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Tetrapropylammonium Perruthenate Catalyzed Glycol Cleavage to Carboxylic (Di)Acids

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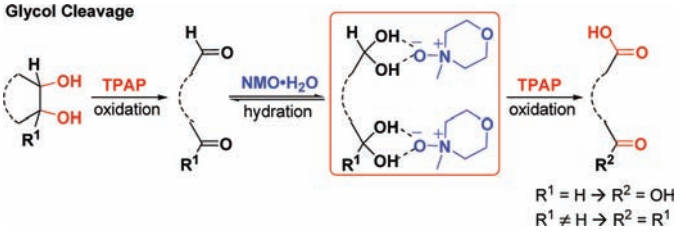
ABSTRACT



A new method to accomplish glycol cleavage to carboxylic (di)acids in one step using catalytic amounts of tetrapropylammonium perruthenate (TPAP) together with *N*-methylmorpholine *N*-Oxide (NMO) as the stoichiometric oxidant is presented. In addition to regenerating the active catalyst, the *N*-oxide stabilizes intermediary carbonyl hydrates and thereby shifts a crucial equilibrium. The mild oxidation protocol is applicable to a broad range of substrates providing the respective acids, diacids, or keto acids in high yields.

The oxidative cleavage of vicinal diols to the corresponding carbonyl compounds is a frequently used transformation in synthetic organic chemistry.[1] Lead tetraacetate (Criegee oxidation)[2] and, more importantly, periodic acid or its salts (Malaprade reaction)[3] are the reagents of choice and generally give the corresponding aldehydes or ketones in good yields. However, if the carboxylic (di)acid is the desired product (Scheme 1), usually two consecutive oxidation reactions are required. There are only a few methods that accomplish this transformation in a single step. The reagent systems used include Co(II)/O_2,[4] PCC (stoichiometric),[5] ruthenium pyrochlore oxides/O_2,[6] $MoO_2(acac)_2$/*t*BuOOH,[7] and WO_4^{2-}/PO_4^{3-}/H_2O_2.[8] These methods, however, suffer from serious drawbacks such as toxicity of reagents, harshness of reaction conditions, lack of selectivity, or limited compatibility with sensitive functional groups.

Tetrapropylammonium perruthenate (TPAP) in combination with *N*-methylmorpholine *N*-oxide (NMO) is a well-established mild and efficient catalyst for alcohol oxidations.[9] So far, a TPAP-catalyzed oxidative cleavage of vicinal diols to carbonyl compounds has only been observed as an unwanted side reaction, particularly with strained

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(1) Shing, T. K. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, p 703.
(2) Criegee, R. *Ber.* **1931**, *64B*, 260.
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(7) Kandeda, K.; Morimoto, K.; Imanaka, T. *Chem. Lett.* **1988**, *17*, 1295.
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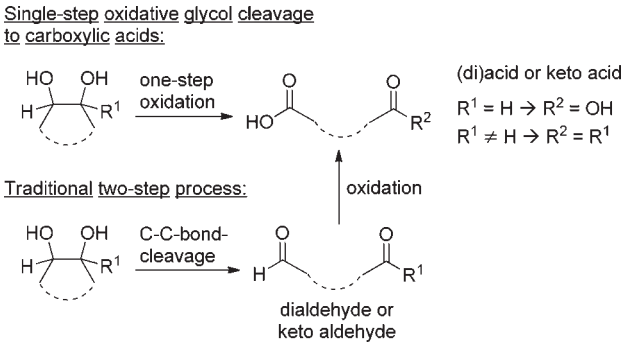
cyclic substrates.[10] In these cases, the corresponding dialdehydes or keto aldehydes were obtained as the products (Scheme 1).

Scheme 1. Envisaged Glycol Cleavage to the Corresponding Carboxylic (Di)Acids or Keto Acids vs Stepwise Process



We have recently developed a protocol for the TPAP-catalyzed direct oxidation of primary alcohols to carboxylic acids.[11] With 10 mol % TPAP and 10 equiv of NMO·H_2O in acetonitrile a wide range of substrates can be converted to the corresponding acids.[11] The key feature of our method is the stabilization of the intermediate aldehyde hydrate which was accomplished by using an excess of NMO containing 1 equiv of water of crystallization. Hydration experiments support our assumption that NMO·H_2O not only serves as the co-oxidant but also, and uniquely, stabilizes the aldehyde hydrate.[12] This stabilization most likely occurs through hydrogen-bonding between the geminal diol and the Lewis basic oxygen of the *N*-oxide (Figure 1).[13]

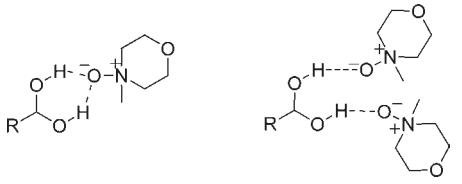
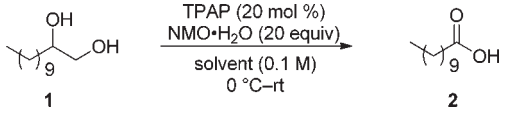


Figure 1. Possible modes of carbonyl hydrate stabilization by NMO.

