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Photocatalytic direct oxygen-isotopic labelings of carbonyls in ketones and aldehydes with oxygen-isotopic waters

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ABSTRACT

Oxygen-isotopic labelings play important roles in identifying and understanding chemical and biological processes. Direct C=O to C=^{18}O or C=^{17}O conversion in a single step leading to labeled compounds can alleviate synthetic burdens without the need for resynthesis. Here we describe a photocatalytic oxygen-isotopic labeling protocol that can efficiently and selectively install ^{18}O and ^{17}O on carbonyls of ketones and aldehydes *via* oxygen isotope exchange with oxygen-isotopic waters ($H_2{}^{18}O$ or $H_2{}^{17}O$) as the sources of oxygen isotopes, in which light and oxygen-enabled sodium alkanesulfinates catalyzed this process. This strategy was extended to the *in-situ* formed ketones from the photocatalytic aerobic oxidation of alkyl arenes and secondary alcohols. Furthermore, reduction of the oxygen-isotopically labeled aldehydes with $NaBH_4$ provided the corresponding oxygen-isotopically labeled primary alcohols. We believe that the oxygen-isotopically labeling method will be widely used in chemistry, biology and medicine fields.

The isotopes of elements have become important tools in chemistry, biology and medicine fields, and they are widely used in spectroscopy, mass spectrometry and mechanistic and pharmacokinetic investigations [1]. Beyond the widespread applications, there has been much attention in incorporating isotopes into drug molecules [1]. For example, a deuterated drug, deutetrabenazine approved by the United States' Food and Drug Administration, is used in the treatment of Huntington's disease [2]. The replacement of hydrogen with its isotopes has received much attention as a way to change the absorption, distribution, metabolism and excretion (ADME) properties of drug candidates [1,3–5]. However, there has been less attention in the oxygen-isotopic labeling relative to the hydrogen-isotopic labeling [6–8]. In fact, ^{18}O and ^{17}O-labeled molecules for high resolution mass spectrometry (HRMS) and ^{17}O-labeled molecules for nuclear magnetic resonance (NMR) spectroscopy are advantageous in rapid identifying drug metabolites in very complex samples [9]. $^{18}O_2$ and $^{17}O_2$ are the simplest oxygen sources, and they have been used in the transition metal-catalyzed aerobic oxidation [10,11]. However, the aerobic oxidation with the gaseous reagents that are not easily stored and taken is incompatible with many common functional groups and suffers from some environmental problems for use of harmful transition metals. Water is a green and cheap medium or reactant for chemical transformation [12–14], the bench-stable waters, $H_2{}^{18}O$ and $H_2{}^{17}O$, are idea oxygen isotope sources, and they have been used in labeling of organic molecules [15–20]. The direct conversion of widespread C=O bonds into C=^{18}O and C=^{17}O bonds with $H_2{}^{18}O$ and $H_2{}^{17}O$ as the oxygen-isotopically labeled sources is simple, convenient and environmentally friendly. Furthermore, direct C=O to C=^{18}O or C=^{17}O conversion in a single step leading to labeled compounds should alleviate synthetic burdens without the need for resynthesis. Although the oxygen-isotopical labeling of carbonyls in aldehydes and ketones in the presence of acid was reported before, the labeling rates for ketones were lower, and the scope of substrates was limited [21].

Visible light photocatalysis has become a thriving area of chemical research for its simplicity, economy and reaction novelty [22–30], and the efficiency of reactions highly depends on the suitable photocatalysts [31–34]. The existing photocatalysts mainly are precious transition-metal complexes [35–37] and elaborate organic dyes [38]. Very recently, we have developed the efficient and environmentally friendly light and oxygen-enabled sodium trifluoromethanesulfinate-mediated selective aerobic oxidations of alkyl arenes and alcohols for the first time [39,40]. Later, several research groups used our photocatalytic systems to develop some useful reactions [41–45]. Here, we want to explore a new strategy for direct oxygen-isotopic labeling of carbonyls in ketones and aldehydes (**1**) with oxygen-isotopic waters ($H_2{}^{18}O$ or $H_2{}^{17}O$) by using our photocatalytic systems (Scheme 1A). In our previous in-

