

Selective Ruthenium-Catalyzed Oxidation of 1,2:4,5-Di-*O*-isopropylidene- β -D-fructopyranose and Other Alcohols with NaOCl

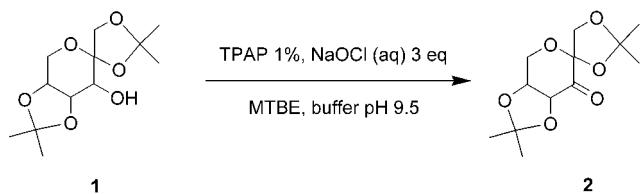
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ABSTRACT



The asymmetric epoxidation catalyst 1,2:4,5-di-*O*-isopropylidene- β -D-*erythro*-2,3-hexadiulo-2,6-pyranose 2 was obtained in high yield from 1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose 1 via a recyclable ruthenium-catalyzed hypochlorite oxidation protocol under biphasic conditions (MTBE/water) in the presence of an alkaline buffer (pH 9.5). Other secondary alcohols were also oxidized selectively to the corresponding ketones.

The selective oxidation of alcohols to aldehydes (primary) and ketones (secondary) is a highly desired conversion in industry and academia. From economical and environmental standpoints, there is a need for catalytic systems able to achieve this transformation working at low concentration of transition metals and releasing the lowest amount of byproducts and waste (i.e., atom-efficient processes¹). Both heterogeneous² and homogeneous³ catalytic systems using clean terminal oxidants such as O₂ or H₂O₂ have been successfully

applied to the oxidation of activated and unactivated alcohols. RuO₄ is a selective stoichiometric oxidant for alcohols, comparable to dichromate⁴ or KMnO₄,⁵ still utilized in many industrial applications. It can be generated in situ by addition of an oxidant such as NaIO₄ or NaBrO₃ to a ruthenium precursor and used in catalytic amounts. The major drawback of these systems is usually the cost of the oxidant and the large amount of waste salts produced. NaOCl, which can also be used to generate RuO₄, is a cheap oxidant, and its byproduct is sodium chloride. Oxidation of organic substrates via sodium hypochlorite has been reported, with⁶ or without⁷ a catalytic amount of ruthenium.

The selective conversion of 1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose 1 into 1,2:4,5-di-*O*-isopropylidene- β -D-

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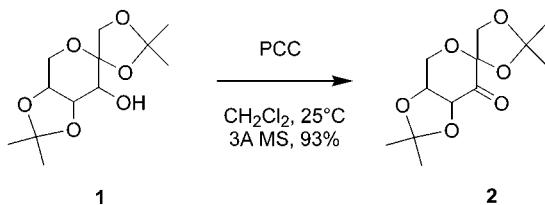
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erythro-2,3-hexadiulo-2,6-pyranose **2** is a particularly interesting target reaction for alcohol oxidation. Ketone **2** was used as a precursor for transition-metal-free catalytic asymmetric olefin epoxidation by Shi and co-workers⁸ and was obtained from fructose diacetone **1** in 93% yield by use of an excess of pyridinium chlorochromate (Scheme 1).^{8,9}

Scheme 1. Stoichiometric Oxidation of **1** to **2** via Pyridinium Chlorochromate (PCC)



Catalytic oxidation of **1** has proved particularly difficult, probably because of steric reasons. Methods such as $\text{Co}/\text{NHPI}/\text{O}_2$,¹⁰ TPAP/ O_2 ,³ Ru/TEMPO/ O_2 ,¹¹ Pd(L-L)(AcO) $_2$ (L-L = bathophenanthroline),¹² and NaOCl/TEMPO,¹³ which were successfully applied to oxidation of alcohols, failed to convert **1** into **2**. The bulkiness of **1** may hinder coordination to Ru and hence catalytic activity. Mio et al.¹⁴ reported the successful oxidation of **1** to **2** using $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (3 mol %) and NaIO_4 (1.5 equiv) in $\text{CHCl}_3/\text{H}_2\text{O}$ under phase transfer conditions at reflux (99% yield). Moderate selectivity to **2** was obtained by Fung et al.¹⁵ using $[\text{Cn}^*\text{Ru}(\text{CF}_3\text{CO}_2)_3 \cdot \text{H}_2\text{O}]$ (1 mol %, Cn* = *N,N',N''*-trimethyl-1,4,7-triazacyclononane) with 'BuOOH (1–1.2 equiv) in CH_2Cl_2 at 40°C (58% yield). However, these methods involve the use of an expensive oxidant/catalyst and/or unattractive conditions.

