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All-at-once arrangement of both oxygen atoms of dioxygen into aliphatic $C(sp^3)$–$C(sp^3)$ bonds for hydroxyketone difunctionalization

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Both β- and γ- hydroxyketone structures are important units in biologically active molecules, synthetic drugs and fine chemicals. Although there are some routes available for their manufacture from pre-functionalized groups on one or two matrix molecule(s), the approaches to simply and simultaneously deposit two oxygen atoms from dioxygen into two specific $C(sp^3)$ positions of pure saturated hydrocarbons have rarely succeeded because they are involved in the targeted activation of three inert C–H σ bonds all at once. Here, we show that a TiO_2-CH_3CN photocatalytic suspension system enables the insertion of dioxygen into one $C(sp^3)$–$C(sp^3)$ bond of strained cycloparaffin derivatives, by which difunctionalized hydroxyketone products are obtained in a one-pot reaction. With the cleavage event to release strain as the directional driving force, as-designed photocatalytic reaction systems show 21 examples of β-hydroxyketone products with 31%–76% isolated yields for three-membered ring derivatives and 5 examples of γ-hydroxyketone products with 30%–63% isolated yields for four-membered ring substrates. ^{18}O isotopic labeling experiments using $^{18}O_2$, $Ti^{18}O_2$ and intentionally added $H_2{}^{18}O$, respectively, indicated that both oxygen atoms of hydroxyketone products were exclusively from dioxygen, suggesting a previously unknown H^+/TiO_2-e^- catalyzed arrangement pathway of the hydroperoxide intermediate to convert dioxygen into hydroxyketone units.

TiO_2 photocatalysis, β- or γ-hydroxyketones, strained cycloalkanes, dioxygen activation

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1 Introduction

There has been considerable interest in the direct oxidation of inert but readily available hydrocarbons to form alcohols, aldehydes and ketones for oxygenation functionalization [1]. Dioxygen, as a green, safe and low-cost oxidant, has been widely applied for various hydrocarbon oxygenation functionalizations [1e,1h,2]. Generally, oxygenation conversions with dioxygen use one of its two oxygen atoms, while the other oxygen atom abstracts hydrogen atoms from substrates or auxiliaries into the H_2O by-product, leading to easy cleavage of the O–O bond (based on the model of mono-oxygenase) [3]. Incorporation of both oxygen atoms of dioxygen all at once to form two oxygen-containing functional groups within a hydrocarbon molecule for oxygenation difunctionalization is the shortest process with the best atom economy without the loss of both hydrogen and C atoms (as dioxygenase reactions), such as hydroxyketone preparation from simple $C(sp^3)$–H compounds by dioxygenase enzyme catalysis [4]. However, it is very challenging to catalytically reduce the two oxygen atoms of dioxygen into one alcoholic hydroxyl and one carbonyl in one substrate molecule due to

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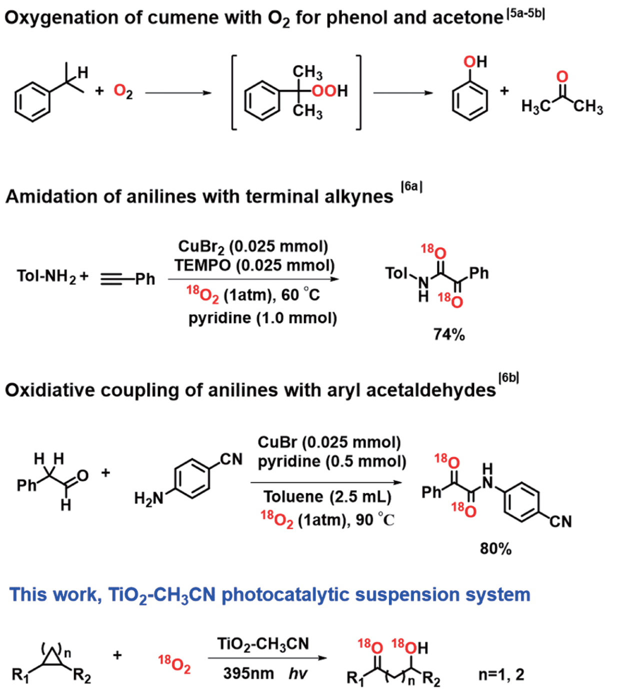
*Corresponding author (email: whma@iccas.ac.cn) fairly restrict incorporation followed by the fracture mode of the O–O bond with simple C(sp^3)–H σ-bonds. The most successful use of both oxygen atoms of dioxygen for the difunctionalization of hydrocarbons is cumene oxidation for the production of the important industrial materials, phenol and acetone, albeit the two oxygen atoms are not assigned to one product molecule (Scheme 1, top). In this way, two oxygen atoms of dioxygen insert into the C(sp^3)–H bond through a ternary C–OOH hydroperoxide arrangement catalyzed by proton acids at 150–200 °C [5]. Contrary to this very successful achievement in the industrial practice, the catalytic placement of both oxygen atoms of dioxygen within one hydrocarbon molecule for preparations of difunctionalized oxygenation fine chemicals is very rare. Until 2010, Jiao and co-workers [6] reported that both oxygen atoms of dioxygen could be transformed into a α-ketoamide unit *via* a Cu-catalyzed oxidative amidation-diketonization reaction of terminal alkynes (Scheme 1), although the substrates require certain functional groups (–NH$_2$, $-\equiv$, and C=O) and the process results in partial hydrogen or oxygen atom loss from the substrates. However, few strategies on inserting both oxygen atoms of dioxygen into two genuine σ-C(sp^3) positions within one organic molecule in a one-pot reaction have been reported so far.