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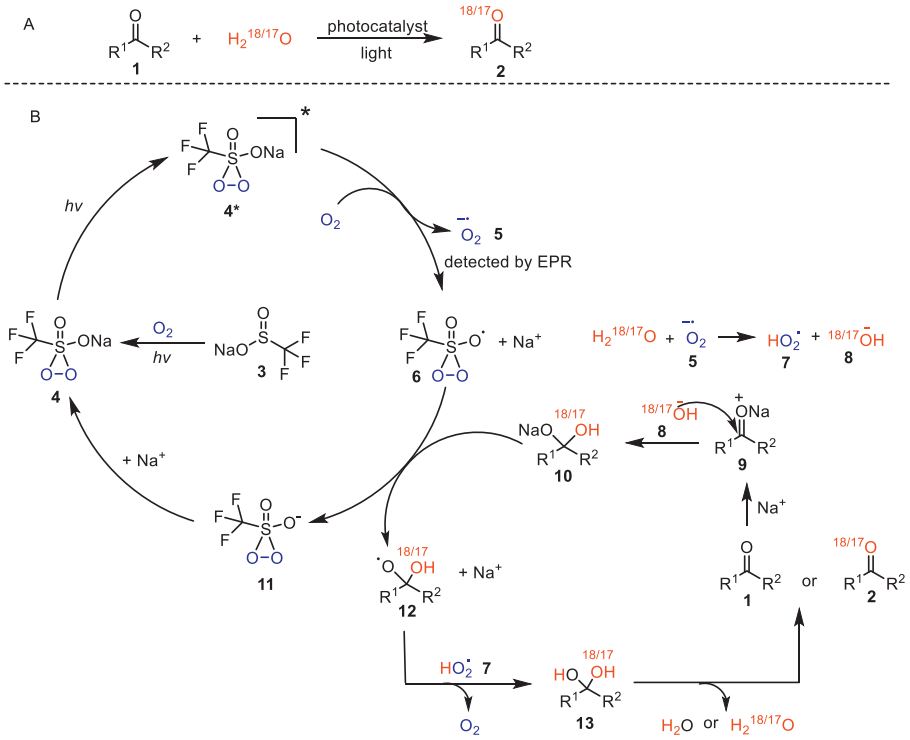


Scheme 1. Our design on photocatalytic direct oxygen-isotopic labeling of carbonyls in ketones and aldehydes with oxygen-isotopic waters. (A) Reaction route. (B) Proposed catalytic cycle for the photoredox-catalyzed protocol.

