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Nitroxyl Radical/PhI(OAc)$_2$: One-Pot Oxidative Cleavage of Vicinal Diols to (Di)Carboxylic Acids

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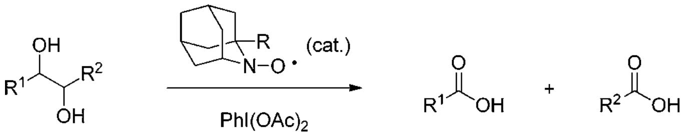
ABSTRACT



A mild and user-friendly one-pot oxidative cleavage of vicinal diols to their corresponding (di)carboxylic acids using AZADOs and PhI(OAc)$_2$ is described. 1,2-Diols and 2,3-diols as well as 1,2,3-triol gave one- or two-carbon-unit-shorter carboxylic acids. Internal vicinal diols also smoothly underwent one-pot oxidative cleavage to afford the corresponding dicarboxylic acids. Cyclic vicinal diols are converted to their corresponding open-form dicarboxylic acids.

The oxidative cleavage of vicinal diols to the corresponding carbonyl compounds is a useful transformation, offering design latitude in organic synthesis. Typically, this transformation is conducted using hypervalent iodine reagents, i.e., $NaIO_4$, HIO_4, $PhI(OAc)_2$,[1,2] and lead tetraacetate $Pb(OAc)_4$[3] to obtain the intended aldehydes/ketones in a dehomologated or ring-opening fashion. To prepare a corresponding (di)carboxylic acid, an additional oxidation from a (di)aldehyde to a (di)carboxylic acid is required. Moreover, the lability of aldehydes often causes a decline in overall yield from a diol to its corresponding (di)carboxylic acid. From these points of view, one-pot oxidative cleavage from vicinal diols to their corresponding (di)carboxylic acids is a promising reaction to improve the efficiency of organic synthesis.

Recently, Stark et al. have developed a practical one-pot oxidative cleavage using catalytic amounts of tetrapropylammonium perruthenate (TPAP) together with *N*-methylmorpholine *N*-oxide (NMO) as a stoichiometric oxidant, which can be applied to a broad range of vicinal diols under mild conditions.[4] However, large excess amounts of NMO and precious rare metals are required. In the preceding letter, we disclosed the 1-methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO)(**3**)/$NaOCl$/$NaClO_2$ method for one-pot oxidative cleavage from 1,2-diols to one-carbon-unit-shorter carboxylic acids, which offered mild, clean, and transition-metal-free oxidative dehomologation.[5] However, this method is specific to terminal vicinal diols. To expand the

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utility of nitroxyl-radical-catalyzed one-pot oxidative cleavage, we pursued a method applicable to internal vicinal diols to demonstrate that the combination of catalytic AZADO (**2**)[6−8] and stoichiometric PhI(OAc)$_2$ efficiently enables one-pot oxidative cleavage from terminal diols as well as from internal vicinal diols to corresponding (di)carboxylic acids (Figure 1, Scheme 1).

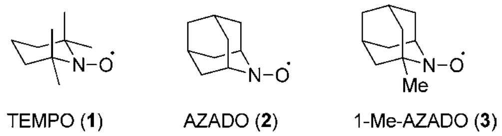


Figure 1. Structures of nitroxyl radicals.

Scheme 1. Traditional Oxidative Cleavage and Method Used in This Study

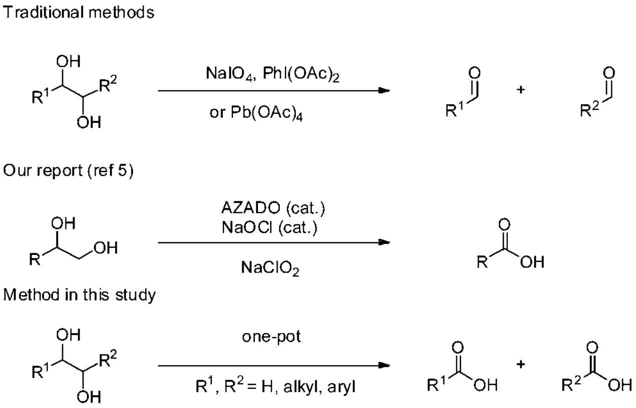
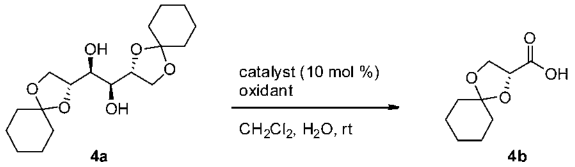


Table 1. Initial Optimization of Reaction Conditions



entry	catalyst	oxidant	yield/time[a]
1	AZADO (**2**)	PhI(OAc)$_2$ (3 equiv)	83%/2 h
2	AZADO (**2**)	NaIO$_4$ (3 equiv)	52%/2 h
3	AZADO (**2**)	PhI(OAc)$_2$ (5 equiv)	90%/1 h
4	none	PhI(OAc)$_2$ (5 equiv)	0%/1 h
5	TEMPO (**1**)	PhI(OAc)$_2$ (5 equiv)	89%/1 h
6	1-Me-AZADO (**3**)	PhI(OAc)$_2$ (5 equiv)	90%/1 h

[a] **4b** was isolated as a methyl ester after treatment with CH$_2$N$_2$.

