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Transition-Metal-Free and Chemoselective NaO^{t}Bu−O$_2$-Mediated Oxidative Cleavage Reactions of *vic*-1,2-Diols to Carboxylic Acids and Mechanistic Insight into the Reaction Pathways

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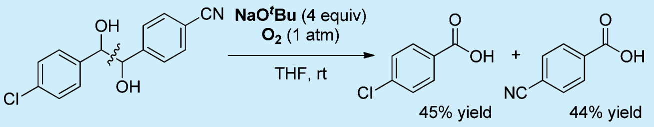
Supporting Information

ABSTRACT: A method for efficient oxidative cleavage of *vic*-1,2-diols using a NaO^{t}Bu−O$_2$ system resulted in the formation of carboxylic acids in high yields. The present protocol is an eco-friendly alternative to a conventional transition-metal-based method. This new strategy allows large-scale production with nonchromatographic purification while also suppressing competitive reaction pathway such as benzilic acid rearrangement.



The development of transition-metal-free, chemoselective reactions is one of the most important and fundamental tasks in organic synthesis, as it contributes significantly to green chemistry practices.[1] To keep pace with scientific advancement on green processes, we recently reported the transition-metal-free oxidation of primary allylic alcohol to α,β-unsaturated carboxylic acids utilizing NaO^{t}Bu under oxygen atmosphere.[2a,2] This protocol has distinctive advantages over existing methodologies because it replaces precious transition-metal catalysts (e.g., Au, Pt, Ru, Cu, or Pd), has a lower reaction temperature, and has a shorter reaction time. Transition-metal-free oxidations of a variety of allylic alcohols with high chemoselectivities were fully investigated for the first time.

As part of a wider research program aimed at designing and developing transition-metal-free processes, we became interested in the oxidative cleavage reaction of *vic*-1,2-diol in combination with alkali metal *tert*-butoxide and oxygen.[3] In general, the most common oxidizing agents for oxidative cleavage of *vic*-1,2-diols are sodium periodate (NaIO$_4$), periodic acid (HIO$_4$), and lead tetraacetate [Pb(OAc)$_4$], which lead to aldehydes or ketones as major products (Scheme 1, eq 1).[4] Several different types of oxidants including transition-metal catalysts also facilitate the direct conversion of *vic*-1,2-diols to carboxylic acids (Scheme 1, eq 2).[5] For such reactions, either a high oxidation metal−oxo catalyst (i.e., Cr, V, Mn, Ru, W) or a transition metal (Pt) catalyst is still accompanied by high temperature (~70 °C).[6] In some cases, low product selectivity between aldehydes and carboxylic acids is also observed.[6b−d]

Recently, a transition-metal-free version of oxidative cleavage of *vic*-1,2-diols to carboxylic acids was reported by utilizing

Scheme 1. Utility of NaO^{t}Bu-O$_2$ System for Oxidative Cleavage of *vic*-1,2-Diol

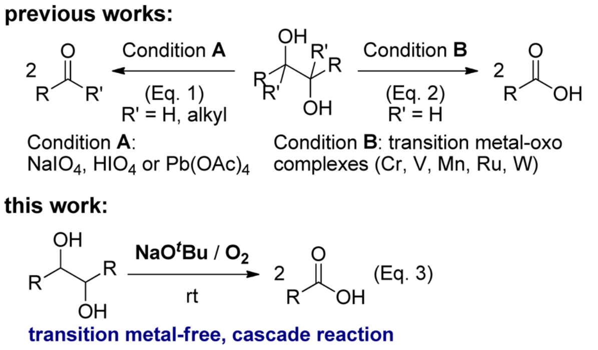
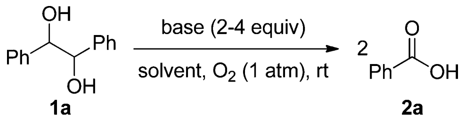


