


Cite this: *RSC Adv.*, 2021, **11**, 13848

Received 13th March 2021
Accepted 5th April 2021

DOI: 10.1039/d1ra02007b
rsc.li/rsc-advances

Poly(ethylene glycol) dimethyl ether mediated oxidative scission of aromatic olefins to carbonyl compounds by molecular oxygen†

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A simple, and practical oxidative scission of aromatic olefins to carbonyl compounds using O_2 as the sole oxidant with poly(ethylene glycol) dimethyl ether as a benign solvent has been developed. A wide range of monosubstituted, *gem*-disubstituted, 1,2-disubstituted, trisubstituted and tetrasubstituted aromatic olefins was successfully converted into the corresponding aldehydes and ketones in excellent yields even with gram-scale reaction. Some control experiments were also conducted to support a possible reaction pathway.

Introduction

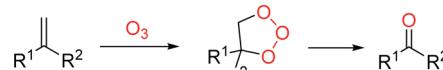
The selective oxidative scission of olefins is a practiced transformation in organic synthesis. The produced carbonyl compounds are valuable intermediates in pharmaceuticals, fragrances, agrochemicals and bulk chemical industries.¹ The two-step ozonolysis is the conventional method to convert olefins into carbonyl compounds (Scheme 1a).² In recent years, the ozone was replaced by other oxidants, such as H_2O_2 ,³ oxone,⁴ TBHP,⁵ *m*-CPBA,⁶ $KMnO_4$,⁷ $PhIO/HBF_4$,⁸ (Scheme 1b). However, the super stoichiometric use of expensive and toxic oxidants leads to a large amount of resource waste and environmental pollution.

Molecular oxygen is regarded as an ideal oxidant due to its easy availability, cheapness, environmental benignity and good functional-group tolerance. Recently, a series oxidative scission of olefins to carbonyl compounds with O_2 as the sole oxidant, catalysed by organocatalysts NHPI,⁹ AIBN,¹⁰ B_2Pin_2 ,¹¹ TEMPO,¹² transitional-metal complexes Pd,¹³ Cu,¹⁴ Fe,¹⁵ Ni,¹⁶ CAN,¹⁷ as well as photocatalysts¹⁸ and electrocatalysts,¹⁹ have been reported (Scheme 1c). However, some shortcomings including non-commercial available catalysts, expensive additives, inevitable residual transitional-metals, and excess amount of volatile organic solvents limit their application in industry. Very recently, although a 1,2-diethoxyethane catalysed oxidative scission of olefins to ketones by air has been achieved, the

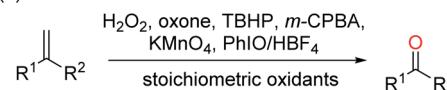
olefins are limited to *gem*-disubstituted aromatic alkenes.²⁰ Therefore, developing a wide applicable strategy for the oxidative scission of olefins to aldehydes and ketones is highly desirable but still remains a challenge.

Poly(ethylene glycol) dimethyl ether (PEGDME) has been attracting increasing interest due to its benign characteristics involving lower cost, non-volatilization, and non-toxicity, *etc.*²¹ To continue our interest in developing environmental benign synthetic reactions.²² Herein we report a simple and practical oxidative scission of a wide range of monosubstituted, *gem*- and 1,2-disubstituted, trisubstituted, and tetrasubstituted aromatic olefins to the corresponding aldehydes and ketones by O_2 with PEGDME as a benign solvent.

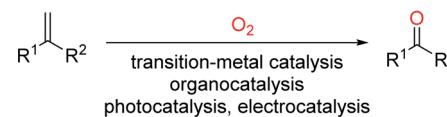
(a) Traditional ozonolysis method



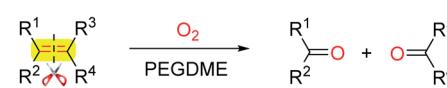
(b) Chemical oxidation method



(c) Catalytic method



(d) This work



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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra02007b

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Scheme 1 Oxidative scission of olefins to carbonyl compounds.