We focused on the characteristics of the nitroxyl radical catalyst, i.e., enabling the use of various stoichiometric oxidants: NaOCl, *m*CPBA, TCCA, I$_2$, Oxone, O$_2$, and others.[9−11] NaIO$_4$ and PhI(OAc)$_2$, which induce the oxidative cleavage of vicinal diols to their corresponding (di)aldehydes, also work as co-oxidants for nitroxyl-radical-catalyzed oxidation.[11,12] Thus, we envisaged that the one-pot oxidative cleavage of a vicinal diol to its corresponding (di)carboxylic acid is feasible, if the hypervalent-iodine-reagent-induced oxidative cleavage and AZADO-catalyzed oxidation of an aldehyde to its corresponding carboxylic acid along with an identical hypervalent iodine reagent as a co-oxidant could synergetically work in the same reaction vessel.

We commenced by examining the efficiencies of the AZADO (**2**)/NaIO$_4$ and AZADO (**2**)/PhI(OAc)$_2$[12] systems for the one-pot oxidative cleavage of internal vicinal diol **4a** (Table 1). AZADO (**2**, 10 mol %) and 3 equiv of PhI(OAc)$_2$ caused one-pot oxidative cleavage of **4a** to afford the desired carboxylic acid **4b** in good yield within 2 h after the simultaneous addition of AZADO (**2**) and the hypervalent iodine reagent (entry 1). On the other hand, 10 mol % AZADO (**2**) and 3 equiv of NaIO$_4$ gave the desired carboxylic acid **4b** in moderate yield (entry 2). Although the oxidative cleavage of diols to aldehydes proceeded smoothly, partial decomposition was accompanied by the oxidative cleavage presumably because the oxidation of aldehydes to carboxylic acids was slow.[13] After increasing the amount of PhI(OAc)$_2$ to 5 equiv, the reaction was completed within 1 h and gave the desired carboxylic acid **4b** in high yield (entry 3). The treatment of **4a** with PhI(OAc)$_2$ in the absence of AZADO (**2**) did not produce the carboxylic acid **4b** after 1 h (entry 4). TEMPO (**1**) and 1-Me-AZADO (**3**) also efficiently catalyzed one-pot

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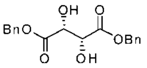
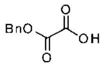
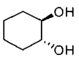
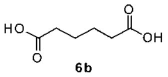
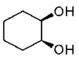
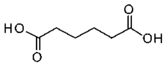
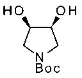
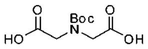
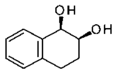
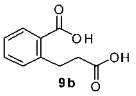
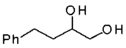
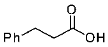
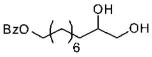
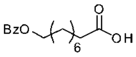
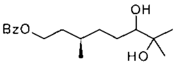
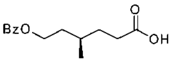
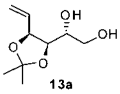
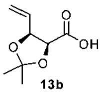
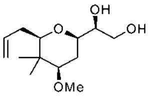
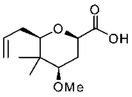
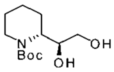
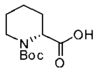
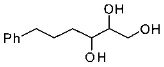
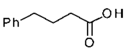
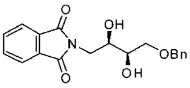
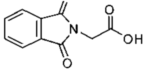
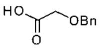
(14) The results under TEMPO and PhI(OAc)$_2$ conditions are shown in Table S1 (Supporting Information).

Table 2. Scopes of AZADO (**2**)- and 1-Me-AZADO (**3**)-Catalyzed One-Pot Oxidative Cleavages

entry	diol	product	yield[a] / time AZADO **(1-Me-AZADO)**
1	 **5a**	 **5b**	88%[b] / 40 min
2	 **6a**	 **6b**	89%[c] / 1 h
3	 **7a**	 **6b**	87%[c] / 1.5 h
4	 **8a**	 **8b**	91%[c] / 1 h
5	 **9a**	 **9b**	85%[c,d] / 4 h
6	 **10a**	 **10b**	84% / 1 h
7	 **11a**	 **11b**	94% / 1 h
8	 **12a**	 **12b**	68%[c] / 1 h **(87%[c] / 1 h)**
9	 **13a**	 **13b**	75%[c] / 1 h **(87%[c] / 1 h)**
10	 **14a**	 **14b**	78%[c] / 2 h **(85%[c] / 1 h)**
11	 **15a**	 **15b**	65%[c] / 2 h **(87%[c] / 1 h)**
12	 **16a**	 **16b**	62%[c] / 1 h, **99%[d,e] / 2 h** **(64%[e] / 2 h)**
13	 **17a**	 **17b**	92%[c] / 1 h
		 **17d**	94%[c] / 1 h

[a] Isolated yield. [b] Carboxylic acids were isolated as methyl esters after treatment with TMSCHN$_2$. [c] Carboxylic acids were isolated as methyl esters after treatment with CH$_2$N$_2$. [d] Bu$_4$NBr was added, and MeCN was used as the solvent. [e] 6 equiv PhI(OAc)$_2$ were used.

