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Ag(I)-catalyzed widely applicable aerobic 1,2-diol oxidative cleavage

Zhong-zhen Zhou,‡ [a,b] Mingxin Liu,‡[a] Leiyang Lv, ‡[a, c] and Chao-Jun Li *[a]

‡ These authors contributed equally.

Abstract: The oxidative cleavage of 1,2-diol is one of the fundamental organic transformations. Up to now, stoichiometric oxidants such as H_5IO_6, $Pb(OAc)_4$, or $KMnO_4$ are still predominantly employed to carry out such oxidative cleavage, which generate stoichiometric hazardous waste. Herein, we have developed a widely applicable and highly selective Ag(I)-catalyzed oxidative cleavage of 1,2-diol that consumes atmospheric oxygen as the sole oxidant, serving as a potentially greener alternative to the classical fundamental transformations

The oxidative cleavage of 1,2-diols is one of the most important methods in organic chemistry.[1] The pioneering work for achieving such a cleavage is the Criegee oxidation and the Malaprade reaction, developed by Criegee in 1931[2] and Malaprade in 1934,[3] respectively. Those reactions achieved exceptional efficiency, functional tolerance, and established among the most fundamental organic reactions in modern organic chemistry. However, stoichiometric oxidants such as high-valent iodine[4] or lead[5] are necessary, which generate stoichiometric hazardous waste (Fig. 1a). Other useful classical reagents in oxidative cleavage of diols, such as $KMnO_4$, also share the same limitation.[6] Hence, there are many efforts on the development of new catalysts or oxidants in attempt to overcome these limitations.[7] Nevertheless they generally suffer from poor selectivity and adaptability. Up till today, no method provides full substrate scope covering aliphatic-, aromatic-, terminal-, internal-, and cyclic-1,2-diols for catalytic aerobic oxidative cleavage of 1,2-diols under atmospheric or low pressure and at mild temperature. Very recently, Escande and Anastas reported an elegant sodium-manganese layered mixed oxide (Na-Mn LMO)-catalyzed aerobic oxidative cleavage of 1,2-diols into the corresponding aldehydes (Fig. 1b).[7a] Despite achieving significant adaptability over benzylic and allylic diols, aliphatic (linear or cyclic) cyclic diols were inactive. The cleavage also requires higher reaction temperature(100 °C) and only producing aldehyde products. Although precedent work has achieved the oxidative cleavage of certain 1,2-diols into both aldehydes and carboxylic acids,[7o] a cleavage method that can afford both good selectivity and wide adaptability, at the same time consumes non-hazardous and greener oxidant (such as aerobic oxygen) under mild conditions, is still highly desirable but challenging to develop.

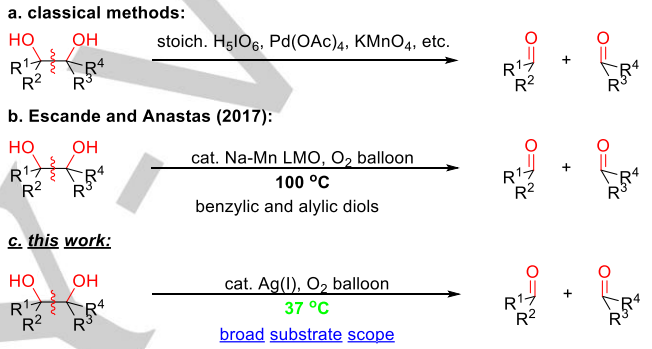

Figure 1. Methods for 1,2-diol oxidative cleavage

In 2015, we demonstrated the use of a silver(I) catalyst in the aerobic oxidation of aldehyde.[8] The catalyst showed powerful adaptability with a wide range of different aldehydes. Inspired by the adaptability of silver(I) as aerobic oxidation catalyst, we were interested in further exploring the catalyst for other oxidations of great importance. Herein, we wish to report the first silver(I)-catalyzed aerobic cleavage of 1,2-diols efficiently and selectively, into the corresponding carbox-ylic acids, complementing Escande and co-workers' method (Fig. 1c).