Table 1. Optimization of Reaction Conditions[a]



entry	base (equiv)	solvent	time (h)	yield[b] (%)
1		THF	24	ND
2	KO^{t}Bu (2)	THF	24	42
3	NaO^{t}Bu (2)	THF	24	50
4	NaO^{t}Bu (3)	THF	24	56
5	NaO^{t}Bu (4)	THF	3	75
6	NaO^{i}Pr (4)	THF	24	42
7	NaOMe (4)	THF	24	34
8	NaH (4)	THF	24	71
9	KHMDS (4)	THF	24	<5
10	Cs$_2$CO$_3$ (4)	THF	24	ND
11	NaO^{t}Bu (4)	CH$_2$Cl$_2$	3	ND
12	NaO^{t}Bu (4)	toluene	3	55
13	NaO^{t}Bu (4)	1,4-dioxane	3	54
14	NaO^{t}Bu (4)	Et$_2$O	3	64
15	NaO^{t}Bu (4)	DMSO	3	67
16[c]	NaO^{t}Bu (4)	THF	3	ND

[a]General conditions: **1a** (0.5 mmol), base (2−4 equiv), solvent (3 mL), O$_2$ (1 atm), rt. [b]Isolated yield. [c]Anaerobic conditions.

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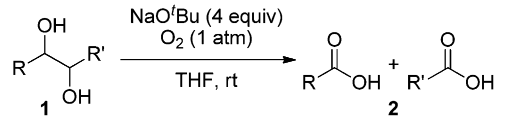
Table 2. Reaction Scope[a]



a: R = R′ = Ph
b: R = R′ = 4-Cl-C_6H_4
c: R = R′ = 3-Cl-C_6H_4
d: R = R′ = 2-Cl-C_6H_4
e: R = R′ = 4-F-C_6H_4
f: R = R′ = 4-Br-C_6H_4
g: R = R′ = 4-CF_3-C_6H_4
h: R = R′ = 4-CN-C_6H_4
i: R = R′ = 4-NO_2-C_6H_4
j: R = R′ = 4-Me-C_6H_4
k: R = R′ = 4-OMe-C_6H_4
l: R = 4-Cl-C_6H_4; R′ = 4-CN-C_6H_4
m: R = 4-NO_2-C_6H_4; R′ = *n*-Pentyl
n: R = 4-Cl-C_6H_4; R′ = H
o: R = R′ = Ph$(CH_2)_4$

entry	substrate	product	time (h)	yield[b] (%)
1	**1a**	**2a**	3	75
2	**1b**	**2b**	5	91
3	**1c**	**2c**	5	96
4	**1d**	**2d**	7	70
5	**1e**	**2e**	3	70
6	**1f**	**2f**	6	75
7	**1g**	**2g**	3.5	89
8	**1h**	**2h**	2.5	91
9	**1i**	**2i**	2	96
10	**1j**	**2j**	5	60
11	**1k**	**2k**	5	60
12	**1l**	1/2 **2b** + 1/2 **2h**	2	45 (**2b**) + 44 (**2h**)
13[c]	**1m**	1/2 **2i** + 1/2 **2m′**[d]	8	39 (**2i**) + 39 (**2m′**)
14	**1n**	1/2 **2b**	2	44 (**2b**)
15[e]	**1o**	**2o**	6	40[f]

[a] General conditions: **1** (0.5 mmol), NaO^{t}Bu (4 equiv), solvent (3 mL), O_2 (1 atm), rt. [b] Isolated yield. [c] Using NaO^{t}Bu (6 equiv). [d] **2m′** is *n*-hexanoic acid. [e] Using NaO^{t}Bu (6 equiv). [f] Determination of the yield by Fisher esterification with H_2SO_4−MeOH.

organocatalysis [nitroxyl radical as organocatalyst and PhI$(OAc)_2$ (5 equiv)/or $NaClO_2$ (3 equiv) as oxidants], photooxidation [2-chloroanthraquinone as catalyst, O_2, *hν* (400-W Hg lamp)], aqueous sodium hypochlorite (10 equiv), hydroperoxide [*tert*-butyl hydroperoxide (4 equiv), KO^{t}Bu (3 equiv), 80 °C], and sodium perborate [$NaBO_3{\cdot}4H_2O$ (10 equiv) as oxidant in AcOH (2−3 mL per oxidant) under reflux conditions].[7] Therefore, multifarious ways to accomplish oxidative cleavage of *vic*-1,2-diols into carboxylic acids without the need for transition-metal catalysts, costly oxidants, and power supply instruments are highly desirable.

Herein, we report a scalable, transition-metal-free, and chemoselective cascade of reactions utilizing NaO^{t}Bu and O_2 as oxidant, which are both readily available and inexpensive. This could potentially address the shortcomings of the aforementioned transition metal-based methodologies (Scheme 1, eq 3). The labeling experiment with $^{18}O_2$ was performed to elucidate the pathway for the preferential mechanism.

