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Organo-photocatalytic C–H bond oxidation: an operationally simple and scalable method to prepare ketones with ambient air†

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Oxidative C–H functionalization with O₂ is a sustainable strategy to convert feedstock-like chemicals into valuable products. Nevertheless, eco-friendly O₂-utilizing chemical processes, which are scalable yet operationally simple, are challenging to develop. Here, we report our efforts, *via* organo-photocatalysis, in devising such protocols for catalytic C–H bond oxidation of alcohols and alkylbenzenes to ketones using ambient air as the oxidant. The protocols employed tetrabutylammonium anthraquinone-2-sulfonate as the organic photocatalyst which is readily available from a scalable ion exchange of inexpensive salts and is easy to separate from neutral organic products. Cobalt(II) acetylacetonate was found to be greatly instrumental to oxidation of alcohols and therefore was included as an additive in evaluating the alcohol scope. The protocols employed a nontoxic solvent, could accommodate a variety of functional groups, and were readily scaled to 500 mmol scale in a simple batch setting using round-bottom flasks and ambient air. A preliminary mechanistic study of C–H bond oxidation of alcohols supported the validity of one possible mechanistic pathway, nested in a more complex network of potential pathways, in which the anthraquinone form – the oxidized form – of the photocatalyst activates alcohols and the anthrahydroquinone form – the relevant reduced form of the photocatalyst – activates O₂. A detailed mechanism, which reflected such a pathway and was consistent with previously accepted mechanisms, was proposed to account for formation of ketones from aerobic C–H bond oxidation of both alcohols and alkylbenzenes.

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Introduction

Ketone is a chemical function group frequently found in bioactive molecules,¹ and ketone-containing compounds are routinely employed as building blocks in syntheses of complex molecules.² Among different means of preparation,³ C–H bond oxidation, converting alcohols and alkylbenzenes to corresponding ketones, offers a direct route towards this class of compounds. Despite successes of traditional stoichiometric oxidants,^{4,5} molecular oxygen (O₂), because of its abundance, low cost, and environmentally benign nature, is preferred as a waste-free oxidant for C–H bond oxidation of alkylbenzenes and alcohols.⁶ However, due to the inertness of O₂ towards closed-shell organic molecules and limited solubility of O₂ in organic solvents under ambient pressure,⁷ a unified approach, capable of delivering scalable aerobic C–H bond oxidation in an operationally simple fashion such as batch setting with ambient air, is highly valuable but challenging to develop. Many thermal methods for C–H bond oxidation of alcohols and alkylbenzenes

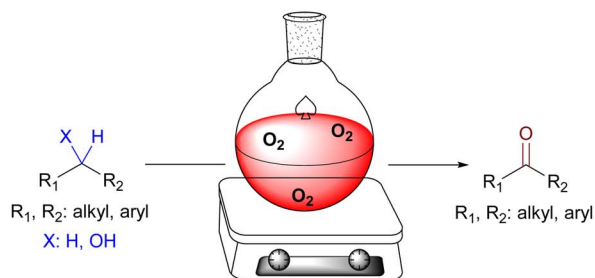
require pure O₂ atmosphere or high pressure of inert-gas-diluted O₂,⁸ elevated temperature,⁹ toxic/corrosive solvents,¹⁰ expensive transition metal catalysts,¹¹ and prolonged reaction time¹² which are undesirable from cost and safety considerations especially when large-scale applications are concerned (Fig. 1A).

Over the last two decades, various photocatalytic modes of activation have emerged to activate otherwise unreactive molecules through intermediacy of C-centered organic radicals.¹³ By rendering organic molecules open-shell, energetic barriers was significantly lowered for O₂ incorporation step into organic substrates.¹⁴ Many photocatalytic procedures, capable of activating C–H bonds in unactivated aliphatic alcohols and less electron-rich alkylbenzene derivatives, relied on indirect hydrogen atom transfer catalysis (HAT)¹⁵ due to inertness of the aforementioned substrates toward photo-induced electron transfer. In this activation mode, “secondary” reactive species, which activate C–H bonds of organic substrates such as singlet O₂ or heteroatom-centered radicals, formed from O₂ and radical precursors upon quenching a photocatalyst in its excited state.¹⁶ These redox cascades, despite being elegant and capable of effectively harnessing alcohols and alkylbenzenes into many chemical transformations, might be kinetically compromised from a low concentration of “secondary” reactive species,