Results and discussion

Our studies were started with *gem*-diphenylethylene (**1a**) as a model substrate (Table 1). When the oxidation scission of **1a** was performed in *N,N*-dimethylformamide (DMF), methyl *tert*-butyl ether (MTBE), tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF) at 130 °C or under reflux condition with O₂ as the sole oxidant, only trace amount of diphenylmethanone (**2a**) was observed (entries 1–4). To our delight, the desired product **2a** was detected by HPLC with 73% yield in 1,4-dioxane at 100 °C for 10 hours (entry 5). However, when 1,4-dioxane was replaced by morpholine, the yield decreased to 49% (entry 6). To improve the reaction efficiency, ethylene glycol (EG), triethylene glycol (TEG), and a series of ethers including ethylene glycol dimethyl ether (EGDME), ethylene glycol diethyl ether (EGDEE), diethylene glycol monomethyl ether (DEGMME), diethylene glycol dimethyl ether (DEGDME), dipropylene glycol monomethyl ether (DPGMME), dipropylene glycol dimethyl ether (DPGDME), poly(ethylene glycol) (average *M_n*, 400) (PEG₄₀₀), poly(ethylene glycol) dimethyl ether (average *M_n*, 250) (PEGDME₂₅₀). ^b Reaction conditions: **1a** (0.5 mmol), solvent (1 mL), O₂ balloon. ^c The yields were determined by HPLC.

Table 1 Optimization of the reaction conditions^{a,b}

Entry	Solvent	Temp. (°C)	<i>t</i> (h)	Yield ^c (%)
1	DMF	130	10	<2%
2	MTBE	55	10	<2%
3	THF	66	10	<2%
4	2-MeTHF	78	10	<2%
5	1,4-Dioxane	100	10	73
6	Morpholine	130	10	49
7	EG	130	10	54
8	TEG	130	10	85
9	EGDME	86	10	61
10	EGDEE	130	10	90
11	DEGMME	130	10	91
12	DEGDME	130	10	93
13	DPGMME	130	10	94
14	DPGDME	130	10	94
15	PEG	130	10	96
16	PEGDME	130	10	99
17	PEGDME	110	10	99
18	PEGDME	100	10	78
19	PEGDME	110	8	99
20	PEGDME	110	6	83
21 ^d	PEGDME	110	8	35
22 ^e	PEGDME	110	8	64
23 ^f	PEGDME	110	8	52

^a Abbreviation: *N,N*-dimethylformamide (DMF), methyl *tert*-butyl ether (MTBE), tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF), ethylene glycol (EG), triethylene glycol (TEG), ethylene glycol dimethyl ether (EGDME), ethylene glycol diethyl ether (EGDEE), diethylene glycol monomethyl ether (DEGMME), diethylene glycol dimethyl ether (DEGDME), dipropylene glycol monomethyl ether (DPGMME), dipropylene glycol dimethyl ether (DPGDME), poly(ethylene glycol) (average *M_n*, 400) (PEG₄₀₀), poly(ethylene glycol) dimethyl ether (average *M_n*, 250) (PEGDME₂₅₀). ^b Reaction conditions: **1a** (0.5 mmol), solvent (1 mL), O₂ balloon. ^c The yields were determined by HPLC.