Strained ring cycloparaffin units, such as three- or four-membered rings, are versatile building blocks in modern organic synthesis [7] because their unique bonding and inherently high ring strain (the strain energy of cyclopropane is ~29.0 kcal/mol and cyclobutene is ~26.3 kcal/mol relative to cyclopentane at 7.4 kcal/mol) confer diverse possibilities exactly to construct delicate functional structures by means of ring-opening operations [7g,8]. Especially, it is very easy to structure difunctionalized groups at the broken ends of the strained ring. Nevertheless, difunctionalized oxygenations of strained cycloparaffins with dioxygen in traditional catalysis never came to be realized unless using some special oxidants such as hypervalent iodine reagents [8c]. We envision that the most plausible way to introduce dioxygen into both a hydroxyl and carbonyl group within a genuine C(sp^3) hydrocarbon chain would be to rearrange one C–C bond of a cycloalkane ring unit contained in a hydrocarbon substrate (Scheme 1, bottom), a feat that pushes two oxygen atoms of dioxygen into C–H and C–C bonds without losing any atoms from the reactants. For this purpose, photosensitization and photocatalysis should be employed since both are common and effective ways to activate dioxygen at room temperature [1c,1d,9]. These mild reaction conditions may prevent overoxidation once the strained ring is opened under high oxidation pressure. For instance, König and co-workers [9b] reported that β-chloro-ketones could be realized from opening ring of aryl cyclopropanes through sodium anthraquinone-2-sulfonate sensitized activation of dioxygen in the presence of HCl and HNO$_3$ under visible-light irradiation. In contrast, 9,10-dicyanoanthracene-sensitized photooxygenation of 1,2-diarylcyclopropanes with dioxygen only resulted in endoperoxide formation (3,5-diaryl-1,2-dioxolane) in the presence of Mg(ClO$_4$)$_2$ [9c]. We herein report that the preparation of β- or γ-hydroxyketone units can be achieved all at once from strained cycloparaffin derivatives through aerobic TiO$_2$-CH$_3$CN photocatalysis in a concerted free radical and hydroperoxide rearrangement route. This strategy will provide, in principle, a new method to incorporate dioxygen into the σ-C(sp^3)–C(sp^3) chain of alkanes in a one-pot reaction without the loss of any hydrogen or carbon atoms of the substrate or an O atom of activated dioxygen.



Scheme 1 Arranging both oxygen atoms of O$_2$ for difunctionalized oxygenation (color online).

2 Experimental

2.1 Materials and instruments

TiO$_2$ (Degussa P25) was provided by Acros Company (Belgium) and used as received. D$_2$O and H$_2{}^{18}$O were purchased from Aladdin Company (China). ^{18}O$_2$ was purchased from Cambridge Isotope Laboratories, Inc. (USA). The isotopic enrichment was greater than 97%. Diethyl zinc, diiodomethane, and trifluoroacetic acid were purchased from TCI Company (Japan). Acetonitrile (99.9%, extra dry with molecular sieves, water ≤50 ppm) was purchased from InoChem Company (China). Tetrahydrofuran (THF) was distilled with Na, and dichloromethane (DCM) was distilled with CaH$_2$.

An light-emitting diode (LED) lamp (395±10 nm, 30 W) from a domestic manufacturer was used as the light source. The light intensity irradiated on the reaction vial was measured using a light intensity meter (model CEL-NP2000-10; Au light, China), and the value was found to be approximately 60 mW cm^{-2}. Quantitative measurements of the conversions of the substrates and yields of the products were made on a gas chromatograph (Agilent 7890A) equipped with a flame ionization detector (FID) and an Agilent Technology 19091J-413 (USA) capillary column (30 m× 0.32 mm×0.25 μm) using high purity N_2 as the carrier gas. The standard analysis conditions were as follows: injector temperature 250 °C, detector temperature 300 °C, and a column temperature program of 50 °C (hold for 1.5 min) after which increased to 300 °C (hold for 5 min) at a rate of 20 °C min^{-1}. ^{1}H nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra in $CDCl_3$ at 20 °C were obtained using a Bruker 300/400/500 MHz Fourier transform NMR spectrometer (Germany). The diastereomeric ratios (d.r.) for all compounds were determined by ^{1}H NMR analysis based on the peak areas of the isomers. Gas chromatography-mass spectrometry (GC-MS) measurements were conducted using a Shimadzu QP2010 SE system (Japan) equipped with an HP-5 capillary column (30 m×0.32 mm×0.5 μm). High-resolution electrospray ionization mass spectrometry (HR-ESI-MS) measurements were performed on an Agilent quadrupole time-of-flight (Q-TOF) 6510 instrument (USA).

