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A sodium trifluoromethanesulfinate-mediated photocatalytic strategy for aerobic oxidation of alcohols

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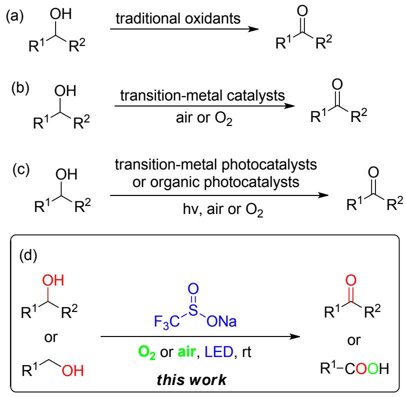
Xianjin Zhu, Can Liu, Yong Liu, Haijun Yang and Hua Fu*

A sodium trifluoromethanesulfinate-mediated photocatalytic strategy for the aerobic oxidation of alcohols has been developed for the first time, and the photoredox aerobic oxidation of secondary and primary alcohols provided the corresponding ketones and carboxylic acids, respectively, in high to excellent yields.

The functions of organic compounds are highly dependent on their functional groups, so the transformation of functional groups is one of the most important chemical processes in organic chemistry. Alcohols are ubiquitous in nature and chemical field, and ketones and carboxylic acids are key chemicals and intermediates in the synthesis of diverse organic compounds.[1] Therefore, the selective oxidation of alcohols represents one of the most addressed problems in organic synthesis. However, the traditional methods for oxidation of alcohols often use stoichiometric amount of environmentally unfriendly oxidants (Scheme 1a)[2] such as metal oxides,[2a] methyl hypervalent iodine,[2b,2c] sulfoxides,[2d] and peroxides.[2e,2f] In sharp contrast, molecular oxygen including oxygen and air is economic and environmentally benign oxidant. However, molecular oxygen in the ground state is inactive to organic substrates, so it should previously be activated to transform into reactive oxygen species such as singlet oxygen, superoxide anion radical, hydrogen peroxide, and hydroxy radical.[3] Although many catalytic aerobic oxidations of alcohols to the corresponding carbonyl compounds have been developed, the expensive and toxic transition metal catalysts, such as ruthenium,[4] palladium[5] copper[6a,b] and cobalt[6c] complexes are usually required (Scheme 1b). Over the past decades, the photocatalytic organic reactions have attracted great attention because they are atom-economic and environmentally friendly alternatives to the conventional catalytic strategies,[7] and some photocatalytic aerobic oxidations of alcohols to carbonyl compounds have been developed (Scheme 1c).[8] However, most organic compounds do not absorb light in the visible light region (400-800 nm), so use of photocatalysts is necessary to realize the organic reactions.[9] The common photocatalysts are the expensive and toxic transition metal complexes[7b,7c,10-12] and elaborate organic dyes,[13-16] which restricts photochemical widespread applications for high cost.



Scheme 1 Oxidation of alcohols to carbonyl compounds.

Very recently, we have developed a light and oxygen-enabled sodium trifluoromethanesulfinate-mediated selective oxidation of C-H bonds.[17] Inspired by the results above, we had speculated that the sodium trifluoromethanesulfinate photocatalytic system could promote aerobic oxidation of alcohols to carbonyl compounds (Scheme 1d). A detailed description of our suggested mechanistic photocatalytic cycle is shown in Figure 1. We imagined that initial light-irradiation of pentacoordinate sulfide intermediate **4** would yield the photoexcited state **4***, and energy transfer (ET) bettwen **4*** and molecular oxygen would regenerate **4** releasing singlet oxygen $^1O_2$ (**5**). Single-electron transfer (SET) of **4*** to oxygen would produce radical **6** and superoxide anion radical **7**.[17] Abstraction of the hydrogen atom at the same carbon of hydroxyl in **1** by **6** would lead to an α-hydroxyl radical **8**[8] releasing **9**, and exchange of the proton in

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Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China. E-mail: fuhua@mail.tsinghua.edu.cn

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9 with Na$^+$ would regenerate photocatalyst **4**. Reaction of **8** with **7** in the presence of a proton would give an α-hydroxy peroxyl radical **10**, and desorption of hydroperoxide from **10** would provide the target product (**2**). Meanwhile, treatment of **8** with O_2 or **5** would afford radical **10'**, and then reaction of **10'** with **1** would form intermediates **8** and **10** mentioned above.