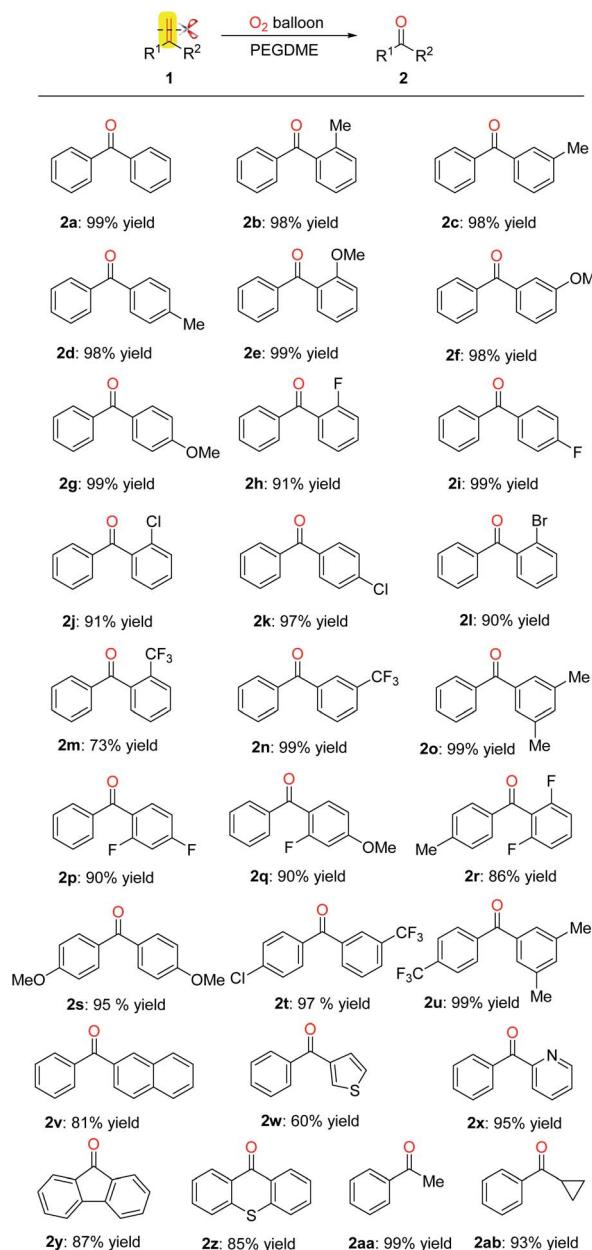
^d Under air atmosphere. ^e 1 mmol of **1a**. ^f 5 mmol of **1a**.

monomethyl ether (DPGMME), and dipropylene glycol dimethyl ether (DPGDME) were screened as a solvent at 130 °C for 10 hours, providing 54–94% yields (entries 7–14). Moreover, it was found that the environmentally friendly poly(ethylene glycol) (PEG) and poly(ethylene glycol) dimethyl ether (PEGDME) gave 96% and 99% yield, respectively (entries 15–16). Therefore, PEGDME was demonstrated to be the best solvent. Next, the effect of the reaction temperature was examined. The yield of **2a** remained at 99% when the reaction temperature dropped to 110 °C, but lower yield of 78% was observed at 100 °C (entries 17–18). Shorter reaction time was also attempted, the results revealed that the yield remained at 99% at 8 hours (entries 19–20). When the reaction was performed under air atmosphere, the yield decreased to 35% (entry 21). In addition, it was found that the higher concentration of **1a** led to lower yield of **2a** (entries 22–23). Finally, the entry 19 was regarded as the optimal reaction conditions: **1a** (0.5 mmol), PEGDME (1 mL), under O₂ atmosphere, 110 °C, and 8 hours.

With the optimized reaction conditions in hand, the scope of various olefins was investigated. As shown in Scheme 2, the oxidative scission of *gem*-diphenylethylenes bearing electron-donating group (Me, OMe) at the *ortho*-, *meta*- or *para* position, of the phenyl proceeded successfully to give the corresponding **2b–2g** with >98% yield. In addition, the halogen element (F, Cl, Br) substituted *gem*-diphenylethylenes were also gave corresponding ketones **2h–2l** in 90–99% yields. The halogen substituents are useful entities amenable to further transformation in organic synthesis. The *gem*-diphenylethylenes with *meta*-substituted electron-withdrawing group CF₃ gave higher yield than the *ortho*-substituted one (**2m**: 73%, **2n**: 99%). The *gem*-diphenylethylenes with two or three substituents on the phenyls also gave the desired products **2o–2u** in 86–99% yields. When phenyl of *gem*-diphenylethylene was replaced by naphthyl, thienyl and pyridyl, the oxidative scission also proceeded smoothly, affording the corresponding products **2v–2x** in 60–95% yields. To our delighted, the substrates containing fluorene or thioxanthene moiety also provided the desired ketones **2y** and **2z** in 87% and 85% yields. Furthermore, the aryl-alkyl disubstituted olefins like α -methylstyrene and α -cyclopropylstyrene were also applicable to this oxidative scission. The corresponding ketones **2aa** and **2ab** were obtained in 99% and 93% yields.

