The Effect of pH Control on the Selective Ruthenium-Catalyzed Oxidation of Ethers and Alcohols with Sodium Hypochlorite

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Abstract: Highly selective oxidations of ethers to esters or lactones and of secondary alcohols to ketones were achieved using catalytic amounts of various Ru precursors and the theoretical amount of NaOCl. Reactions were carried out in biphasic solvent mixtures at constant pH 9–9.5 *via* either feed-on-demand addition of HCl and NaOH or in the presence of $NaHCO_3/Na_2CO_3$ buffer. The catalyst could be easily recycled for at least 4 times with only minor loss in selectivity. Products were generally recovered by simple phase separation and evaporation of the organic solvent. The effects of catalyst precursor, additives and pH control method are also described.

Keywords: alcohols; esters; ethers; ketones; lactones; oxidation; pH effect; ruthenium

Introduction

Oxidations are ubiquitous reactions in both inorganic and organic chemistry. These transformations are of great importance not only in the laboratory, but also in industry, where they account for a majority of the applied processes in bulk and fine chemistry. Stoichiometric amounts of oxidants are still applied, despite the fact that a wealth of research has focused on catalytic systems for organic oxidations. Our group has a longstanding interest in the area of catalytic oxidations, including radical processes, metal-mediated homogeneous and heterogeneous catalysis for oxidation of organic substrates such as alkenes, alcohols, etc.[1]

Recently we have focused our attention on the selective α-oxidation of ethers to esters. This reaction can be applied in fine chemical industry for the production of complex natural products and, in principle, to carbohydrate chemistry, where it may enable efficient oxidative deprotection of carboxyl groups. The most efficient oxidant for this transformation is RuO_4.[2] Classical use involves stoichiometric amounts of this reagent, but RuO_4 can also be conveniently generated *in situ via* a combination of ruthenium precursors, usually $RuCl_3 \cdot H_2O$ or $RuO_2 \cdot H_2O$, with an inorganic oxidant such as $NaIO_4$,[3] $NaBrO_3$[4] or NaOCl.[5] In practice these systems involve biphasic conditions, typically CCl_4/H_2O,[6a] often in the presence of phase transfer agents such as tetraalkylammonium salts.[6b] The method has been successfully applied to the oxidation of many different substrates, including linear and cyclic saturated hydrocarbons,[7] olefins and dienes,[8] alkynes,[9] alcohols and diols,[10] carbohydrates,[11] amino compounds,[12] α-amino acids (to α-aminodicarboxylic acids),[13] and steroids.[14]

The $Ru/NaIO_4$ method was substantially improved by Sharpless and co-workers[15] by addition of MeCN to the traditional CCl_4/H_2O system. The higher catalytic activity was explained by the coordinating properties of MeCN, thus preventing the formation of insoluble Ru species which caused catalyst deactivation. This strategy has become a general procedure in oxidation protocols described since then. In spite of the improvement, however, literature methods still suffer from drawbacks: the need for high ruthenium concentrations, and the use of expensive or toxic oxidants ($NaIO_4$, $NaBrO_3$), often in large excess (NaOCl), which in turn generate copious amounts of waste by-products giving high *E*-factors and poor atom efficiencies.[16] In addition, some substrates were oxidized with medium to poor selectivity, as is the case of ethers and acetals.[17]

We found that for ether oxidation these methods could be dramatically improved both in activity and selectivity to esters by simple pH control.[18] This allows for (a) low concentrations of Ru precursors; (b) use of a stoichiometric quantity (2 equivs.) of oxidant, i.e., NaOCl; (c) easy product recovery by simple phase separation and (d) efficient catalyst recycling. The

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protocol was also successfully applied to the oxidation of alcohols, in particular giving spectacular results for the otherwise difficult conversion of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**1**) into 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexadiulo-2,6-pyranose (**2**).[19] Hereby we describe the effect of catalyst precursor, additives and pH control method on the oxidation of aliphatic and aromatic ethers, together with mechanistic considerations.