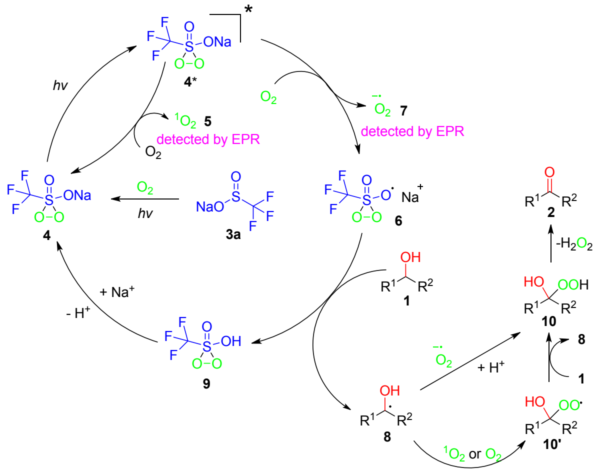
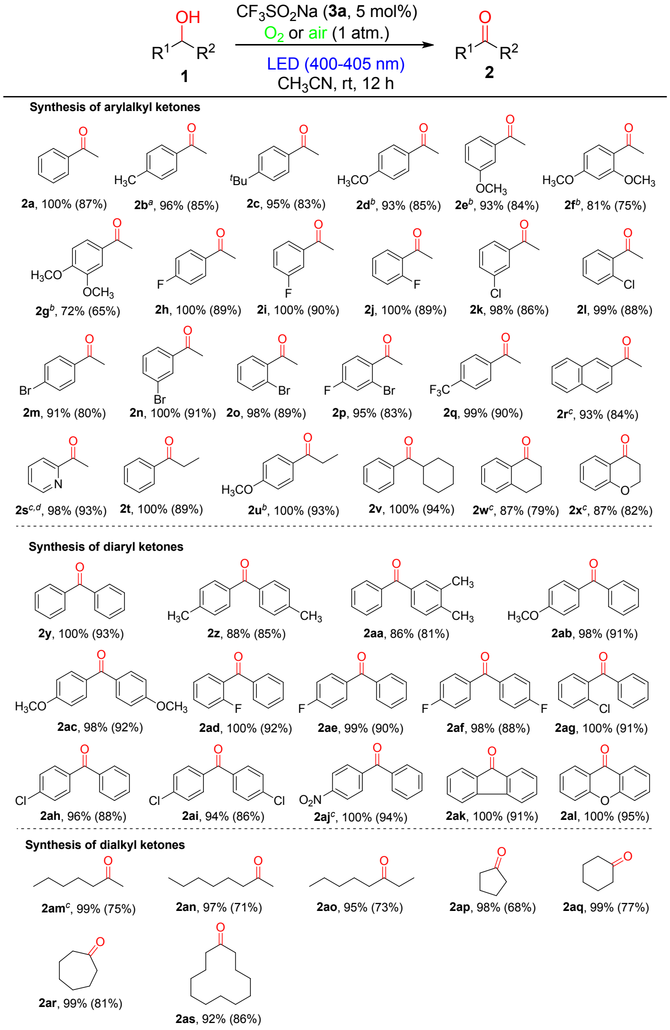
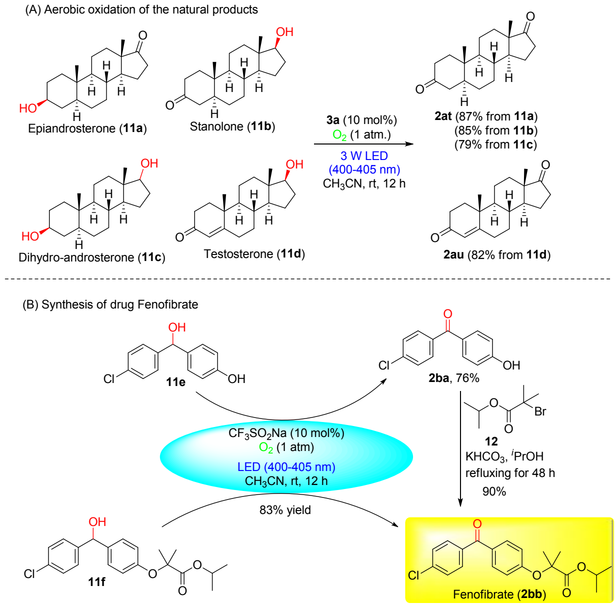


Figure 1 Proposed mechanistic pathway of photocatalytic aerobic oxidation of alcohols (**1**) to carbonyl compounds (**2**).

