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TPAP-Catalyzed Direct Oxidation of Primary Alcohols to Carboxylic Acids through Stabilized Aldehyde Hydrates

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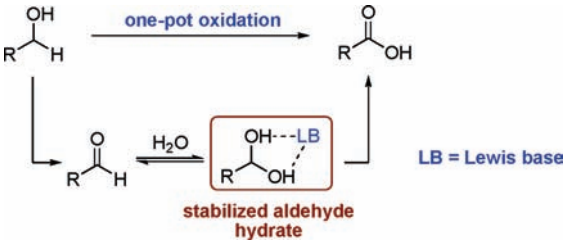
ABSTRACT



We present a simple, mild, and highly effective method for the direct conversion of primary alcohols to carboxylic acids. TPAP serves as the catalyst, and NMO·H_2O plays a dual role, acting as the co-oxidant and as a reagent for aldehyde hydrate stabilization. This previously unknown stabilizing effect of geminal diols by *N*-oxides is the key for the efficiency of the overall transformation.

The oxidation of primary alcohols to carboxylic acids represents one of the most fundamental transformations in organic chemistry.[1] Generally, two separate steps are necessary to accomplish this functional group interconversion: oxidation of the alcohol to the (potentially sensitive) aldehyde and oxidation of the resulting aldehyde to the desired carboxylic acid. Despite recent progress in the direct conversion of primary alcohols into carboxylic acids, the number of methods available is still limited, and often harsh reaction conditions with low functional group compatibility have to be employed.[1] Apparently, in most syntheses of complex target molecules the stepwise process seems to be preferred.

In biological systems, the oxidation of aldehydes to carboxylic acids is an important and highly efficient reaction, e.g., in the context of detoxification processes involving aldehyde dehydrogenases (ALDHs).[2] In the case of these oxidations, the aldehyde hydrate (or a covalently linked analogue) represents a key intermediate and is in fact one reason for the high efficiency of such oxidations. With the aim of developing an efficient and at the same time mild procedure, we decided to search for reagents and conditions to stabilize aldehyde hydrates and in that mimic the biological process. As the hydrates of carbonyl compounds are fairly acidic,[3] we were seeking nonbasic hydrogen bond acceptors for their stabilization. Obviously, this is a unique challenge as the formation of aldehyde hydrates is both entropically and enthalpically disfavored.[4] Geminal diols are therefore usually only formed in minute amounts even when water is used as a solvent.[5] After some

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[‡] Initial experiments were carried out at Freie Universität Berlin.

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(1) For selected methodological approaches, see: (a) Mannam, S.; Sekar, G. *Tetrahedron Lett.* **2008**, *49*, 2457. (b) Hunsen, M. *Synthesis* **2005**, 2487. (c) Tashino, Y.; Togo, H. *Synlett* **2004**, 2010. (d) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031. (e) Yasuda, K.; Ley, S. V. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 1024. (f) Mazitschek, R.; Mülbaier, M.; Giannis, A. *Angew. Chem.* **2002**, *114*, 4216. *Angew. Chem., Int. Ed.* **2002**, *41*, 4059. (g) Thoma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem.* **2000**, *112*, 1362. *Angew. Chem., Int. Ed.* **2000**, *39*, 1306. (h) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *5*, 399. (i) Heyns, K.; Paulsen, H. *Angew. Chem.* **1957**, *69*, 600. (j) Heilbron, I.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1949**, 604.

(2) (a) Crabb, D. W.; Matsumoto, M.; Chang, D.; You, M. *Proc. Nutr. Soc.* **2004**, *63*, 49. (b) Olson, L. P.; Luo, J.; Almarson, O.; Bruice, T. C. *Biochemistry* **1996**, *35*, 9782.

(3) The pK_a of acetaldehyde hydrate has been determined as 13.87: Bell, R. P.; Onwood, D. P. *Trans. Faraday Soc.* **1962**, *58*, 1557.

(4) (a) Hilal, S. H.; Bornander, L. L.; Carreira, L. A. *QSAR Comb. Sci.* **2005**, *24*, 631. (b) Williams, I. H.; Spangler, D.; Femec, D. A.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 31.