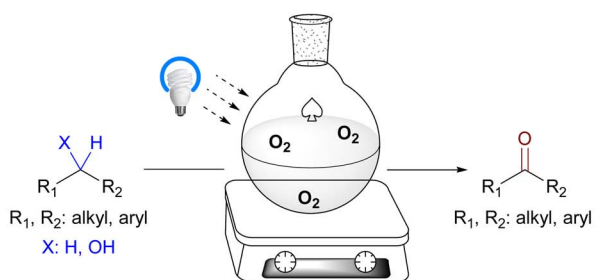
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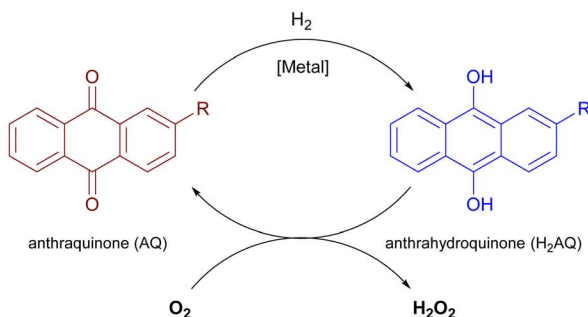
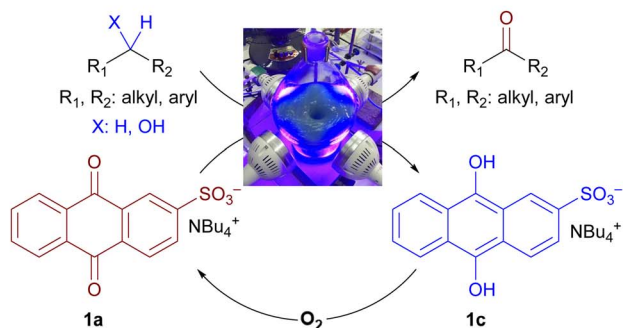


A. Thermal Aerobic C-H Oxidation: Scalability Challenges in Batch

✓ Operationally Simple ✗ Problematic Scalability in Batch

✗ Limited [O₂] ✗ Expensive Transition Metal Catalysts ✗ Inefficient O₂ Activation**B. Photocatalytic Aerobic C-H oxidation: Scalability Challenges in Batch**

✓ Operationally Simple ✗ Problematic Scalability in Batch

✗ Limited [O₂] ✗ Limited Light Penetration ✗ Inefficient Substrate Activation**C. Industrial Application of Anthraquinone: H₂O₂ Production**✓ Facile H₂AQ-mediated O₂ activation**D. Design Plan: Scalable Aerobic AQ-catalyzed C-H Bond Oxidation**

✓ Operationally Simple

✓ Scalability in Batch

✓ Direct Substrate Activation ✓ Facile O₂ Activation ✓ Available, easy-to-separate Catalyst

Fig. 1 Challenges in developing scalable yet operationally simple protocols for catalytic C–H bond oxidation with ambient air.

rendering substrate activation step inefficient. This, along with inherent challenges associated with an aerobic photochemical process such as light penetration¹⁷ and low dissolved oxygen concentration,⁷ might hamper the scalability of developed aerobic photocatalytic procedures (Fig. 1B). Indeed, scalable yet operationally simple procedures for aerobic C–H bond photo-oxidation of alcohols and alkylbenzenes are rarely reported.