To investigate the viability of the envisioned direct oxidative cleavage reaction of *vic*-1,2-diol, hydrobenzoin **1a** was selected as a model substrate. First, various bases and solvents were screened. The results are summarized in Table 1. In a controlled experiment it was found that the reaction did not proceed in the absence of either base or oxygen as oxidant (Table 1, entries 1 and 16).

The use of NaO^{t}Bu gave a slightly better chemical yield than the use of KO^{t}Bu (Table 1, entries 2 and 3). Product yield was significantly influenced by varying the equivalents of NaO^{t}Bu (Table 1, entries 3−5). The influence of the alkoxide nature was also examined. For instance, sodium isopropoxide and sodium methoxide gave low product yield (Table 1, entries 6−7). Interestingly, the chemical yield of product increased in the following order of alkoxide ion basicity: *tert*-butoxide > isopropoxide > methoxide. NaH gave results comparable to those obtained from reaction mediated by NaO^{t}Bu, but a much longer reaction time (24 h) was required (Table 1, entry 8). However, KHMDS and Cs_2CO_3 showed negligible conversion. A number of other solvents, including CH_2Cl_2, toluene, 1,4-dioxane, Et_2O, and DMSO, were subsequently investigated, but they were inferior to THF in terms of yield (Table 1, entries 11−15).

We next explored the scope of this reaction of *vic*-1,2-diols with NaO^{t}Bu under optimized conditions [NaO^{t}Bu (4 equiv), O_2 (1 atm), THF, rt]. The results are summarized in Table 2. A

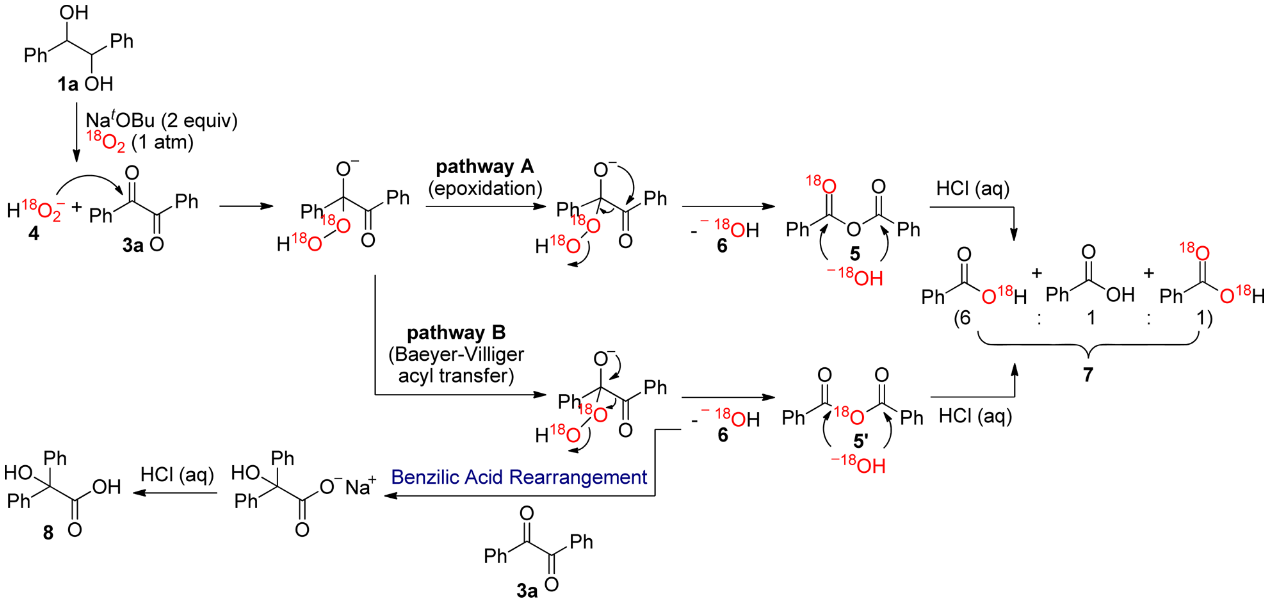


Figure 1. Proposed mechanism for the oxidative cleavage of *vic*-1,2-diols to carboxylic acids.