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experimentation, we found that *N*-oxides and among them especially *N*-methylmorpholine *N*-oxide (NMO) allow for an efficient stabilization of the desired water adducts (Figure 1).

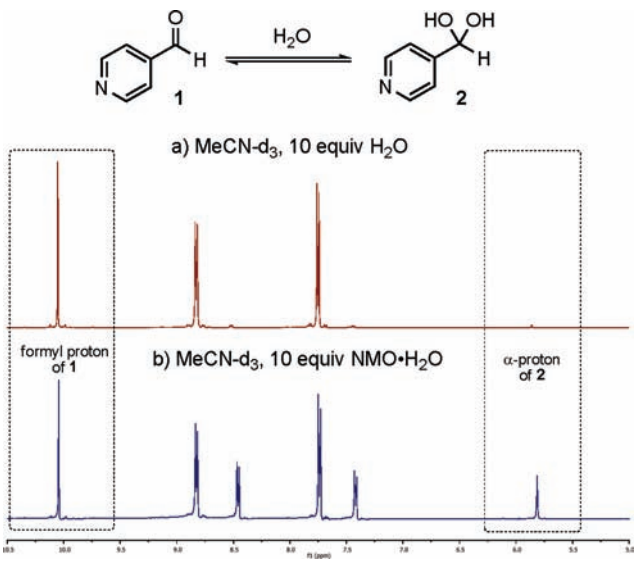
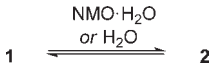


Figure 1. NMR spectra of **1** in MeCN-d_3 with (a) 10 equiv of H_2O; (b) 10 equiv of NMO-hydrate.

An investigation of the hydration equilibrium of 4-pyridine carboxaldehyde by ^{1}H NMR-spectroscopy[6] showed that the presence of NMO (containing 1 equiv of water of crystallization) leads to a considerable shift toward the hydrate (Figure 1). Notably, this previously unknown effect[7] is irrespective of the solvent used. In acetonitrile, dichloromethane, or DMF, one third of the aldehyde is converted to the hydrate if NMO·H_2O is added (Table 1).

Table 1. Aldehyde Hydrate Stabilization by NMO[a]



entry	solvent	NMO·H_2O (equiv)	H_2O (equiv)	aldehyde **1**/hydrate **2**[b]
1	MeCN-d_3	10		67:33
2	MeCN-d_3		10	99:1
3	DCM-d_2	10		67:33
4	DCM-d_2		10	100:0
5	DMF-d_7	10		66:34
6	DMF-d_7		10	>99:1

[a] Sample preparation: aldehyde (1.0 equiv) and NMO·H_2O (10 equiv) or H_2O (10 equiv) in deuterated solvent (0.25 M with respect to the aldehyde). For details, see the Supporting Information. [b] Determined by ^{1}H NMR using the signals at 10.05 ppm (formyl proton of **1**) and 5.91 ppm (α-proton of **2**).

Without NMO but in the presence of 10 equiv of water, only traces of hydrate were detectable in acetonitrile, dichloromethane, and DMF.[8] The stabilization of the aldehyde hydrate is most likely due to hydrogen bonding between the geminal diol and the Lewis-basic oxygen of the *N*-oxide (Figure 2). It is worth mentioning that a similar kind of interaction makes NMO one of the most potent organic solvents for cellulose and polysaccharide materials.[9]

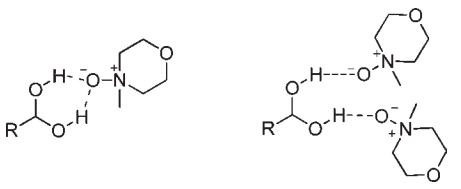


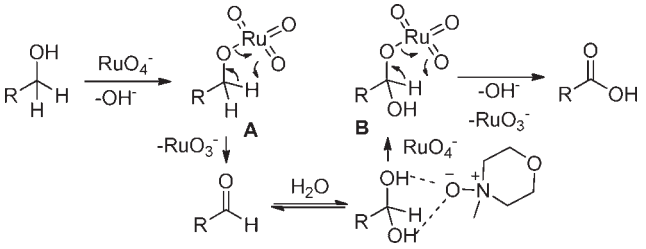
Figure 2. Possible modes of hydrate stabilization by NMO.