We commenced our research by using 5-phenoxy-1,2-pentanediol (**1a**) as a model substrate, THF as major solvent, 3 equiv NaOMe as base (added as solution in MeOH, giving an overall 50:1 THF/MeOH mixed solvent), under 1 atm oxygen at 50 °C (See Table S1 of Supporting Information for complete condition optimization data). After 11 h, 10 mol% AgOTf as catalyst gave 64% of the desired 4-phenoxy-butanoic acid product (**2a**, Table 1, entry 1). Lowering the reaction temperature to 37 °C, increased the yield to 85% (entry 2). This temperature enables the compatibility of our reaction with most commercially available incubators. The attempt to lower the catalyst loading to 5 mol% only slightly reduced the yield to 72% (entry 3). We then noticed that increasing the amount of MeOH in the mixed solvent (5:1 THF/MeOH) gave an increased 94% yield (entry 4). After the reaction time was shortened by half, 96% yield (92% after purification) was obtained (entry 5). We also examined more common silver salt such as Ag_2CO_3 as catalyst (entry 6), but gave inferior yields even with prolonged reaction time. Control experiments indicated that the reaction was shut down when either base, catalyst, or oxygen was absent (entries 7, 8 and 9).

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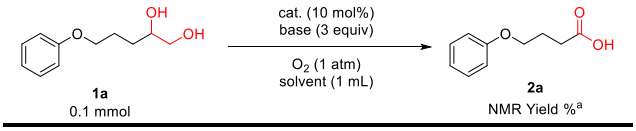
Experiment in dark did not affect the result of the reaction, excluding the possible involvement of light (entry 10).

Table 1. Optimization of reaction conditions



1a
0.1 mmol

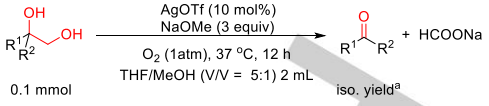
2a
NMR Yield %[a]

entry	base	cat	solvent	T(°C)	t(h)	yield
1	NaOMe	AgOTf	THF/MeOH[b]	50	11	64
2	NaOMe	AgOTf	THF/MeOH[b]	37	11	85
3[c]	NaOMe	AgOTf	THF/MeOH[b]	37	11	72
4	NaOMe	AgOTf	THF/MeOH[d]	37	11	94
5	NaOMe	AgOTf	THF/MeOH[d]	37	6	96 (92)[e]
6	NaOMe	Ag_2CO_3	THF/MeOH[d]	37	12	51
7	NaOMe	-	THF/MeOH[d]	37	6	0
8	-	AgOTf	THF/MeOH[d]	37	6	0
9[f]	NaOMe	AgOTf	THF/MeOH[d]	37	6	0
10[g]	NaOMe	AgOTf	THF/MeOH[d]	37	6	97

[a] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. See Supporting Information for complete data; [b] 50:1 solvent mixture; [c] 5 mol% AgOTf was used; [d] 5:1 solvent mixture; [e] Isolated yield; [f] Performed under argon; [g] Performed in dark.

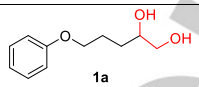
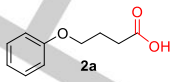
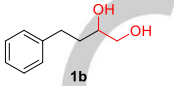
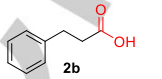
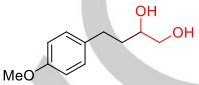
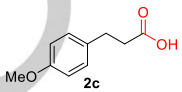
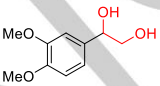
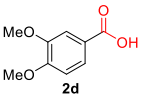
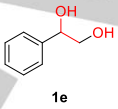
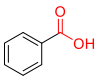
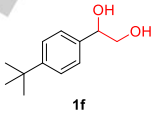
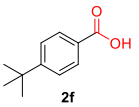
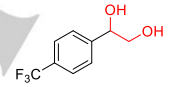
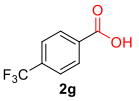
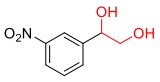
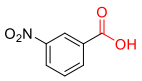
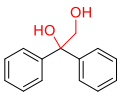
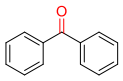
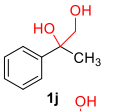
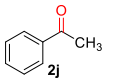
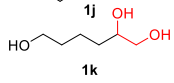
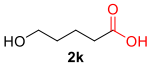
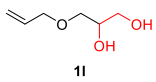
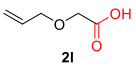
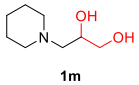
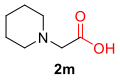
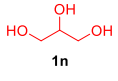
With the optimized reaction conditions in hand, the substrate scope was then examined (Table 2). Various terminal 1,2-diols were first investigated. Besides 5-phenoxy-1,2-pentanediol (**1a**), which gave 96% of the corresponding 4-phenoxybutanoic acid (**2a**), 4-phenyl-1,2-butanediol (**1b**) gave 81% of the corresponding cinnamic acid (**2b**). 4-(4-Methoxyphenyl)-1,2-butanediol (**1c**) also gave 81% 4-methoxycinnamic acid (**2c**). Aromatic diols, such as 1-(3,4-dimethoxyphenyl)-1,2-ethanediol (**1d**), 1-phenyl-1,2-ethanediol (**1e**), 1-(4-tert-butylphenyl)-1,2-ethanediol (**1f**), 1-(4-α, α, α-trifluoro-methylphenyl)-1,2-ethanediol (**1g**), and 1-(3-nitrophenyl)-1,2-ethanediol (**1h**) gave quantitative yields of the corresponding 3,4-dimethoxybenzoic acid (**2d**), benzoic acid (**2e**), 4-tert-butylbenzoic acid (**2f**), 4-α, α, α-trifluoromethylbenzoic acid (**2g**) and 3-nitrobenzoic acid (**2h**), respectively. 1,1-Diphenyl-1,2-ethanediol (**1i**) gave the corresponding benzophenone (**2i**) in 82% yield. 2-Phenyl-1,2-propanediol (**1j**) gave 73% yield of the corresponding acetophenone (**2j**). 1,2,6-Trihydroxyhexane (**1k**) gave selective oxidation of the 1,2-diol into the corresponding 5-hydroxypentanoic acid (**2k**). 3-Allyloxy-1,2-propanediol (**1l**) gave a reduced 48 % yield of 2-(prop-2-en-1-yloxy)acetic acid (**2l**), possibly due to the C=C bond oxidation. 3-Piperidino-1,2-propanediol (**1m**) also gave a good 65 % yield of piperidin-1-yl-acetic acid (**2m**), showing good tolerance of amine group. For all the terminal 1,2-diols, formic acid (**2n**) was also observed in all the corresponding ^{1}H-NMR of the crude reaction mixture with an amount of 0.03 mmol (for 0.1 mmol scale reaction), indicating minor oxidation of NaOMe/MeOH. Deducting the background reaction, glycerol (**1n**) gave about 56% cleavage into formic acid.

