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Manganese dioxide can oxidise unactivated alcohols under *in situ* oxidation–Wittig conditions

Leonie Blackburn, Xudong Wei and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: rjkt1@york.ac.uk

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The *in situ* alcohol oxidation–Wittig reaction using manganese dioxide as the oxidant has been applied to semi-activated and, for the first time, unactivated alcohols to furnish the corresponding α,β-unsaturated esters.

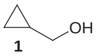
Manganese dioxide is an extremely useful oxidant in organic chemistry.[1] Oxidations using manganese dioxide are particularly easy to perform as the oxidant is heterogeneous and the reaction work-up usually involves simple filtration and evaporation of the solvent. An important use of manganese dioxide is to convert primary alcohols into the corresponding aldehydes, although the process is limited to activated systems of the allylic/benzylic type. Recently, we described the development of an *in situ* manganese dioxide oxidation–Wittig process in which activated alcohols were treated with manganese dioxide in the presence of a stabilised Wittig reagent: the resulting aldehyde was trapped as it was formed to produce the homologated α,β-unsaturated ester [eqn. (1)].[2] This procedure is particularly useful in cases where the intermediate aldehyde is difficult to isolate (*e.g.* for reasons of volatility, toxicity, liability to oligomerisation).

$$RCH_2OH \xrightarrow[Ph_3P{=}CHE]{MnO_2,\ CH_2Cl_2,\ \text{room temp.}} RCH{=}CHE \qquad (1)$$

$$R = \text{vinyl, alkynyl, phenyl;} \quad E = CO_2Et, \textit{etc.}$$

Coincidentally, at around the same time, Barrett *et al.* reported the combined use of the Dess–Martin periodinane and stabilised phosphoranes,[3] and Matsuda's group employed barium permanganate in a similar process.[4]†

The simplicity of the manganese dioxide procedure referred to above, coupled with the toxicity of barium permanganate and the sensitivity, and hazardous preparation, of the Dess–Martin oxidant, prompted us to attempt to extend the scope of the process (Tables 1 and 2). Initial studies concentrated on alcohols which might be classified as 'semi-activated' (Table 1).‡ Thus, as expected, cyclopropylmethanol **1** underwent smooth *in situ* oxidation–Wittig reaction giving enoates **2** and **3**, as did the corresponding diol **4** producing dienoate **5**.



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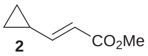

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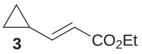

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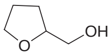

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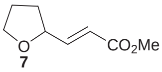

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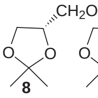

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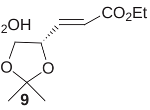

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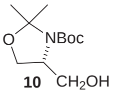

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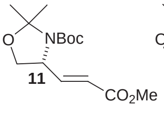

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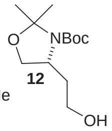

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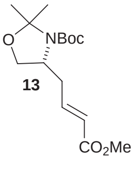

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Such reactions should prove useful in the synthesis of cyclopropyl-based natural products.[3a]

Table 1 *In situ* oxidation–Wittig reactions on 'semi-activated' alcohols[a]

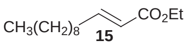
Substrate	Product	Solvent	*t*/h	Yield (%)	Configuration
1	**2**	toluene	4	80	>99% *E*
1	**3**	toluene	4	86	>99% *E*
4	**5**	$CHCl_3$	18	81	>99% *E*
6	**7**	$CHCl_3$	24	66	6:1 *E*:*Z*
8	**9**	toluene	20	74	3:1 *E*:*Z*[b]
10	**11**	toluene	18	58	>95% *E*[c]
12	**13**	$CHCl_3$	20	70	>95% *E*[d]

[a] Activated MnO_2 (Aldrich, *ca.* 10 equiv.) was added in three equal portions to a mixture of the alcohol and the stabilised Wittig reagent, Ph_3PCHCO_2R (1.2 equiv.), in the specified solvent which was heated under reflux for the specified time. [b] $[\alpha]_D^{20}$ +40.5 (*c* 1, $CHCl_3$); lit.,[6] +38.3 (*c* 2, $CHCl_3$). [c] $[\alpha]_D^{20}$ −65.5 (*c* 1, $CHCl_3$); lit.,[7] −65 (*c* 4.2, CH_2Cl_2). [d] $[\alpha]_D^{20}$ −27.9 (*c* 1.15, $CHCl_3$).

In this same study (Table 1), we also investigated the oxidation of alcohols containing a proximal heteroatom which might activate the alcohol to oxidation inductively and/or by providing a coordination site for the oxidant. Encouragingly, tetrahydrofurfuryl alcohol **6** furnished the desired α,β-unsaturated ester **7** in good yield. In contrast, oxidation of this alcohol to the corresponding aldehyde is reported to be problematic and at best yields of *ca.* 50% are obtained using tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO).[5] The *in situ* reaction was also successfully applied to several related enantiomerically pure primary alcohols **8**, **10** and **12**. No racemisation was observed according to polarimeteric measurements[6,7] and good yields were obtained. During the course of this study McKervey *et al.* utilised our *in situ* oxidation–Wittig methodology to convert non-racemic protected γ-amino alcohols into the corresponding α,β-unsaturated esters and ketones without loss of stereochemical integrity.[8]

In order to establish the limitations of this process we treated a completely unactivated alcohol, decanol **14**, under the *in situ* manganese dioxide–Wittig conditions.