2.2 General procedure for photocatalytic reactions

In a 15 mL Pyrex reaction vial, 0.15 mmol of substrate and 25 mg of TiO_2 were dispersed in 3.0 mL of acetonitrile. The vial was sealed with a butyl stopper and purged with O_2; an oxygen balloon was used for the continuous supply of O_2 during the reaction. Afterwards, the vial was cooled in an ice bath, magnetically stirred and irradiated from the side. After certain intervals, an aliquot of the solution was withdrawn with a syringe and analyzed by thin-layer chromatography (TLC) and/or GC-MS. After completion of the reaction, the mixture was filtered through celite to remove the TiO_2 and concentrated to produce a residue that was purified by column chromatography for further analysis (*e.g.*, GC-MS and NMR). The weight calculation to determine the isolate yield was measured using an analytical balance.

2.3 Preparation of $Ti^{18}O_2$

$Ti^{18}O_2$ was prepared according to procedures described by Kavan *et al*. [10]. The synthesis of $Ti^{18}O_2$ was carried out in a closed all-glass vacuum apparatus. $TiCl_4$ (99.98%, Acros, Belgium) was distilled twice under vacuum before use. One gram of $H_2{}^{18}O$ (97 atom% ^{18}O, Aladdin) was frozen under high vacuum by cooling in a liquid nitrogen bath, and the ice came in contact with 2.8 mL of $TiCl_4$ vapor through a glass-breakable valve. After both reactants had mixed completely, the cooling bath was removed, and the reaction product was kept at room temperature overnight. The HCl formed as a byproduct was collected in a side ampoule cooled with liquid nitrogen. Subsequently, the solid product was heated to 200 °C overnight in the still-closed vacuum apparatus, while the HCl trap remained permanently cooled in the liquid nitrogen bath. Finally, the apparatus was opened in a glove box under Ar, and the solid white powder was collected.

2.4 Synthesis of the substrates

(1R,2S)-1,2-diphenylcyclopropane. The cyclopropane substrates were prepared according to procedures described by Murphy *et al*. [11]. Commercially unavailable styrenes were synthesized using the Wittig Olefination protocol. A solution of trifluoroacetic acid (2.46 mL, 32 mmol, 4.6 eq.) in 20 mL of dry dichloromethane was very slowly added at 0 °C to a solution of diethyl zinc (32 mL, 32 mmol, 4.6 eq.) in 35 mL of dry DCM, and the mixture stirred at 0 °C for 30 min to form a solid on the side of the flask. A solution of diiodomethane (2.57 mL, 32 mmol, 4.6 eq.) in 15 mL of dry DCM was added to the previous mixture at 0 °C. The resulting mixture stirred for 45 min at 0 °C. A solution of (*Z*)-1,2-diphenylethene (1.91 g, 10.7 mmol, 1.5 eq.) in 7 mL of dry DCM was then added to the mixture at 0 °C. The final mixture stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (50 mL) and the aqueous layer was extracted with DCM (3×100 mL). The organic phases were combined, washed with $NaHCO_3$ (3×60 mL), water (80 mL) and brine (3×60 mL), and dried over Na_2SO_4. Column chromatography was used to obtain the desired pure product (1.5 g, 70%).

6-(4-Chlorophenyl)-7-(4-methoxyphenyl)-3-oxabicyclo [3.2.0]heptane. The cyclobutene was prepared according to procedures described by Yoon *et al*. [12]. A 50 mL Schlenk flask containing $MgSO_4$ (300 mg) was flame-dried under vacuum and cooled under dry N_2. Bis(styrene) (280 mg, 0.89 mmol), $MV(PF_6)_2$ (61 mg, 0.131 mmol), and $Ru(bpy)_3(PF_6)_2$ (61 mg, 0.131 mmol) were then added to the cooled flask. The flask was charged with 8 mL of $MeNO_2$, and the solution reacted for approximately 3.5 h. Column chromatography was used to obtain the desired pure product (220 mg, 80%).