Our next aim was to apply these findings in the context of the envisaged direct oxidation of primary alcohols to carboxylic acids. Based on our experience in the field of ruthenium-mediated oxidation reactions,[10,11] we considered Ru(VII) reagents and among these tetra-*n*-propylammonium perruthenate (TPAP)[12] to be the most suitable oxidation catalyst. TPAP (together with NMO as a co-oxidant) is typically used under anhydrous conditions as a selective and mild oxidant for primary and secondary alcohols to aldehydes and ketones, respectively.[12] There are, however, only a few examples of TPAP-catalyzed oxidations of primary alcohols to carboxylic acids,[13] and so far, a systematic investigation of reaction conditions and substrate scope has not been reported. In addition, the simple addition of water to TPAP-catalyzed oxidations of primary alcohols in order to push carboxylic acid formation is not expected to be effective (vide infra). We

(5) (a) Gomez-Bombarelli, R.; Gonzalez-Perez, M.; Perez-Prior, M. T.; Calle, E.; Casado, J. *J. Phys. Chem A* **2009**, *113*, 11423. (b) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1.
(6) Abe, K.; Endo, H.; Hirota, M. *Bull. Chem. Soc. Jpn.* **1981**, 466.
(7) It is, however, known that pyridinecarboxaldehyde *N*-oxides form the hydrate more readily when the carbonyl group is located in the 2-position because of the possibility of forming an intramolecular hydrogen bond: Okano, V.; Toma, H. E.; do Amaral, L. *J. Org. Chem.* **1981**, *46*, 1021.
(8) The effect was also observed in $CDCl_3$, DMSO-d_6, and CD_3OD.
(9) (a) Fink, H.-P.; Weigel, P.; Purz, H. J.; Ganster, J. *Prog. Polym. Sci.* **2001**, *26*, 1473. (b) Chanzy, H.; Maia, E. *Acta Crystallogr.* **1982**, *B38*, 852. (c) Maia, E.; Peguy, A.; Pérez, S. *Acta Crystallogr.* **1981**, *B37*, 1858.
(10) (a) Göhler, S.; Roth, S.; Cheng, H.; Göksel, H.; Rupp, A.; Haustedt, L. O.; Stark, C. B. W. *Synthesis* **2007**, 2751. (b) Göhler, S.; Stark, C. B. W. *Org. Biomol. Chem.* **2007**, *5*, 1605. (c) Göksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433. (d) Roth, S.; Stark, C. B. W. *Angew. Chem.* **2006**, *118*, 6364. *Angew. Chem., Int. Ed.* **2006**, *45*, 6218. (e) Roth, S.; Göhler, S.; Cheng, H.; Stark, C. B. W. *Eur. J. Org. Chem.* **2005**, 4109.
(11) (a) Cheng, H.; Stark, C. B. W. *Angew. Chem.* **2010**, *122*, 1632. *Angew. Chem., Int. Ed.* **2010**, *49*, 1587.
(12) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. For rewiews, see:(a) Langer, P. *J. Prakt. Chem.* **2000**, *342*, 728. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(13) (a) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302. (b) Hu, T.; Panek, J. S. *J. Org. Chem.* **1999**, *64*, 3000.

therefore supposed that NMO could play a dual role in our envisaged oxidation procedure: (i) stabilization of the aldehyde hydrate intermediate and (ii) co-oxidant to recycle the active Ru(VII) catalyst.[12] Scheme 1 shows the corresponding reaction pathway. The two oxidative steps are believed to proceed via similar intermediates, Ru(VII) esters **A** and **B** (Scheme 1). The efficiency of the overall transformation relies on an effective formation and stabilization of the aldehyde hydrate.[14,15]

Scheme 1. Proposed Mechanism for the Direct Oxidation of Primary Alcohols to Carboxylic Acids