To verify our hypothesis in Figure 1, aerobic oxidation of 1-(4-fluorophenyl)ethanol (**1h**) to 1-(4-fluorophenyl)ethanone (**2h**) was used as the model to optimize conditions, and the results showed that optimal conditions for the photoredox aerobic oxidation of secondary alcohols to ketones were as follows: 5-25 mol% of sodium trifluoromethanesulfinate (**3a**) as the precursor of photocatalyst, MeCN or DMF as the solvent, LED (400-405 nm) as the light source under oxygen or air atmosphere (1 atm.) at room temperature for 12 h (see Tables S1-S7 in ESI for details). Subsequently, substrate scope for the sodium trifluoromethanesulfinate-mediated photocatalytic aerobic oxidation of secondary alcohols was investigated. As shown in Scheme 2, a myriad of secondary alcohols containing an aryl and an alkyl were first investigated. In general, all the substrates could smoothly perform this aerobic oxidation under the standard conditions giving the corresponding ketones in high to excellent yields (see **2a**-**2x**, 72-100% conversion yields) with good functional group tolerance. The substrates containing methoxyl groups on aryl rings needed 25 mol% sodium trifluoromethanesulfinate (**3a**) as the precursor of photocatalyst and DMF as the solvent (see **2d-2g** and **2u**, 72-100% conversion yields), and those containing two methoxyl groups on aryl rings provided lower yields (see **2f** and **2g,** 75 and 72% conversion yield, respectively). Notably, aerobic oxidation of 1-(*p*-tolyl)ethanol (**1b**) in MeCN gave small amount of 4-acetylbenzoic acid (about 30% conversion yield), while the reaction in DMF afforded 1-(*p*-tolyl)ethanone (**2b**) in 96% conversion yield without 4-acetylbenzoic acid appearing. Moreover, the substrate containing a pyridyl that was subjected to the reaction under LED (400-405 nm) irradiation exhibited lower reactivity, and a 98% conversion yield was provided under irradiation of LED (380-385 nm) (see **2s**). It should be noted that no obvious steric effect and electronic effect were observed for this transformation. Subsequently, the secondary alcohols containing two aryl groups were investigated, and they afforded excellent yields under the standard conditions (see **2y**-**2al,** 86-100% conversion yields). However, the substrates containing methyl on the aryl rings gave slightly low yields because of oxidation of small amounts of methyl to carboxyl (see **2z** and **2aa,** 88% and 86% conversion yields, respectively). Next, the photocatalytic aerobic oxidations of aliphatic secondary alcohols including acyclic and cyclic alcohols were surveyed, and they were also suitable substrates giving the corresponding products (see **2am-2as**) in excellent conversion yields (92-99%). Gratifyingly, the present reaction could tolerate various functional groups including ether, CF_3 and nitro groups, C-F, C-Cl and C-Br bonds and *N*- and *O*-heterocycles.