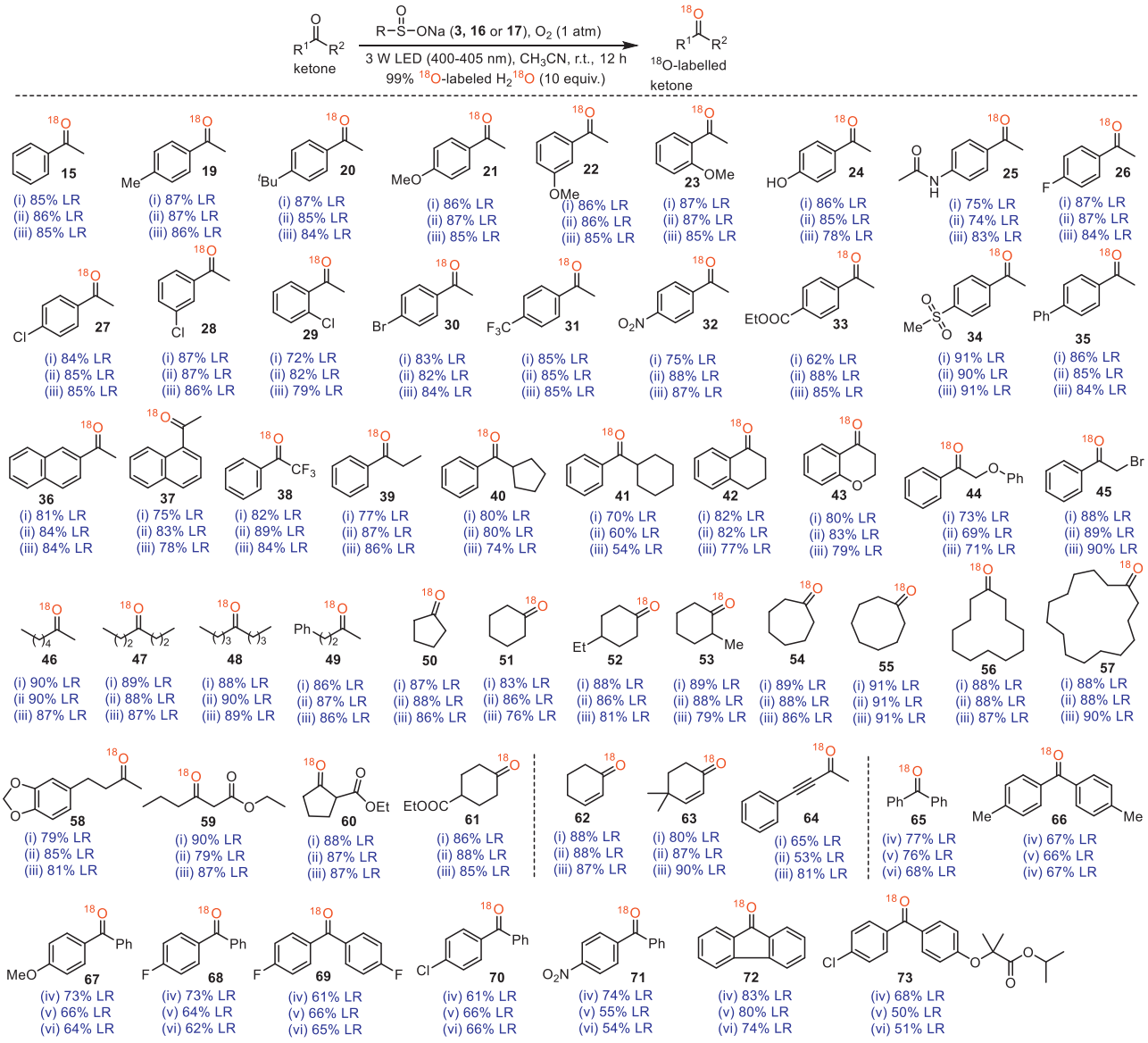
vestigations [39,40], we found that the *in situ* formed pentacoordinate sulfide (**4**) derived from sodium trifluoromethanesulfinate (**3**) and oxygen could act as the photocatalyst. A detailed description of our proposed mechanistic cycle is outlined in Scheme 1B. Initial photoexcitation of **4** would generate **4***, and single-electron transfer (SET) of **4*** to oxygen would lead to superoxide anion radical **5** and radical **6** leaving Na^+ (At this time, two electron-deficient groups, radical **6** and Na^+, should be separated each other). A proton transfer from oxygen-isotopic water to **5** would form radical **7** and oxygen-isotopic hydroxyl anion (**8**) [38], complexation of carbonyl compound (**1**) with Na^+ would give **9**, and nucleophilic attack of **8** to **9** would lead to **10**. SET of **10** to **6** would provide **11** freeing radical **12** and Na^+, and combination of **11** with Na^+ would regenerate **4**. Meanwhile, transfer of hydrogen radical in **7** to **12** would afford hydrate **13** releasing oxygen, and dehydration of **13** would give the oxygen-isotopically labeled carbonyl compound (**2**) or unlabeled **1**. Addition of excess amount of oxygen-isotopic water (10 equiv.) in the reaction system would greatly improve yield of **2**.

With this mechanistic design in hand, we first screened various conditions for ^{18}O-labeling of acetophenone (**14**) (see Tables S1-S7 in Supporting information for details). Here, we summary some key reaction parameters (Table 1). The results showed that the conditions, using 2 mol% sodium trifluoromethanesulfinate (**3**) relative to **14** as the precursor of photosensitizer, acetonitrile as the solvent with irradiation of a 3 W light emitting diode (LED) bulb (400–405 nm) under oxygen atmosphere (1 atm), gave ^{18}O-labeled acetophenone (**15**) in 85% ^{18}O-labeling rate (LR) with 15% of unlabeled acetophenone (**14**) remaining without occurrence of any by-product (entry 1). When 5 mol% sodium benzenesulfinate (**16**) or 10 mol% sodium ethanesulfinate (**17**) replaced 2 mol% **3** as the precursor of photosensitizer, and 86% and 85% LRs were provided, respectively (entries 2 and 3). This transformation did not work in the presence of 10 mol% sodium trifluoromethanesulfonate (CF_3SO_3Na) (**18**) instead of **3** (entry 4). No ^{18}O-labeled product was observed in the absence of sulfinate (entry 5). Irradiation with 530–535 nm LED could not induce this transformation (entry 6). When 450–455 nm, 420–425 nm, 380–385 nm LED or compact fluorescent light (34 W) bulbs were used as the light sources, 82%, 82%, 79% and 75% LRs were afforded, respectively (entries 7–

Table 1
Investigations of key reaction parameters.[a]