series of symmetrical and unsymmetrical *vic*-1,2-diols were examined. In general, the symmetrical *vic*-1,2-diols bearing electron-withdrawing substituents smoothly transformed to corresponding products in high yields ranging from 70% to 96%. However, those with electron-donating substituents resulted in relatively lower yields (60%). Interestingly, unsymmetrical *vic*-1,2-diols (**1l** and **1m**) can be oxidatively cleaved with NaO^{t}Bu-O_2 to form two different acids (Table 2, entries 12 and 13). Specifically, 4-chlorobenzoic acid **2b** and 4-cyanobenzoic acid **2h** were obtained in virtually identical yields (~45%) when hydrobenzoin derivative **1l** was employed. Unsymmetrical *vic*-1,2-diol bearing both aryl and alkyl substituents also gave the corresponding products (**2i** and **2m′**).

Styrene-derived terminal 1,2-diol **1n** gave one-half the product **2b** with 44% yield (Table 2, entry 14). Aliphatic internal 1,2-diol **1o** proved suitable candidate for this transformation. The yield of actual product **2o** was determined by Fischer esterification of the resulting 5-phenylpentanoic acid with MeOH in the presence of catalytic amounts of H_2SO_4 (Table 2, entry 15). During the oxidative cleavage reaction of *vic*-1,2-diol, small amounts of benzilic acid (10%) were detected in most cases.

To ascertain mechanistic insights into the nature of oxidant, an ^{18}O isotopic labeling experiment was conducted with $^{18}O_2$ gas (Figure 1).

Double deprotonation of the hydroxyl group in *vic*-1,2-diol with 2 equiv of NaO^{t}Bu presumably generated 1,2-diketone **3** and ^{18}O-labeled hydroperoxide anion **4** via hydride transfer from the α-carbon of alcohol to the ^{18}O-labeled oxygen. The subsequent nucleophilic attack of ^{18}O-labeled hydroperoxide anion **4** to the carbonyl group of 1,2-diketone would form two different ^{18}O-labeled anhydride **5** and **5′** as transient intermediate and ^{18}O-labeled hydroxide ion **6** via epoxidation mechanism (pathway A) or Baeyer–Villiger mechanism with acyl group migration (pathway B), leading to three main categories of carboxylic acids **7** after simple acid-workup.[8] The resulting products were subjected to GC/MS analysis (Hewlett-Packard Agilent 6890, 5973 MSD). The ^{16}O and ^{18}O compositions of individual carboxylic acids were determined by the relative abundances of mass peaks at m/z = 122 for $^{16}O^{16}O$, m/z = 124 for $^{16}O^{18}O$, and m/z = 126 for $^{18}O^{18}O$.

As shown in Figure 2 and proposed in Figure 1, it was revealed that the relative abundances of isotopic masses for each product **7** are identical to those of isotopic masses (theoretical ratio of benzoic acid isotopes [$^{16}O^{16}O$:$^{16}O^{18}O$:$^{18}O^{18}O$] = 1:6:1, experimental ratio of [$^{16}O^{16}O$:$^{16}O^{18}O$:$^{18}O^{18}O$] = 1:6.2:1.3).

During the reaction course, small amounts of benzilic acid derivative **8** were observed. This indicates that the released hydroxide ion **6** serves as a formidable competitor to the formation of carboxylic acid **7** and α-hydroxy acid **8**. Namely, the benzilic acid rearrangement had clearly occurred, in which 1,2-diketone **3** was converted to α-hydroxy acid **8** upon treatment with hydroxide ion **6**. This information provides crucial evidence of the existence of 1,2-diketone and hydroxide ion while allowing a better understanding of the reaction mechanism.

