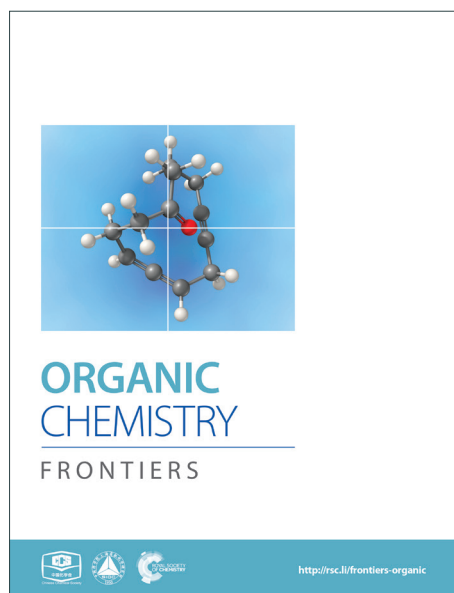
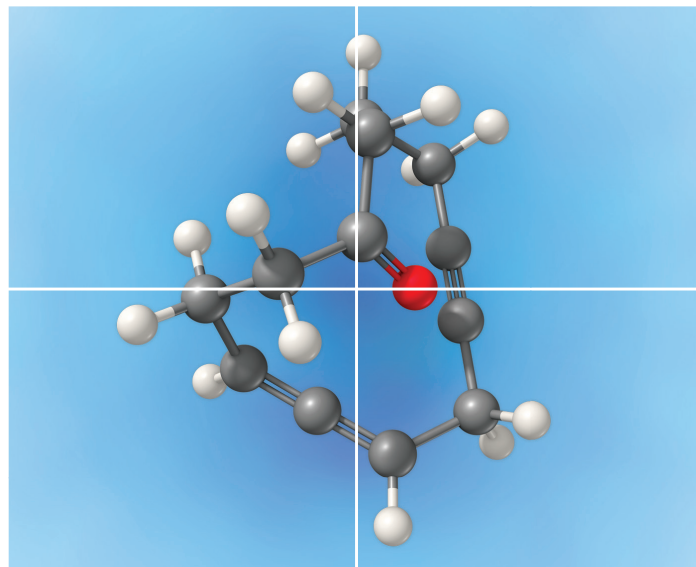


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ARTICLE TYPE

Ozonation of Methylenecyclopropanes

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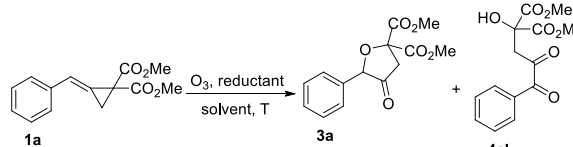
Ozonation of methylenecyclopropanes bearing gem-disubstituted electron-withdrawing groups (EWG) gave ring-opened oxidative products in moderate to good yields. As for MCPs in which EWGs are two methoxycarbonyl groups, the ozonation gave oxidative cyclization products in methanol at -78 °C in the presence of CuCl; as for MCPs in which EWGs are one methoxycarbonyl and one trifluoromethyl group, the ozonation produced α -diketones in ethyl acetate (EA) at -78 °C.

Methylenecyclopropanes (MCPs) as highly strained but easily available small rings have been widely used in organic synthesis as a versatile building block through a variety of ring-opening processes.¹ After careful survey of the reaction patterns of MCPs, we found that the oxidative ring-opening modes of MCPs are limited. The well known examples are the oxidation of MCPs with peracids or SeO₂ and H₂O₂ or other oxidants to give cyclobutanone derivatives.^{2a-e} Another important issue is the oxidative addition of 1,3-dicarbonyl compounds with MCPs via one electron transfer process mediated by Mn(OAc)₃ or CAN^{2f-j} as well as the photo-induced oxidation of MCPs with O₂ to give the corresponding 1,2-dioxolane via charge transfer complex.³ On the other hand, the ozonolysis of alkylidenecyclopropanes to give the corresponding oxidative ring-opened products has been also disclosed by several groups.⁴ In this paper, we wish to report two different oxidative ring-opening modes of MCPs, in which the cyclopropane has a gem-disubstituted ester groups [(CO₂Me)₂] (MCPs **1**) or a gem-disubstituted ester and trifluoromethyl group [CF₃(CO₂Me)] (MCPs **2**) as electron-withdrawing groups (EWG),⁵ upon treating with ozone. We will disclose in this paper that the two different ring-opening oxidation products can be exclusively obtained under different conditions.

