

## Highly efficient use of NaOCl in the Ru-catalysed oxidation of aliphatic ethers to esters

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**The selectivity of  $\alpha$ -oxidation of ethers to esters via Ru–NaOCl can be dramatically improved by pH control, at high substrate to catalyst ratios using a stoichiometric amount of hypochlorite in biphasic media at room temperature.**

$\alpha$ -Oxidation of ethers and acetals is a potentially interesting conversion in the fine chemical industry for the production of complex natural products and for use in carbohydrate chemistry, where this reaction is frequently applied for the oxidative deprotection of hydroxy groups. A mild and selective oxidant for this conversion is  $\text{RuO}_4$ , which can be conveniently generated *in situ* using a Ru precursor and  $\text{NaIO}_4$  or hypochlorite salts.<sup>1</sup>

The methods described in the literature required either a large amount of ruthenium<sup>2</sup> (25 mol%) or an excess of hypochlorite<sup>3</sup> (9 equiv.), giving moderate selectivity toward ester formation often at incomplete conversion and long reaction times.  $\text{LiClO}$  was reported as the most efficient oxidative agent at high catalytic ratio (0.2 mol% Ru) but long reaction times and repeated additions of hypochlorite were required to achieve complete conversion.<sup>4</sup> The use of an excess of hypochlorite leads to the formation of copious amounts of sodium chloride waste and hence to a high *E* factor<sup>5</sup> which decreases the environmental acceptability of the process.

We reasoned that efficient use of NaOCl (*i.e.* 2:1 ratio to the substrate) should be achieved by optimising the reoxidation of the catalyst from its reduced form, presumably  $\text{RuO}_2$ , avoiding decomposition to inactive insoluble species. In other words, the rate of the reaction  $\text{Ru(IV)} - \text{Ru(VIII)}$ , namely  $k_{\text{ox}}$ , should be much larger than the rate of decomposition,  $k_{\text{dec}}$ , throughout the catalytic run (Scheme 1). We found that simple pH control is the key to improve the catalytic process and obtain fast selective  $\alpha$ -oxidation of aliphatic symmetrical and unsymmetrical ethers to esters.

We generated  $\text{RuO}_4$  in solution by dissolving  $[\text{RuCl}_2(\text{dmsO})_4]$  **1**, 0.05 mmol, in  $\text{CH}_2\text{Cl}_2$ , 2  $\text{cm}^3$ , to which aqueous NaOCl (1.0 M), 0.2 mmol, was added quickly under stirring at room temperature. After a few minutes the pH of the stirred biphasic mixture was measured as *ca.* 9.

In a separate experiment, *n*-butyl ether (5 mmol) was added to a solution of **1** (1 mol%) which was preactivated as described above, under vigorous stirring at 0 °C. To this solution, NaOCl (10 mmol) was added dropwise over 2 hours, during which the temperature was maintained at 0 °C and pH was monitored. After this time, the conversion stopped and was accompanied by a sharp decrease of pH from 8.5 to 4.8, as indicated by the reaction profile, shown in Fig. 1, with formation of a black precipitate. The reaction mixture was allowed to warm up to

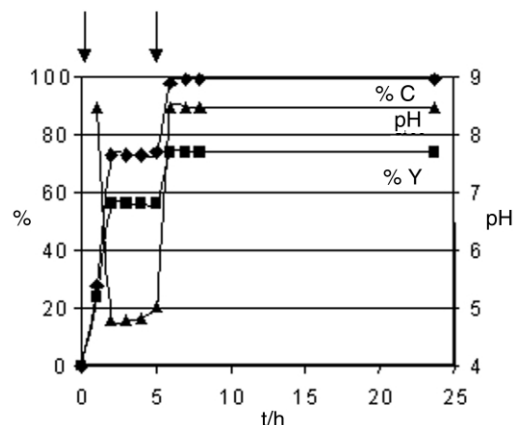
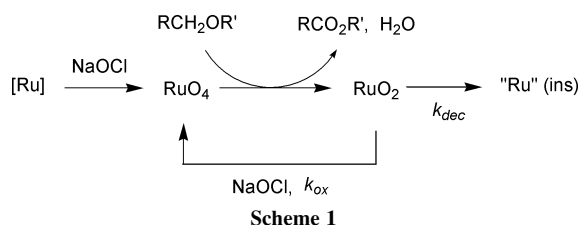
room temperature for 3 h, during which no further conversion was observed and the pH stayed in the acidic region. The addition of another aliquot of NaOCl (10 mmol) caused the precipitate to dissolve and led to complete conversion and a final selectivity of 74% to the ester, with the pH back at the original value of 8.5.

