A new catalytic oxidative cleavage reaction to furnish lactones†

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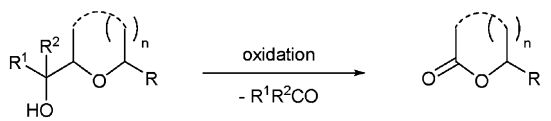
A highly efficient oxidative cleavage reaction of THF and THP alcohols to γ- and δ-lactones using catalytic PCC (1 mol%) and periodic acid as terminal oxidant is presented.

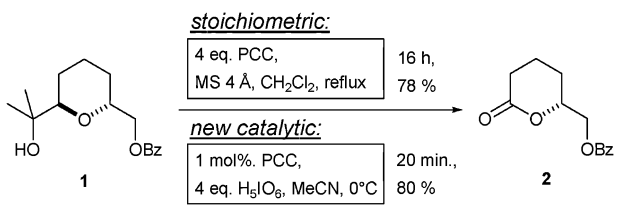
The selective cleavage of carbon–carbon bonds represents an invaluable tool in organic synthesis.[1] Such transformations play a significant role as they often provide an unusual and complementary entry to certain functional groups. As part of our interest in oxidation catalysis we were seeking a method for the cleavage of β-hydroxy ethers. This process can be regarded as an extension of the glycol cleavage and Criegee oxidation[2] of vicinal diols and constitutes an oxidative ester forming strategy[3,4] (Scheme 1).

Due to the relevance of substituted lactones[5] as structural motifs in different classes of natural products, this investigation focused on cyclic ethers as substrates. The starting materials, heterocycles with neighbouring hydroxy groups, are easily accessible *e.g.* through oxidative cyclization of 1,5- and 1,6-dienes.[6–8]

Based on previous studies in the area[9] we investigated the reactivity of Cr(VI)-reagents under different conditions.[10] Among the reagent systems tested, an excess (4 eq.) of pyridinium chlorochromate (PCC) under anhydrous conditions in CH_2Cl_2 at reflux temperature proved to be most efficient in promoting the cleavage reaction. Under these conditions initially reported by Chandrasekaran *et al.*[9b] for tetrahydrofuran methanols, model substrate **1** was converted to lactone **2** in 78% yield (Scheme 2, top box).[11]



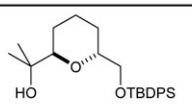
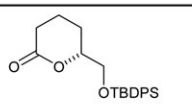
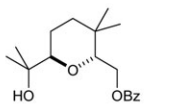
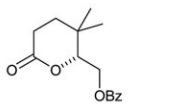
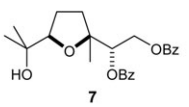
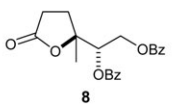
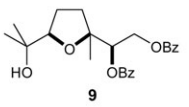
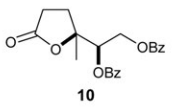
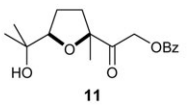
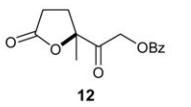
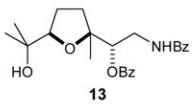
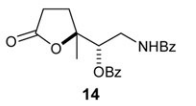
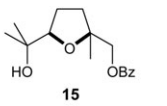
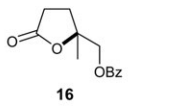
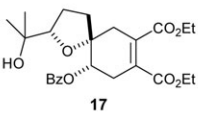
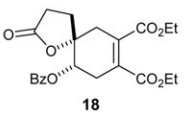
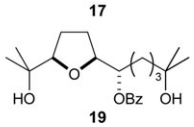
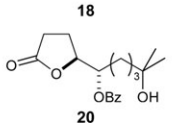
Scheme 1 Oxidative cleavage of β-hydroxy ethers.



Scheme 2 Oxidative cleavage of a tertiary THP-alcohol to the corresponding δ-lactone; Bz = benzoyl.

The fairly harsh conditions and long reactions times, however, appeared not to be compatible with a broader range of

Table 1 Catalytic oxidative cleavage of tertiary THP and THF alcohols to the corresponding δ- and γ-lactones[a]

Entry	Substrate	Lactone	Yield (%)[b]
1	 **3**	 **4**	95
2	 **5**	 **6**	92
3	 **7**	 **8**	97
4	 **9**	 **10**	98
5	 **11**	 **12**	98
6	 **13**	 **14**	98
7	 **15**	 **16**	92
8	 **17**	 **18**	90
9	 **19**	 **20**	72

[a] *Reagents and conditions*: 0.5 mmol substrate in 10 mL MeCN, 1 mol% PCC, 4 eq. H_5IO_6, 0 °C, 10–30 min. reaction time. [b]Isolated yields after filtration over $Na_2S_2O_3$/silica (see ESI[1]† for details). TBDPS = *tert*-butyldiphenylsilyl.