3 Results and discussion

A typical photocatalytic reaction was performed in a 15 mL Pyrex reaction vial. 0.15 mmol of substrate (1*R*,2*S*)-1,2-diphenylcyclopropane (**1**) and 25 mg (0.31 mmol) of commercially available TiO_2 (Degussa P25) were dispersed in 3.0 mL of a solvent such as acetonitrile. The vial was sealed with a butyl stopper and purged with 1 atm of O_2; an oxygen balloon was used for the continuous supply of O_2 during the reaction. Afterwards, the vial was cooled in a bath to control the reaction temperature, magnetically stirred and irradiated from the side with a 30 W ultraviolet (UV) LED lamp. To inhibit the overoxidation, the reaction conditions were further optimized (Table S1, Supporting Informaiton online) according to the yield of **1a** by varying the solvent polarity, reaction temperature and irradiation wavelength. Under the optimized conditions (acetonitrile as the solvent, reaction temperature of 0 °C, and 395 nm UV irradiation), **1** showed a nearly exponential decay against irradiation times, which is typical of a pseudo-first-order photocatalytic reaction (Figure 1, and Figure S1, Supporting Informaiton online), while the yield of the desired product **1a** increased as the photocatalytic reaction proceeded, and the isolated yield of **1a** reached 71%. From the inset in Figure 1, the other by-products, benzaldehyde and acetophenone, accounted for nearly all of the rest of the transformation of **1**. The yield of **1a** displayed some decline after complete transformation of the substrate with extended irradiation. Control experiments confirmed that the oxidation reaction was not possible in the absence of light or the TiO_2 photocatalyst. As expected, TiO_2 photocatalyst showed as remarkable stability and recyclability as ever. TiO_2 photocatalyst is readily recycled by simply filtration and shows only a slight decrease in β-hydroxyketone yield after five trials (<5%) and little changes in X-ray diffraction (XRD) patterns and adsorption spectra (Figure S2). There was no **1a** formation in the absence of dioxygen, suggesting that dioxygen is the obligatory oxygen source in this transformation (Table S1).

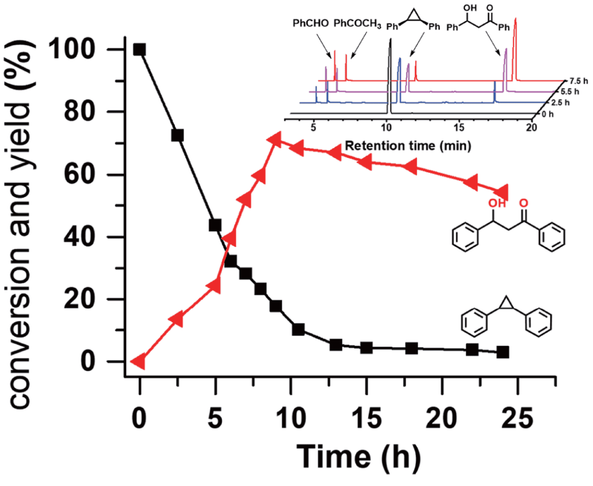
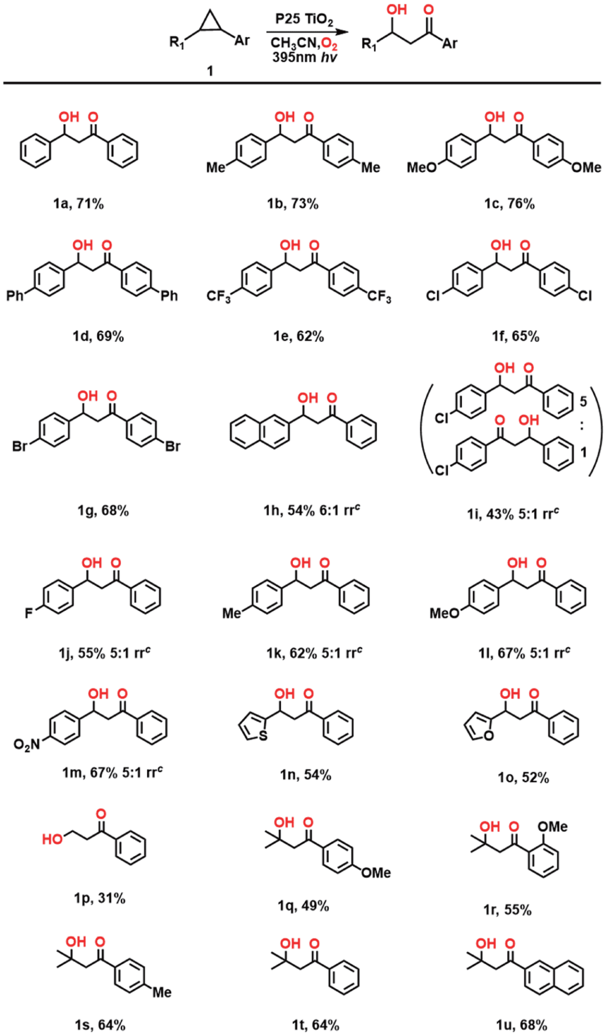


Figure 1 Plot of the kinetic profile of the photocatalytic reaction of diphenylcyclopropane (**1**). Conditions: 0.15 mmol of **1**, 25 mg of TiO_2, 3.0 mL of acetonitrile, and 1.0 atm O_2 at 0 °C. Inset: GC spectra for the determination of the transformation of **1** and **1a** formation with different irradiation times (color online).

