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Organocatalytic One-Pot Oxidative Cleavage of Terminal Diols to Dehomologated Carboxylic Acids

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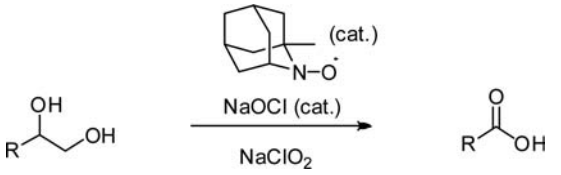
ABSTRACT



The organocatalytic one-pot oxidative cleavage of terminal 1,2-diols to one-carbon-unit-shorter carboxylic acids is described. The combination of 1-Me-AZADO (cat.), NaOCl (cat.), and $NaClO_2$ caused smooth one-pot oxidative cleavage under mild conditions. A broad range of substrates including carbohydrates and *N*-protected amino diols were converted without epimerization. Terminal triols and tetraols respectively underwent cleavage of their C-2 and C-3 moieties to afford their corresponding two- and three-carbon-unit-shorter carboxylic acids.

The 1,2-diol is a useful structural motif in organic synthesis that offers flexible access to various functional groups, such as α-hydroxy-carbonyl[1,2] or α-dicarbonyl compounds,[3] epoxides,[4] alkenes,[5] and others[6,7] on the basis of judicious choices of reagents and conditions. Because of our research interest in developing nitroxyl radical/oxoammonium salt-catalyzed alcohol oxidation processes,[8,9] we examined the applicability of TEMPO oxidation to the selective conversion of 1,2-diols to 2-hydroxy acids using the primary alcohol selectivity of TEMPO.[1a,c] During our experimentation, we found that terminal 1,2-diols are cleanly converted to dehomologated carboxylic acids via the oxidative decarboxylation of α-keto-carboxylic acids.

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(1) For selected examples, see: (a) Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stockle, M.; Kessler, H. *Chem.—Eur. J.* **2002**, *8*, 4365–4376. (b) Tanaka, H.; Sawayama, A. M.; Wandless, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 6864–6865. (c) Liang, S.; Xu, Z.; Ye, T. *Chem. Commun.* **2010**, *46*, 153–155. (d) Soulé, J. F.; Mathieu, A.; Norsikian, S.; Beau, J.-M. *Org. Lett.* **2010**, *12*, 5322–5325. (e) Yu, L.-F.; Hu, H.-N.; Nan, F.-J. *J. Org. Chem.* **2011**, *76*, 1448–1451.

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We now describe the first organocatalytic one-pot oxidative cleavage of terminal 1,2-diols to dehomologated carboxylic acids with a wide range of substrate applicabilities, featuring the combined use of cat.1-Me-AZADO/cat.NaOCl/$NaClO_2$.

Nitroxyl-radical-catalyzed alcohol oxidation has attracted much attention owing to its versatile utility supported by diverse sets of catalyst and terminal oxidant availabilities.[10−13] 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO, **1**) is a representative of this type of catalyst. A less hindered class of nitroxyl radical 2-azaadamantane *N*-oxyls (AZADOs) (**2**, **3**),[8a,b,f,g] 9-azabicyclo[3.3.1]-nonane *N*-oxyl (ABNO) (**4**),[8c] and 9-azanoradamantane *N*-oxyl (Nor-AZADO) (**5**)[8e] have been developed as more reactive nitroxyl radical catalysts (Figure 1).

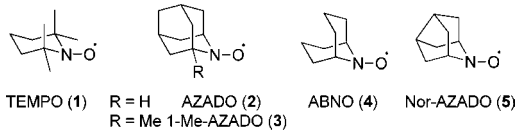


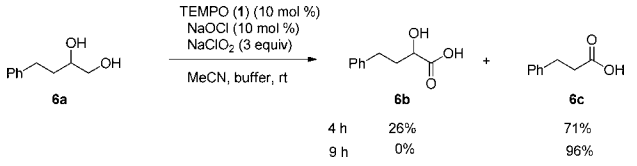
Figure 1. Structures of nitroxyl radicals.