Entry	Variation of the standard condition	^{18}O-Labeling rate (%)
1	None	85
2	5 mol% $PhSO_2Na$ (**16**) instead of **3**	86
3	10 mol% $EtSO_2Na$ (**17**) instead of **3**	85
4	10 mol% CF_3SO_3Na (**18**) instead of **3**	NR
5	Without sulfinate	NR
6	530–535 nm LED instead of 400–405 nm LED	NR
7	450–455 nm LED instead of 400–405 nm LED	82
8	420–425 nm LED instead of 400–405 nm LED	82
9	380–385 nm LED instead of 400–405 nm LED	79
10	Compact fluorescent light (34 W)	75
11	Without light	NR
12	Air (1atm) instead of oxygen	82
13	Ar atmosphere instead of oxygen	NR
14	CH_2Cl_2 instead of CH_3CN	78
15	$ClCH_2CH_2Cl$ instead of CH_3CN	73
16	Tetrahydrofuran instead of CH_3CN	69
17	CH_3COOEt instead of CH_3CN	59
18	DMSO instead of CH_3CN	58

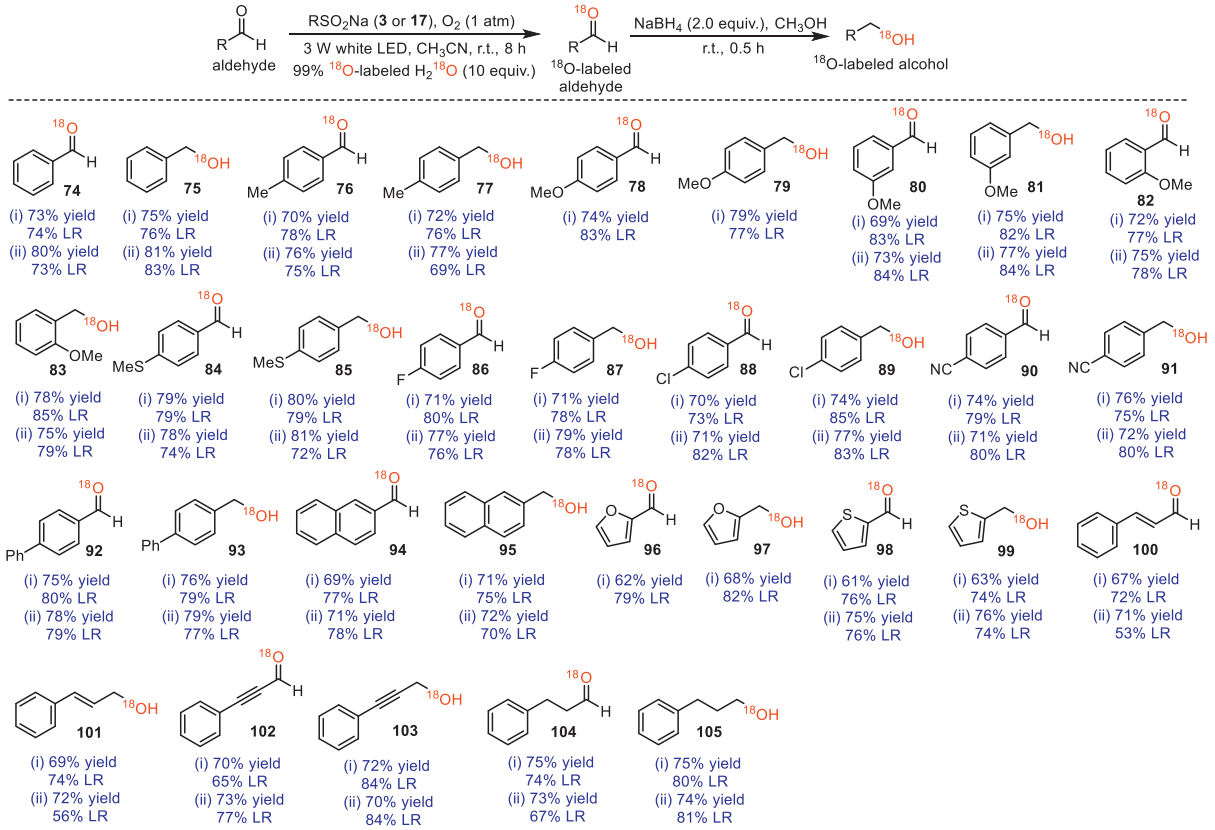
[a] Reaction conditions: acetophenone (**14**) (0.1 mmol), **3**, **16**–**18** (2–10 mol%), 99% ^{18}O-labeled $H_2{}^{18}O$ (1.0 mmol, 10 equiv.), solvent (1.0 mL) at room temperature for 12 h. The ^{18}O-labeling rates (LRs) were determined by GC–MS (See Supporting information for calculation of ^{18}O-labeling rates (LRs)). NR = no reaction.