Aldehydes are also important building blocks in fine chemicals. And then, we examined this oxidative scission of olefins to prepare aldehydes. As shown in Scheme 3, the mono-substituted, 1,2-disubstituted, trisubstituted and tetrasubstituted aromatic olefins were also subjected to this transformation. For example, the monosubstituted aromatic olefine **1ac** was cleavaged to give 4-bromobenzaldehyde (**2ac**) in 92% yield under standard conditions. Benzaldehyde **2ad** was obtained as the sole product in 95% yield by the oxidative scission of 1,2-disubstituted aromatic olefine **1ad**. Interestingly, the 1,4-bis(2-methylstyryl)benzene (**1ae**) can be cleavaged to 1,4-phthalaldehyde (**2ae**) and 2-methylbenzaldehyde (**2ae'**) in 83% and 82% yield. When trisubstituted 1,1-diphenyl-2-(4-bromophenyl)ethene (**1af**) and triphenylethylene (**1ag**) were used as substrates, the corresponding products **2af** and **2ag** were obtained in 93% and 90% yields.

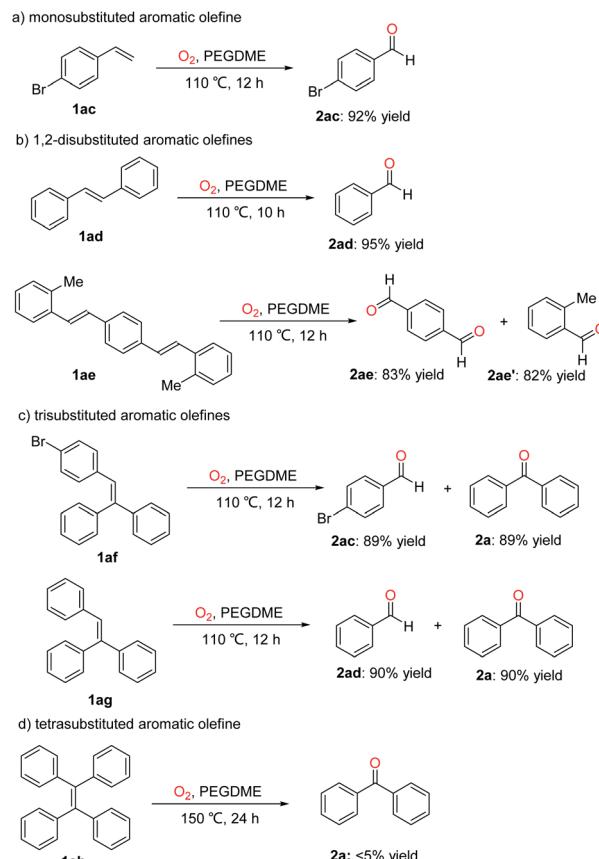




Scheme 2 Scope of *gem*-disubstituted aromatic olefins. Reaction conditions: 1 (0.5 mmol), PEGDME (1 mL), O_2 balloon, $110\text{ }^\circ\text{C}$, 8 hours, isolated yield.

bromobenzaldehyde (**2ac**), benzaldehyde (**2ad**) and diphenylmethanone (**2a**) were obtained in about 90% yields. Finally, the tetraphenylethylene (**1ah**) was also subjected to this oxidative scission, less than 5% yield was obtained even if elevating the temperature to $150\text{ }^\circ\text{C}$ and extending the reaction time to 24 hours.

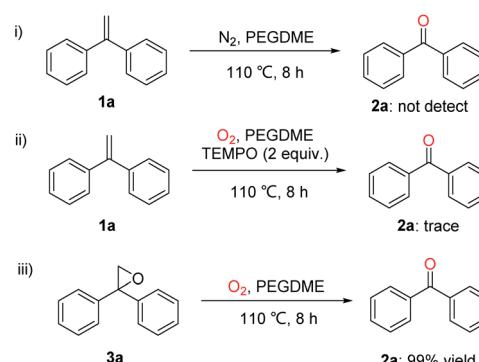
To understand the reaction pathway, control experiments were conducted. As shown in Scheme 4, when the oxidative scission of *gem*-diphenylethylene (**1a**) was carried out under N_2 atmosphere, no product **2a** was observed. Only a trace amount of oxidation product **2a** was detected in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) under



Scheme 3 Scope of mono, di-, tri-, and tetrasubstituted aromatic olefins.