In light of the inherent stereodiscriminable properties of TEMPO,[1] we first evaluated the possibility of TEMPO-catalyzed oxidation to conduct the selective oxidation of 1,2-diols to their corresponding 2-hydroxy acids, employing cat.NaOCl/$NaClO_2$ (Zhao's procedure),[13b,d] which offers an efficient one-pot oxidation of primary alcohols to their corresponding carboxylic acids. While attempting the oxidation of 1,2-diol **6a** under Zhao's conditions, we unexpectedly found that smooth and clean oxidative C−C cleavage from the 2-hydroxy acid **6b** to the one-carbon-unit-shorter carboxylic acid **6c** takes place (Scheme 1).

At the outset of this reaction, only 2-hydroxy acid was detected by analytical TLC. As the reaction approached completion, C−C bond cleavage took place exclusively to afford the one-carbon-unit-shorter carboxylic acid **6c** without any intermediate other than the 2-hydroxy acid **6b** being detected. One report including a nitroxyl-radical-catalyzed direct cleavage reaction from 1,2-diol to dehomologated carboxylic acid has been published;[14] however, it focused on the development of a column-flow alcohol oxidation system using immobilized TEMPO with few examples of oxidative cleavage. Stark et al. have also recently reported TPAP-catalyzed vicinal diol cleavage to carboxylic acids as a new synthetic method.[15] Because of the efficiency and mildness of the nitroxyl-radical-catalyzed method as well as its eco- and user-friendliness, we thought it useful to clarify the scope of nitroxyl-radical-catalyzed oxidative cleavage.[16] Furthermore, highly active AZADOs could expand the scope of TEMPO-catalyzed oxidative cleavage.

Comparing 1-Me-AZADO (**3**) with TEMPO (**1**), we examined the substrate applicability of this method (Table 1).[17−19] As expected, the simple 1,2-diols **6a**, **7a**, and **8a** efficiently underwent the desired reaction using either catalyst. The phenylacetylene **9a** yielded its corresponding one-carbon-unit-shorter carboxylic acid **9c** accompanied by less than 5% benzoic acid under the 1-Me-AZADO-catalyzed conditions, whereas 12% benzoic acid was obtained under the TEMPO-catalyzed conditions (entry 4). For the entries 5−7, 9, and 10, the differences between 1-Me-AZADO and TEMPO became clear. The conversions from 2-hydroxy acids to one-carbon-unit-shorter carboxylic acids were more efficiently promoted under the 1-Me-AZADO-catalyzed conditions than under

Scheme 1. Unexpected Oxidative Cleavage



TEMPO-catalyzed conditions. Thus, the corresponding 2-hydroxy acids were obtained after 24 h under the TEMPO-catalyzed conditions in moderate yield (the yields are shown in Table 1). No epimerization of an adjacent stereocenter was detected under either set of catalyst-catalyzed conditions (entries 5−10). Note that the methoxy diol **13a** and the *N*-protected amino diols **14a** and **15a** efficiently underwent one-pot oxidative cleavage without racemization under the 1-Me-AZADO-catalyzed conditions (entries 8−10).[20,21] The optically active diols **13a** and **14a** were prepared by Sharpless asymmetric epoxidation and acid-catalyzed nucleophilic ring opening

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(15) Schmidt, A.-K. C.; Stark, C. B. W. *Org. Lett.* **2011**, *13*, 5788–5791.