Table 1 Scope of the photocatalytic oxygenation of cyclopropane derivatives [a),b),c)]

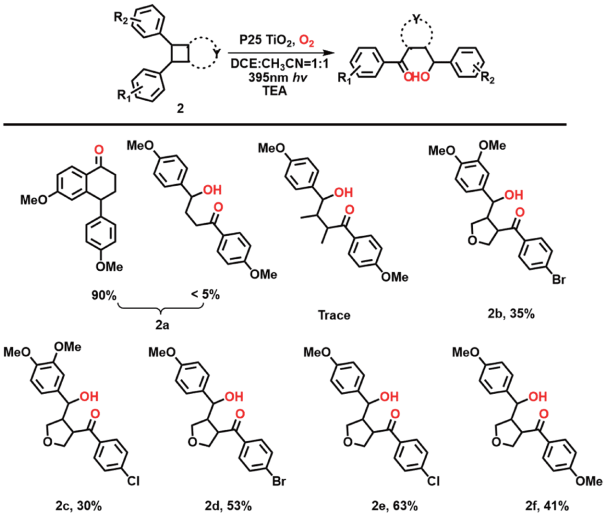


1a, 71%
1b, 73%
1c, 76%
1d, 69%
1e, 62%
1f, 65%
1g, 68%
1h, 54% 6:1 rr[c]
1i, 43% 5:1 rr[c]
1j, 55% 5:1 rr[c]
1k, 62% 5:1 rr[c]
1l, 67% 5:1 rr[c]
1m, 67% 5:1 rr[c]
1n, 54%
1o, 52%
1p, 31%
1q, 49%
1r, 55%
1s, 64%
1t, 64%
1u, 68%

a) Isolated yields if not specified. The regioselectivity was determined by ^{1}H NMR. b) Optimized conditions: P25 (25 mg, 0.25 mmol), 0 °C, 10 h, 395 nm LED, and 0.15 mmol of substrate in 3.0 mL of CH_3CN. c) The isolated yield of the major isomer is listed.

To test the viability of this method, we expanded the scope of the cyclopropane substrates. As presented in Table 1, 1,2-diaryl cyclopropanes possessing electron-donating groups at the *para*-position of the phenyl ring, such as alkyl (**1b**), methoxy (**1c**), and 4-Ph (**1d**), reacted smoothly and provided the corresponding β-hydroxyketone in good yields (69%–76%), while electron-withdrawing substituents gave moderate yields (**1e**–**1g**). In the case of unsymmetrical 1,2-diaryl cyclopropanes (**1h**–**1m**), the regioisomeric ratio (r.r.) was approximately 5–6:1, the major isomer derived from definitive hydroperoxidating of the cyclopropane that preferentially takes place at the carbon site of the cyclopropane bearing the less substituted aryl group. Thiophene and furan derivatives (**1n**, **1o**) could also be converted with fair yields, and this might be useful for the synthesis of functionalized hydroxyketone frameworks. Up to now, all transformations have been limited to diaryl cyclopropane derivatives, which seems to be obligatory for dioxygen insertion into the C–C

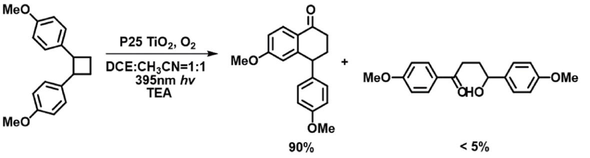
Table 2 Scope of the photocatalytic oxygenation of cyclobutanes a), b)



a) Reaction conditions: P25 (25 mg, 0.25 mmol), 0 °C, 10 h, 395 nm LED, 3 μL of triethylamine (TEA) and 0.15 mmol of substrate in 3.0 mL of CH$_3$CN and 1,2-dichloroethane (DCE) (1:1). b) Isolated yields.

bond of the three-membered ring unit of the substrate. Unexpectedly, a substrate with a single aryl substituent could also be transformed into a β-hydroxyketone (**1p**). In addition, a variety of single aryl-containing cyclopropanes bearing *gem*-dimethyl substituents were also examined, affording the desired products in moderate yields (**1q**–**1u**).

To extend this method to the preparation of γ-hydroxyketones, we set out to enable substrates containing cyclobutane units, which should be theoretically feasible (Table 2). We then used 1,2-bis(4-methoxyphenyl) cyclobutane as the substrate to execute the photocatalytic oxygenation reaction under identical conditions to the case of 1,2-diarylpropane. However, this reaction gave the 4-phenyltetralone derivative (Table 2, **2a**) as the major oxidation product, while γ-hydroxyketone was present in only a tiny minority (<5%) (Eq. (1)).



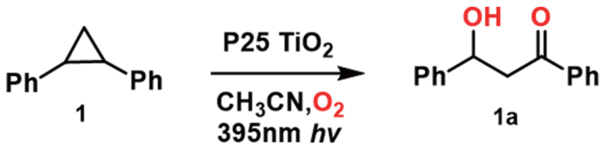
(1)