We recently discovered that for the biphasic ruthenium-catalyzed hypochlorite α -oxidation of aliphatic ethers, a narrow pH range (8–10) is required to achieve the best selectivity to esters.¹⁶ The pH can be kept constant throughout the catalytic run by either (a) use of a $\text{NaHCO}_3/\text{Na}_2\text{CO}_3$ buffer solution or (b) feed-on-demand addition of HCl (during the addition of NaOCl) and NaOH (afterward) via a pH-stat device. The best Ru precursor proved to be $(\text{Pr}_4\text{N})\text{RuO}_4$, TPAP, which was synthesized according to the literature.¹⁷

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The method was applied to the oxidation of **1** to **2** and, for comparison, to a series of unfunctionalized secondary alcohols. The results, summarized in Table 1, show that all

Table 1. Oxidation of Secondary Alcohols via TPAP/NaOCl^a

substrate	product	% conv ^b	% yield ^b
1^c	2	98	90
2-octanol	2-octanone	99	99
borneol	camphor	99	99
cyclohexanol	cyclohexanone	99	88
1-phenyl ethanol	acetophenone	90	89
2-adamantanol ^d	2-adamantanone	97	96

^a Reactions were carried out over 4 h at rt in a 50-mL two-necked pear-shaped flask containing the substrate (5 mmol), TPAP (0.25 mol %), EtOAc (5 mL), and $\text{NaHCO}_3/\text{Na}_2\text{CO}_3$ buffer solution (pH 9.5, 5 mL). The flask was equipped with a pH electrode and a dropping funnel from which the oxidant (NaOCl 0.7 M, 1 equiv) was added dropwise over 2 h. ^b GC conversions and yields, based on pure samples. ^c TPAP 1 mol %, NaOCl 3 equiv, MTBE instead of EtOAc. ^d TPAP 0.5 mol %, MTBE instead of EtOAc.

substrates are converted into the corresponding ketones in high yield and selectivity when the reaction is carried out at pH 9.5 in the presence of the appropriate buffer solution.

For simple secondary alcohols, the reactions proceed smoothly under optimized conditions using a stoichiometric amount of NaOCl and 0.25 mol % of ruthenium. At the end of the reaction, the catalyst is present as RuO_2 in the water phase, and this permits the recovery of the products by simple phase separation and evaporation of the solvent.¹⁸ We have reduced the environmental impact of the process using EtOAc or methyl *tert*-butyl ether (MTBE) instead of CH_2Cl_2 or other chlorinated solvents still commonly used in oxidations involving RuO_4 . Other sources of Ru, i.e., RuCl_3 and RuO_2 , can also be used, but in this case approximately two times higher concentrations of Ru will be required compared to TPAP.¹⁶ Solvent-free oxidation of 2-octanol to 2-octanone was also successfully carried out (conversion at 4 h, 99%, isolated yield 97%). Catalysis still occurs in the organic phase, in this case the substrate itself. The effect of pH on activity and selectivity was investigated. Oxidation of **1** at acidic pH in the presence of TPAP (1 mol %) yielded **2** in lower selectivity than at basic pH, while the blank reaction showed decomposition of the substrate, probably due to deprotection. For the oxidation of 2-octanol, higher conversions and selectivities were obtained at pH 6 with or without Ru, in agreement with data reported by Stevens et al.⁷ (Table 2). These observations suggest that the efficiency of the process depends more on the stability of the substrate at different pH rather than on the stability and solubility of the catalyst. No byproducts of the oxidation of **1** to **2** could be identified under the various conditions applied. We assume that the major side reaction is deprotection followed by destructive over-oxidation to CO_2 .

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(18) In a scaled-up experiment under the conditions described in Table 1, 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).