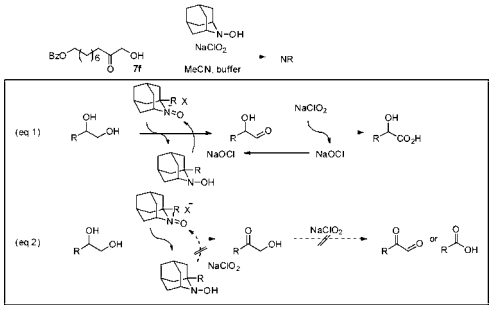
(16) Selected recent examples of two-step transformation of 1,2-diol to one-carbon-unit-shorter carboxylic acid: (a) Parker, K. A.; Lim, Y. H. *J. Am. Chem. Soc.* **2004**, *126*, 15968–15969. (b) Koizumi, Y.; Kobayashi, H.; Wakimoto, T.; Furuta, T.; Fukuyama, T.; Kan, T. *J. Am. Chem. Soc.* **2008**, *130*, 16854–16855. (c) Ramana, C. V.; Khaladkar, T. P.; Chatterjee, S.; Gurjar, M. K. *J. Org. Chem.* **2008**, *73*, 3817–3822. (d) Mohapatra, D. K.; Sahoo, G.; Ramesh, D. K.; Rao, J. S.; Sastry, G. N. *Tetrahedron Lett.* **2009**, *50*, 5636–5639. (e) Lu, Y.; Woo, S. K.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13876–13879. (f) Zhang, Y. A.; Rohanna, J.; Zhou, J.; Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 3208–3216.

from the corresponding allylic alcohol (see Supporting Information). These results showcase the use of this method for preparing optically active α-amino acids and α-alkoxy acids. The piperidinodiol **15a** was also prepared from D-mannitol according to Kamal's report,[22] which indicates the use of this one-pot oxidative cleavage as a preparation method for α-amino acids from a chiral pool. Unfortunately, **16a** having a sensitive trisubstituted olefin under oxidative conditions and the internal diol **17a** did not afford the desired products.

To investigate the applicability of this one-pot oxidative cleavage to terminal triols and tetraols, we examined the reactions of the triol **18** and the tetraol **20** (Scheme 2). Two- and three-carbon dehomologations effectively proceeded to afford the corresponding carboxylic acids.

To probe the reaction mechanism, we examined the reactivity of oxoammonium salts (1-Me-AZADO$^+$X$^-$), which are active species of 1-Me-AZADO (**3**), NaOCl,[23] and $NaClO_2$,[24,25] toward the 2-hydroxy acid **7b** and the keto acid **7e** (Scheme 3). Neither 1-Me-AZADO$^+$Cl$^-$ nor NaOCl-$NaClO_2$ caused the C−C bond cleavage of the 2-hydroxy acid **7b** (eqs 1, 2). Although 1-Me-AZADO$^+$Cl$^-$ also did not cause the C−C bond cleavage of the keto acid **7e**, $NaClO_2$ did promote the C−C bond cleavage of the keto acid **7e** (eqs 3, 4). These results show that C−C bond

(17) AZADO (**2**) also smoothly catalyzed one-pot oxidative cleavage. By mixing the hydroxy ketone **7f** and the hydroxyamine of AZADO (AZADOH) and $NaClO_2$, neither C−C bond cleavage nor alcohol oxidation occurred, which indicates that the oxidation of a secondary alcohol prior to a primary alcohol could shut down the catalytic cycle (eq 2). NaOCl generated from $NaClO_2$ by the oxidation of an aldehyde to a carboxylic acid is necessary for the regeneration of oxoammonium species in this reaction (eq 1). Thus, we used 1-Me-AZADO (**3**) because of its moderate bulkiness as a catalyst.



(18) The catalytic efficiency of 1-Me-AZADO is shown in the Supporting Information (Table S1). **7a** effectively underwent the one-pot oxidative cleavage with 1 mol % 1-Me-AZADO.

(19) In our previous study,[8b] sometiomes one-pot oxidation of primary alcohols to carboxylic acids suddenly stopped in low ion concentration buffter (<0.1 M ion concentration) accompanied by acidification of the reaction mixture. It was confirmed that one-pot oxidation proceeded in 1 M phosphate buffer with high reproducibility.

(20) **13a** and **14a** were prepared from the corresponding 90% ee 2,3-epoxy alcohol. The enantiomeric excess of **13c** obtained from either the 1-Me-AZADO- or TEMPO-catalyzed reaction was determined to be 90% ee. The enantiomeric excess of **14c** obtained from the 1-Me-AZADO (**3**) catalyzed reaction was also determined to be 90% ee, although the TEMPO (**1**) catalyzed condition afforded 87% ee **14c**.

(21) Optically pure **15c** was obtained from chiral **15a** under either the 1-Me-AZADO (**3**)- or TEMPO (**1**)-catalyzed conditions.