This result is highly consistent with the findings reported previously in which the secondary C–C bond of the four-membered ring unit is cracked followed by cyclization with parent benzene [13]. This suggested that intramolecular attack and cyclization were more likely than the intermolecular dioxygen insertion reaction after breaking the C–C bond of the four-membered ring. We argue that two measures are likely to significantly promote the aimed γ-hydroxyketone yield. One is to screen the suitable substrates with substantial steric hindrance installed in the cyclobutane unit that could prevent intramolecular cyclization events, which may be beneficial to the oxidation of cyclobutanes into γ-hydroxyketones. The other is to accelerate the possible proton shift involved in placing hydroxyl or carbonyl oxygen at C(sp^{3})–H or C(sp^{3})–C(sp^{3}) positions during opening-ring process of cyclobutene. Thus, we first selected substrates containing oxabicyclo[3.2.0] units to repeat the photocatalytic transformation. The yield of γ-hydroxyketone was indeed increased relative to **2a** case; however, it was still lower (appr. 20%) when the reaction conditions were the same as the selective oxidation of cyclopropane (Table S1). Then, we added 0.1% (*v*/*v*) triethylamine as proton transfer reagent to the reaction system, and the yield was dramatically improved and a maximum isolated yield reached up to 63% (**2b**–**2f**, Table 2). In this way, we obtained the main products **2b-2f** in 30%–63% isolated yields. We did not carry out more transformations of four-membered ring derivatives due to substrate limitations. However, successful examples **2b**–**2f** displayed the primary potential for the preparation of the designated C(sp^{3})-site hydroxyketones of hydrocarbon compounds *via* oxygenation with dioxygen in a one-pot photocatalytic reaction. In addition, the oxidative cyclobutane reaction presents with excellent stereoselectivity. Using a 6-(4-bromophenyl)-7-(4-methoxyphenyl)-3-oxabicyclo [3.2.0] heptane substrate, the ^{1}H NMR data showed that the value of d.r. was greater than 10:1 (see the spectrum in the Supporting Information online). Such a one-pot catalytic oxidation of the C(sp^{3})–C(sp^{3}) bond generates both β- and γ-hydroxyketone products, which, to the best of our knowledge, had scarcely been reported before.

Furthermore, we attempted to extend this photocatalyzed dioxygen insertion reaction to five- or six- membered ring substrates that have little strain, and we did not achieve the expected δ- or ε-hydroxyketone ring-opening products, whereas the corresponding cyclopentanones or cyclohexanones were produced in less than 5% yield. Approximately 95% of the substrate was cracked into fewer carbon number deep-oxidation products. This was highly consistent with all TiO$_2$-photocatalyzed pure aliphatic hydrocarbon reactions with dioxygen as the sole oxidant [1c,13,14]. That is, simultaneous difunctionalized oxygenations of saturated carbon chains with dioxygen mediated by TiO$_2$ photocatalysts occur for these substrates that only contain strained ring units. Nonetheless, dioxygen insertion into one C(sp^{3})–C(sp^{3}) bond of the strained ring should be a novel reaction pathway that is significantly different from the previously well-known routes of catalytic activation of dioxygen. To confirm that the important properties are exclusively related to opening strained rings by TiO$_2$ photocatalysis, we will in detail investigate how both oxygen atoms of dioxygen insert into the strained ring unit of aliphatic compounds all at once without the necessary assistance of the leaving of both hydrogen and carbon atoms.

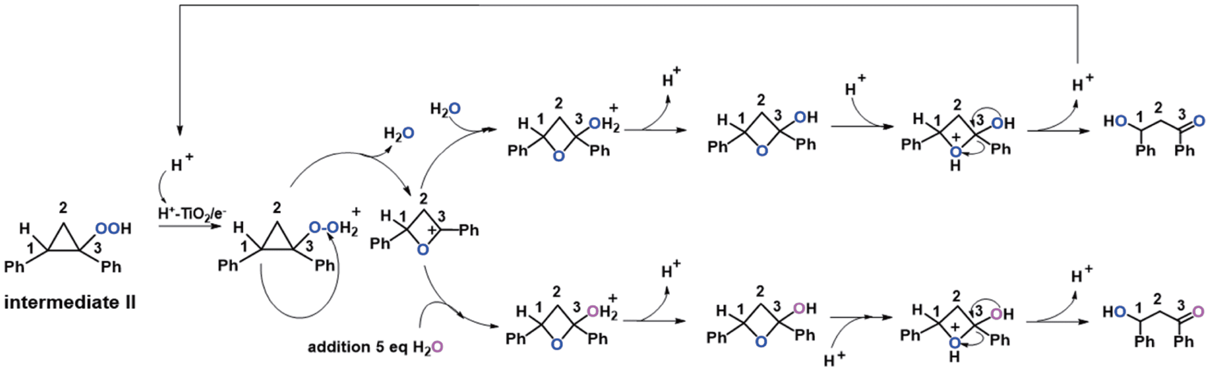
To elaborate the dominant mechanism and determine if the oxygen atoms in **1a** exclusively originate from O_2 rather than from the oxygen atom on the TiO_2 surface or residual or possibly formed intermediate H_2O, several 18-oxygen isotopic labeling experiments were performed, as summarized in Table 3. When the vial was purged with $^{18}O_2$, the [M+4] product approached 99% yield, indicating that all oxygen atoms of the β-hydroxyketone were from dioxygen (entry 2), which is significantly different from the >99% normal molecule weight [M] product from $^{16}O_2$ (Table 3, entry 1). The surface oxygen of TiO_2 is not incorporated or exchanged into the products, as we specially prepared the $Ti^{18}O_2$ photocatalyst (entry 3). This is apparently not in accordance with the Mars-Van Krevelen mechanism, in which the lattice oxygen is always incorporated into the carbonyl and the consumed oxygen is restored from molecular oxygen in the gas phase [15]. We argue that the O–O was divided into two independent C–OH and C=O units should be through a H_2O intermediate leaving and rebounding (Scheme 2). Thus, we intentionally added a small amount of H_2O to this transformation to observe whether the oxygen atom of H_2O participates in hydroxyketone formation. In the $^{16}O_2$ photocatalytic reaction system, the addition of 5 eq. of $H_2{}^{18}O$ led to an [M]:[M+2] close to 1:1 (entry 4), indicating that although H_2O was incorporated into the product molecule, at least half of the product ([M]) was formed from the initial dioxygen, which maintained to the end of the reaction. In other words, the formation of half of the [M+2] product and no [M+4] product indicated that H_2O participation only occurred in a step parallel to that of dioxygen after the substrate had primarily incorporated dioxygen (*i.e.*, after hydroperoxide intermediate formation in Eq. (9), Scheme 2). This speculation was further confirmed by the use of $^{18}O_2$ with 5 eq. of $H_2{}^{16}O$ to repeat this transformation (entry 5). No [M] product appearance and half of the [M+4] product generation indicated that $^{18}O_2$ dominated the oxygenation reaction throughout. Furthermore, when 5 eq. of deuterated water was added, it was found that the molecular weight of the product had not changed (entry 6); namely, both hydrogen atoms of the ternary C–H of the cyclopropane ring were maintained until the end of the reaction and were not replaced by additional D_2O. It should be mentioned that we isolated the hydroxyketone product from the photocatalytic system and

