Tandem oxidation processes: a combined phosphorus- and sulfur-ylide approach to polysubstituted cyclopropanes

Magalie F. Oswald, Steven A. Raw and Richard J. K. Taylor*

A new manganese dioxide-mediated tandem oxidation process (TOP) has been developed which, by suitable combination of stabilised phosphorus- and sulfur-ylides, allows the direct conversion of allylic alcohols or α-hydroxyketones into polysubstituted cyclopropanes.

We have a long-standing interest in the development of manganese dioxide-mediated tandem oxidation processes (TOPs) for the elaboration of alcohols.[1] These TOP methodologies offer a number of advantages to the organic chemist: they are operationally simple, the MnO_2 and its by-products being removed by a simple filtration; they result in a reduced number of operations, giving significant time–cost benefits; they allow the use of "difficult" carbonyl intermediates (i.e. those that are volatile, toxic or noxious) as they are prepared and elaborated in situ. Initial studies concentrated on 1,2-additions to the carbonyl, e.g. olefination[1a,c] and imine-formation.[1d] We have recently, however, described a MnO_2–TOP methodology for the conversion of a variety of allylic alcohols into cyclopropanes via oxidation and 1,4-trapping of the so-formed acroleins in situ with stabilised sulfur-ylides (Scheme 1).[2]
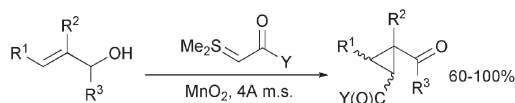

Scheme 1 TOP–cyclopropanation methodology.

We were intrigued by the possibility that the so-formed cyclopropanecarboxaldehydes could be exploited in further in situ transformations. We decided to first examine the Wittig reaction, as we have already established the compatibility of phosphorus-ylides with MnO_2.[1c]

In general, the addition of ylides to α,β-unsaturated systems can occur via two modes; fast but reversible 1,2-addition or slow but irreversible 1,4-addition. We hoped to tune the reaction conditions so that both sulfur- and phosphorus-ylides could be used in situ, in the presence of MnO_2, to allow first oxidation, followed by cyclopropanation then olefination.

In pursuit of this concept, we examined the reaction of 2-methylprop-2-en-1-ol **1a** with S-ylide **2a**,[3a] P-ylide **3a** and activated MnO_2. We were delighted to observe, in our first attempt, the formation of the desired cyclopropane **4a** as a ~1.4:1 mixture of isomers in a yield of 62% (Scheme 2). This was

accompanied by a small but significant amount of dienoate **5a**. We are of the opinion that cyclopropanation occurs faster than olefination for two reasons: (1) TLC analysis indicates complete oxidation–cyclopropanation, giving the known aldehyde,[2] before significant olefination is observed. (2) When dienoate **5a** was exposed to S-ylide **2a** under similar conditions, only ∼50% conversion to **4a** was observed after 16 h.
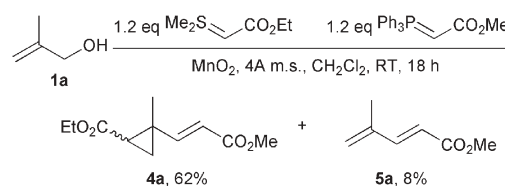
Scheme 2 TOP–cyclopropanation–olefination.

A brief optimisation study was then carried out, varying temperature and equivalents of ylides **2a** and **3a**. It was quickly established that use of a two-fold excess of S-ylide and carrying out the reaction at reflux gave the best yield of **4a**, 81%, with no dienoate **5a** being observed. These optimum conditions were then shown to work well with a variety of alcohols **1**, S-ylides (**2a**[3a] and **2b**[3b]) and P-ylides **3** (Table 1).

We have previously described a TOP–olefination approach to γ-ketocrotonates[6] from α-hydroxyketones **6** and, with the success of our initial aims, we were keen to expand the current methodology to this concept: We envisaged a complementary sequence whereby cyclopropanes are produced by a "queuing process" in which olefination, subsequent to oxidation, necessarily precedes cyclopropanation (Scheme 3).
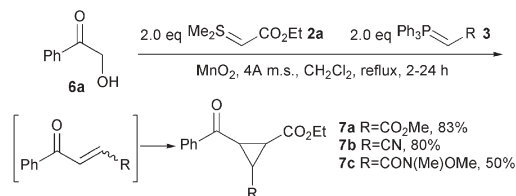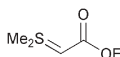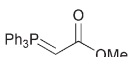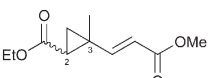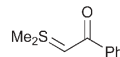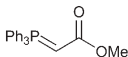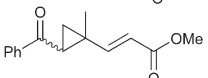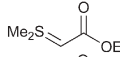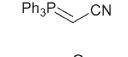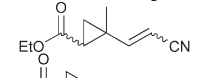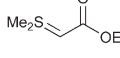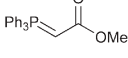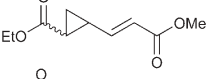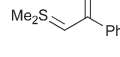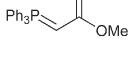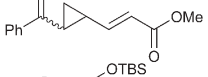

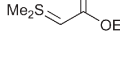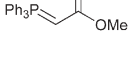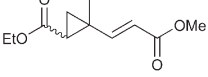**Scheme 3** TOP–olefination–cyclopropanation.

