Organic Letters
Letter
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Chemoselective Catalytic Oxidation of 1,2-Diols to α-Hydroxy Acids Controlled by TEMPO−ClO_2 Charge-Transfer Complex

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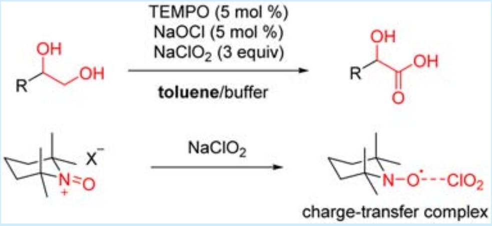
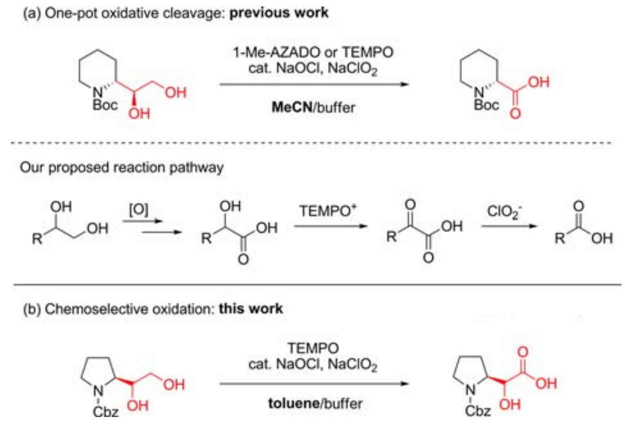
Supporting Information

ABSTRACT: Chemoselective catalytic oxidation from 1,2-diols to α-hydroxy acids in a cat. TEMPO/cat. NaOCl/$NaClO_2$ system has been achieved. The use of a two-phase condition consisting of hydrophobic toluene and water suppresses the concomitant oxidative cleavage. A study of the mechanism suggests that the observed selectivity is derived from the precise solubility control of diols and hydroxy acids as well as the active species of TEMPO. Although the oxoammonium species $TEMPO^+Cl^-$ is hydrophilic, the active species dissolves into the organic layer by the formation of the charge-transfer (CT) complex TEMPO−ClO_2 under the reaction conditions.



α-Hydroxy acids are important subunits contained in biologically active compounds.[1,2] Selective direct oxidation from 1,2-diols to the corresponding α-hydroxy acids without protecting groups is a potentially highly useful method for their preparation. This is because 1,2-diols are readily accessible from biomass such as carbohydrates and glycerol, and from the dihydroxylation of terminal alkenes,[3,4] the hydration of epoxides,[5] and other methods.[6] However, most oxidants cause inevitable side reactions such as oxidative cleavage[7,8] and oxidation of the secondary alcohol,[9] especially when a 1,2-diol consists of a primary alcohol and a secondary alcohol. Hence, a general oxidation method from 1,2-diols to the corresponding α-hydroxy acids is still unknown, although a limited number of examples have been reported.[10−12] Among the variety of one-pot oxidation methods from primary alcohols to the corresponding carboxylic acids that have been developed, Merck's method using cat. TEMPO/cat. NaOCl/$NaClO_2$ and Widlanski's method using cat. TEMPO/$PhI(OAc)_2$, and the corresponding AZADO-catalyzed methods, are the most reliable in recent organic syntheses.[13−15] However, the oxidation of 1,2-diols produces one-carbon-shorter carboxylic acids instead of α-hydroxy acids through the inevitable oxidative cleavage under the one-pot oxidation conditions, as we previously reported (Scheme 1a).[8] In the previous studies, we also made two important observations from mechanistic experiments on the cat. 1-Me-AZADO/cat. NaOCl/$NaClO_2$ condition: (a) the oxoammonium species itself does not induce the oxidative cleavage of a C−C bond; (b) the oxidative cleavage occurs from keto acids, not from hydroxy acids.[8b] These observations suggest that high chemoselectivity toward the oxidation of the 1,2-diols compared with α-hydroxy acids could achieve a desired selective oxidation. Herein, we disclose the successful implementation of an efficient chemoselective catalytic oxidation of 1,2-diols to α-hydroxy acids (Scheme 1b). In this reaction system, it was found that the TEMPO−ClO_2 charge-transfer (CT) complex plays an important role in the chemoselectivity.