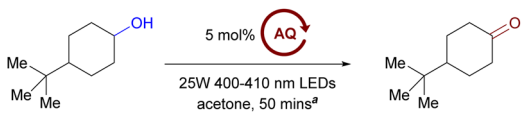
We anticipated that an efficient catalytic approach for C–H bond photo-oxidation would require a facile direct hydrogen atom transfer (HAT) between the excited state of the photocatalyst and organic substrates. Accordingly, we expected that a strong thermodynamic driving force for HAT step would be necessary for efficient catalysis. In addition, an effective oxidative recycling of the photocatalyst by O₂ is crucial to the overall success of the catalytic protocol. Anthraquinone (AQ) derivatives have been employed as mediators for industrial hydrogen peroxide production, which takes advantages of a spontaneous aerobic oxidation of anthrahydroquinone (H₂AQ) – one reduced form of anthraquinone (Fig. 1C).¹⁸ Therefore, we envisioned that thanks to the facile redox reaction of H₂AQ with O₂, AQ derivatives, which are commercially and synthetically available with diverse substituents and substitution patterns,¹⁹ represent a rich pool of potential catalysts for oxidative transformations with O₂. Furthermore, the triplet state of photoexcited AQ* possesses high triplet energy of 62.9 kcal mol^{−1} and therefore should have enough thermodynamic driving force for

a hydrogen atom transfer with alcohols and alkylbenzenes.^{20,21} Therefore, in this study, we sought to develop scalable yet operationally simple protocols for aerobic C–H bond oxidation of alcohols and alkylbenzenes based on photocatalytic reactivity of anthraquinone derivatives (with an oversimplified design plan outlined tentatively in Fig. 1D).

Results and discussion

We initiated our study by subjecting different anthraquinone derivatives to catalytic oxidation of 4-*tert*-butylcyclohexanol (commercially available as mixture of *cis* and *trans* diastereomers) at 2 mmol scale using ambient air as the oxidant and acetone as the solvent (Table 1). To our delight, while catalytic oxidations mediated by AQ derivatives with strong electron-donating substituents provided diminished yields of ketones (Table 1, entries 1–3, 0–11% yield), those employed AQ derivatives with weak electron-donating or electron-withdrawing substituents afforded higher than 30% yield of ketone and with almost 100% selectivity (Table 1, entries 4–8, 34–54% yield). This was promising, given only 5 mol% of catalysts were used and samples were merely irradiated for 50 min. This result prompted us to try another cheap commercially available anthraquinone derivative, sodium anthraquinone-2-sulfonate monohydrate (2-AQ-SO₃Na·H₂O) which possesses a strong electron-withdrawing group, for catalytic oxidation.

Table 1 Evaluation of anthraquinone derivatives in alcohol oxidation



Entry	AQ derivatives	Conversion ^b	Yield ^b
1	2-NH ₂ -AQ	2%	0%
2	2-OH-AQ	2%	2%
3	2-OMe-AQ	12%	11%
4	2- <i>t</i> -Bu-AQ	42%	38%
5	2-Me-AQ	59%	54%
6	AQ	35%	34%
7	2-Cl-AQ	35%	34%
8	2-AQ-COOH	38%	37%
9	2-AQ-SO ₃ Na·H ₂ O ^c	18%	15%
10	2-AQ-SO ₃ Na·H ₂ O ^d	59%	57%
11	1a	54%	53%
12	1a ^e	100%	94%
13	2-AQ-SO ₃ Na·H ₂ O ^f	100%	90%

^a 2 mmol scale in 10 mL acetone, ambient air, with one 25 W 400–410 nm Lamp. ^b ¹H NMR yield with 1,3,5-trimethoxybenzene as internal standard. ^c Prestir 30 min. ^d With 5 mol% NBu₄Cl, prestir 30 min. ^e With 1 mol% Co(acac)₃. ^f With 5 mol% NBu₄Cl and 1 mol% Co(acac)₃, prestir 30 min.

Nevertheless, due to low solubility of this salt in acetone, only 15% yield of ketone was achieved (Table 1, entry 9). By adding 5 mol% tetrabutylammonium chloride, NBu₄Cl, as a phase transfer catalyst, the catalytic oxidation afforded 57% of ketone (Table 1, entry 10) which is in accordance with catalytic trend of other AQ derivatives (Table 1, entries 4–8). Independent ion exchange between 2-AQ-SO₃Na·H₂O and NBu₄Cl (see ESI†) provided a previously undocumented compound, tetrabutylammonium anthraquinone-2-sulfonate (**1a**) (Fig. 1D), which was as effective at catalysing alcohol oxidation (Table 1, entry 11, 53% yield) as an equimolar mixture of 2-AQ-SO₃Na·H₂O and NBu₄Cl (Table 1, entry 10, 57% yield). Among these three best catalytic systems 2-Me-AQ, an equimolar mixture of 2-AQ-SO₃Na·H₂O and NBu₄Cl, and **1a** (Table 1, entries 5, 10 and 11), we considered **1a** to be most convenient for preparative synthesis for two reasons. First, **1a** is easy to make in large scale, bench-stable, highly soluble, and non-hygroscopic so it should be easier to handle than an equimolar mixture of insoluble 2-AQ-SO₃Na·H₂O and a highly hygroscopic NBu₄Cl salt in both small scale synthesis and upscale synthesis using flow reactors. Second, **1a** is ionic and should be easy to separate from the neutral organic substrates and products by simple filtration through a silica gel plug, while neutral anthraquinone derivatives are notorious for low solubility in conventional organic solvents and might present a purification challenge when used in higher loadings.