Scheme 2. Investigations of substrate scope on the ^{18}O-labeling of ketones. Reaction conditions: ketone (**1**) (0.1 mmol), 99% ^{18}O-labeled $H_2{}^{18}O$ (1.0 mmol, 10 equiv.), MeCN (1.0 mL) under O_2 atmosphere and light irradiation at room temperature for 12 h. (i) In the presence of 2 mol% CF_3SO_2Na (**3**). (ii) In the presence of 5 mol% $PhSO_2Na$ (**16**). (iii) In the presence of 10 mol% $EtSO_2Na$ (**17**). (iv) In the presence of 25 mol% CF_3SO_2Na (**3**). (v) In the presence of 25 mol% $PhSO_2Na$ (**16**). (vi) In the presence of 50 mol% $EtSO_2Na$ (**17**). The ^{18}O-labeling rates (LRs) were determined by GC–MS (see Supporting information for calculation of ^{18}O-labeling rate (LR)).

10). This transformation was not performed without irradiation of light (entry 11). 82% LB was provided with air instead of oxygen atmosphere (entry 12). This transformation did not occur in the absence of oxygen (entry 13). The results above showed that none was dispensable for oxygen, light and sulfinate in this transformation. Other solvents, dichloromethane (CH_2Cl_2), 1,2-dichloroethane ($ClCH_2CH_2Cl$), tetrahydrofuran (THF), ethyl acetate (CH_3COOEt) and dimethyl sulfoxide (DMSO), were attempted (entries 14–18), and they were inferior to acetonitrile. More investigations on the reaction parameters were performed in Tables S1-S7. Therefore, the optimal conditions for the oxygen-isotopic labeling of ketones are as follows: 3 W LED bulb (400–405 nm) as the light source, catalytic amount of sulfinate (2 mol% sodium trifluoromethanesulfinate (**3**), 5 mol% sodium benzenesulfinate (**16**) or 10 mol% sodium ethanesulfinate (**17**)) as the precursor of photosensitizer in acetonitrile under atmosphere of oxygen at room temperature.

Having established the optimal conditions for this ^{18}O-labeling of ketones, we investigated scope of substrates. As shown in Scheme 2, various ketones are amenable to this light and oxygen-enabled sulfinate-mediated selective ^{18}O-labeling strategy, they were performed well, and almost no side-products were observed. First, twenty aryl methyl ketones underwent this ^{18}O-labeling under the optimal conditions in Table 1 (**15**, **19–37**), and three sulfinates (**3**, **16** and **17**) as the precursors of photocatalysts were effective. Substituents on aromatic rings of the aryl methyl ketones did not obviously affect ^{18}O-labeling rates of ketones including neutral (**15**, **35**–**37**, 75%–86% LRs), electron-rich (**19–25**, 74%–87% LRs), weak electron-deficient (**26**–**30**, 72%–87% LRs), and strong electron-deficient (**31**–**34**, 62%–91% LRs) groups. Interestingly, ^{18}O-labeling of **25** containing amide group selectively occurred on the ketone rather than on the amide because hydrate formation of the amide was much more difficult than formation of the ketone hydrate (**13** in Scheme 1). Other carbonyl compounds including carboxylic acids, esters, amides, thioamide, ureas and anhydrides were attempted to perform this ^{18}O-labeling, and they did not work, which indicated that the present method exhibited high

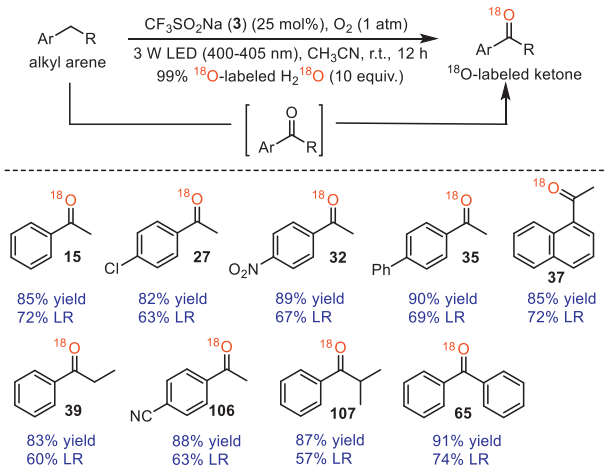


Scheme 3. ^{18}O-Labeling of aldehydes. Reaction conditions: aldehyde (0.2 mmol), 99% ^{18}O-labeled $H_2{}^{18}O$ (2.0 mmol, 10 equiv.), MeCN (1.0 mL) under O_2 atmosphere and irradiation with 3 W white LED at room temperature for 8 h. (i) In the presence of 2.0 mol% CF_3SO_2Na (**3**). (ii) In the presence of 10 mol% $EtSO_2Na$ (**17**). Isolated yields. The ^{18}O-labeling rates (LRs) were determined by GC–MS (see Supporting information for calculation of ^{18}O-labeling rates (LRs)).