$CH_3(CH_2)_8CH_2OH$ **14**



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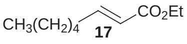
$CH_3(CH_2)_4CH_2OH$ **16**



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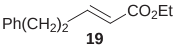
$Ph(CH_2)_3OH$ **18**



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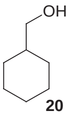

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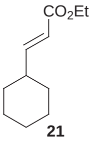

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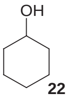

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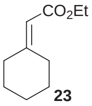

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To our amazement (Table 2), enoate **15**[9] was obtained in 80% yield after 24 h reflux in toluene.§ This result was extremely surprising given the generally accepted view that manganese dioxide is not an effective oxidant for unactivated primary alcohols.[1] We therefore studied other unactivated primary

Table 2 *In situ* oxidation–Wittig reaction on unactivated alcohols[a]

Substrate	Product	Solvent	*t*/h	Yield(%)	Configuration
14	**15**	toluene	24	80	$>95\%$ *E*
16	**17**	toluene	24	70	$>95\%$ *E*
18	**19**	toluene	6	86	$>95\%$ *E*
20	**21**	$CHCl_3$	20	51	$>99\%$ *E*
22	**23**	toluene	24	<1	

[a] Activated MnO_2 (Aldrich, *ca*. 10 equiv.) was added in three equal portions to a mixture of the alcohol and the stabilised Wittig reagent, Ph_3PCHCO_2R (1.2 equiv.), in the specified solvent which was heated under reflux for the specified time.

alcohols. Both hexanol **16** and 1-phenylpropan-3-ol **18** furnished the desired products **17** and **19**, respectively, in excellent yield. With cyclohexylmethanol **20**, the expected product **21** was obtained in reduced yield (51%); it seems likely that alkyl substitution at the β-position relative to the alcohol is responsible for the reduction in efficiency. A limitation to the process was realised when secondary alcohols were studied. As shown in Table 2, treatment of cyclohexanol **22** under the *in situ* oxidation–Wittig conditions gave only trace amounts of the desired enoate **23**. Similar results were also observed with pentan-3-ol and dihydrocholesterol, which both failed to yield the corresponding enoates. These results were not unexpected as both the oxidation of secondary alcohols and the Wittig reactions of stabilised phosphoranes with ketones are known to be difficult compared with the corresponding sequence commencing with primary alcohols.

We have carried out preliminary studies to try to rationalise these results. The most important point is that on treatment with manganese dioxide in the absence of a Wittig reagent, but under otherwise identical conditions, the primary alcohols gave only low yields of the corresponding aldehydes: for example, after reflux in toluene with manganese dioxide for 24 h, decanol gave decanal in only 12% yield, unreacted alcohol accounting for the balance of material. One possible explanation for the high conversions observed in the presence of the stabilised phosphoranes is that the primary alcohols are being converted into the corresponding aldehydes in small equilibrium quantities with the *in situ* Wittig reagent immediately trapping out the aldehyde. Alternatively it is possible that the phosphorane may be activating the oxidant or the alcohol (or the intermediate complex) to oxidation. Further mechanistic studies are in progress.¶

In summary, we have shown for the first time that unactivated primary alcohols can be efficiently oxidised using manganese dioxide under *in situ* Wittig conditions. Similar results are reported with 'semi-activated' alcohols producing a range of synthetically useful α,β-unsaturated esters.

We thank the EPSRC for a research fellowship (X. W.) and research studentship (L. B.). We are also grateful to Pfizer for additional financial support and to A. D. Campbell for carrying out the conversion of **12** into **13**.

Notes and references

† In preliminary studies, we have shown that chromium dioxide (Magtrieve™) can also be used for *in situ* oxidation–Wittig reactions.

‡ All new compounds were fully characterised spectroscopically and by HRMS.

§ Representative procedure: Activated manganese dioxide (0.3 g) was added to a stirred solution of decanol (158 mg, 1 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (418 mg, 1.2 mmol) in toluene (25 ml) and the mixture was heated to reflux. Two further portions of manganese dioxide (*ca.* 0.3 g each) were added to the reaction over the first hour and then it was stirred and heated until TLC indicated that reaction was complete (*ca.* 24 h). The manganese dioxide was removed by filtration through Celite, the Celite was washed well with toluene, and the combined organic portions were concentrated *in vacuo* to *ca*. 1–2 ml. Column chromatography (light petroleum–Et_2O 5:1) gave ethyl *trans*-dodec-2-enoate (181 mg, 80%) as a colourless oil with spectroscopic data consistent with those published (ref. 9).

¶ Addition of Ph_3PO or pyridine to the manganese dioxide oxidation of decanol under toluene reflux (24 h) increases the yield from 12 to *ca.* 40%.

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