For the aforementioned reasons, **1a** was employed for further optimization. We were pleased to find that an inclusion of merely 1 mol% of Co(acac)₃ in catalytic oxidation with **1a** gave full conversion of 4-*tert*-butylcyclohexanol and 94% of ketone (Table 1, entry 12). A similar effect of Co(acac)₃ was also

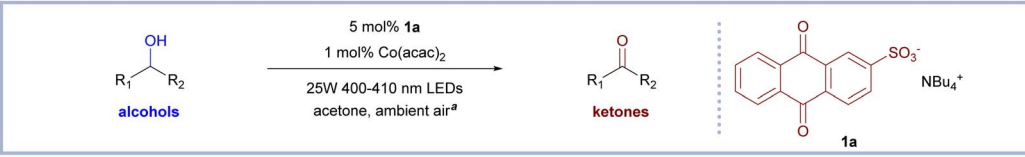
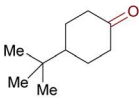
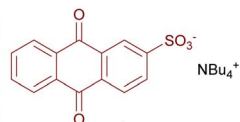
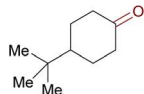
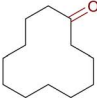
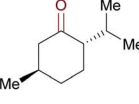
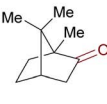
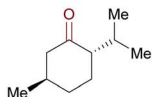
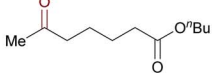
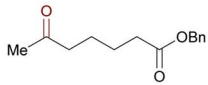
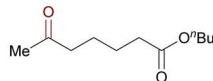
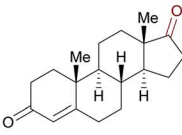
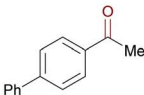
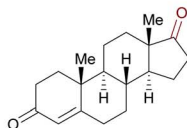
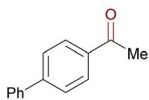
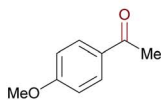
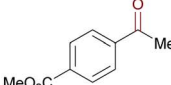
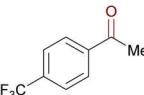
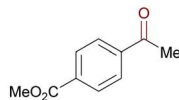
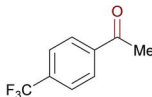
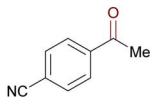
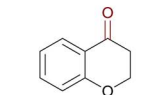
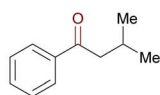
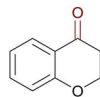
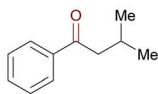
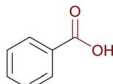
observed when an equimolar mixture of 2-AQ-SO₃Na·H₂O and NBu₄Cl was employed to afford a comparable ketone yield of 90% (Table 1, entry 13).