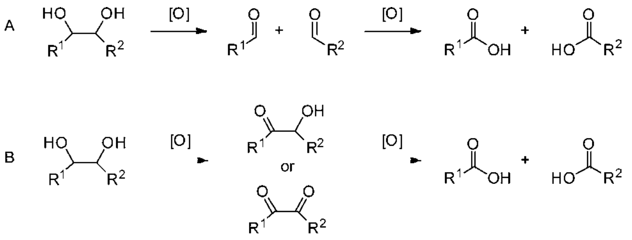
oxidative cleavage (entries 5, 6).[14] Because AZADO (**2**) shows the highest catalytic activity for alcohol oxidation, we selected AZADO (**2**) as the catalyst and examined its applicability to a series of diols.

Various vicinal internal and terminal diols smoothly underwent one-pot oxidative cleavage to afford their corresponding (di)carboxylic acids. The sensitive double bond, acetonide, and *N*-Boc group were tolerated under these reaction conditions. Because the oxidation rate of aromatic aldehydes to carboxylic acids observed was relatively slow, we used MeCN as a solvent and added Bu$_4$NBr to promote the formation of a geminal diol (entry 5 in Table 2 and entry 3 in Table S1). Furthermore, neither epimerization nor racemization was detected (entries 9–11). In entry 8, the yield of the desired product **12b** is moderate, because 32% hydroxy ketone **12c** was produced as a major byproduct. The diol **13a**, **14a**, and **15a** produced the desired one-carbon-unit-shorter carboxylic acids in moderate yields along with unidentified byproducts (entries 9–11). Interestingly, the use of 1-Me-AZADO (**3**) instead of AZADO (**2**) improved the efficiency to afford the corresponding carboxylic acids in high yield (entries 8–11). The terminal triol **16a** also afforded the desired two-carbon-shorter carboxylic acid **16b** in high yield in the presence of Bu$_4$NBr (entry 12). Nonsymmetrical interior diol **17a** afforded **17b** and **17d** in high yields (entry 13).

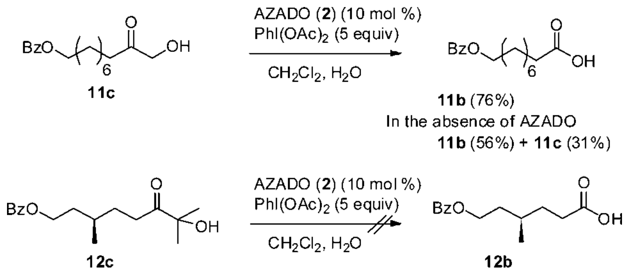
There are two possible pathways for one-pot oxidative cleavage (Scheme 2). One is that the oxidative cleavage of a diol to the dialdehyde proceeds prior to the oxidation of the dialdehyde to its corresponding dicarboxylic acids (path A). The other is that the oxidation of a diol to a hydroxy ketone or a diketone proceeds prior to oxidative cleavage (path B). By TLC analysis, it was observed that the oxidative cleavage of a diol to a (di)aldehyde mainly took place prior to alcohol oxidation.

We were interested in determining whether it is necessary for oxidative cleavage to occur prior to alcohol oxidation (Scheme 3). To clarify this point, the hydroxy ketone **11c** was treated with AZADO and PhI(OAc)$_2$. **11c** underwent oxidative cleavage, which means that path B is also possible. It was confirmed that the oxidative cleavage of **11c** was caused by PhI(OAc)$_2$ in the absence of AZADO. On the other hand, the C–C bond cleavage of the tertiary hydroxy ketone **12c** did not proceed. In this case, the C–C bond cleavage needs to proceed prior to the alcohol oxidation, which is consistent with the result that 1-Me-AZADO (**3**) with moderate reactivity gave a better result than AZADO (**2**).

Scheme 2. Reaction Pathway for One-Pot Oxidative Cleavage



Scheme 3. Reactivities of Hydroxy Ketone **11c** and **12c**



In summary, we have developed a method for the one-pot oxidative cleavage reaction of vicinal diols to their corresponding (di)carboxylic acids with catalytic amounts of AZADOs and stoichiometric amounts of $PhI(OAc)_2$ under mild and transition-metal-free conditions. This method can be applied not only to the dehomologation of terminal diols and triols but also to the ring opening of cyclic vicinal diols. 1-Me-AZADO (**3**) often afforded better results than AZADO (**2**). This method will be a useful tool in organic synthesis.

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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.