The initial examinations were carried out upon treating MCP **1a** or MCP **2a** with ozone in the presence of a variety of reductants and the results are shown in Table 1 and Table 2, respectively. We found that the oxidative cyclization product **3a** and α -diketone **4a'** were obtained in dichloromethane (DCM) upon treatment of **1a** with ozone in a variety of reductants at -78 °C (**1a**:reductant = 1:1.3) (Table 1, entries 1-8). To get **3a** as the sole product, we carefully examined

the solvent effects using CuCl as the reductant and found that in ethanol or methanol, **3a** could be obtained exclusively in 87% or 88% yield, respectively (Table 1, entries 9-16). Reductant CuCl is crucial in this reaction to give **3a** exclusively and using NiCl₂ or FeCl₂ as the reductant gave **3a** and **4a'** as a product mixture (Table 1, entries 17-19). The examination of the employed amount of CuCl and the reaction temperature revealed that using 2.0 equiv of CuCl afforded **3a** in 89% yield under the standard conditions and the oxidation reaction should be carried out at -78 °C (Table 1, entries 20-23). The structure of **3a** has been fully assigned by NMR spectroscopic data (see Supporting Information).

Table 1. Optimization of the Reaction Conditions for the Ozonation of Methylenecyclopropane **1a**



The reaction scheme shows MCP **1a** (gem-disubstituted with two CO₂Me groups) reacting with O₃ and a reductant in a solvent at temperature T to produce two products: **3a** (a 5-membered ring with a lactone-like structure and two CO₂Me groups) and **4a'** (an α -diketone with two CO₂Me groups).

entry ^a	reductant	1a :reductant	solvent	T (°C)	yield (%) ^b	
					3a	4a'
1	S	1:1.3	DCM	-78	42	41
2	Ph ₃ P	1:1.3	DCM	-78	67	31
3	Zn	1:1.3	DCM	-78	42	29
4	S	1:1.3	DCM	-78	52	30
5	NaNO ₂	1:1.3	DCM	-78	55	37
6	Na ₂ SO ₃	1:1.3	DCM	-78	60	22
7	Na ₂ S ₂ O ₃	1:1.3	DCM	-78	62	25
8	CuCl	1:1.3	DCM	-78	80	18
9	CuCl	1:1.3	EA	-78	55	31
10	CuCl	1:1.3	THF	-78	-	-
11	CuCl	1:1.3	Acetone	-78	83	14
12	CuCl	1:1.3	Et ₂ O	-78	68	30
13	CuCl	1:1.3	PE	-78	32	5
14	CuCl	1:1.3	toluene	-78	62	22
15	CuCl	1:1.3	EtOH	-78	87	-
16	CuCl	1:1.3	MeOH	-78	88	-
17	NiCl ₂	1:1.3	MeOH	-78	59	17
18	FeCl ₂	1:1.3	MeOH	-78	67	4
19	CuCl	1:0	MeOH	-78	33	41
20	CuCl	1:0.5	MeOH	-78	52	27
21	CuCl	1:2	MeOH	-78	89	-
22	CuCl	1:3	MeOH	-78	88	-
23	CuCl	1:2	MeOH	0	80 ^c	-

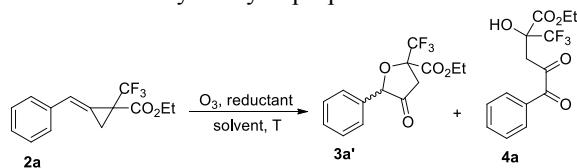
^[a] MCP **1a** (0.5 mmol, 1 equiv) was dissolved in 5.0 mL solvent at T °C, and then O₃ was bubbled until the solvent became blue. The reductant (x equiv) was then added at T °C. The reaction mixture naturally returned to room temperature and was further stirred for 5 h. ^[b] Isolated yields. ^[c] The crude product containing some other complex mixtures.