Results and Discussion

In order to optimize the existing ether oxidation methods based on Ru/NaOCl, we reasoned that efficient use of NaOCl (i.e., 2:1 ratio *vs.* substrate for ethers, 1:1 for alcohols) could be achieved by optimizing the reoxidation of the catalyst from its reduced form, thus avoiding decomposition to inactive insoluble species. It was previously shown that the nature of high valent Ru oxo species generated by addition of an oxidant in biphasic solvent systems strongly depends on pH.[20] In a first catalytic experiment, *n*-butyl ether (5 mmol) was added to a solution of [RuCl$_2$(dmso)$_4$] (1 mol %) which was pre-activated by addition of a few drops of NaOCl, under vigorous stirring at 0 ^{0}C. To this solution (pH 8.5), NaOCl (10 mmol) was added dropwise over 2 hours at 0 ^{0}C and pH was monitored. After this time, the conversion stopped and a sharp decrease of pH from 8.5 to 4.8 was observed (Figure 1) together with formation of a black precipitate.

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 butyl butyrate, with the pH back at the original value of 8.5. Our experimental setup was therefore modified in order to keep the pH constant in the range 8.5–9.5, using a pH-stat device for the whole duration of the catalytic run (see Experimental Section). In this way, the reaction could be carried out at room temperature from the beginning with a stoichiometric amount of NaOCl (2 equivs.), without the need for phase transfer agents. Nearly complete conversion and highly selective ester formation was achieved for a series of symmetrical and unsymmetrical aliphatic, cyclic and benzylic ethers. Experimental data are summarized in Table 1, while the reaction profile of a typical high-performance run for ether oxidation is shown in Figure 2.

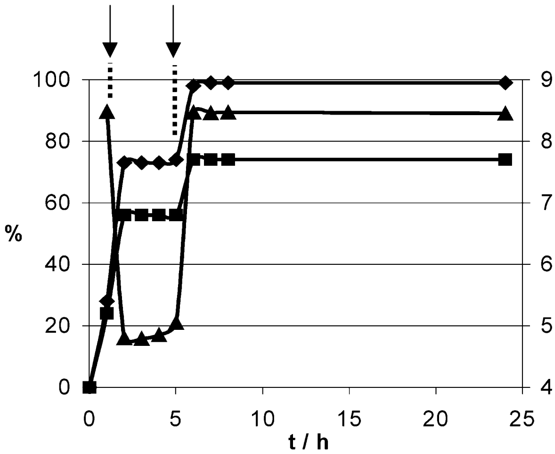


Figure 1. Conversion (◆), yield (■) and pH change (▲) in the oxidation of (n-Bu)$_2$O in the presence of RuCl$_2$(dmso)$_4$ (1 mol %), NaOCl (4 equivalents), CH$_2$Cl$_2$, 0 °C (2 h) – RT. The oxidant was added in two aliquots (2 equivs. each, arrows) at t = 0 and t = 5 h, dropwise at *ca.* 0.1 cm^3/min rate.

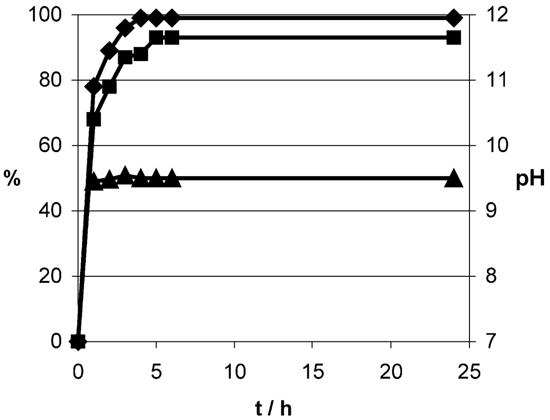


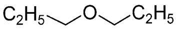
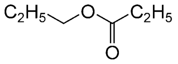
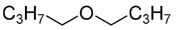
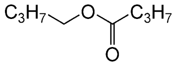
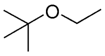
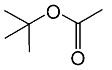
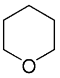
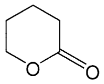
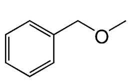
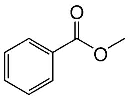
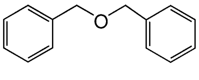
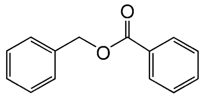
Figure 2. Conversion (◆), yield (■) and pH change (▲) in the oxidation of (n-Bu)$_2$O in the presence of RuCl$_2$(dppp)$_2$ (0.2 mol%), NaOCl (2 equiv.), pH-stat control, CH$_2$Cl$_2$, RT.