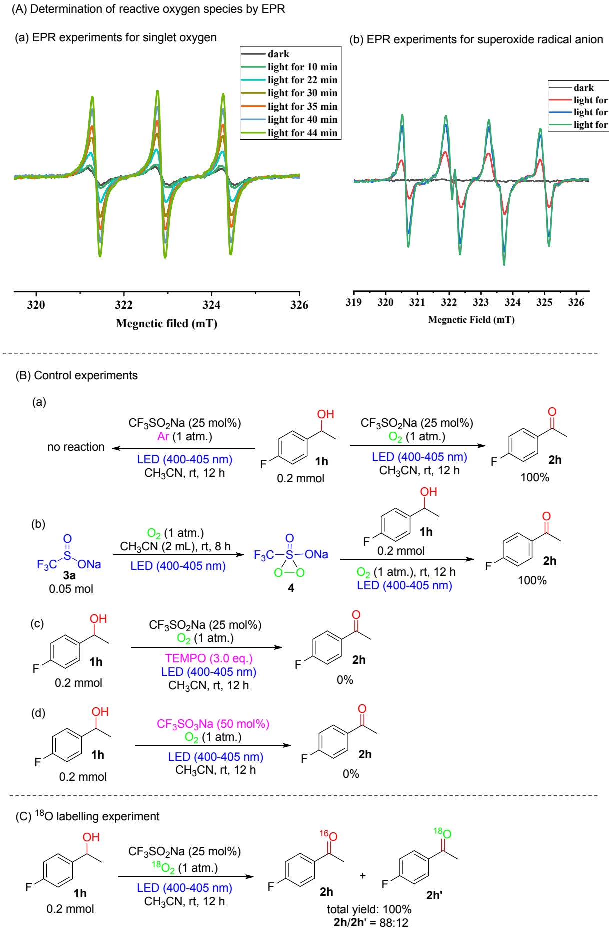
Scheme 2 Substrate scope for the photocatalytic aerobic oxidation of secondary alcohols (**1**) to ketones (**2**). Reaction conditions: under O_2 or air atmosphere (1 atm.), secondary alcohol (**1**) (0.1 mmol), CF_3SO_2Na (**3a**) (5 mol%), MeCN (1.0 mL), room temperature (~25 °C), time (12 h) in a sealed tube under irradiation of 3 W LED (400-405 nm). The conversion yields were determined by GC-MS using dodecane as the internal standard (isolated yields in the parentheses). ^{a}Using DMF (1.0 mL) as the solvent. ^{b}Using DMF (1.0 mL) as the solvent in the presence of 25 mol% CF_3SO_2Na (**3a**). ^{c}In the presence of 10 mol% CF_3SO_2Na (**3a**). ^{d}Using 3 W LED (380-385 nm) as the light source.



Scheme 3 Applications of our method in late-stage modifications of natural products and synthesis of fenofibrate **(2bb).**

To further demonstrate the utility of this protocol, we performed the late-stage modifications of four natural products (Scheme 3A). To our delight, the biologically relevant natural products[18] (epiandrosterone (**11a**), stanolone (**11b**), dihydro-androsterone (**11c**) and testosterone (**11d**)) underwent the selective aerobic oxidation giving the corresponding ketones (**2at** and **2au**) in high yields (79-87%). Finally, we prepared an effective marketed hypolipidemic drug, fenofibrate (**2bb**)[19] by using the present method (Scheme 3B). Aerobic oxidation of **11e** provided ketone **2ba** in 76% yield, and coupling of **2ba** with **12** in the presence of base gave fenofibrate (**2bb**) in 90% yield. The other route is aerobic oxidation of **11f** leading to **2bb** in 83% yield.

To explore reaction mechanism on the sodium trifluoromethanesulfinate-mediated photocatalytic aerobic oxidation of secondary alcohols (**1**) to ketones (**2**), some experiments were carried out as follows: (A) To confirm the species of active oxygen involved in the aerobic oxidation, we performed the electron paramagnetic resonance (EPR) experiments. When a solution of sodium trifluoromethanesulfinate (**3a**) and 2,2,6,6-tetramethylpiperidin-4-one (TMPD) as the trapping agent of $^{1}O_2$ in acetonitrile was irradiated with full wavelength light (400-700 nm) under oxygen atmosphere, we found that the characteristic signal of $^{1}O_2$ adduct with TMPD gradually became strong with extension of irradiation time (Scheme 4Aa); When solution of **3a** and 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as the trapping agent of $O_2^{\bullet-}$ in acetonitrile was irradiated with the full wavelength light under oxygen atmosphere, we also observed a characteristic signal of $O_2^{\bullet-}$ adduct with DMPO (Scheme 4Ab). (B) Several control experiments were conducted as follows: (a) No reaction occurred when 1-(4-fluorophenyl)ethanol (**1h**) was treated under argon atmosphere instead of oxygen atmosphere, and the subsequent reaction under oxygen atmosphere gave **2h** in a quantitative conversion yield (Scheme 4Ba), which indicated that oxygen plays an important role in this transformation; (b) After irradiation of **3a** in acetonitrile with 3 W LED (400-405 nm) for 8 h under oxygen atmosphere, ^{19}FNMR spectrum showed **3a** was converted into **4**,[17] then **1h** was added to the system, and a continued irradiation under the same condition for 8 h provided **2h** in a quantitative conversion yield (Scheme 4Bb). The result indicated that **4** could be the actual photocatalyst for this transformation; (c) As shown in Scheme 4Bc, the reaction did not work in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical scavenger, which showed that a radical pathway can be involved in the transformation in Scheme 2. (C) To further understand the role of O_2 for the reaction, isotopic labelling experiment was carried out (Scheme 4C). When $^{18}O_2$ replaced $^{16}O_2$ as the oxygen source, **2h** containing ^{16}O-carbonyl was a dominated product, which indicated that oxygen of carbonyl in **2h** was from hydroxyl of **1h** rather than O_2. Based on the experiments above, we rationalized that the proposed mechanism in Figure 1 is reasonable.