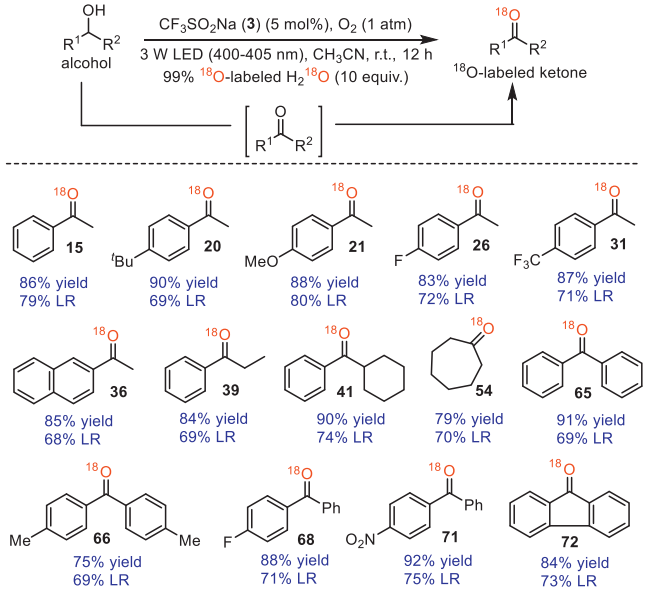
selectivity (Scheme S1 in Supporting information). Subsequently, aryl alkyl ketones containing different alkyls were tested under the standard conditions, and we found that different alkyls including trifluoromethyl (**38**, 82%–89% LRs), ethyl (**39**, 77%–87% LRs), cyclopentyl (**40**, 74%–80% LRs) and cyclohexyl (**41**, 54%–70% LRs) showed some different ^{18}O-labeling efficiency. Next, two cyclic ketones were used as the substrates, and they provided the satisfactory ^{18}O-labeling rates (**42** and **43**, 77%–83% LRs). Ketones containing ether (**44**) and bromo (**45**) groups were tested, and 69%–90% LRs were achieved. Thirteen aliphatic ketones including chain (**46–49**, **58**) and cyclic (**50–57**) ketones were applied, and this ^{18}O-labelings were performed well (76%–91% LRs). Three aliphatic ketones containing ester groups were selectively labeled on the carbonyls of the ketones rather than on those of the ester groups (**59–61**, 79%–90% LRs). We attempted three α,β-unsaturated ketones (**62–64**), and 53%–90% LRs were obtained. Finally, various diaryl ketones were investigated, and we found that more amounts of sulfinates (25 mol% CF_3SO_2Na (**3**), 25 mol% $PhSO_2Na$ (**16**), 50 mol% $EtSO_2Na$ (**17**)) were needed and ^{18}O-labeling rates of the diaryl ketones (**65–73**, 50%–77% LRs) were lower than those of the aryl alkyl ketones and aliphatic ketones above. The results can be attributed to conjugative effect and steric hindrance of two aryls in the diaryl ketones, which is unfavorable for formation of the corresponding hydrates. It is worthwhile to note that the ^{18}O-labeling of fenofibrate (**73**) (an effective marketed hypolipidemic drug [46]) containing an ester group also was selectively performed on the ketone rather than on the ester.