Table 2. Substrate scope investigations



0.1 mmol

iso. yield[a]

entry	substrate	product	yield (%)
1	 1a	 2a	96
2	 1b	 2b	81
3	 1c	 2c	81
4	 1d	 2d	>99
5	 1e	 2e	>99
6	 1f	 2f	>99
7	 1g	 2g	>99
8	 1h	 2h	>99
9	 1i	 2i	82
10	 1j	 2j	73
11	 1k	 2k	92
12	 1l	 2l	48%
13	 1m	 2m	65%
14	 1n	 2n	56%[b]

[a] Reaction conditions: diol (0.1 mmol), Ag catalyst (0.01 mmol, 10 mol%), NaOMe (0.3 mmol, 3 equiv) were mixed in 1 mL THF/MeOH (5:1) in sealed reaction vessel equipped with a magnetic stir bar and a balloon filled with oxygen. The mixture was stirred at 37 °C for 12 h. The products were isolated using prep-TLC or column chromatography and yields were calculated accordingly. [b] ^{1}H-NMR yield after correction from background, measured using sodium benzenesulfonate as internal standard in D_2O.

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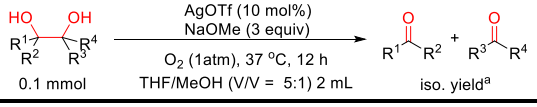
Table 3. Oxidative cleavage of internal diols