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On the other hand, using MCP **2a** as the substrate, the presence of reductant gave the corresponding **3a'** and **4a** as a product mixture in 64-78% total yields in methanol or DCM at -78 °C (Table 2, entries 1-7). We also identified that **4a** could be obtained as a major product in 68% yield along with trace of **3a'** in the absence of reductant (Table 2, entry 8). Its structure could be proved by the condensation of ethyl 3,3,3-trifluoro-2-oxopropanoate (0.5 mmol, 1 equiv) and 1-phenylpropane-1,2-dione in the presence of DABCO (see Supporting Information). The examination of solvent effects revealed that carrying out the reaction in ethyl acetate (EA) afforded **4a** in 70% yield and this served as the best conditions for the formation of **4a** (Table 2, entries 8-13). The different oxidation products obtained from **1a** and **2a** are presumably due to the different EWGs.

Table 2. Optimization of the Reaction Conditions for the Ozonation of Methylene cyclopropane **2a**



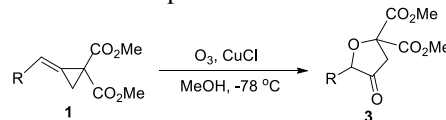
entry ^a	reductant	2a:reductant	solvent	T (°C)	yield (%) ^b	
					3a'	4a
1	CuCl	1:1.3	MeOH	-78	27	37
2	S	1:1.3	DCM	-78	12	62
3	Ph ₃ P	1:1.3	DCM	-78	8	70
4	Zn	1:1.3	DCM	-78	20	47
5	S	1:1.3	DCM	-78	23	42
6	NaNO ₂	1:1.3	DCM	-78	17	51
7	Na ₂ SO ₃	1:1.3	DCM	-78	15	57
8	-	-	DCM	-78	trace	68
9	-	-	acetone	-78	trace	65
10	-	-	EA	-78	trace	70
11	-	-	toluene	-78	trace	63
12	-	-	Et ₂ O	-78	4	58
13	-	-	MeOH	-78	trace	53

^[a] MCP **2a** (0.5 mmol, 1 equiv) was dissolved in 5 mL solvent at -78 °C, and then O₃ was slowly bubbled until the solvent became blue. The reductant was then added at -78 °C. The reaction mixture naturally returned to room temperature with stirring and was further stirred for 5 h. ^[b] Isolated yields.

With the identification of the best reaction conditions, we next turned our effort to study the scope and limitations of these two oxidative ring-opening reactions and the results are summarized in Tables 3 and 4, respectively. A variety of MCPs **1** and **2** with aryl groups bearing different substituents have been tested and the corresponding oxidative products **3a-3g** and **4a-4g** were obtained in moderate to good yields without the observation of significant electronic effects (Table 3, entries 1-6 and Table 4, entries 1-6). As for substrates **1h** and **2h** having naphthyl substituent, and substrates **1i** and **2i** in which the aryl groups have two substituents, the reactions also proceeded smoothly, delivering the corresponding products **3h** and **4h** in 43% and 73% yields and **3i** and **4i** in 87% and 58% yields, respectively (Table 3, entries 7 and 8 and Table 4, entries 7 and 8). Employing **1k** as the substrate gave the desired product **3k** in 38% yield (Table 3, entry 10). In the cases of aliphatic MCP **1j**, in which R = benzyl group, the corresponding oxidative cyclized product **3j** was obtained in

61% yield (Table 3, entry 9). However, in the case of **2j**, the ozonation also gave the corresponding oxidative cyclized product **3j'** as a single diastereoisomer on the basis of NMR spectroscopic data rather than the desired α -diketone product **4j** (see Supporting Information) (Table 4, entry 9). At the present stage, we can not perfectly explain this observation, perhaps due to that aromatic group is also required to stabilize the cyclic species **B1** or **B2** to give the corresponding α -diketone product (Scheme 3).

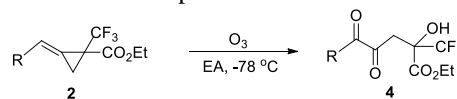
Table 3. Substrate Scope for the Ozonation of MCPs **1**



entry	R	3, yield/%
1	4-BrC ₆ H ₄ , 1b	3b , 57
2	4-ClC ₆ H ₄ , 1c	3c , 62
3	4-MeC ₆ H ₄ , 1d	3d , 62
4	3-MeC ₆ H ₄ , 1e	3e , 70
5	2-MeC ₆ H ₄ , 1f	3f , 67
6	4-MeOC ₆ H ₄ , 1g	3g , 67
7	2-naphthyl, 1h	3h , 43
8	3,5-Me ₂ C ₆ H ₃ , 1i	3i , 87
9	Bn, 1j	3j , 61
10	3,5-Br ₂ C ₆ H ₃ , 1k	3k , 38

^[a] MCP **1** (0.5 mmol, 1 equiv) was dissolved in 5 mL MeOH at -78 °C, and then O₃ was slowly bubbled until the solvent became blue. CuCl (2 equiv) was added at -78 °C and the reaction mixture naturally returned to room temperature with stirring and was further stirred for 5 h. ^[b] Isolated yields.