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(23) Veisi, H. *Synlett* **2007**, 2607–2608 and references cited therein.

(24) de Ferreira, M. L. *Synlett* **2011**, *5*, 730–731 and references cited therein.

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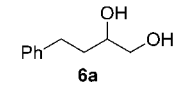
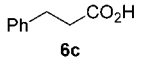
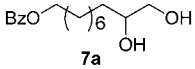
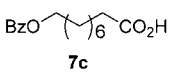
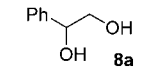
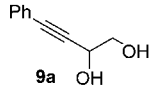
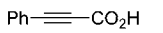
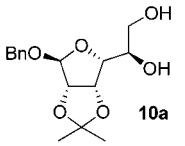
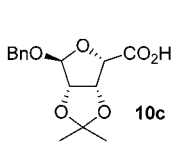
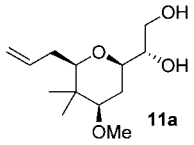
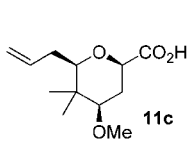
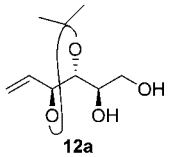
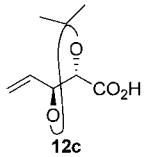
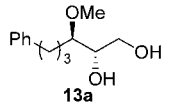
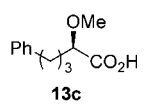
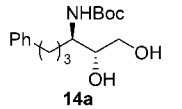
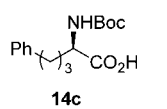
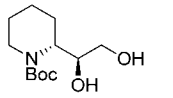
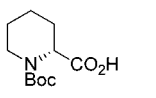
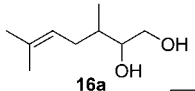
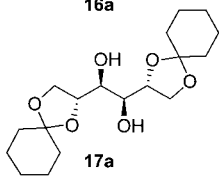
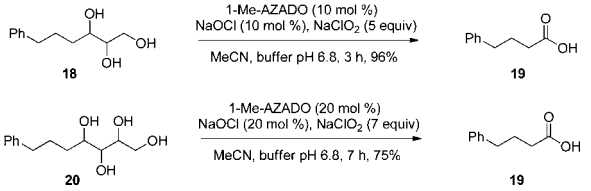
Table 1. Scopes of TEMPO- and 1-Me-AZADO-Catalyzed One-Pot Oxidative Cleavages[a]

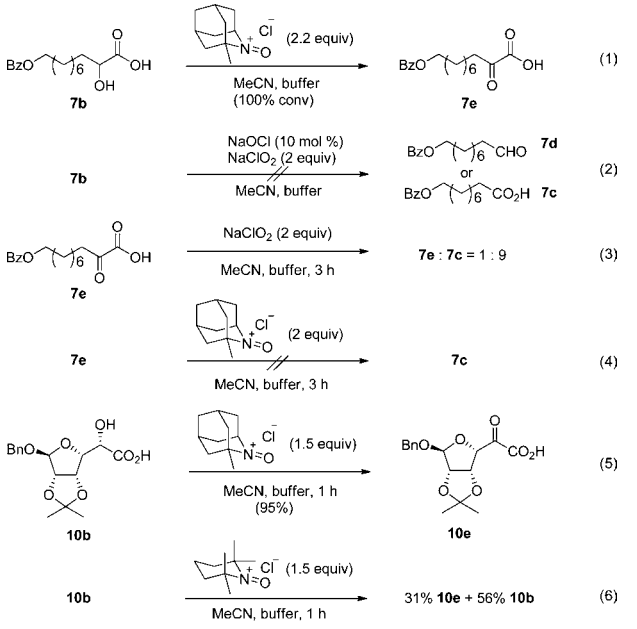
entry	diol	product	time (h) yield (%)[b] 1-Me-AZADO	TEMPO
1	 **6a**	 **6c**	**2.5**	**96**
			9	96
2	 **7a**	 **7c**	**3**	**98**
			3	100
3	 **8a**	$PhCO_2H$ **8c**	**24**	**90[c]**
			24	85[c]
4	 **9a**	 **9c**	**3**	**83[c]**
			20	78[c]
5	 **10a**	 **10c**	**5**	**89[c]**
			24	33(64)[c,d]
6	 **11a**	 **11c**	**2**	**79[c]**
			24	55(22)[c,d]
7	 **12a**	 **12c**	**1**	**91[c]**
			72	25(<41)[c,d]
8	 **13a**	 **13c**	**2**	**98[c]**
			8	96[c]
9	 **14a**	 **14c**	**5**	**100[c]**
			24	48(35)[c,d]
10	 **15a**	 **15c**	**3**	**82[c,e]**
			24	50(28)[c,d,e]
11	 **16a**		24	0
			-	-
12	 **17a**		24	0
			-	-