With the optimized condition in hands, we sought to explore the substrate scope of the developed C–H bond oxidation protocol for alcohol using 5 mol% of **1a** and 1 mol% of Co(acac)₃. Secondary unactivated aliphatic alcohols showed excellent reactivity under the optimized condition to afford ketones in good to excellent yields (Table 2). Catalytic oxidations were fast with virtually full conversion in 1–2 mmol scales within less than 2 h in all cases, even in challenging cases of sterically hindered alcohols (Table 2, entries 6–8, 13, 70–92% yield) which previously required pure O₂ atmosphere and either prolonged irradiation or elevated temperature.^{8c,16a,22} A range of functional groups were well tolerated, including large-ring cyclic secondary alcohol (Table 2, entry 5, 80% yield), tertiary C–H bonds (Table 2, entries 2, 4, 6–8, 12 and 13, 76–92% yield), TBS-protected ether (Table 2, entry 9, 53% yield), ester (Table 2, entries 10 and 11, 78–95% yield), electronically deactivated benzylic C–H bond (Table 2, entry 11, 78% yield), ketone (Table 2, entry 12, 89% yield), and enone (Table 2, entry 13, 80% yield). After assessing the scope of aliphatic alcohols, a variety of secondary benzylic alcohols were subjected to the developed alcohol oxidation protocol. Secondary benzylic alcohols, bearing both electron-donating and electron-withdrawing substituents, was readily oxidized in excellent yields (>90%) in 1–2 mmol scale (Table 2, entries 14–20 and 22–23, 92–99% yield) with time to completion of less than 1 h. Nitro-group-bearing benzylic alcohol (Table 2, entry 21), which is electronically deactivated by a strong electron-withdrawing group and has a relatively colored ketone product, while proved to be challenging to other aerobic photo-oxidation,^{16a} was amenable to our developed procedure to yield 96% of ketone. Secondary benzylic alcohol substrates with aromatic ether (Table 2, entry 23, 99% yield) and tertiary C–H bond (Table 2, entry 24, 94% yield) were well tolerated and afforded excellent yields of ketones. Benzylic alcohol substrates containing benzylic C–H bonds were more challenging with a diminished 72% yield of ketone (Table 2, entry 25), and the analogous oxidation of 1-(4-ethylphenyl)ethan-1-ol (Table 2, entry 26) provided 82% of 1,4-diacetylbenzene, where alcohol oxidation was concurrent with oxygenation of benzylic C–H bonds. As a representative example of primary benzylic alcohol (Table 2, entry 27), catalytic oxidation of benzyl alcohol resulted in a good 70% yield of benzoic acid in 2 mmol scale.

From the results of catalytic oxidation of 1-(4-ethylphenyl)ethan-1-ol (Table 2, entry 26), we noticed the reactivity of benzylic C–H bonds toward oxidation under the standard condition. Further control experiments suggested that while Co(acac)₃ was still instrumental to photochemical aerobic benzylic oxidation, its effect in benzylic oxidation is less dramatic than that in alcohol oxidation (Table 3, entry 28). Therefore, we decided to explore the scope of alkylbenzene oxidation using a sole organocatalytic approach with **1a** as the catalyst and no additives (Table 3). To our delight, ethylbenzene derivatives bearing a variety of functional groups were amenable to catalytic aerobic oxidation with **1a** (Table 3, entries



Table 2 Photocatalytic aerobic C–H bond oxidation of aliphatic and benzylic alcohols