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substrates. Moreover, Cr(VI)-reagents are carcinogenic and environmentally hazardous, the development of catalytic oxidations is therefore desirable.[12–14]

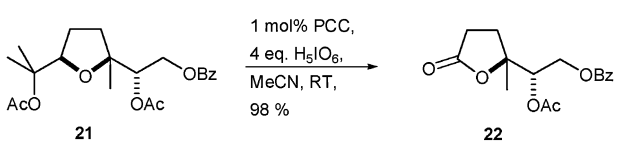
Based on these considerations we tested various co-oxidants as well as different conditions in conjunction with catalytic amounts of PCC. In addition, these investigations were aimed at an *in situ activation* of the Cr(VI)-catalyst in order to broaden the substrate scope and functional group compatibility. After extensive screening, we found that 1 mol% PCC together with four equivalents of periodic acid[14] in acetonitrile represents a powerful reagent combination to accomplish the oxidative scission. Other co-oxidants and solvents were less efficient and led to sluggish conversion or left the starting materials unreacted. Remarkably, using this catalytic method, THP-derivative **1** was converted to the δ-lactone within minutes at 0 °C, as opposed to 16 h at reflux in the stoichiometric system (Scheme 2).

As often observed in PCC oxidations we initially encountered problems to isolate chromium-free products.[13] We found, however, that lactones obtained *via* filtration over $Na_2S_2O_3$ adsorbed on silica (see ESI† for details) were analytically pure and an additional chromatographic purification was not required. We believe that this simple but highly efficient work-up procedure will be useful to other PCC oxidations.

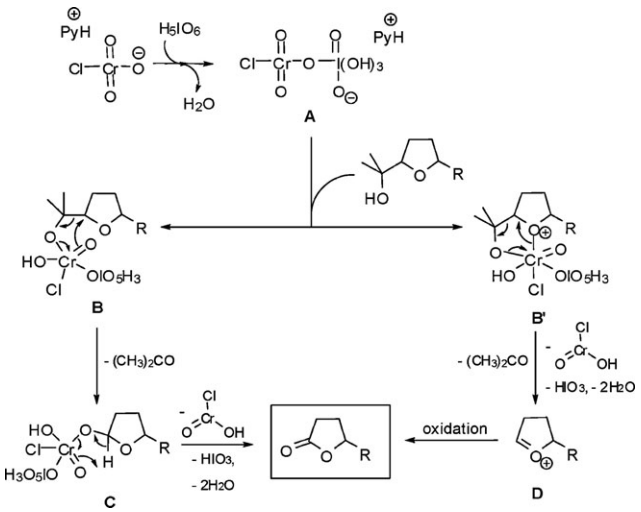
We next applied the optimized protocol to a set of different cyclic hydroxy ether substrates.[15] As summarized in Table 1 both THP-[8] and THF-derivatives[7] reacted equally well and resulted in the formation of the corresponding lactones. Yields were generally high and no side products could be detected. Thus, silyl ethers, esters, ketones, amides, and electron deficient double bonds proved to be compatible with the reaction conditions. Even elaborate spiro-lactone **18** could be obtained in high yield (Table 1, entry 8). In addition, it is worth noting that a remote tertiary alcohol function (*cf*. substrate **19**, Table 1, entry 9) did not interfere with the cleavage reaction. No side product owing to the additional alcohol function could be detected.

An acetate protected[16] β-hydroxy ether (substrate **21**, in Scheme 3) resulted in a prolonged reaction time (16 h), nevertheless, high yields of γ-lactone **22** (98%) were isolated. At the same time, the secondary acetate remained intact (Scheme 3). Presumably, oxidative cleavage occurs after slow hydrolysis of the tertiary acetate unit under the reaction conditions.

In accord with other reactions where PCC is used along with periodic acid, we suggest that chlorochromate is first activated as a mixed anhydride (**A** in Scheme 4) which exhibits an enhanced oxidative strength as compared to PCC itself.[17] This assumption is supported by the fact that periodic acid in the absence of PCC did not produce any lactone while PCC in the absence of periodic acid resulted in a very sluggish conversion.



Scheme 3 Oxidative cleavage of an acetate protected tertiary alcohol.



Scheme 4 Proposed cleavage mechanism.

After activation a nucleophilic attack of the alcohol to the strongly Lewis-acidic chromium centre occurs (**B** or **B′**). For the subsequent C–C–bond cleavage either a cationic or neutral pathway appears feasible (Scheme 4). After scission of the C–C–bond the resulting lactol-type intermediate (**C** or **D**) is oxidized to the corresponding lactone. Finally, the low-valent chromium species is reoxidized and reactivated by periodic acid to re-enter the catalytic cycle.[18]

In summary, we have presented a novel catalytic cleavage reaction of β-hydroxy ethers. The cyclic ether starting materials are converted to the corresponding γ-butyrolactones and δ-valerolactones within minutes and isolated in excellent yield. It is important to note that this catalytic reagent system is significantly more reactive than stoichiometric protocols. We have also presented a novel and very effective work-up procedure for PCC oxidations using a solid supported reducing agent. Our current research in the area is focused on mechanistic aspects of this oxidative fission reaction as well as synthetic applications.

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