As shown, after brief optimisation, conditions were found that allowed conversion of α-hydroxyacetophenone **6a** to the intermediate γ-ketocrotonates by olefination with P-ylides **3a–c**, subsequent in situ cyclopropanation (with **2a**) gave the desired products **7a–c** in good to excellent yields. These conditions were

Table 1 TOP–cyclopropanation–olefination methodology[4,5]

Entry	Alcohol	S-ylide	P-ylide	Product	2,3-trans:cis[a]	Yield
i	1a	2a	3a	4a	~3.5:1	81%[b]
ii	1a	2b	3a	4b	~3.0:1	66%
iii	1a	2a	3b	4c	—[c]	88%
iv	1b	2a	3a	4d	~6.5:1	61%
v	1b	2b	3a	4e	~3.5:1	74%
vi	1c	2a	3a	4f	~1.8:1	64%
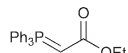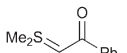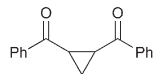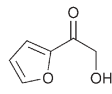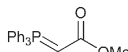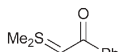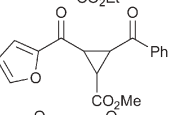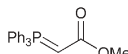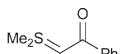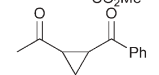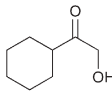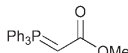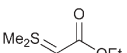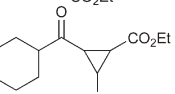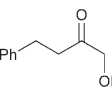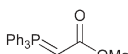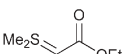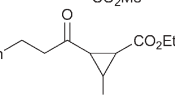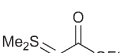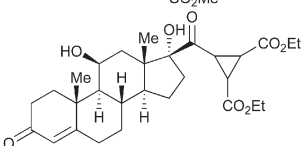
[a] Ratio determined by integration of ^{1}H NMR spectra. [b] When Ph$_3$PCHCO$_2$^{t}Bu was used in place of **3a**, the desired cyclopropane was formed (56% yield), accompanied by the corresponding dienoate (27%). [c] Alkene also showed *E*- and *Z*-isomers. *trans*/*E*:*cis*/*E*:*trans*/*Z*:*cis*/*Z* ~8.5:4.4:3.6:1.0.

then applied to a variety of α-hydroxyketones **6**, P-ylides **3** and S-ylides **2** to give cyclopropanes **7d–i** in similar yields (Table 2). The so-formed cyclopropanes are structurally interesting, being 1,2,3-trisubstituted with differentiated carbonyl groups. Of particular note is the use of hydrocortisone **6f** (entry vi), showing the applicability of this methodology to complex, multi-functional substrates. Moreover, NMR spectroscopy shows that just one isomer of the product **7i** predominates, implying regio- and stereoselectivity in the *in situ* cyclopropanation step.

In conclusion, we have developed two related MnO$_2$-mediated TOP methodologies which exploit the combination of sulfur- and phosphorus-ylides to give polysubstituted cyclopropanes. These methodologies both comprise three discrete transformations in a single manipulation, which is followed by simple work-up and

Table 2 TOP–olefination–cyclopropanation methodology[4,5]

Entry	α-Hydroxyketone	P-ylide	S-ylide	Product[a]	Yield
i	6a	3e	2b	7d	81%
ii	6b[7]	3a	2b	7e	63%[b]
iii	6c	3a	2b	7f	60%[c]
iv	6d[7]	3a	2a	7g	60%
v	6e[7]	3a	2a	7h	51%
vi	6f	3e	2a	7i	78%

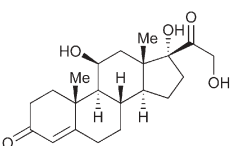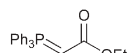[a] Isolated as a mixture of isomers about the cyclopropane. [b] When S-ylide **2a** was used, the corresponding cyclopropane was isolated in 54% yield. [c] When S-ylide **2a** was used, the corresponding cyclopropane was isolated in 55% yield.

purification. We are currently optimising this methodology and applying it to target synthesis.

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Notes and references

1 For examples see: (*a*) S. A. Raw, M. Reid, E. Roman and R. J. K. Taylor, *Synlett*, 2004, 819; (*b*) S. A. Raw, C. D. Wilfred and R. J. K. Taylor, *Org. Biomol. Chem.*, 2004, **2**, 788; (*c*) X. Wei and R. J. K. Taylor, *J. Org. Chem.*, 2000, **65**, 616; (*d*) L. Blackburn and R. J. K. Taylor, *Org. Lett.*, 2001, **3**, 1637 and references therein.
2 M. F. Oswald, S. A. Raw and R. J. K. Taylor, *Org. Lett.*, 2004, **6**, 3997.
3 (*a*) G. B. Payne, *J. Org. Chem.*, 1967, **32**, 3351; (*b*) J. Quintana, M. Torres and F. Serratosa, *Tetrahedron*, 1973, **29**, 2065.
4 General procedure: to a solution of alcohol (**1** or **6**) in CH_2Cl_2 was added sequentially powdered 4Å molecular sieves (1.0 g per mmol of alcohol), S-ylide **2** (2.0 eq.), P-ylide **3** (1.2 eq. for alcohol **1**, 2.0 eq. for **6**) and activated MnO_2 (10.0 eq.). The mixture was heated to reflux and monitored by TLC. After complete consumption of starting material and all expected intermediates (*i.e.* cyclopropanecarboxaldehydes or γ-ketocrotonates), the mixture was cooled, filtered through Celite® and concentrated *in vacuo*. The crude reaction mixture was then purified by column chromatography, giving the product (**4** or **7**).
5 All known compounds gave satisfactory data, all novel compounds were fully characterized by spectroscopic methods and HRMS.
6 K. A. Runcie and R. J. K. Taylor, *Chem. Commun.*, 2002, 974.
7 Non-commercially available α-hydroxyketones[5] were synthesised according to a literature procedure: R. M. Moriaty, B. A. Berglund and R. Penmaster, *Tetrahedron Lett.*, 1992, **33**, 6065.