The catalyst is entirely confined in the organic phase upon addition of NaOCl, as is evident from simple visual analysis, so that the reoxidation of the catalyst occurs at the phase boundary and is facilitated by fast magnetic stirring. In contrast with early observations by Sharpless and co-workers,[15] the presence of a chlorinated solvent is not mandatory. Replacement of CH$_2$Cl$_2$ with EtOAc or methyl *t*-butyl ether (MTBE), without the need for additional MeCN, showed comparable or better catalytic activity and selectivity to the desired product under the same conditions (Table 1, entries 6, 9). It can be expected that these polar coordinating solvents act, in the words of Sharpless, "to disrupt the insoluble carboxylate complexes and return the ruthenium to the catalytic cycle", analogous to acetonitrile.

The results of catalyst screening using a series of ruthenium complexes with different oxidation states of the metal in the oxidation of dibutyl ether are summarized in Table 2. The best catalyst precursors under the pH-stat conditions were found to be *cis*-Ru(dmso)$_4$Cl$_2$, *trans*-Ru(dppp)$_2$Cl$_2$ [dppp = 1,3-(diphenylphosphino)propane] and [n-Pr$_4$N][RuO$_4$] (TPAP). We attribute this to a higher stability of the precursors under catalytic conditions, and slow conversion to RuO$_4$ by acting as a reservoir.

For lactones hydrolysis may occur at basic pH, thus in the case of tetrahydropyran (entry 10) the reaction was performed at pH 7.5, which in turn gives a slower

Table 1. Oxidation of aliphatic and aromatic ethers via TPAP/NaOCl, pH-stat control.[a]

Entry	Substrate	Product	Catalyst[b] (mol %)	% C[c]	% Y[c]
1			**1** (0.5)	82	80
2			**1** (0.5)	85	70
3			**2** (0.5)	99	93
4			**3** (0.25)	88	77
5			**4** (0.5);	77	59
6			**1** (0.25)[d]	98	95
7			**1** (0.5)	99	73
8			**2** (0.25)	86	51
9			**1** (0.25)[d]	86	71
10			**1** (0.5)[e]	67[f]	44
11			**1** (0.5)	60	42
12			**1** (0.5)	41	22

[a] Conditions: substrate (5 mmol), NaOCl (10 mmol), CH_2Cl_2 (2 cm^3), RT, pH 9.5, 5 h.

[b] **1**: $[RuCl_2(dmso)_4]$, **2**: $[RuCl_2(dppp)_2]$, **3**: TPAP, **4**: $RuO_2 \cdot H_2O$.

[c] Determined by GLC based on pure samples, isolated yields usually 2–3% lower.

[d] EtOAc instead of CH_2Cl_2, 3 h.

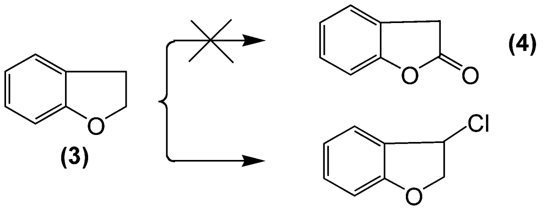
[e] At pH 7.5.

[f] At 20 h.

reaction rate. Ethers containing aromatic moieties such as benzyl methyl ether and dibenzyl ether, were also oxidized, albeit with moderate selectivity as RuO_4 is known to degrade aromatic rings to carboxylic acids (Table 1, entries 11, 12). Oxidation of dihydrobenzofuran (**3**) (81% conversion) using TPAP 0.5%, in the presence of 2 equivalents of NaOCl, yielded after 5 h a single product in 92% selectivity, which was identified as the 1-chlorohydrobenzofuran by GC-MS (Scheme 1). The blank reaction showed lower conversion (73%) and selectivity (77%) to the same product again without formation of coumaranone (**4**).

Apparently, chlorination of the benzylic position takes place (elemental chlorine is always present in solutions of NaOCl).

A possible drawback of our oxidation method could be the cumbersome way to maintaining a constant pH during the catalytic run through alternate Dosimat addition of acid and base. This was solved by replacing the pH control either with adequate buffer solutions or by adding $NaHCO_3$ to the NaOCl solution (pH 9–10). Control experiments were carried out and the results are summarized in Table 3. The three different methods showed results comparable within the experimental error, so we conclude that Dosimat control can be replaced with the buffer solution. For comparison,



Scheme 1.