Scheme 1. Nitroxyl-Radical-Catalyzed Oxidation of 1,2-Diols

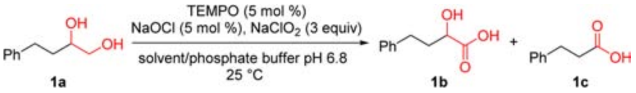


In the course of our studies to investigate the optimal conditions for chemoselective oxidation from 1,2-diols to α-hydroxy acids, solvent screening provided us with fascinating results (Table 1). While oxidative cleavage was inevitably induced to give one-carbon-shorter carboxylic acids in amphiphilic MeCN, which is generally used as a solvent in Merck's method,[13a] higher selectivity was observed in hydrophobic solvents. In particular, toluene, xylene, benzene, and Et_2O produced α-hydroxy acids with excellent selectivities (α-hydroxy acid/one-carbon-shorter carboxylic acid ≥ 20:1). Note that the reaction rate in hydrophobic solvents tended to be faster than that in amphiphilic solvents. We selected low-cost and easy-to-use toluene as the optimal solvent and evaluated the substrate scope.

Received: April 7, 2015
Published: April 17, 2015

DOI: 10.1021/acs.orglett.5b01003
Org. Lett. 2015, 17, 2282−2285

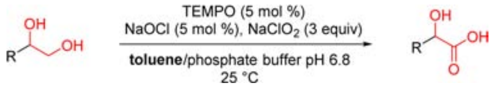
Table 1. Solvent Screening

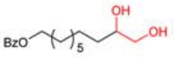
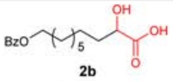
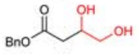
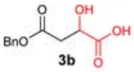
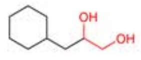
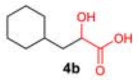
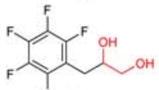
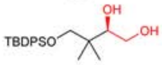
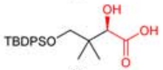
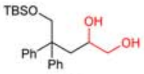
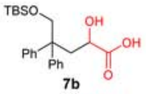
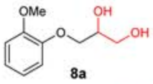
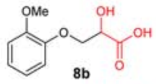
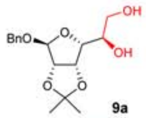
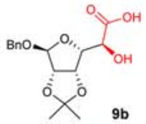
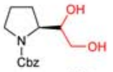
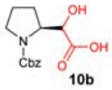
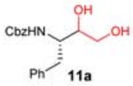
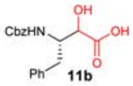
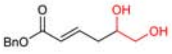
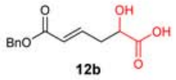
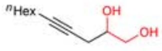
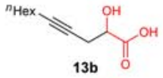
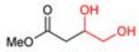
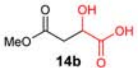


solvent	time (h)	yield (%)[a] 1b	1c	selectivity[b]	solubility in water (%)[c]
1,4-dioxane	22	29	71	0.4	soluble
MeCN	12	30	51	0.6	soluble
AcOEt	7	75	25	2.9	8.08
3-pentanone	3	64	24	2.7	5.10
CH_2Cl_2	3	79	13	6.1	1.96
Et_2O	**3.5**	**95**	**4.7**	**>20**	**1.2**
$ClCH_2CH_2Cl$	2.5	82	17	4.8	0.86
$CHCl_3$	3	84	13	6.5	0.8
benzene	**2**	**82**	**3.1**	**>20**	**0.18**
toluene	**4**	**95**	**4.7**	**>20**	**0.05**
xylene	**8**	**83**	**2.6**	**>20**	**0.02**

[a] Yield determined by NMR. [b] **1b** yield/**1c** yield. [c] Reported values in MSDS of Kanto Chemical Co., Inc.