From this experiment, it appears that unproductive hypochlorite decomposition occurs at low pH, and this could in turn decrease the amount of oxidant available for efficient catalyst reoxidation. The catalyst is deposited as a precipitate ( $k_{\text{dec}} > k_{\text{ox}}$ ), presumably  $\text{RuO}_2 \times \text{H}_2\text{O}$  with a water content less than 10% which is virtually inert to oxidation as observed by Mills and co-workers.<sup>7</sup> The low pH may also have a detrimental effect on the selectivity toward ester formation, as acid and alcohol are formed as by-products under these conditions. These data suggest that the best catalytic performance for ether oxidation can be obtained in a narrow pH range at alkaline values (8–9.5).

A similar pH effect was observed for the oxidation of octan-2-ol to octan-2-one<sup>8</sup> via Ru– $\text{NaBrO}_3$  and for the Os-catalysed aerobic dihydroxylation of olefins.<sup>9</sup> Our experimental setup was therefore modified in order to keep the pH constant at 9.5, using a pH-stat device for the whole duration of the catalytic run.<sup>†</sup>

In a typical experiment, a Ru precursor (see Table 1) was dissolved in  $\text{CH}_2\text{Cl}_2$  and activated with a 4-fold excess of hypochlorite at room temperature. To this mixture, the substrate was added quickly, followed by dropwise addition of the oxidant, at a rate of *ca.* 0.1  $\text{cm}^3 \text{min}^{-1}$ . During this phase, pH was adjusted by addition of HCl 2.0 M. After complete addition of NaOCl (2 equiv. overall), pH was observed to drop and was therefore kept constant by addition of NaOH 2.0 M until the end of the experiment.

The most relevant results are summarised in Table 1. Aliphatic symmetrical ethers such as (*n*-Pr)<sub>2</sub>O and (*n*-Bu)<sub>2</sub>O could be oxidised to the corresponding esters with very good selectivity in 5 hours (Entries 1–5). (*t*-Bu)O(Et) (unsymmetrical) was similarly converted to *tert*-butyl acetate, the lower selectivity being ascribed to partial hydrolysis of the product



**Fig. 1** Oxidation of (*n*-Bu)<sub>2</sub>O in the presence of **1** (1 mol%), NaOCl (4 equiv.),  $\text{CH}_2\text{Cl}_2$ , 0 °C (2 h)–RT. The oxidant was added in two aliquots (arrows) at  $t = 0$  and  $t = 5$  h, dropwise at *ca.* 0.1  $\text{cm}^3 \text{min}^{-1}$  rate.

**Table 1** Catalytic oxidation of aliphatic ethers to esters<sup>a</sup>

Entry	Substrate	Product	Catalyst <sup>b</sup> /mol%	%C <sup>c</sup>	%Y <sup>c</sup>	%S
1	<i>n</i> -Propyl ether	Propyl propionate	<b>1</b> (0.5)	82	80	98
2	<i>n</i> -Butyl ether	Butyl butyrate	<b>1</b> (0.5)	85	70	82
3			<b>2</b> (0.5)	99	93	93
4			<b>3</b> (0.25)	88	77	88
5			<b>4</b> (0.5)	77	59	78
6			<b>1</b> (0.25) <sup>d</sup>	98	95	97
7	<i>t</i> -Butyl ethyl ether	<i>t</i> -Butyl acetate	<b>1</b> (0.5)	99	73	73
8			<b>2</b> (0.25)	86	51	59
9			<b>1</b> (0.25) <sup>d</sup>	86	71	83
10	Tetrahydropyran	$\delta$ -Valerolactone	<b>1</b> (0.5) <sup>e</sup>	67 <sup>f</sup>	44	66

<sup>a</sup> Conditions: substrate (5 mmol), NaOCl (10 mmol), CH<sub>2</sub>Cl<sub>2</sub> (2 cm<sup>3</sup>), RT, pH 9.5, 5 h. <sup>b</sup> **1**: [RuCl<sub>2</sub>(dmsO)<sub>4</sub>], **2**: [RuCl<sub>2</sub>(dppp)<sub>2</sub>], **3**: TPAP, **4**: RuO<sub>2</sub> × H<sub>2</sub>O.