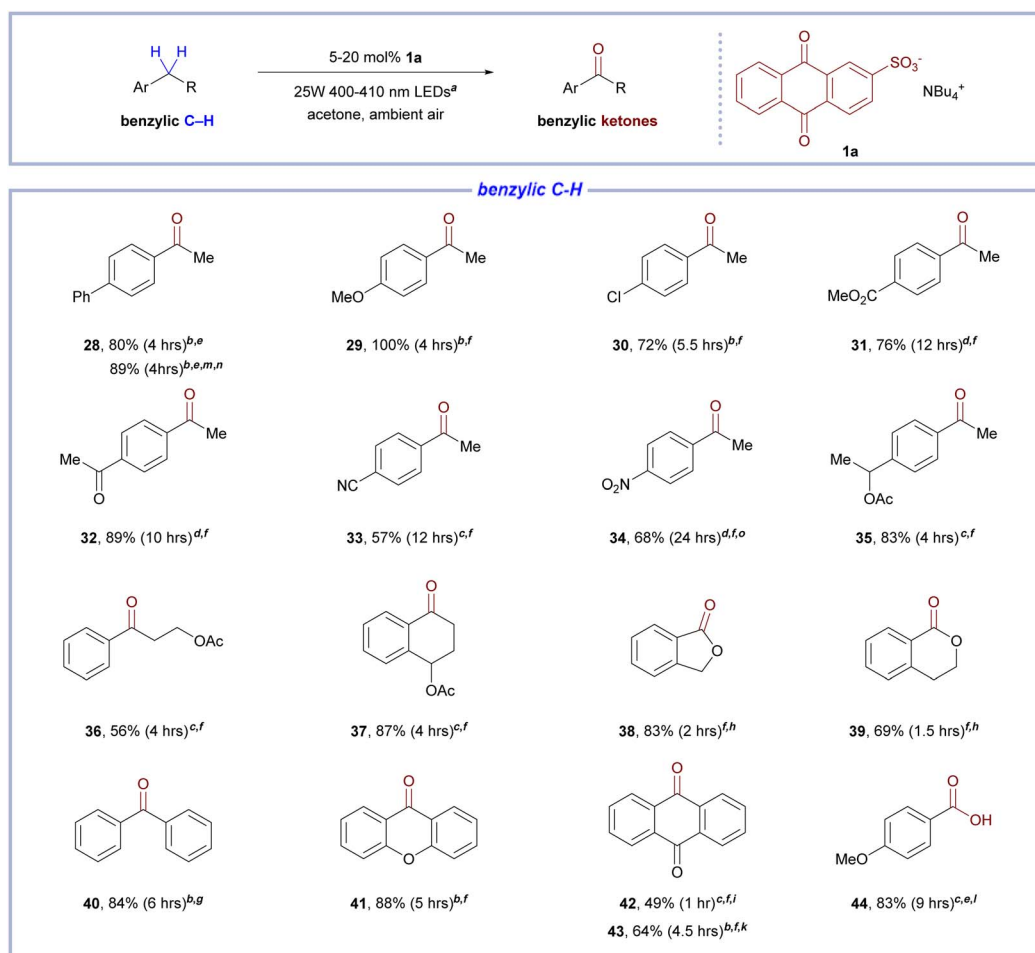
	
aliphatic alcohols	
 2, 91% (50 mins)	 3, 88% (1 hr) ^b
 4, 76% (45 mins)	 5, 80% (1 hr) ^c
 6, 70% (2 hrs)	 7, 91% (40 mins) ^d 8, 92% (40 mins) ^e
 9, 53% (3 hrs) ^c	 10, 95% (1.5 hrs) ^c
 11, 78% (2 hrs) ^c	 12, 89% (45 mins) ^f
 13, 80% (105 mins) ^{c,g}	
benzylic alcohols	
 14, 99% (1hr)	 15, 96% (45 mins)
 16, 94% (40 mins)	 17, 92% (1hr) ^c
 18, 98% (50 mins)	
 19, 92% (45 mins)	 20, 98% (45 mins)
 21, 96% (8 hrs) ^{c,h}	 22, 99% (40 mins)
 23, 99% (45 mins)	
 24, 93% (1.5 hrs)	 25, 72% (1.5 hrs)
 26, 82% (12 hrs) ^{c,i}	 27, 70% (9hrs)

^a 2 mmol scale in 10 mL acetone with one 25 W 400–410 nm LEDs lamp. ^b In MeCN, isolated as 2,4-dinitrophenylhydrazones due to product volatility. ^c 1 mmol scale in 10 mL acetone. ^d From *rac*-borneol. ^e from *rac*-isoborneol. ^f 2 mmol scale in 15 mL acetone. ^g With 3 mol% Co(acac)₃. ^h With two 25 W 400–410 nm LEDs Lamps. ⁱ From 1-(4-ethylphenyl)ethan-1-ol. All yield values are yields of the isolated compounds.