Table 2. Substrate Scope of the TEMPO-Catalyzed Chemoselective Oxidation



entry	1,2-diol	α-hydroxy acid	time (h)	yield (%)
1[a]	 **2a**	 **2b**	1.5	85
2	 **3a**	 **3b**	8	87
3	 **4a**	 **4b**	0.8	92
4[a]	 **5a**	 **5b**	2.5	84
5[b]	 **6a**	 **6b**	4	88
6[c]	 **7a**	 **7b**	3	78
7[a]	 **8a**	 **8b**	24	73 (10)[d,e]
8[b,c]	 **9a**	 **9b**	1	96
9	 **10a**	 **10b**	5	82
10[a]	 **11a**	 **11b**	1	85
11	 **12a**	 **12b**	3.5	81
12[b]	 **13a**	 **13b**	1	80
13	 **14a**	 **14b**	5	0

[a] Reaction temp 50 °C. [b] 20 mol % NaOCl was slowly added using a syringe pump over 1 h. [c] Isolated as methyl ester by treatment with CH_2N_2. [d] NMR yield. [e] Yield of one-carbon-shorter carboxylic acid.

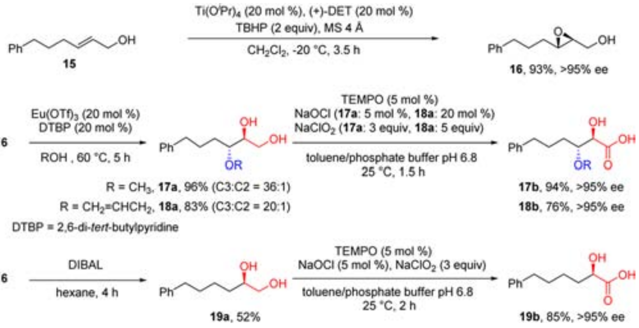
A broad range of 1,2-diols were selectively oxidized to afford the corresponding α-hydroxy acids in high yields accompanied by less than 5% one-carbon-shorter carboxylic acids (Table 2). In the case of **8a**, although 10% of the one-carbon-shorter carboxylic acid **8c** was produced, the desired α-hydroxy acid **8b** was obtained in high yield (entry 7). Various functional groups such as ester, silyl ether, benzyl ether, Cbz carbamate, and unsaturated bonds are compatible (entries 2, 5, 6, and 8−12). Although **2a**, **5a**, **8a**, and **11a** were insoluble in the reaction solvents at room temperature, the desired oxidation effectively proceeded at 50 °C (entries 1, 4, 7, and 10). Water-soluble diol **14a** did not produce the desired product **14b** (entry 13).

Optically active α-hydroxy acids can also be prepared by a three-step reaction sequence consisting of Sharpless-Katsuki asymmetric epoxidation,[16] C3-selective ring opening,[6] and chemoselective oxidation (Scheme 2). Neither epimerization nor racemization was observed.

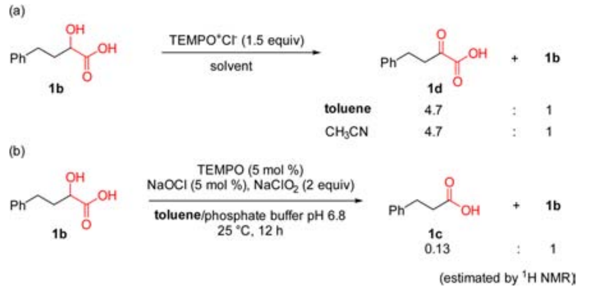
We initially considered the chemoselectivity derived from the difference between the oxidation rate of an α-hydroxy acid by oxoammonium species in a hydrophobic solvent and that in a hydrophilic solvent. To compare the oxidation rate in toluene with that in MeCN, hydroxy acid **1b** was subjected to oxidation by a stoichiometric amount of $TEMPO^+Cl^-$ in each solvent. However, a significant difference in the oxidation rates that could explain the observed chemoselectivity was not observed (Scheme 3a), whereas the oxidation of α-hydroxy acid **1b** under the TEMPO/NaOCl/$NaClO_2$ condition was substantially slow in toluene (Scheme 3b).