Table 3 Abundance of ^{18}O in **1a**$^{a) b) c)}$



Entry	Cat.	O_2	Additive	Percentage of ^{16}O and ^{18}O in **1a** (%)		
				M	M+2	M+4
1	TiO_2	$^{16}O_2$	None	>99	0	0
2	TiO_2	$^{18}O_2$	None	0	0	>99
3	$Ti^{18}O_2$	$^{16}O_2$	None	>99	0	0
4	TiO_2	$^{16}O_2$	5 eq. $H_2{}^{18}O$	47.7	52.3	0
5	TiO_2	$^{18}O_2$	5 eq. $H_2{}^{16}O$	0	48.9	0
6	TiO_2	$^{16}O_2$	5 eq. D_2O	>99	0	0

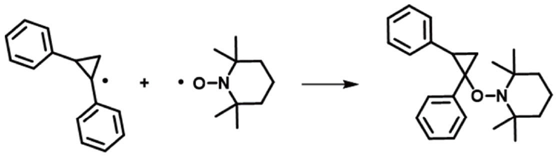
a) Under the same conditions as Table 1; b) abundance of ^{18}O in **1a** was determined by HR-ESI-MS; c) see Figure S4 and discussion for HR-ESI-MS spectra and data analyses.



Scheme 2 A plausible photocatalytic reaction mechanism (color online).

then added 5 eq. of D_2O or 5 eq. of $H_2{}^{18}O$ and stirred the mixtures overnight in the dark, and found that the molecular weight of the product did not change. This control experiment showed that there was no exchange of isotope either the hydroxyl functional group or the ketone functional group in the products after treatment with $H_2{}^{18}O$ or D_2O (Figure S3).

To summarize briefly, the above several lines of evidence imply that: (1) the two oxygen atoms from dioxygen have priority insertion into the C–C bond of the strained ring regardless of adding an excess of H_2O; (2) the hydroxyketone formation reaction has experienced two distinct stages together (the early stage of only O_2 participation Eqs. (5)–(9) and later stage of O_2/H_2O participation, namely, the arrangement of intermediate **II**); (3) additional H_2O does not destroy the transformation selectivity and simply takes part in the latter half-reaction after initiating by dioxygen (this is why there was no product with both oxygen atoms from H_2O). With the above isotopic experimental evidence and discussion, a mechanism for TiO_2 photocatalysis was proposed (Scheme 2). In this oxygenation process, the strained three- and four-membered ring transformations into β- and γ-hydroxyketones are divided into two stages: the first is the one-electron oxidation for hydroperoxide **II** formation and this is not consistent with the oxygeneation of bis(styrene), in which the oxidation reaction proceeds through the 1,4-distonic radical cation intermediate [13]. The other is the rearrangement of the hydroperoxide intermediate to form the final product. In the former, the reaction is initiated by one-electron oxidation of **1** by the valence band holes ($h_{vb}{}^+$) [13,16], which has been readily confirmed with the addition of 10 eq. of CH_3OH to completely quench the conversion of **1** (Table S1). Meanwhile, the electron transfer from the conduction-band electron ($e_{cb}{}^-$) to O_2 plays an indispensable role in the formation of key intermediate hydroperoxide **II** (Eqs. (5)–(9)). This could be indirectly confirmed with the addition of typical electron acceptor decamethylferrocenium (Cp_2Fe^+) to our O_2/diaryl cyclopropane derivative reaction system to react with $e_{cb}{}^-$ prior to O_2, which resulted in benzaldehyde (~89% yield) rather than target β-hydroxyketone product (Eq. (4) and Scheme S1, Supporting Informait on online). In the sequential radical chain propagation reaction period (Eqs. (5) and (6)), the depletion and regeneration of ternary carbon free radical intermediate **I** is crucial to activate dioxygen into both hydroperoxide intermediate **II** and the final product. Firstly, we captured this free radical with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and determined by ESI-MS (Figure 2, Eq. (2)) as the vial was purged with 1 atm of ${}^{18}O_2$ or ${}^{16}O_2$.