On the basis of these findings we decided to investigate the potential of TPAP and the hydrate stabilization concept for the direct conversion of vicinal diols to the corresponding (di)acids or keto acids[14] (Scheme 1). Indeed, when simple 1,2-diols were subjected to catalytic amounts of TPAP in the presence of NMO·H_2O, along with other oxidation products, the formation of corresponding acids was observed. This prompted us to carry out a systematic investigation of the reaction conditions.

A solvent screening was conducted using 1,2-dodecanediol as the test substrate in the presence of 20 mol % catalyst and 20 equiv of NMO·H_2O (Table 1). The screening included solvents that provided good results in the TPAP-catalyzed oxidation of primary alcohols to carboxylic acids.[11] The best results (70 and 69% yield, respectively) were obtained when the classic TPAP-solvents dichloromethane and acetonitrile were used (Table 1, entries 1 and 2). Reducing the catalyst loading or the amount of co-oxidant/hydrate stabilizing agent lead to diminished yields.

Table 1. Solvent Screening



1 2

entry	solvent	isolated yield of **2** (%)
1	CH_2Cl_2	70
2	MeCN	69
3	DMF	64
4	acetone	54
5	THF	62

We next applied our optimized conditions (20 mol % TPAP, 20 equiv of NMO·H_2O, in CH_2Cl_2 (0.1 M)) to various 1,2-diols containing different functionalities. As summarized in Table 2, a range of acyclic vicinal diols gave the respective cleavage products in good yields (Table 2, entries 1–6). Products were isolated either as free acids or, after treatment with TMS-diazomethane,[15] as the resulting methyl esters (see Table 2 and Supporting Information for details). In the case of substrate **7**[16] (Table 2, entry 4) the initially obtained hydroxy acid was cyclized under Brønsted acid catalysis and isolated as bicyclic lactone **8**[17] (see Table 2 and Supporting Information for details). Cleavage of dihydroxyolefin **11** resulted in the corresponding acid **12**[18] as the major product in 41% yield (Table 2, entry 6).

(11) Schmidt, A.-K. C.; Stark, C. B. W. *Org. Lett.* **2011**, *13*, 4164.

(12) An investigation of the hydration equilibrium of 4-pyridine carboxaldehyde by ^{1}H NMR spectroscopy showed that the presence of 10 equiv of NMO·H_2O leads to a considerable shift towards the carbonyl hydrate. This effect is largely irrespective of the solvent used; see ref 11 for details.

(13) For related hydrogen bond acceptor properties of NMO, see: Fink, H.-P.; Weigel, P.; Purz, H. J.; Ganster, J. *Prog. Polym. Sci.* **2001**, *26*, 1473.

(14) For a related catalytic oxidative cleavage of hydroxy ethers yielding cyclic esters, see: Roth, S.; Stark, C. B. W. *Chem. Commun.* **2008**, 6411.

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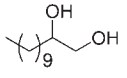
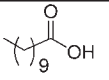
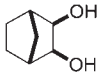
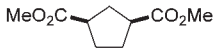
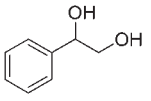
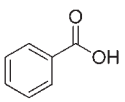
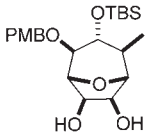
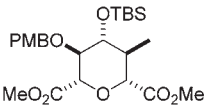
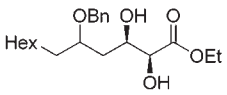
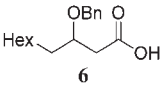
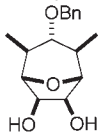
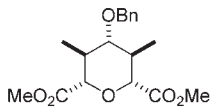
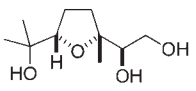
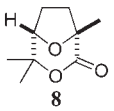
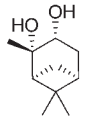
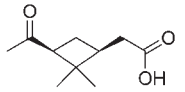
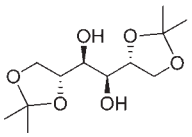
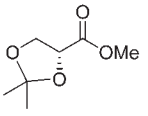
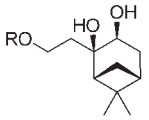
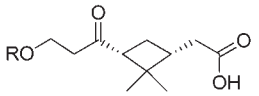
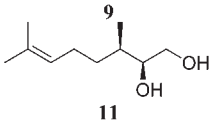
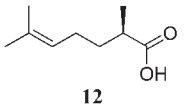
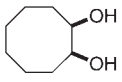
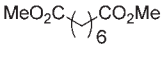
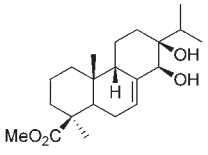
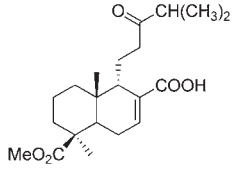
(18) (a) Burger, B. V.; Petersen, W. G. B.; Weber, W. G.; Munro, Z. M. *J. Chem. Ecol.* **2002**, *28*, 2527. (b) Flachsbart, B.; Fritzsche, M.; Weldon, P. J.; Schulz, S. *Chem. Biodiversity* **2009**, *6*, 1.