Even though, in theory (with respect to its role as a co-oxidant), only 2 equiv should be sufficient for the oxidation reaction, we found that 10 equiv of NMO·H_2O was required (see also Table 1) for the reaction to go to completion[16] using octanol as a representative model substrate (Table 2, entries 1–4). A 94% yield of octanoic acid was isolated when the reaction was performed in acetonitrile.[17] A slight excess of NMO·H_2O (3 equiv) gave only a moderate yield of the acid (44%, Table 2, entry 1). The same trend was observed when octanal was used as the substrate (Table 2, entries 6 and 7). These data indicate that a significant amount of hydrate-stabilizing agent has to be added in order to produce a reasonable concentration of the hydrate intermediate during the lifetime of the Ru(VII) catalyst. Most importantly, we found that simply adding water (7 equiv) along with 3 equiv of NMO·H_2O significantly diminished the yield of octanoic acid (28%, Table 2, entry 5). This result is not surprising since it is known that the presence of water reduces catalytic turnovers, an effect that might be explained on the basis of the finding that (stoichiometric) TPAP oxidations are strongly autocatalytic in colloidal RuO_2 formed during the reaction.[18] Small amounts of water reduce its catalytic nature, thereby decreasing the reaction rate. Thus, in addition to its stabilizing effect on aldehyde hydrates, NMO·H_2O also seems to allow for the presence of water without adverse effects on the overall catalytic process.

Table 2. Influence of the Amount of NMO·H_2O and Additional Water on the Oxidation of Octanol and Octanal to Octanoic Acid[a]

entry	substrate	NMO·H_2O[b] (equiv)	H_2O[b] (equiv)	time (h)	yield of acid (%)
1	octanol	3		24	44[c]
2	octanol	5		4	87[d]
3	octanol	7.5		0.8	99[d]
4	octanol	10		1	94[c] (100)[d]
5	octanol	3	7	3	28[c]
6	octanal	1		3	41[c]
7	octanal	3		3	75[c]

[a] Reaction conditions: substrate (1.0 equiv, 0.5 or 1.0 mmol scale), TPAP (10 mol %), NMO·H_2O, MeCN (0.25 M). [b] Equivalents added relative to the substrate. [c] Isolated yield of octanoic acid. [d] Conversion determined by GC–FID.

We next applied our standard conditions to various substrates containing different functionalities (Table 3). Simple aliphatic alcohols are oxidized to the corresponding carboxylic acids in good to excellent yields in short reaction times (usually 1 h or less). Alcohols containing double and triple bonds are also viable substrates with, for example, the *cis*-double bond of 4-decen-1-ol staying untouched under the reaction conditions (Table 3, entry 4). β-Branched alcohols and substrates containing functionalities such as epoxides, halides, or Boc-protected amines are oxidized to the corresponding acids in excellent yields. Also, α- and β-stereocenters remain intact (Table 3, entries 8 and 9).

The method can be employed for benzylic alcohols as well. However, the efficiency strongly depends on the nature of the substituents on the aromatic ring. Donor-substituted benzylic alcohols provide only moderate yields, whereas acceptor substituted benzylic alcohols give the respective benzoic acid derivatives in excellent yields (Table 3, entries 13–18). We have included the weak results using *para*-donor-substituted benzylic alcohols (Table 3, entries 14 and 15) as these data not only show the limitations of our direct oxidation protocol but are also a negative result in support of the involvement of aldehyde hydrates. Finally, we applied our method to more complex substrates (Table 3, entries 19 and 20) including acetonide-protected galactose which, after esterification of the crude product using TMS-diazomethane, gave ester **22** in 66% yield. The oxidation of an alcohol[19] containing a chiral

(14) This has been established for Cr(VI) oxidants: (a) Roček, J.; Ng, C.-S. *J. Am. Chem. Soc.* **1974**, *96*, 1522. (b) Roček, J.; Ng, C.-S. *J. Org. Chem.* **1973**, *38*, 3348.

(15) A radical mechanism or a Baeyer–Villiger-like process are also possible: Bäckvall, J.-E., Ed. *Modern Oxidation Methods*, 1st ed.; Wiley-VCH: Weinheim, 2004. Another possible pathway may involve the nucleophilic addition of NMO to the aldehyde intermediate. The resulting species $[RCH(O^-)(ON^+R'_3)]$ would then be oxidized to an active ester followed by hydrolysis. Detailed investigations are currently underway.