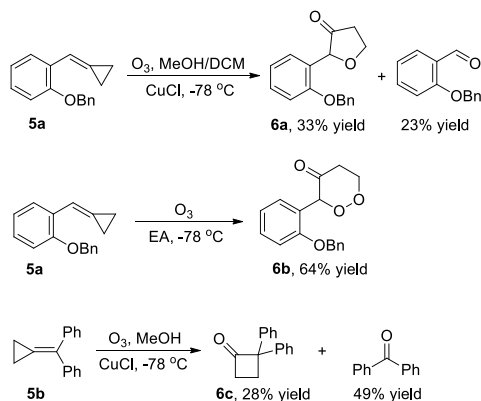
Table 4. Substrate Scope for the Ozonation of MCPs **2**



entry	R	4, yield/%
1	4-BrC ₆ H ₄ , 2b	4b , 64
2	4-ClC ₆ H ₄ , 2c	4c , 61
3	4-MeC ₆ H ₄ , 2d	4d , 63
4	3-MeC ₆ H ₄ , 2e	4e , 65
5	2-MeC ₆ H ₄ , 2f	4f , 67
6	4-MeOC ₆ H ₄ , 2g	4g , 72
7	2-naphthyl, 2h	4h , 73
8	3,5-Me ₂ C ₆ H ₃ , 2i	4i , 58
9	Bn, 2j	3j' , 21

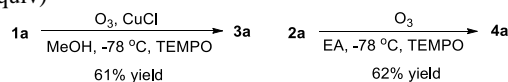
^[a] MCP **2** (1 mmol, 1 equiv) was dissolved in 5 mL EA at -78 °C, and then O₃ was slowly bubbled until the solvent became blue. The reaction mixture naturally returned to r.t. with stirring and was further stirred for 5 h. ^[b] Isolated yields. ^[c] The structure of **4j'** is the oxidative cyclized product similar as that of **3j**.

As for MCP **5a**, the reaction gave the corresponding oxidative cyclization product **6a** in 33% yield along with a double bond cleaved aldehyde in 23% yield in the presence of reductant under the standard conditions (Scheme 1).^{4c} In the absence of reductant, the corresponding oxidative cyclized product **6b** was formed in 64% yield (Scheme 1). In the case of disubstituted MCP **5b**, 2,2-diphenylcyclobutanone **6b** was formed in 28% yield along with benzophenone in 49% yield (Scheme 1).^{4c} In all these cases, none of the corresponding α -diketone could be identified.

Scheme 1. Ozonation of MCPs **5a** and **5b**

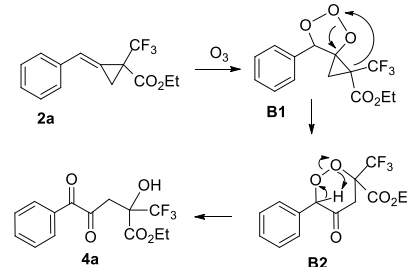
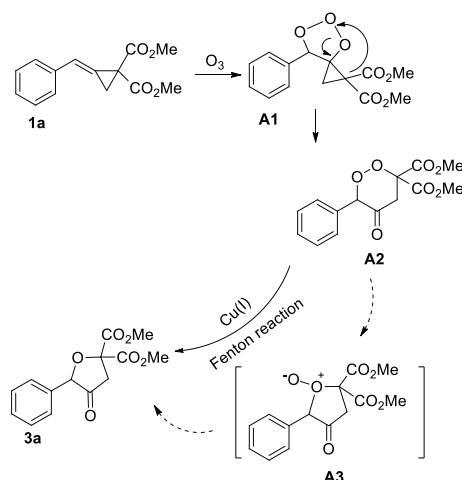
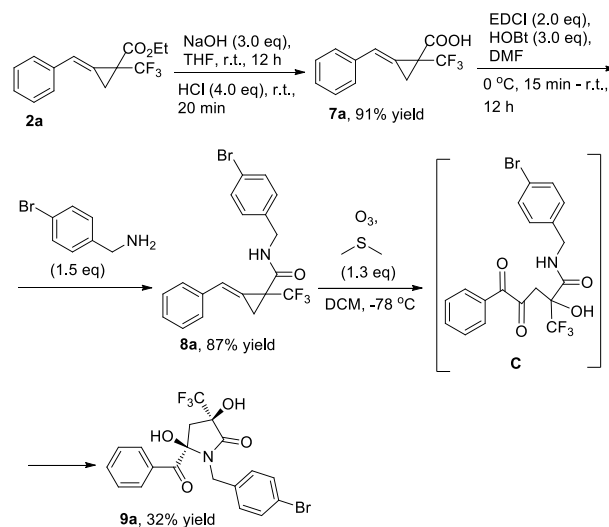
The control experiment has confirmed that these reactions under the optimized conditions was unaffected by the addition of the radical inhibitor such as TEMPO (1.0 equiv), rendering unlikely the intervention of a radical pathway (Scheme 2).