Table 2. Pre-catalyst screening for oxidation of Bu_2O under pH-stat control conditions.[a]

[Ru]	T [h]	% C	% Y	% S
cis-Ru(dmso)$_4$Cl$_2$	5	97	83	86
	20	97	83	86
trans-Ru(dppp)$_2$Cl$_2$	5	99	93	93
	20	99	93	93
trans-Ru(PPh$_3$)$_3$Cl$_2$	5	72	57	79
	20	73	57	79
[*n*-Pr$_4$N][RuO$_4$]	5	92	80	87
	20	94	82	87
cis-[Ru(dmp)$_2$(MeCN)$_2$](BF$_4$)$_2$	5	78	58	74
	20	87	68	77
Ru/C (5% w/w)	5	52	42	81
	20	64	48	75
RuO$_2$ · H$_2$O	5	79	59	75
	20	81	59	73

[a] Conditions: Bu_2O, 5 mmol; [Ru], 0.5 mol %; NaOCl 2 equivs., CH_2Cl_2 5 mL, TCB (standard) 1 mmol, RT, pH 9.5.

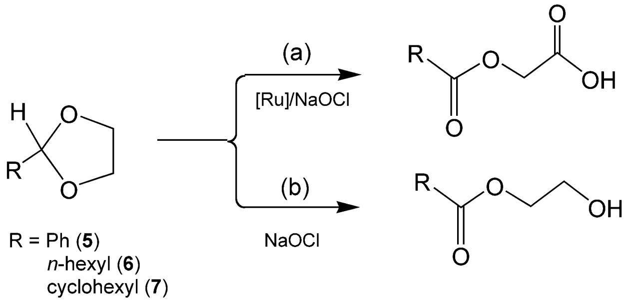
Table 3. Different methods to maintain constant pH during Ru/NaOCl oxidation of Bu_2O.[a]

Cat (mol %)	Method 1		Method 2		Method 3	
	% C	% Y	% C	% Y	% C	% Y
Ru(dmso)$_4$Cl$_2$ (0.5)	85	70	81	65	82	64
TPAP (0.25)	88	77	83	74	81	78
RuO$_2$ · H$_2$O (0.5)	77	59	75	58	73	58

[a] Conditions: Bu_2O, 5 mmol; TPAP, 0.5 mol %; NaOCl 2 equivs., CH_2Cl_2 5 mL, TCB (standard) 1 mmol, RT, 5 h. *Method 1*: Dosimat addition of HCl 2 M (during addition of NaOCl) then NaOH 2 M. *Method 2*: NaOCl 0.7 M solution buffered to pH 10 by addition of $NaHCO_3$ (s). *Method 3*: $NaHCO_3$/Na_2CO_3 buffer (pH 9.5), 1 : 1 v/v ratio to the solvent.

Morris and Kiely reported the use of a small amount of K_2CO_3 together with RuO_2/$NaIO_4$ in biphasic H_2O/CCl_4 media for the oxidation of the C-5 hydroxy group in a series of protected carbohydrates, although the presence of a phase transfer agent (benzyltriethylammonium chloride) was necessary to bring about catalysis and no rationale for the use of the base was given.[21]

The mechanism of ether α-oxidation with RuO_4 was studied in detail by Bakke and Frohaug,[22] who proposed two possible pathways to ester formation, namely (a) concerted reaction similar to S_E2, involving a front-side attack of the electrophile or (b) two-step reaction consisting of a reversible oxidative addition of the ether to a RuO_4 followed by a slow second step with a concerted mechanism to eliminate the ester. The effect of pH on the nature of Ru oxo species in equilibrium was examined by Mills in a recent paper,[20a] showing that perruthenate $Ru^{VII}O_4^-$ is the main species in biphasic H_2O/CCl_4 solutions in the pH range 8 – 10. Although we cannot rule out RuO_4^- as the active oxidant we favor RuO_4 based on the following experimental evidence. We performed the stoichiometric reaction of Bu_2O with TPAP under nitrogen and observed no substrate conversion; moreover, the combination TPAP (10 mol %)/O_2, active for alcohol oxidation,[31b] is inactive for ether oxidation. Oxidation of acrolein dimethyl acetal gave extensive decomposition, as expected for C=C double bond cleavage by RuO_4. Furthermore, a black precipitate, typical of RuO_4, was often observed on the side of the flask when the stirring rate was decreased during the catalytic tests.