Table 2. Substrate Scope[a]

entry	substrate	product	yield (%)[b]	entry	substrate	product	yield (%)[b]
1	 **1**	 **2**	70	8	 **15**	 **16**	90[c,d]
2	 **3**	 **4**	73	9	 **17**	 **18**	72[d]
3	 **5**	 **6**	83	10	 **19**	 **20**	55[d]
4	 **7**	 **8**	66[e]	11	 **21**	 **22**	67
5	 **9**	 **10**	78[d]				
6	 **11**	 **12**	41	12	**23**, R = TBS	**24**, R = TBS	65
				13	**25**, R = Ac	**26**, R = Ac	78
				14	**27**, R = Bn	**28**, R = Bn	90
7	 **13**	 **12**	82[c,d]	15	 **29**	 **30**	40

[a] Reagents and conditions: 0.5−1.0 mmol scale; diol (1 equiv) in CH_2Cl_2 (0.1 M), TPAP (20 mol %), NMO·H_2O (20 equiv), addition of TPAP at 0 °C, and then stirring at rt. [b] Isolated yield. [c] Conducted at a higher concentration (0.25 M). [d] Isolated as methyl ester after esterification of the crude product with $TMSCHN_2$ (3 equiv). [e] Isolated after *p*-TsOH-catalyzed lactonization of the crude product.

However, a number of side products were detected. Although double bonds are usually compatible with TPAP oxidations,[9] the double bond in this particular distance to the vicinal diol is likely the reason for the somewhat lower selectivity.[19] We next focused on the conversion of cyclic substrates. Diols **13** and **15** gave the respective cleavage products in excellent yields (Table 2, entries 7 and 8). The release of ring strain is expected to favor the oxidative scission reaction.[10] The more complex oxygen-bridged bicyclic diols **17** and **19**[20] were also successfully cleaved to the corresponding tetrahydropyran diacids and isolated as diesters **18** and **20** after treatment with TMS-diazomethane[15] (Table 2, entries 9 and 10). It is worth noting that the oxidation-sensitive *p*-methoxybenzyl ether of diol **17** remained unaffected. (+)-*cis*-Pinonic acid (**22**) and other substituted cyclobutaneacetic acids were obtained in good to high yields (65−90%) from the corresponding 2,3-pinanediols (Table 2, entries 11−14). In general, a variety of functional groups as well as typical protecting groups such as ethers, silyl ethers, ketals, esters, and remote tertiary alcohols proved to be compatible with the oxidative cleavage protocol. Moreover, potentially labile stereocenters were not affected under the standard reaction conditions (Table 2, entries 5, 6, and 8−14).

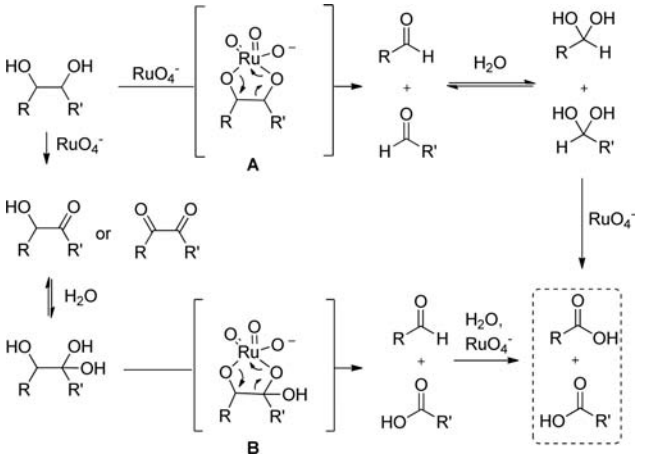
(19) Cheng, H.; Stark, C. B. W. *Angew. Chem.* **2010**, *122*, 1632. *Angew. Chem., Int. Ed.* **2010**, *45*, 1587.