To obtain insight into the chemoselectivity, the distribution ratio of the 1,2-diol **1a**, the α-hydroxy acid **1b**, and the catalyst between toluene and phosphate buffer was investigated. After each material dissolved into the two-phase solution (toluene/phosphate buffer = 1.4:1), it was vigorously stirred for 10 min and left to stand until it separated clearly into two phases. The concentrations of 1,2-diol **1a** and α-hydroxy acid **1b** were determined by NMR experiments. It was found that the 1,2-diol **1a** was mainly distributed in the organic layer (organic layer/aqueous layer = ca. 8:2). The α-hydroxy acid **1b** was entirely distributed in the aqueous layer, as it was not detected in the organic layer. To examine the distribution ratio of the active species of the catalyst, yellow oxoanmmonium salt $TEMPO^+Cl^-$ was dissolved into a toluene/buffer solution (Figure 1a). The aqueous layer changed from a colorless solution to yellow, and the absorption of oxoammonium species in the wavelength range of 450−500 nm (λ_{max} = 473 nm) was observed by UV−vis measurement of the aqueous layer, while no absorption was detected at the organic layer (Figure 1b). Notably, the addition of $NaClO_2$ to the $TEMPO^+Cl^-$ solution led to a clear change in the appearance (Figure 1a). The organic layer became dark red. The observation of the dark red color was noted in Zhao's original report.[13a] However, the dark red species was not identified. UV−vis measurement of the organic layer showed the characteristic of

Scheme 2. Preparation of Enantioenriched Hydroxy Acids



Scheme 3. Mechanistic Experiments



very strong absorption in the range of 350—400 nm (Figure 1c). Similar absorption was reported by Ganiev et al.[17] They reported that ClO_2 and TEMPO form a dark red CT complex in an organic solvent with inherent absorption in the range 450—500 nm. In addition, ClO_2 provides such strong absorption in the range 350—400 nm. On the basis of their reports, we prepared ClO_2 and obtained its UV−vis spectrum to compare the absorption of ClO_2 and the CT complex with the spectrum obtained from the organic layer of $TEMPO^+Cl^-/NaClO_2$ solution. The strong absorption in the range 350—400 nm shows good agreement with that of ClO_2, and the subtraction spectra of the ClO_2 absorption from the UV−vis spectrum of the organic layer indicated the formation of the CT complex ($TEMPO−ClO_2$) (λ_{max} = 478 nm) (Figure 1d). These results indicate that hydrophilic $TEMPO^+Cl^-$ and $NaClO_2$ form the hydrophobic CT complex through single-electron transfer and that the active species of TEMPO dissolves into the organic layer.

On the basis of the above observations, a plausible explanation for the chemoselective oxidation of 1,2-diols to α-hydroxy acids is proposed in Scheme 4. 1,2-Diols are mainly distributed in the organic layer, and α-hydroxy acids are entirely distributed in the aqueous layer. The hydrophilic oxoammonium species generated from TEMPO/TEMPOH immediately reacts with ClO_2^- and forms a hydrophobic CT complex ($TEMPO−ClO_2$). The gradually generated oxoammonium species ($TEMPO^+ClO_2^-$) in equilibrium selectively oxidizes 1,2-diols to the corresponding α-hydroxyaldehydes in the organic layer, and the subsequent oxidation of α-hydroxyaldehydes by $NaClO_2$ affords the corresponding α-hydroxy acids, whereas the resultant α-hydroxy acids remain intact because they are distributed in the aqueous layer.