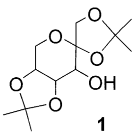
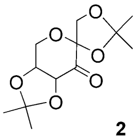
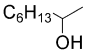
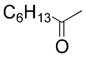
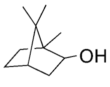
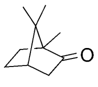
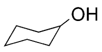
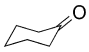
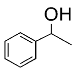
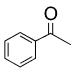
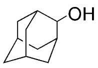
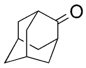


Scheme 2.

Cyclic acetals such as 2-phenyl-1,3-dioxolane (**5**), 2-hexyl-1,3-dioxolane (**6**) and 2-cyclohexyl-1,3-dioxolane (**7**), synthesized according to known procedures,[23] could be oxidized to the corresponding aryl- or alkyl carboxylic acid carboxymethyl esters, albeit in modest yields (Scheme 2). For example, the oxidation of **7**, at buffered pH 9.5 in the presence of Ru(dmso)$_4$Cl$_2$ (0.1 mol %) in EtOAc gave 67% conversion and 19% yield of the acid, whereas 71% conversion and 10% yield were observed at pH 6.5 (acid buffer, see Experimental Section) using 0.5 mol % of Ru(dmso)$_4$Cl$_2$. Lower yields at pH 6.5 could be due to hydrolysis of the substrate, hence leading to unidentified side products. The blank reaction without Ru results in oxidation by NaOCl at the tertiary carbon atom, giving almost quantitative formation of the carboxylic acid 2-hydroxyethyl ester derivatives under the same conditions both at pH 9.5 and 6.5 (Scheme 2).

Alcohol oxidations with Ru/NaOCl were also improved using the pH control method, compared to reported data.[6b] Although "greener" methods for alcohol oxidation using O_2 or H_2O_2 as terminal oxidants are available nowadays[24,25] the modified Ru/NaOCl system is extremely efficient for recalcitrant substrates such as 1,2 : 4,5-di-*O*-isopropylidene-β-D-fructopyranose **1**. For its conversion into 1,2 : 4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexadiulo-2,6-pyranose **2**, other catalytic methods fail.[19] Oxidation of the sterically hindered alcohol group in **1**, is apparently highly favored over oxidation of the C–H bonds adjacent to the various

Table 4. Oxidation of secondary alcohols *via* TPAP/NaOCl.[a]

Entry	Substrate	Product	% C[b]	% Y[b]	% S
13	 [c] **1**	 **2**	98	90	92
14			99	99	100
15			99	99	100
16			99	88	89
17			90	89	99
18	 [d]		97	96	99

[a] Conditions: substrate (5 mmol), TPAP (0.25 mol %), EtOAc (5 cm^3), $NaHCO_3/Na_2CO_3$ buffer solution (pH 9.5, 5 cm^3), 4 h, RT, NaOCl 0.7 M, 1 equiv., dropwise over 2 h.

[b] GC conversions and yields, based on pure samples.

[c] TPAP 1 mol %, NaOCl 3 equivs., MTBE instead of EtOAc.

[d] TPAP 0.5 mol %, MTBE instead of EtOAc.

ether and acetal O-atoms in this RuO_4-based system. It is a potentially interesting target reaction, as ketone **2** is a precursor for transition metal-free catalytic asymmetric olefin epoxidation, developed by Shi and co-workers.[26] So far, this compound was obtained from fructose diacetonide **1** in 93% yield by use of an excess of pyridinium chlorochromate (PCC) which is more expensive and toxic. In a typical experiment **1** (5 mmol), was oxidized to **2** (98% conversion, 90% isolated yield) over 4 hours at RT in the presence of TPAP (1 mol %), MTBE (5 cm^3), $NaHCO_3/Na_2CO_3$ buffer solution (pH 9.5, 5 cm^3), using 3 equivalents of NaOCl 0.7 M. In a large-scale experiment under the same conditions, oxidation of **1** (10.4 g, 40 mmol) afforded **2** as a NMR-pure white precipitate after solvent evaporation in 85% isolated yield (8.8 g, 34 mmol). For simple secondary alcohols, the reactions proceed smoothly under optimized conditions using a stoichiometric amount of NaOCl and 0.25 mol % of TPAP, which is the precatalyst giving the best performance (Table 4). For liquid substrates such as 2-octanol, organic solvent-free oxidation was also successfully carried out (conversion at 4 h, 99%, isolated yield of 2-octanone 97%). Catalysis still occurs in the organic phase, in this case the substrate itself.