(20) The diols were obtained by dihydroxylation of the respective olefins which were prepared through a [4 + 3]-cycloaddition route according to: (a) Kim, H.; Hoffmann, H. M. R. *Eur. J. Org. Chem.* **2000**, 2195. (b) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem.* **2004**, *116*, 1968. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934. See also: Hoffmann, H. M. R.; Dunkel, R.; Mentzel, M.; Reuter, H.; Stark, C. B. W. *Chem.—Eur. J.* **2001**, *7*, 4771.

(21) Haslinger, E.; Hüfner, A. *Monatsh. Chem.* **1995**, *126*, 1109.

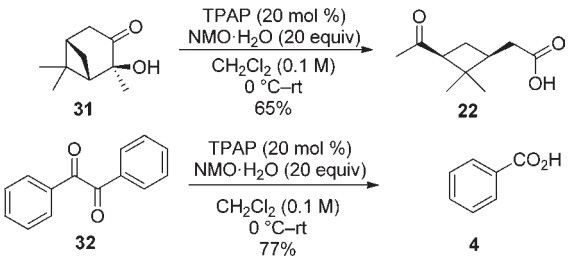
Abietic acid derived diol **29** was cleaved to keto acid **30** with a moderate yield of 40% (Table 2, entry 15).[21] Simple oxidation of the secondary hydroxy group was also observed, resulting in a considerable amount (36%) of uncleaved hydroxy ketone. The stability of this side product against oxidative degradation is expected to result from the carbonyl group being in conjugation to the double bond. Thus, the ketone does not easily form hydrates (*vide infra*; cf. also Scheme 2).

Scheme 2. Proposed Glycol Cleavage Mechanism Involving Carbonyl Hydrates



We propose a mechanism that involves initial formation of a cyclic perruthenate diester (**A** in Scheme 2)[19] which then oxidatively collapses under cleavage of the C−C bond to give the corresponding carbonyl compounds (Scheme 2). Hydration of the latter and subsequent oxidation give the desired carboxylic acid (or diacid).[11] It is also conceivable that the diol is first oxidized to the hydroxy ketone (or diketone) which, after hydration, could also form a cyclic perruthenate diester (**B** in Scheme 2). The oxidative fragmentation of this Ru(VII) diester would result in a carboxylic acid (two carboxylic acids in the case of a diketone precursor) and an aldehyde which could then be oxidized further.[11] In any case, the success of the overall process is strongly dependent on the efficiency of the hydrate formation (Scheme 2). We have previously shown that effective formation of geminal diols from aldehydes can be achieved by adding an excess of NMO·H_2O.[11] In order to test whether the bottom half of the mechanism depicted in Scheme 2 is a realistic pathway, we subjected starting materials (already) containing one or two carbonyl groups to our standard cleavage procedure (Scheme 3). Both the tertiary hydroxy ketone **31** and the diketone **32** underwent smooth conversion to the corresponding acids (Scheme 3). These control experiments not only provide some mechanistic insight but also demonstrate that competing alcohol oxidations to ketols or dicarbonyls do not necessarily lead to any loss of material. Apparently, such initial side products can be converted to the same target compounds by an analogous mechanistic pathway as for the original starting material (Scheme 2). Moreover, these results (Scheme 3) imply further applications of our cleavage procedure.

Scheme 3. Oxidative Cleavage of a Hydroxy Ketone and a Diketone



In summary, we have developed a mild protocol for the direct oxidative glycol cleavage to carboxylic (di)acids. TPAP serves as the catalyst, and NMO as the stoichiometric oxidant. In addition, the *N*-oxide acts as a reagent to stabilize intermediary aldehyde hydrates and thereby pushes carboxylic acid formation. The same effect may be operative in converting initial shunt products such as hydroxy ketones or diketones to the desired target molecules. The mild reaction protocol is applicable to a wide range of substrates providing the respective acids, diacids (or diesters), or keto acids in good to high yields. Vicinal diols containing primary, secondary, and tertiary alcohols are smoothly oxidized to the expected cleavage products. Under the standard conditions many functional as well as protecting groups are tolerated and potentially labile stereocenters remain intact. We therefore believe that the method presented here is a valuable alternative to existing procedures.

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Supporting Information Available. Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.