Table 2. pH Tolerance and Blank Reactions in the Oxidation of **1** to **2** and of 2-Octanol to 2-Octanone via TPAP/NaOCl

substrate	pH	TPAP (mol %)	% conv ^c	% yield ^c
1 ^a	6.0		57	0
	6.0	1.0	95	64
	9.5		12	7
	9.5	1.0	98	90
	2-octanol ^b		89	70
2-octanol ^b	6.0	1.0	99	98
	6.0		60	28
	9.5	1.0	95	94

^a **1** (5 mmol), MTBE (20 mL), NaOCl 0.7 M (3 equiv dropwise over 2 h), buffer solution (5 mL), rt, 4 h. ^b 2-Octanol (5 mmol), EtOAc (5 mL), NaOCl 0.7 M (1 equiv dropwise over 1 h), buffer solution (5 mL), rt, 2 h. Buffers: NaHCO₃/Na₂CO₃ (pH 9.5), NaH₂PO₄/Na₂HPO₄ (pH 6.0). ^c GC conversions and yields, based on pure samples, 1,2,4-trichlorobenzene internal standard.

The protocol was also applied to the oxidation of 1-octanol **3** as a model for primary alcohols. The blank reaction at pH 6 in EtOAc gave 73% conversion in 3 h, yielding 1-octanal **4** (27%), octanoic acid **5** (15%), and octyl octanoate **6** (20%). In the presence of TPAP (1 mol %), similar conversions and selectivities were observed at pH 6 (conversion at 3 h, 78%; yields, **4**, 25%; **5**, 30%; **6**, 12%) and pH 9.5 (conversion at 3 h, 70%; yields, **4**, 20%; **5**, 28%; **6**, 8% after workup).

The use of buffer solutions proved to be more efficient than the feed-on-demand addition of HCl/NaOH (Table 3,

Table 3. Effect of TPAP Concentration and Use of Promoters in the Oxidation of **1** to **2** via TPAP/NaOCl^a

entry	promoter (mol %)	TPAP (mol %)	% conv	% yield
1	none	1.0	99	83
2	none	0.5	77	49
3	none	0.1	35	27
4	KBr (5)	0.5	99	74
5	KBr (2.5)	0.25	88	63
6	KBr (1)	0.1	57	36
7	pyridine oxide (5)	0.5	87	60

^a **1** (5 mmol), MTBE (20 mL), NaOCl 0.7 M (3 equiv dropwise over 2 h), rt, 4 h. The pH was kept constant at 9.5 by feed-on-demand addition of HCl (during the addition of NaOCl) and NaOH (afterward) via Dosimat.

entry 1) and should be preferred. Promoters such as KBr and pyridine oxide (10:1 ratio to TPAP) could be used to decrease the amount of catalyst, e.g. from 1.0 to 0.5 mol %, without loss of activity and moderate decrease in selectivity to **2** (Table 3, entry 4).

Efficient catalyst recycling was also possible. After the organic phase was separated, RuO₂ was back-extracted as RuO₄ with fresh solvent from the water phase by acidification and addition of a few drops of NaOCl. The new organic phase so obtained could be used directly for a new cycle.¹⁹ The results shown in Figure 1 demonstrate that there is a

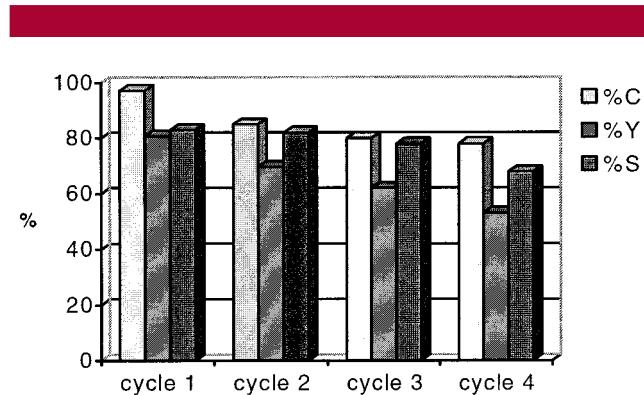


Figure 1. Catalyst recycling in the oxidation of **1** (2 mmol) to **2** (not optimized). TPAP (cycle 1) 1 mol %, MTBE (10 mL), NaOCl 0.7 M (3 equiv), room temperature, 4 h, pH 9.5 (Dosimat).

small loss in activity after four cycles. We attribute this to mechanical losses owing to the small scale of the reaction (**1**, 2 mmol; TPAP, 0.02 mmol); however, the loss in selectivity is moderate (from 83% to 72% after four cycles).

In summary, our study provides an efficient, cheap, and recyclable catalytic method for the so far troublesome oxidative synthesis of **2**, a catalyst for asymmetric olefin epoxidation.

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Supporting Information Available: Experimental procedure for oxidations, including recycling experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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