entry	substrate	product	yield (%)
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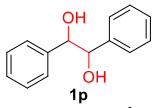
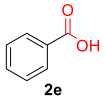
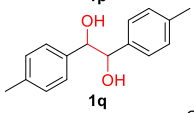
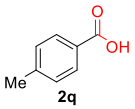
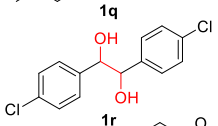
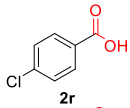
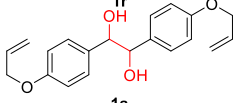
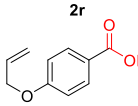
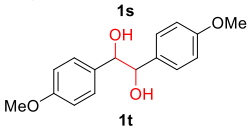
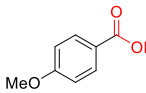
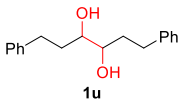
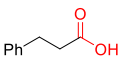
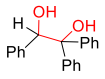
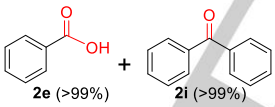
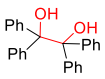
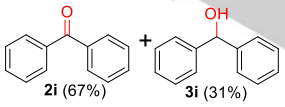
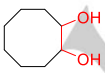
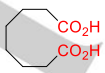
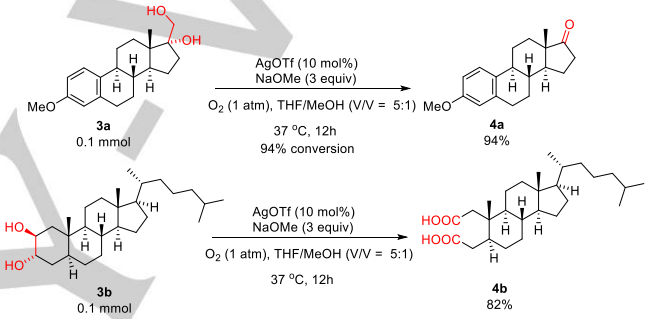
2	 1p	 2e	96
3	 1q	 2q	>99
4	 1r	 2r	90
5	 1s	 2s	77
6	 1t	 2t	75
7	 1u	 2b	86
8	 1v	 2e (>99%) + 2i (>99%)	
9	 1w	 2i (67%) + 3i (31%)	
10	 1x	 2x	88
11	 1y	 2y	45
12	 1z	 2z	52

[a] Reaction conditions: diol (0.1 mmol), Ag catalyst (0.01 mmol, 10 mol%), NaOMe (0.3 mmol, 3 equiv) were mixed in 1 mL THF/MeOH (5:1) in sealed reaction vessel equipped with a magnetic stir bar and a balloon filled with oxygen. The mixture was stirred at 37 °C for 12 h. [b] ^{1}H-NMR yield determined using sodium benzenesulfonate as internal standard in D_2O.

Internal 1,2-diols (pinacols) were also examined towards our aerobic oxidation (Table 3). Simple 2,3-dihydroxybutane (**1o**) gave the corresponding acetic acid (**2o**) in 60 % yield. Hydrobenzoin (**1p**) gave 96% yield of the corresponding **2e**. 1,2-Bis(4-methylphenyl)-1,2-ethanediol (**1q**) gave quantitative cleavage into the corresponding 4-toluic acid (**2q**). 1,2-Bis(4-chlorophenyl)-1,2-ethanediol (**1r**) gave 4-chlorobenzoic acid (**2r**) in 90% yield. 1,2-Bis(4-allyloxyphenyl)-1,2-ethanediol (**1s**) and 1,2-bis(4-methoxyphenyl)-1,2-ethanediol (**1t**) gave their corresponding 4-allyloxybenzoic acid (**2s**) and 4-methoxybenzoic acid (**2t**) in 77% and 75% yields, respectively. It should be noted that no oxidation of C=C was observed for **2o**. 1,6-Diphenyl-3,4-hexanediol (**1u**) gave the corresponding **2b** in 86 % yield. 1,1,2-Triphenyl-1,2-ethanediol (**1v**) underwent quantitative cleavage to give the corresponding **2e** and **2i**. Benzopinacol (**1w**) gave 67% **2i** and 31% α-phenylbenzyl alcohol (**3i**), possibly due to greater steric hindrance of the substrate. Cyclic diols were also examined. Interestingly, cyclohexane-1,2-diol (**1x**) shows better reactivity by giving 88% of the corresponding adipic acid (**2x**) than cyclopentane-1,2-diol (**1y**), which gave 45% of glutaric acid (**2y**). Larger-ring diols such as octane-1,2-diol (**1z**) also gave 52 % of octanedioic acid (**2z**).



Scheme 1. Aerobic 1,2-diol cleavage of complex substrate

To examine the generality of our method, we then applied our aerobic oxidative cleavage conditions towards an estrogen derivative, 17-hydroxy-3-methoxy-estra-1,3,5(10)-triene-17-methanol (**3a**). With an increased amount of silver catalyst, methoxy-estrone (**4a**) was isolated in 94% yield, and the remaining **3a** (~ 6%) was also isolatable from the reaction mixture without undergoing side-reactions, indicating the selectivity of our method. Another natural product derivative, (2β-3α-5α)-cholestane-2,3-diol (**3b**), also gave the corresponding 2,2'-((3R,3aR,5aS,6S,7S,9aR,9bS)-3a,6-dimethyl-3-((R)-6-methylheptan-2-yl)dodecahydro-1H-cyclopenta[a]naphthal-ene-6,7-diyl)diacetic acid (**4b**) in 82 % yield (Scheme 1). We also attempted to scale-up the aerobic cleavage method. Under the optimized reaction conditions, 1 mmol amount of 4-phenyl-1,2-butanediol and 1-phenyl-1,2-ethanediol gave the corresponding **2b** and **2e** in 85% and 98% yields, respectively (Fig. 2a and 2b). Gram-scale examination of 1-phenyl-1,2-ethanediol gave 90% **2e** even with a reduced catalyst loading (Fig. 2c). Pinacol-type substrate, meso-hydrobenzoin, gave 94% of **2e**, along with small quantities of methyl benzoate and benzil (Fig. 2d).