Scheme 2. The Control Experiment in the Presence of TEMPO (1.0 equiv)



The plausible reaction mechanism is depicted as below using **1a** and **2a** as substrate models on the basis of previous literature and the control experiments (Scheme 3).^{4e} The [3+2] cycloaddition of O_3 with **1a** or **2a** gives intermediate **A1** or **B1**, which undergoes a heterolytic O-O bond cleavage and cyclopropane ring opening to afford intermediate **A2** or **B2**, respectively. In the case of MCP **1a**, intermediate **A2** undergoes rearrangement to afford intermediate **A3**, which gives final product **3a** via Fenton reaction.⁶ Intermediate **A2** can also directly afford **3a** via Fenton reaction. In the case of MCP **2a**, intermediate **B2** directly undergoes the O-O bond heterolytic cleavage and proton transfer to give the final product **4a**. Presumably due to the strongly electron-withdrawing effect of CF_3 substituent, the O-O bond heterolytic cleavage in intermediate **B2** can proceed preferentially under the reaction conditions to give **4a**; whereas intermediate **A2** leans to undergo cyclization to give zwitterionic intermediate **A3** or the Fenton reaction. Therefore, the different electronic effects of EWGs in MCPs **1** or **2** cause the different reaction pathways.

MCP **2a** can be easily transformed into MCP **8a** via hydrolysis under basic conditions and condensation with *para*-bromobenzylamine in the presence of EDCI and HOBt in DMF. MCP **8a** can also undergo ring-opening oxidative cleavage to give **9a** in 32% yield via α -diketone intermediate **C** under the standard conditions.⁷ Its structure has been identified by X-ray diffraction and the CIF data are presented in the Supporting Information.⁸

Scheme 3. Plausible Mechanisms for the Formation of **3a** and **4a**Scheme 4. The Further Transformation of MCP **2a** with O_3 

In summary, we have developed two easily available ozonation processes for MCPs **1** and **2** bearing *gem*-disubstituted EWGs. On the control of the oxidative conditions, the ring-opening oxidative cyclization products **3** could be obtained as the sole products for MCPs **1**, in which the *gem*-disubstituted EWGs are two methoxycarbonyl groups, and the ring-opening oxidative α -diketones **4** could be afforded as the major products in most cases for MCPs **2**, in which the *gem*-disubstituted EWGs are one methoxycarbonyl

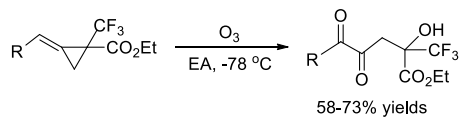
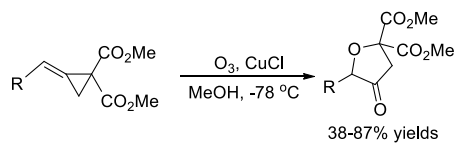
and one trifluoromethyl group, in moderate to good yields. The electronic property of EWG plays a significant effect on the reaction outcomes. The related mechanisms have been also proposed. Further investigations to examining the mechanistic details more extensively and the application of this oxidation method are underway in our laboratory.

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Ozonation of Methylene cyclopropanes

Ozonation of methylenecyclopropanes bearing gem-disubstituted electron-withdrawing groups (EWG) gave ring-opened oxidative products in moderate to good yields

*Rui Sang, Xiang-Ying Tang and Min Shi**