Scheme 4 Investigations on mechanism for the photocatalytic aerobic oxidation of secondary alcohols (**1**) to ketones (**2**).

Inspired by the excellent results above, we next investigated photocatalytic aerobic oxidation of primary alcohols to carboxylic acids. As shown in Scheme 5, arylmethanols were first attempted as the substrates, and the corresponding aryl formic acids were obtained in high to excellent yields with good functional group tolerance (see **13a-13j**, 81-96% yields). Three

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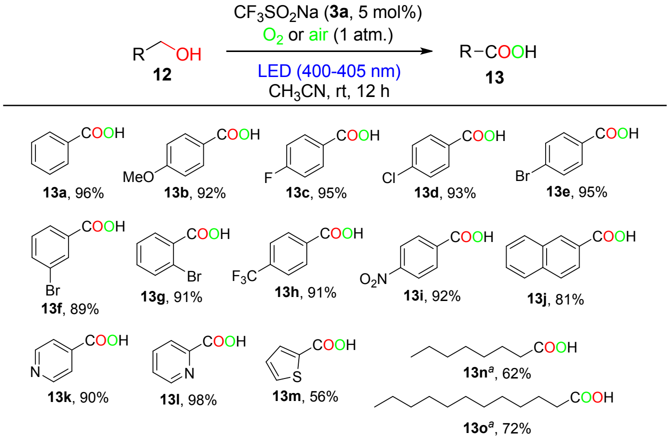
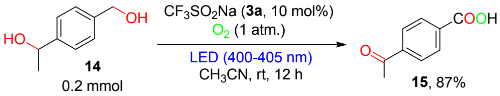
heteroarylmethanols, pyridin-4-ylmethanol, pyridin-2-ylmethanol and thiophen-2-ylmethanol, were attempted as the substrates, and the first two substrates provided excellent yields (see **13k** and **13l**, 90% and 98% yields, respectively). However, thiophen-2-ylmethanol only gave 56% yield because of presence of sulfur atom (see **13m**). Subsequently, two aliphatic primary alcohols were used in the photocatalytic aerobic oxidation, and they also provided the satisfactory results (see **13n** and **13o**, 62% and 72% yields, respectively). Therefore, our sodium trifluoromethanesulfinate-mediated photocatalytic strategy is very useful method for the aerobic oxidation of primary alcohols to carboxylic acids.



Scheme 5 Substrate scope for the photocatalytic aerobic oxidation of primary alcohols (**12**) to carboxylic acids (**13**). Reaction conditions: under O_2 or air atmosphere (1 atm.), primary alcohol (**12**) (0.1 mmol), CF_3SO_2Na (**3a**) (10 mol%), MeCN (1.0 mL), room temperature (~25 °C), time (12 h) in a sealed tube under irradiation of LED (400-405 nm). Isolated yields. [a]Time (48 h).

Finally, we surveyed the photocatalytic aerobic oxidation of alcohol **14** containing two different kinds of hydroxyls (Scheme 6), and product **15** containing a carbonyl and a carboxyl was obtained in 87% isolated yield. The result showed that our method was very practical for synthesis of multi-functional compounds.



Scheme 6 Photocatalytic aerobic oxidation of alcohol containing two different kinds of hydroxyls.

In summary, we have developed a highly efficient sodium trifluoromethanesulfinate-mediated photocatalytic aerobic oxidation of alcohols for the first time and found that the *in-situ* formed pentacoordinate sulfide derived from sodium trifluoromethanesulfinate and oxygen acted as the photocatalyst. The photoredox aerobic oxidation of secondary and primary alcohols provides the corresponding ketones and carboxylic acids, respectively, in high to excellent yields. We believe that the efficient and practical method will be widely used in organic synthesis.

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Conflicts of interest

There are no conflicts to declare.

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