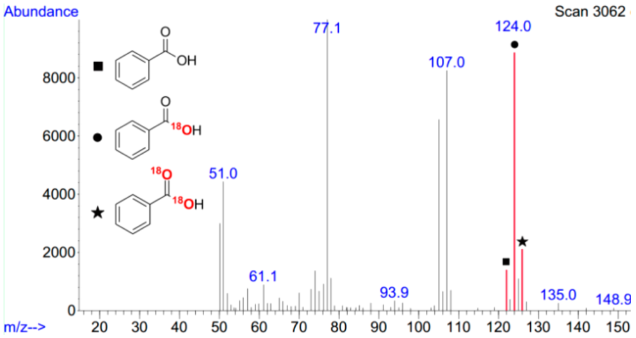
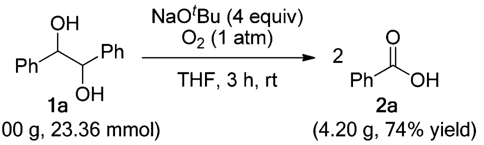
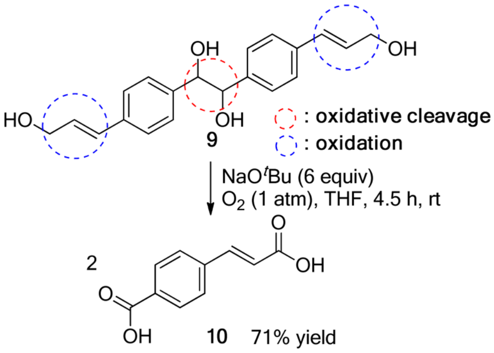


Figure 2. Isotopic labeling results from the oxidative cleavage of *vic*-1,2-diol utilizing a NaO^{t}Bu-$^{18}O_2$ system.

Scheme 2. Large-Scale Production of 2a



Scheme 3. Transition-Metal-Free, Oxidation/Oxidative Cleavage Reaction in a One-Pot Manner Utilizing a NaO^{t}Bu-O_2 System



To verify the existence of 1,2-diketone, a reaction of 4,4′-methoxyhydrobenzoin **1k** was carried out with 4 equiv of NaO^{t}Bu under oxygen atmosphere at −20 °C to produce 4,4′-methoxybenzil **3k** in 11% yield. The product was identified by ^1H and ^{13}C NMR spectroscopy. Despite being hampered by parasitic pathways, such as benzilic acid rearrangement, the desired carboxylic acid was almost selectively formed. The existence of reactive intermediate such as anhydride **5** or **5′**, which are not easily isolable from reaction mixture in the presence of strong nucleophile (such as hydroxide ion[9]), offers the possibility to suppress competing parasitic reactions (benzilic acid rearrangement). The ability to control selectivity while avoiding the use of transition-metal catalyst is one of the most distinctive features of the oxidative cleavage of *vic*-1,2-diols. The presence of trace transition metal elements in NaO^{t}Bu was also examined by ICP-ACE, and the results are shown in ref 10.

A 23-fold scale-up was also demonstrated with substrate **1a** compared to the currently approved reaction under the NaO^{t}Bu–O_2 system. The detailed experimental procedure is described in the Supporting Information. Organic and aqueous layers were clearly separated by salting-out, eliminating the need for additional organic extraction. Moreover, the desired product **2a** was easily isolated from residues due to the insolubility of resulting side product benzilic acid **8** in EtOAc/hexanes (Scheme 2).

Finally, the oxidation/oxidative cleavage reaction of **9** was performed in a one-pot manner. For example, a simple primary allylic alcohol moiety was oxidized to α,β-unsaturated carboxylic acid, and a 1,2-diol moiety was oxidatively cleaved to carboxylic acid (Scheme 3).

In summary, we have developed a transition-metal-free, oxidative cleavage reaction of *vic*-1,2-diols to carboxylic acids with NaO^{t}Bu under oxygen atmosphere. We also demonstrated how to scale-up experiments without organic extraction and chromatographic technique. This protocol was used to perform an oxidation/oxidative cleavage reaction in a one-pot fashion.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedure and characterization of all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(9) The reaction of **1a** was performed in the presence of TEMPO (1−3 equiv) as radical scavenger under optimal conditions, resulted in the formation of the desired product **2a** in high yield. It is crucial evidence to support the involvement of non-free-radical species (e.g., $^-$OH, $^-$O$_2$H) in this transformation.

(10) In order to eliminate the possibility of the presence of trace transition-metal elements in NaO^{t}Bu that would potentially affect our results, we purified the NaO^{t}Bu by sublimation and also examined by inductively coupled plasma-atomic emission spectrometry (ICP-ACE) prior to our investigation. These results clearly show that the contents of transition metals (Pd, Fe, and Cu) were in the range of 0.2−0.5 ppm. After identifying negligible transition metal contents, we carried out the reaction of **1a** with the purified NaO^{t}Bu under oxygen atmosphere to produce the desired product **2a** in a yield similar to that obtained in Table 2.

■ NOTE ADDED AFTER ASAP PUBLICATION

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