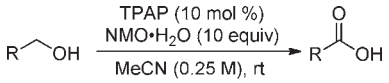
(16) We also found that the amount of water relative to NMO could be reduced. However, it was found to be more convenient to simply use NMO·H_2O. Details will be disclosed in a full account.

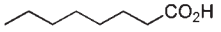
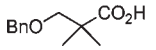
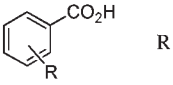
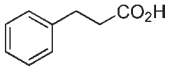
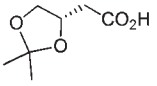
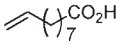
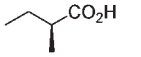
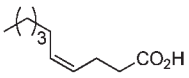
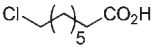
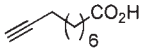
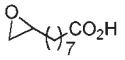
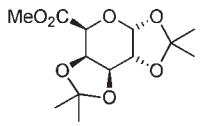
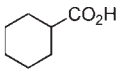
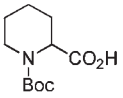
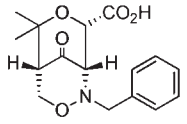
(17) Similarly high yields were obtained when DCM, acetone, or DMF was used. Low yields were obtained in solvents in which TPAP and NMO were poorly soluble. See the Supporting Information for a complete solvent screening.

(18) Lee, D. G.; Wang, Z.; Chandler, W. D. *J. Org. Chem.* **1992**, *57*, 3276.

(19) This starting material was generously provided by Prof. Dr. H.-U. Reissig, Freie Universität Berlin, Germany. For details on the synthesis of this substrate, see: (a) Al-Harrasi, A.; Pfrengle, F.; Prisyazhnyuk, V.; Yekta, S.; Koóš, P.; Reissig, H.-U. *Chem.—Eur. J.* **2009**, *15*, 11632. (b) Yekta, S.; Prisyazhnyuk, V.; Reissig, H.-U. *Synlett* **2007**, 2069. (c) Al-Harrasi, A.; Reissig, H.-U. *Angew. Chem.* **2005**, *117*, 6383. *Angew. Chem., Int. Ed.* **2005**, *44*, 6227.

Table 3. Substrate Scope for the TPAP-Catalyzed Direct Oxidation of Primary Alcohols to Carboxylic Acids[a]



entry	product		yield [%][b]	entry	product		yield [%][b]	entry	product		yield [%][b]
1		**4**	94	7		**10**	84	13	 R = H	**16**	70[f]
2		**5**	92	8		**11**	74[c]	14	R = *p*-Me	**17**	26[f]
								15	R = *p*-MeO	**18**	32[f]
3		**6**	89	9		**12**	100[d,e]	16	R = *p*-Cl	**19**	95
								17	R = *o*-I	**20**	94
								18	R = *p*-NO_2	**21**	91
4		**7**	86	10		**13**	86				
5		**8**	87	11		**14**	99	19		**22**	66[g]
6		**9**	91	12		**15**	98	20		**23**	58

[a] Performed on a 0.5 or 1.0 mmol scale. [b] Isolated yields. [c] Optical rotation in accordance with the literature value of the enantiomerically pure compound. [d] Conversion determined by GC–FID. [e] ee >99%; determined by chiral GC–FID through comparison with a racemic sample. [f] The remainder material in these experiments was the aldehyde intermediate (TLC, GC–MS).

bicyclic core with a labile N–O bond provided acid **23** in 58% yield after recrystallization.

In summary, we have developed an efficient and high-yielding protocol for the direct oxidation of primary aliphatic and aromatic alcohols to carboxylic acids. A wide range of substrates containing sensitive functionalities undergo facile oxidation. The key feature of our method is the stabilization of the intermediary aldehyde hydrates by NMO. Moreover, the NMO–water complex seems to provide "chemically bound water" and thus prevents free water from deactivating the catalyst system. In addition, it is not unlikely that NMO plays a role as a catalyst for hydrate formation.

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