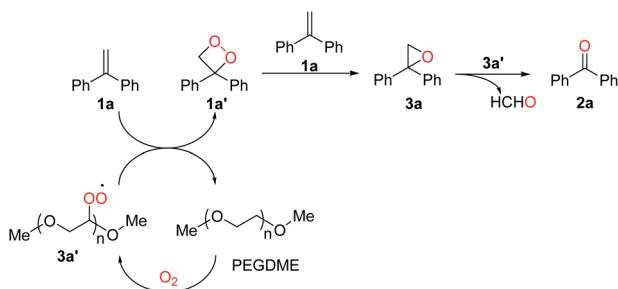
optimal conditions. It means that a radical reaction pathway might be involved. When 2,2-diphenyloxirane (**3a**) was used as the starting material, the desired ketone **2a** could be obtained in 99% yield, indicating that **3a** might be a key intermediate of this oxidative scission reaction.

Based on the control experiments and reported work,²⁰ a plausible reaction pathway was proposed as shown in Scheme 5. Firstly, PEGDME was oxidized by O_2 to produce a peroxy radical **3a'**. Secondly, 3,3-diphenyl-1,2-dioxetane (**1a'**) was formed by the oxidation of *gem*-diphenylethylene (**1a**) with **3a'** as



Scheme 4 Control experiments.





Scheme 5 Plausible reaction pathway.

an oxidant, regenerating PEGDME concurrently. And then, **1a'** is converted to the more stable key intermediate **2,2-diphenyloxirane (3a)** with one equivalent of **1a**. Finally, **3a** was converted to give the product **2a** with **3a'** as an oxidant.

To further demonstrate the practicality of this oxidative scission reaction, as shown in Scheme 6, a gram-scale reaction of *gem*-diphenylethylene (**1a**; 1.80 g, 10 mmol) was conducted under O_2 atmosphere in PEGDME at 110 °C for 10 hours, the product diphenylmethanone (**2a**) was isolated in 96% yield (1.75 g).

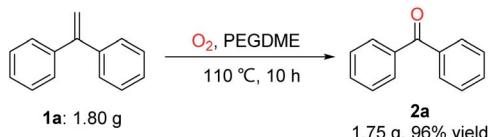
Conclusions

In summary, we have developed an oxidative scission of aromatic olefins to carbonyl compounds using molecular oxygen as the sole oxidant with PEGDME as solvent. A wide range of monosubstituted, *gem*- and 1,2-disubstituted, trisubstituted, and tetrasubstituted aromatic olefins were oxidized to aldehydes and ketones in excellent yields. A reaction pathway was proposed based on some control experiments. A successful gram-scale reaction also demonstrated its practicability.

Experimental section

General information

Unless otherwise noted, all reagents, catalysts and solvents were purchased from commercial suppliers and used without further purification. Column chromatography was performed with silica gel (200–300 mesh). NMR spectra were recorded on Bruker AVANCE III (400 MHz) spectrometers. $CDCl_3$ was the solvent used for the NMR analysis, with tetramethyl silane as an internal standard. Chemical shifts were reported up field to TMS (0.00 ppm) for 1H NMR and relative to $CDCl_3$ (77.0 ppm) for ^{13}C NMR. HPLC analysis was conducted on an Agilent 1200 Series instrument with 5C18-MS-II Packed Column (4.6 mm I.D. \times 250 mm).



Scheme 6 Gram-scale synthesis.

General procedure for oxidation scission of aromatic olefin

The corresponding aromatic olefin **1** (0.5 mmol), PEGDME (1 mL) were added to a 10 mL Schlenk tube. The tube was evacuated and filled with oxygen three times. The mixture was stirred at 110 °C for 8 hours under O_2 atmosphere using a balloon. After cooling, the mixture was subjected to silica gel column chromatography (PE : EA = 15 : 1) to give the product **2**.

Gram-scale oxidation scission of *gem*-diphenylethylene (**1a**)

The *gem*-diphenylethylene (**1a**, 1.80 g, 10 mmol), PEGDME (20 mL) were added to a 50 mL of round-bottomed flask equipped with a three-way jointer. The flask was then evacuated and filled with oxygen three times. The mixture was stirred at 110 °C for 10 hours under O_2 atmosphere using a balloon. After cooling, the mixture was subjected to silica gel column chromatography (PE : EA = 15 : 1) to give the product **2a** (1.75 g, 96% yield).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the 111 Project (D20015) and the Natural Science Foundation of Hubei Province of China (2018CFB241).

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