, 1-Ad) favour the formation of a different diastereomeric cyclopropyl series at these temperatures. The mechanism is currently being fully investigated and will be reported in due course.

Acknowledgements

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Notes and references

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

‡ *Crystal data*: $C_{22}H_{24}O_3$, **7** (Y = Ph, R^1 = *t*-Bu): monoclinic $P2_1/n$, $a = 5.5486(1)$, $b = 17.8452(8)$, $c = 19.0424(8)$ Å, $\beta = 91.930(3)°$, $U = 1884.4(1)$ Å^3, $Z = 4$, $D_c = 1.186$ g cm^{-3} and $\mu = 0.77$ cm^{-1}. Data were collected at 173 K on a Nonius Kappa CCD employing Mo-Kα radiation in the ranges $1.0° < \theta < 30.1°$ and $1.4° < \theta < 27.5°$, respectively. The structure was solved by SAPI91 and refined with the TEXSAN Structure Analysis Package (Molecular Structure Corporation, 1998) of crystallographic programs. A total of 2484 reflections with $I \geq 3.0\sigma(I)$ were used in the refinement which converged with $R = 0.073$ and $Rw = 0.047$. CCDC reference number 207/411. See http://www.rsc.org/suppdata/p1/b0/b001975p/ for crystallographic files in .cif format.

§ ^{31}P NMR chemical shifts referenced to 85% aqueous H_3PO_4 (external) in $CDCl_3$. No such signals are observable for the reaction of the same 1,2-dioxine with non-bulky ylides, ref. 1.

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2 The crystal structure of cyclopropane **4** (Y = Ph, R^1 = *t*-Bu) has been submitted for publication elsewhere; T. D. Avery, G. Fallon, D. K. Taylor and E. R. T. Tiekink, *Z. Kristallogr.*, 2000, in the press. Cyclopropane **8** (Y = Ph, R^1 = *t*-Bu) has been submitted for publication elsewhere; T. D. Avery, G. Fallon, D. K. Taylor and E. R. T. Tiekink, submitted for publication in *Z. Kristallogr.*, 2000.

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4 K. E. O'Shea and C. S. Foote, *J. Org. Chem.*, 1989, **54**, 3475. Also see ref. 1.

5 See for example: J. C. Hanekamp, R. B. Rookhuizen, H. J. T. Bos and L. Brandsma, *Tetrahedron*, 1992, **48**, 5151; W. Adam, H. M. Harrer and A. Treiber, *J. Am. Chem. Soc.*, 1994, **116**, 7581 and references cited therein.