In order to decrease the amount of Ru without loss of activity, we examined the effect of promotors, in particular pyridine oxide and bromide salts. Whilst the first type of additive is expected to increase the solubility and stability of the catalyst in the organic phase, bromide should be converted into hypobromite. The combination of HOCl/HOBr is known to be a more effective oxidant in organic solvents than hypochlorite alone.[27] The results of oxidation of dibutyl ether to butyl butyrate, with 2 equivalents of NaOCl in EtOAc at pH 9.5 using a $NaHCO_3/Na_2CO_3$ buffer at different TPAP concentrations, with or without additives, are summarized in Table 5. From these experiments it can be concluded that efficient ether oxidation can be achieved at high substrate to catalyst ratios (up to 1000:1) using TPAP and pyridine oxide, without the need of an excess of hypochlorite.

Efficient catalyst recycle could also be achieved by a simple series of pH change and extractions (Experimental Section). For the oxidation of **1** to **2**, the decrease in selectivity is moderate (from 83% to 72% after 4 cycles) which we attribute to mechanical losses (starting TPAP, 0.02 mmol). The tests were repeated using dibutyl ether as substrate; in this case the decrease in selectivity to butyl butyrate was negligible (from 99% to 96% after 5 cycles), as shown in Figure 3.

Table 5. Effect of promotors on the oxidation of Bu_2O at different TPAP concentrations.[a]

Additive (mol %)	TPAP (mol %)	% C	% Y	% S
none	0.25	98	95	97
KBr (1)	0.1	67	62	92
Pyridine oxide (1)	0.1	80	78	98

[a] Conditions: Bu_2O, 5 mmol; NaOCl 2 equivs., $NaHCO_3$/Na_2CO_3 buffer (pH 9.5), 5 mL; EtOAc 5 mL, TCB (standard) 1 mmol, RT, 5 h.

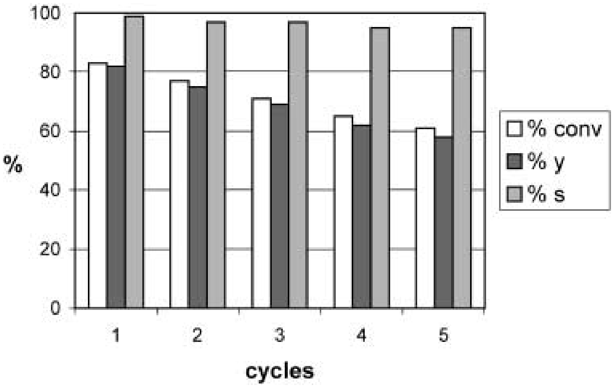


Figure 3. Catalyst recycling in the oxidation of Bu_2O in the presence of TPAP, 0.5 mol %; NaOCl 2 equivs., EtOAc, buffer $NaHCO_3$/Na_2CO_3 1 M (pH 9.5), RT, 3 h.

Conclusions

We have developed a convenient and selective Ru/hypochlorite oxidation protocol for the selective transformation of a series of ethers and alcohols. The catalytic systems described in the literature, especially regarding ether oxidation, have limited reproducibility and/or require an excess of terminal oxidant, i.e., NaOCl solutions (household bleach). When the pH is maintained at 9–9.5 the reactions proceed smoothly, using the theoretical amount of hypochlorite, with fast, complete conversion of substrate and high selectivity to the target molecules at low concentration of Ru precursor. A variety of Ru precursors can be used, although we found that $[Pr_4N][RuO_4]$ (TPAP) gave the best results. The catalyst can also be recycled with negligible loss of selectivity and minimum loss of activity, which can be further optimized by scale-up. Lower selectivities were observed with ethers containing aromatic moieties, which are susceptible to non-selective oxidation by RuO_4.