<sup>c</sup> Determined by GLC based on pure samples, isolated yields usually 2–3% lower. <sup>d</sup> EtOAc instead of CH<sub>2</sub>Cl<sub>2</sub>, 3 h. <sup>e</sup> At pH 7.5. <sup>f</sup> At 20 h.

under basic conditions (Entries 7, 8). Oxidation of tetrahydropyran (cyclic) to  $\delta$ -valerolactone (Entry 10) was carried out at *ca.* neutral pH (7.5) to avoid ring-opening which can occur at high pH, although this decreased the activity of the process and required longer reaction time (20 h). Further studies on the oxidation of cyclic ethers are in progress.

Catalyst screening indicated that numerous precursors can be used, such as Ru(II) complexes *cis*-[RuCl<sub>2</sub>(dmsO)<sub>4</sub>], **1**, and *trans*-[RuCl<sub>2</sub>(dppp)<sub>2</sub>],<sup>10</sup> **2** (dppp = 1,3-bis(diphenylphosphino)propane), the Ru(VII) complex [*n*-Pr<sub>4</sub>N][RuO<sub>4</sub>],<sup>11</sup> TPAP, **3**, and RuO<sub>2</sub> × H<sub>2</sub>O, **4** (as supplied by Acros). For oxidation of butyl ether in CH<sub>2</sub>Cl<sub>2</sub>, **3** proved to be a very active precursor at high catalytic ratio (1:400). For this substrate, the best selectivity was obtained using **2** in 1:200 ratio to the substrate, possibly due to the stabilising effect of the bidentate ligand on the precursor which may function as a reservoir for RuO<sub>4</sub>.

We checked the possibility of replacing CH<sub>2</sub>Cl<sub>2</sub> as the organic phase with more environmentally acceptable solvents. Ethyl acetate can not only be used successfully to obtain a biphasic media, but also has a beneficial effect on catalysis. The selectivity to butyl butyrate increased to 97%, using 0.25 mol% of **1** in 3 h (Entry 6). A similar effect was observed for the oxidation of (*t*-Bu)O(Et), where the selectivity to *tert*-butyl acetate increased to 83% (Entry 9). EtOAc may either stabilise the catalyst in the high oxidation state or decrease the activation barrier of the polar transition state. The pH control procedure could be conveniently replaced by a more user-friendly NaHCO<sub>3</sub>–Na<sub>2</sub>CO<sub>3</sub> buffer (pH 9.5, 1:1 v/v ratio to solvent). Butyl ether was converted to butyl butyrate with 98% selectivity using TPAP (0.25 mol%) in EtOAc.

We are currently investigating the scope of this method, although we envisage that its applicability may be limited to substrates not containing carbon–carbon double or triple bonds which are known to be cleaved by RuO<sub>4</sub>.

In summary, this study shows that Ru-catalysed bleach  $\alpha$ -oxidation of ethers can be carried out without the need of an excess of oxidant (as reported so far) whereas the reaction proceeds at constant pH 9.5; fast complete conversions (as short as 3 h) and high yields in esters (up to 95%) were obtained by efficient reoxidation of Ru to the active catalytic species (RuO<sub>4</sub>) by optimal use of the terminal oxidant (NaOCl) using environmentally-friendly organic solvents.

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## Notes and references

† In a typical experiment, the catalytic run was carried out in a three-necked 50 cm<sup>3</sup> pear-shaped flask containing a magnetic stirrer, equipped with a dropping funnel and connected to a Metrohm pH-stat device consisting of Dosimat, pH meter and Impulsomat. The rate of addition of aqueous NaOCl (1.0 M) by dropping funnel was typically 0.1 cm<sup>3</sup> min<sup>-1</sup>, whilst HCl (2.0 M) and NaOH (2.0 M) were added automatically by Dosimat at 0.5 cm<sup>3</sup> min<sup>-1</sup> rate (usually less than 1 cm<sup>3</sup> each was required) having preset the pH at 9.5.

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