Inspired by the excellent results in Scheme 2, we attempted to extend the substrate scope. First, ^{18}O-labeling of aldehydes was investigated. As shown in Scheme 3, we found that ^{18}O-labeled aldehydes in the presence of 2 mol% CF_3SO_2Na (**3**) or 10 mol% $EtSO_2Na$ (**17**) were major products with small amount of unlabeled aldehydes remaining and newly-formed carboxylic acids appearing. Meanwhile, we also performed one-pot two-step process including ^{18}O-labeling of aldehydes and reduction of the ^{18}O-labeled aldehydes with $NaBH_4$ to the corresponding ^{18}O-labeled alcohols. Eleven aromatic formaldehydes provided satisfactory yields and ^{18}O-labeling rates including neutral (**74**, **75**, **92–95**, 69%–76% yields, 70%–83% LRs), electron-rich (**76–85**, 69%–81% yields, 69%–85% LRs), weak electron-deficient (**86–89**, 70%–79% yields, 73%–85% LRs), and strong electron-deficient (**90** and **91** 71%–76% yields, 75%–80% LRs) groups. Two heteroaryl formaldehydes containing furan or thiophenol rings also were suitable substrates (**96–99**, 61%–76% yields, 74%–82% LRs). Two α,β-unsaturated aldehydes (**100–103**) were attempted, and 67%–73% yields and 53%–84% LRs were provided. An aliphatic aldehyde, 3-phenylpropanal, was used as the substrate, and it gave ^{18}O-labeled products **104** and **105** in 73%–75% yields with 67%–81% LRs.

In our previous research, we developed the light and oxygen-enabled sodium trifluoromethanesulfinate-mediated selective aerobic oxidation of alkyl arenes and secondary alcohols to ketones [39,40]. Here, we attempted sequential aerobic oxidation of alkyl arenes and secondary alcohols to ketones and ^{18}O-labeling of the ketones. As shown in Scheme 4, nine examples were performed with 25 mol% sodium trifluoromethanesulfinate (**3**) as the precursor of photocatalyst, and they afforded the satisfactory results (**15**, **27**, **32**, **35**, **37**, **39**, **65**, **106** and **107**, 82%–91% yields, 57%–74% LRs). As shown in Scheme 5, fourteen secondary alcohols were performed this domino strategy, and excellent yields and satisfactory ^{18}O-labeling rates were obtained (**15**, **20**, **21**, **26**, **31**, **36**, **39**, **41**, **54**, **65**, **66**, **68**, **71** and **72**, 75%–92% yields, 68%–80% LRs). Finally, we explored ^{17}O-labeling of ketones and an aldehyde. Here,



Scheme 4. Aerobic oxidative ^{18}O-labeling of alkyl arenes leading to ^{18}O-labeled ketones. Reaction conditions: alkyl arene (0.1 mmol), 99% ^{18}O-labeled $H_2{}^{18}O$ (1.0 mmol, 10 equiv.), CF_3SO_2Na (**3**) (0.025 mmol, 25 mol%), MeCN (1.0 mL) under O_2 atmosphere and irradiation with 3 W 400–405 nm LED at room temperature for 12 h. Isolated yields. The ^{18}O-labeling rates (LRs) were determined by GC–MS (See Supporting information for calculation of ^{18}O-labeling rates (LRs)).



Scheme 5. Aerobic oxidative ^{18}O-labeling of alcohols leading to ^{18}O-labeled ketones. Reaction conditions: alcohol (0.1 mmol), 99% ^{18}O-labeled $H_2{}^{18}O$ (1.0 mmol, 10 equiv.), CF_3SO_2Na (**3**) (0.025 mmol, 25 mol%), MeCN (1.0 mL) under O_2 atmosphere and irradiation with 3 W 400–405 nm LED at room temperature for 12 h. Isolated yields. The ^{18}O-labeling rates (LRs) were determined by GC–MS (See Supporting information for calculation of ^{18}O-labeling rates (LRs)).

we used lower concentration of $H_2{}^{17}O$ (40% ^{17}O-labeled $H_2{}^{17}O$) because of its high sensitivity in ^{17}O NMR spectroscopy and cost concern. As shown in Scheme 6A, five ketones were effectively labeled with 40% ^{17}O-labeled $H_2{}^{17}O$ (**108**–**112**, 25%–36% LRs). Testosterone (**112**) exhibits some biological activity including adjusting the metabolism of carbohydrates, lipids and proteins and influencing muscle growth and adipogenesis [47]. Subsequently, aldehyde **113** was performed one-pot two-step process including ^{17}O-labeling and reduction with $NaBH_4$, and primary alcohol **115** was obtained in 71% yield with 32% LB. Therefore, the results above showed that our environmentally friendly oxygen-isotopically labeling method was effective. We also attempted ^{18}O-labeling of dicarbonyl compound, 1,3-cyclohexanedion (**116**) with 10 equiv. of 99% ^{18}O-labeled $H_2{}^{18}O$ in the presence of 2 mol% CF_3SO_2Na (**3**) or 10 mol% $EtSO_2Na$ (**17**), and the single ^{18}O-labeled (**117**) and double ^{18}O-labeled (**118**) products were obtained in 37.6% or 37.1% and 60.6% or 58.1% LBs, respectively (Scheme 6B).