[a] Conditions: 10 mol % nitroxyl radical, 10 mol % NaOCl, and 3 equiv of $NaClO_2$ were added in MeCN and buffer (pH 6.8, 1.0 M) at rt. [b] Isolated yield. [c] Carboxylic acids were isolated as methyl esters after treatment with CH_2N_2. [d] The numbers in paretheses are the yields of the corresponding 2-hydroxy acids. [e] 6 equiv of $NaClO_2$ were used.

Scheme 2. One-Pot Oxidative Cleavage of Triol and Tetraol



Scheme 3. Reactivity of Oxoammnium Salts, NaOCl, and $NaClO_2$

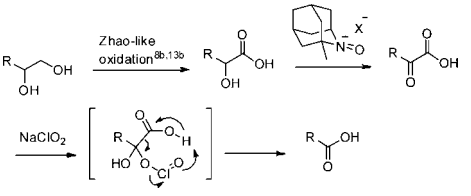


cleavage of 2-hydroxy acids is caused by $NaClO_2$ via the keto acid. Next, to investigate the difference in reaction rate between the 1-Me-AZADO-catalyzed and TEMPO-catalyzed conditions, the 2-hydroxy acid **10b** was treated with either 1-Me-AZADO$^+$Cl$^-$ or TEMPO$^+$Cl$^-$. **10b** was completely oxidized to the corresponding keto acid **10e** by 1-Me-AZADO$^+$Cl$^-$ within 1 h (eq 5). On the other hand, 56% 2-hydroxy acid **10b** was recovered after treatment with TEMPO$^+$Cl$^-$ for 1 h (eq 6). These results indicate that the difference in reaction rate between 1-Me-AZADO (**3**)-catalyzed and TEMPO (**1**)-catalyzed conditions reflects the rate of oxidation from the 2-hydroxy acid to the keto acid.

With the above results taken into consideration, an overall plausible reaction mechanism is shown in Scheme 4. 1,2-Diols are oxidized to 2-hydroxy acids which are the only intermediates detectable by analytical TLC under the reaction conditions. Immediately after 2-hydroxy acids are oxidized to keto acids by the oxoammonium species, the C–C bond is smoothly excised by $NaClO_2$. The one-pot oxidative cleavage is completed in four oxidative steps: oxidation of primary alcohols to aldehydes, oxidation of aldehydes to carboxylic acids, oxidation of hydroxyl acids to keto acids, and oxidative cleavage of keto acids to one-carbon-unit-shorter carboxylic acids.

In summary, we have developed cat.1-Me-AZADO/cat. NaOCl/$NaClO_2$ for the useful one-pot oxidative cleavage reaction of 1,2-diols to dehomologated carboxylic acids under mild conditions. 1-Me-AZADO (**3**) more effectively catalyzed the reaction than TEMPO (**1**). Sensitive groups such as double bonds, triple bonds, acetonides, and *N*-Boc groups were compatible with these reaction conditions. This one-pot oxidative cleavage proceeded without the epimerization of adjacent stereocenters. Furthermore, this method was applicable to terminal triols and tetraols. This reaction will be a useful transformation for 1,2-diols and will also expand the use of nitroxyl radical catalysts.

Scheme 4. Plausible Overall Mechanism



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Supporting Information Available. General experimental procedure, characterization data, and copy of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.