(2)

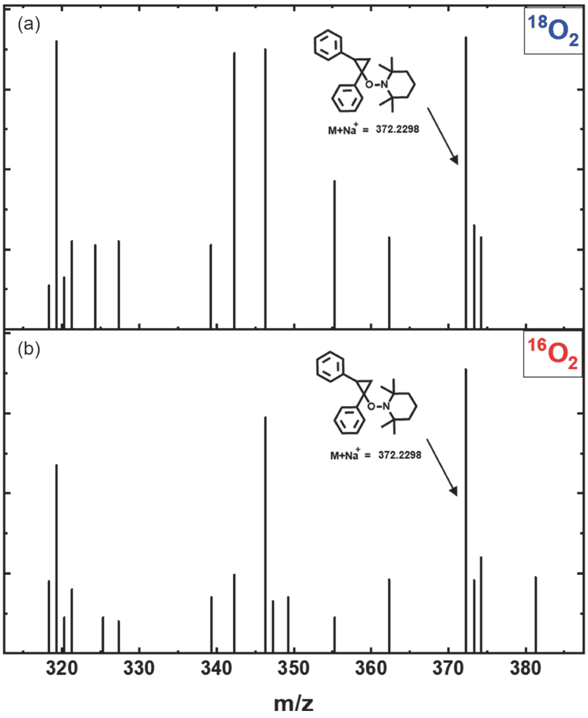


Figure 2 HR-ESI-MS spectra of the ternary carbon free radical intermediate captured by TEMPO after treatment with ${}^{16}O_2$ (a) and ${}^{18}O_2$ (b) (color online).

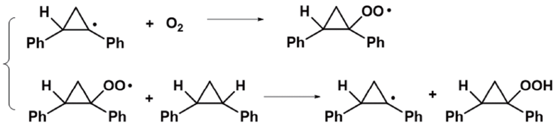
Finally, the chain termination consists of the reaction of $O_2{}^{\bullet-}$ and tertiary carbon free radical **I** (Scheme 2, Eqs. (7)–(9)), resulting in the formation of hydroperoxide intermediate **II**. For the catalytic rearrangement stage, although the rearrangement reaction catalyzed by Lewis and proton acids has been applied for preparations of different oxygenated compounds, such as phenol and acetone from cumine hydroperoxide, there are few examples of the rearrangement of these hydroperoxides established on strained rings because of the difficult cleavage of very strong C–C bonds of three- or four-membered rings (their bond dissociation energy (BDE) is generally greater than 100 kcal/mol) [17]. We argue that the photoinduced H^+/TiO_2-e^- catalyzes the rearrangement of hydroperoxide **II** (Scheme 2 bottom). The photoinduced renascent protons (Eq. (4)) on the TiO_2 surface possess strong Brønsted acid properties owing to the coexisting weak conjugate base. That is, the delocalized conduction-band electron ($e_{cb}{}^-$) functions greater than that of the common conjugated Brønsted base, which enables H^+/TiO_2-e^- to protonate polybrominated benzene rings, as evidenced by our previous work [18]. Apparently, during this rearrangement process, there are no hydrogen, oxygen or carbon atoms that are forced away as leaving groups from the stoichiometric formula of the final product, but the dissociation of protons and H_2O from the available intermediates as well as their recombination is most likely to occur. This proton shift is rather crucial for γ-hydroxyketone formation from less strained four-membered ring. This is why photocatalytic oxygenations of cyclobutanes for preparations of γ-hydroxyketones require TEA as proton shift reagent.

$$TiO_2 + hv \longrightarrow TiO_2\text{-}h_{vb}^{+}/e_{cb}^{-} \quad (3)$$

Initiation:

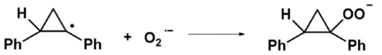

(4)

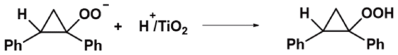
Chain propagation:


(5)
(6)

Chain termination:

$$H^{+}/TiO_2\text{-}e_{cb}^{-} + O_2 \longrightarrow O_2^{-} + H^{+}/TiO_2 \quad (7)$$


(8)


(9)

4 Conclusions

Our experimental results showed the precise arrangement of two oxygen atoms from dioxygen within an organic molecule without C=C, C≡C or C–X pre-functionalized groups for the green manufacture of β- and γ-hydroxyketone units. With an increasing number of synthetic methods available for strained ring units, TiO_2-based photocatalytic strategies to prepare difunctionalized oxygenated products using dioxygen as the sole oxidant would definitely result in special attractiveness because of its powerful activation of C–H and C–C bonds under environmentally-friendly reaction conditions.

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Conflict of interest The authors declare no conflict of interest.

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