We explored mechanism on the photocatalytic direct oxygen-isotopic labeling. In previous study, we conducted density functional theory (DFT) calculations and analysis, and found that pentacoordinate sulfide (**4**) derived from sodium trifluoromethanesulfinate (**3**) and oxygen could act as the photocatalyst [39]. Here, we investigated treatment of $PhSO_2Na$ (**16**) or $EtSO_2Na$ (**17**) with oxygen, and found that formation of the corresponding pentacoordinate sulfides **16′** and **17′** were feasible (Tables S8-S15, Schemes S2 and S3 in Supporting information). When 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was added to the reaction system, no oxygen-isotopic product was observed (Supporting information), which indicated that the present oxygen-labeling underwent a radical process. More controlled experiments were performed (see Supporting information for details). All the results show that the proposed mechanism in Scheme 1 is reasonable.

In conclusion, we have developed a photocatalytic direct oxygen-isotopic labeling protocol, in which ^{18}O and ^{17}O-labelings of carbonyls in ketones and aldehydes were efficient and selective in a single step using oxygen-isotopic waters ($H_2{}^{18}O$ or $H_2{}^{17}O$) as the sources of oxygen isotopes. This strategy was extended to the *in-situ* formed ketones from the aerobic oxidation of alkyl arenes and secondary alcohols. Furthermore, the reduction of the oxygen-isotopically labeled aldehydes with $NaBH_4$ provided the corresponding oxygen-isotopically labeled primary alcohols. The present oxygen-isotopically labeling method shows some advantages including inexpensive and readily available alkanesulfinates as the precursors of photocatalysts, simple and easy operational reaction conditions, use of environmentally friendly chemicals and high selectivity of the reactions. We believe that the oxygen-isotopically labeling method will be widely used in chemistry, biology and medicine fields.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108454.

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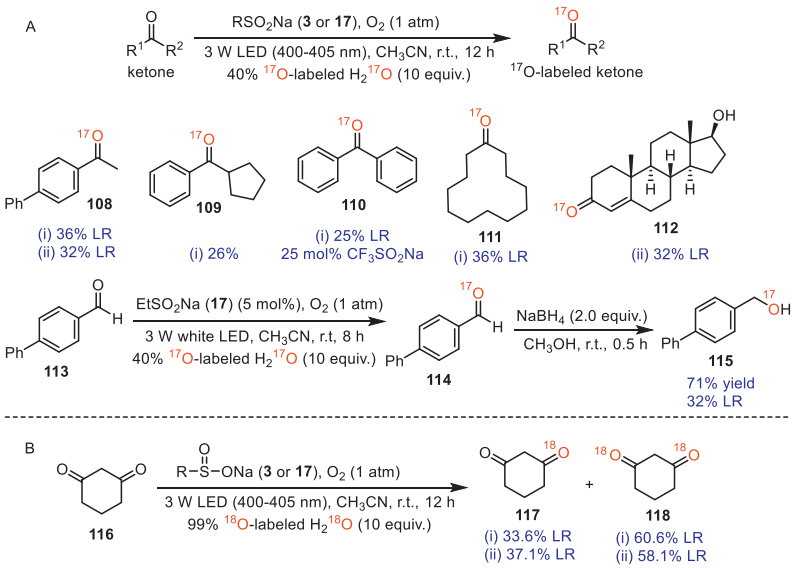

Scheme 6. (A) ^{17}O-Labeling of ketones and an aldehyde. Reaction conditions: ketone (0.1 mmol), 40% ^{17}O-labeled $H_2{}^{17}O$ (1.0 mmol, 10 equiv.), MeCN (1.0 mL) under O_2 atmosphere and irradiation with 3 W white LED at room temperature for 8 h. (i) In the presence of 2.0 mol% CF_3SO_2Na (**3**). (ii) In the presence of 10 mol% $EtSO_2Na$ (**17**). The ^{17}O-labeling rates (LRs) were determined by GC–MS or ESI-MS (See Supporting information for calculation of ^{17}O-labeling rates (LRs)). (B) ^{18}O-Labeling of 1,3-cyclohexanedion. (i) In the presence of 2 mol% CF_3SO_2Na (**3**). (ii) In the presence of 10 mol% $EtSO_2Na$ (**17**). The ^{18}O-labeling rates (LRs) were determined by GC–MS (See Supporting information for calculation of ^{18}O-labeling rates).

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