Experimental Section

Materials

The Ru complexes *cis*-$Ru(dmso)_4Cl_2$,[28] *trans*-$Ru(dppp)_2Cl_2$,[29] *trans*-$Ru(PPh_3)_3Cl_2$,[30] $[n\text{-}Pr_4N][RuO_4]$ (TPAP),[31] *cis*-$[Ru(dmp)_2(MeCN)_2](BF_4)_2$ (dmp = 1,10-dimethylphenanthroline)[32] were synthesized according to literature procedures. Ru/C (5% w/w) and $RuO_2 \cdot H_2O$ were purchased from Aldrich and used without further purification. The commercially available substrates and products (used for GC calibration purposes) were purchased from Acros and Aldrich. All ethers were passed onto a short column of basic alumina to remove stabilizers prior to use. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (**1**) and 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexadiulo-2,6-pyranose (**2**) were supplied by Catalytica Ltd. (presently DSM pharmaceuticals) as white crystalline solids at 97% purity.

Catalytic Tests

Feed-on-demand pH control: In a typical experiment, a 2-necked, pear-shaped flask was equipped with a magnetic stirrer, an addition funnel and a pH electrode, the latter connected to a Metrohm pH stat device, consisting of a pH meter, an Impulsomat and a Dosimat. The following reagents were then added in the order stated: catalyst precursor (prepared according to the literature), organic solvent (containing the GC internal standard) and a few drops of aqueous NaOCl. The biphasic mixture was stirred vigorously until the organic phase assumed a yellow color and the aqueous phase was colorless. The substrate was added rapidly dropwise with a pipette while stirring, once dissolved in the remaining solvent. The pH at this stage was typically in the range 12–13. The oxidant, 0.7 M NaOCl, was then added dropwise *via* the addition funnel, typically over 2 hours. During this phase, the pH was maintained at 9.5 by addition of HCl (2.0 M) via Dosimat. After the addition of the oxidant was completed, the pH was observed to drop and was therefore kept constant at the chosen value by Dosimat addition of NaOH 2.0 M for the rest of the experiment (typically 5 hours overall). The reaction was carried out at room temperature and was monitored by taking samples of the organic phase regularly and analyzing the mixture by GC after adsorption of the catalyst on a Celite pad (retention times and response factors were determined by calibration based on pure samples). When complete conversion was reached (typically after 3–5 h) the final work-up involved phase separation and evaporation of the organic phase to yield the crude product (*ca.* 95% of the final amount). The aqueous phase was extracted with CH_2Cl_2 after neutralization with $NaHCO_3$ followed by evaporation to yield a second crop (*ca.* 5% of the final amount).

Buffer solution pH control: In a typical experiment, a 2-necked, pear-shaped flask was equipped with a magnetic stirrer, an addition funnel and a pH electrode, the latter connected to a Metrohm pH meter. The following reagents were then added in the order stated: buffer solution ($NaHCO_3$/Na_2CO_3, 1.0 M, pH 9.5; NaH_2PO_4/Na_2HPO_4, 1.0 M, pH 6.0), catalyst precursor, organic solvent (containing the GC internal standard) and a few drops of aqueous NaOCl. The biphasic mixture was stirred vigorously until the organic phase assumed a yellow color and the aqueous phase was colorless. The substrate was added rapidly dropwise with a pipette while stirring, once dissolved in the remaining solvent. The oxidant was then added dropwise *via* the addition funnel, typically over 2 hours. The rest of the experiment was carried out as described above.

Catalyst Recycling Tests

A series of experiments was carried out to test the activity of the catalytic system after recycling. The procedure described in a recent patent was used to recycle the catalyst from its low valent state.[33] **1** was used as substrate for recycling tests. Conditions: **1**, 2 mmol; TPAP, 0.02 mmol; NaOCl (0.7 M) 6 mmol (8.6 mL) added over 3 h; MTBE 10 mL; TCB (1,3,5-trichlorobenzene, GC internal standard) 1 mmol, RT, 4 h; pH 9.50. After the run was completed, the organic phase containing **1**, **2** and TCB was separated after addition of NaOH to pH 11, which forces the catalyst into the water phase. Then the catalyst was back-extracted from the aqueous phase by addition of NaOCl (0.2 mmol) and MTBE (10 mL overall), at pH 6. To the yellow solution so obtained, the substrate was added as a solid. The oxidation protocol was then applied as described above. The recycling tests were also carried out using Bu$_2$O as substrate for 5 cycles overall, under the following conditions: Bu$_2$O, 5 mmol; TPAP, 0.5 mol %; NaOCl 2 equivs., EtOAc 5 mL, buffer NaHCO$_3$/Na$_2$CO$_3$ 1 M (pH 9.5), 5 mL; TCB (GC standard) 1 mmol; RT, 3 h.

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