To understand the mechanism of our aerobic oxidative cleavage, an isotope labeling experiment was conducted using $^{18}O_2$ as the sole oxidant. The product showed a 1:2:1 ratio of m:m+2:m+4 in GC-MS (Scheme 2). Along with the detection of benzil in Fig. 2d, we suggest that the reaction might proceed via a mechanism similar to Yang's report in 2014,[7f] where the diol was oxidized into 1,2-dicarbonyl compound first, followed by a Baeyer-Villager-type cleavage. Using benzil as substrate under our aerobic oxidative cleavage conditions gave 74 % yield (Scheme

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3). Time-course reaction also supports the above-mentioned mechanism (see Scheme S1 of Supporting Information). However, our reaction gave a much wider substrate scope compared to Yang's metal-free system (limited to benzylic diols only). The efficient cleavage of most of our substrates cannot proceed without Ag(I) catalyst. This implies the efficiency of silver in activation of oxygen.[9]

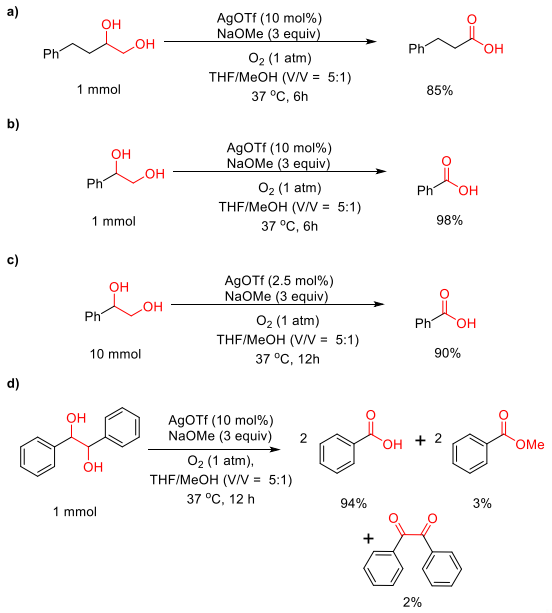
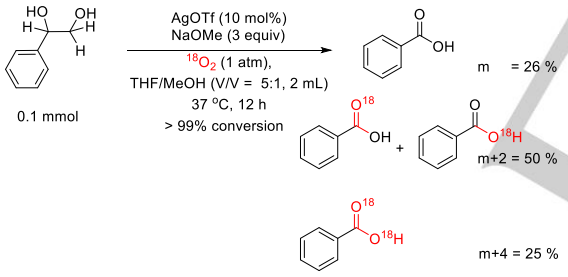
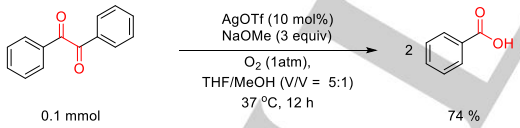


Figure 2. Scaling-up of the aerobic diol oxidative cleavage



Scheme 2. Isotope labelling experiment



Scheme 3. Aerobic oxidative cleavage of benzil

In summary, we have developed a widely adaptable and selective aerobic oxidative cleavage of 1,2-diols. The reaction proceeds under mild conditions with readily available catalyst that exhibits high efficiency. A wide scope of substrates including natural products have been successfully cleaved by the method to generate the corresponding carboxylic acids. Further applications of silver catalyst towards other oxidation processes are underway in our lab.

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Keywords: 1,2-diol • aerobic oxidative cleavage • carboxylic acids • selectivity • silver catalyst

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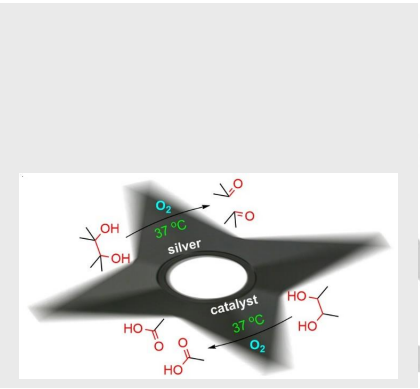

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