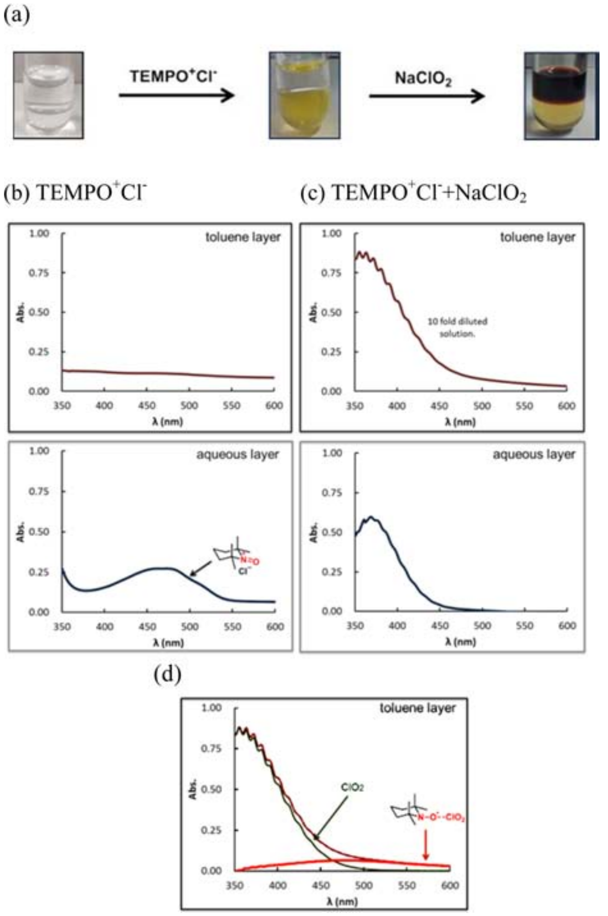
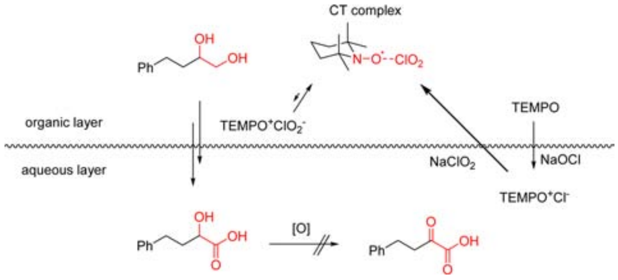


Figure 1. (a) Two-phase toluene/phosphate buffer solution, two-phase solution of $TEMPO^+Cl^-$, and solution after addition of $NaClO_2$. (b) UV−vis spectra before addition of $NaClO_2$ to $TEMPO^+Cl^-$ toluene/phosphate buffer solution. (c) UV−vis spectra after addition of $NaClO_2$ to $TEMPO^+Cl^-$ toluene/phosphate buffer solution. (d) Subtraction spectrum of ClO_2 from that of toluene layer after addition of $NaClO_2$.

Scheme 4. Plausible Explanation for the Chemoselectivity



In conclusion, we have achieved the chemoselective catalytic oxidation of 1,2-diols to α-hydroxy acids, which has been considered as a formidable challenge. A broad range of 1,2-diols are effectively oxidized into the corresponding α-hydroxy acids. The preparation of optically active α-hydroxy acids was also demonstrated. We also identified the interesting chemical property of the CT complex formation under the oxidation conditions, which will be an important finding for further development of a nitroxyl-radical-catalyzed reaction. We believe this reaction will be a useful tool for organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We dedicate this work to the memory of Prof. Tsutomu Katsuki. This work was partially supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" and Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT and by a Grant-in-Aid for Young Scientists (A) (No. 23689001) from JSPS.

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