28–34, 57–100% yield). Noticeably, ethylbenzene derivatives with electron-withdrawing groups, which were normally recalcitrant to or absent in scope of other aerobic benzylic photo-oxidation protocols,²³ could be converted to ketones in average to good yields (Table 3, entries 30–34, 57–89% yield). Benzylic substrates with acetyl-protected benzylic alcohols (Table 3, entries 35 and 37, 83–87% yield) underwent aerobic oxidation smoothly to afford good yields of ketones, while oxidation of

a substrate with acetyl-protected alcohol (Table 3, entry 36, 56% yield), which is positioned in close proximity of benzylic C–H bonds, was less effective. Using 2-methoxyanthraquinone (**1b**) as catalyst, oxygenation can be affected in substrates with benzylic C–H bonds that is at alpha position to aliphatic ether (Table 3, entries 38–39, 69–83% yield). Highly activated benzylic C–H substrates with extended conjugate systems in the ketone products were also amenable to catalytic oxidation with **1a**

Table 3 Photocatalytic aerobic benzylic C–H bond oxidation



^a With one 25 W 400–410 nm LEDs lamp. ^b With 5 mol% **1a**. ^c With 10 mol% **1a**. ^d With 20 mol% **1a**. ^e 2 mmol scale in 10 mL acetone. ^f 1 mmol scale in 10 mL acetone. ^g 2 mmol scale in 20 mL acetone. ^h With 5 mol% 2-OMe-AQ in place of **1a**. ⁱ From anthrone. ^k From 9,10-dihydroanthracene. ^l From 4-methylanisole. ^m With 1 mol% Co(acac)₂. ⁿ HPLC yield with 1,4-dimethoxybenzene as internal standard. ^o With two 25 W 400–410 nm LEDs lamps. All yield values are yields of the isolated compounds, unless noticed.

(Table 3, entries 40–43, 49–88% yield). As a representative example of primary alkylbenzenes (Table 3, entry 44), catalytic oxidation of 4-methylanisole resulted in 83% yield of 4-methoxybenzoic acid in 2 mmol scale.

Mechanistic investigation

After evaluating the substrate scope, we sought to study the mechanism by which **1a** catalyzes aerobic C–H bond oxidation of organic substrates. With alcohols as chosen substrates, we conducted a set of control experiments to evaluate the role of reaction variables (Table 4). A significant difference in yields between experiments under air (Table 4, entries 1 and 4, 53–94% yield) and experiments under Ar (Table 4, entries 6, 8 and 9, 5–7% yield) hinted at a critical role of O₂ as the terminal oxidant. A control experiment without **1a** (Table 4, entry 3, 0% yield) confirmed the necessity of **1a** in the optimized procedure, and no-light experiments (Table 4, entries 2, 5, 7 and 10, 0% yield) confirmed an exclusive photochemical, not thermal,

oxidation of alcohols under conditions of the developed protocol. Non-zero yields in control experiments under Ar (Table 4, entries 8 and 9, 5–7% yield) suggested that **1a** in the presence of a light source can oxidize alcohols even in the absence of O₂. Therefore, we investigated closely the direct photochemical reaction of **1a** and alcohols.

A stoichiometric photo-assisted reaction between **1a** and cyclooctanol under inert atmosphere afforded tetrabutylammonium anthrahydroquinone-2-sulfonate (**1c**) as a yellow precipitate (Fig. 2), of which the structural assignment was consistent with ¹H and ¹³C NMR data of the isolated solid (see ESI†). This corresponds to a formal reduction of AQ core by one alcohol molecule. It is worth mentioning that the Hollman group proposed a putative mechanism for aerobic oxidation with sodium anthraquinone-2-sulfonate in which the catalyst cycles between AQ form and 9,10-dihydroxy-9,10-dihydroanthracene form which corresponds to a formal reduction of AQ core by two alcohol molecules.^{24f} We therefore studied the photochemical reaction between **1a** and alcohols



Table 4 Control experiments for photocatalytic alcohol oxidation

Entry	Deviations	Conversion ^b	Yield ^b
1	None	100%	94%
2	No light	0%	0%
3	No 1a	0%	0%
4	No Co(acac) ₃	54%	53%
5	No light, no Co(acac) ₃	0%	0%
6	Under Ar	5%	5%
7	Under Ar, no light	1%	0%
8	Under Ar, no Co(acac) ₃ , 5 mol% 1a	5%	5%
9	Under Ar, no Co(acac) ₃ , 10 mol% 1a	8%	7%
10	Under Ar, no Co(acac) ₃ , no light, 10% 1a	0%	0%

^a 2 mmol scale in 10 mL acetone, ambient air, with one 25 W 400–410 nm LEDs lamp. ^b ¹H NMR yield with 1,3,5-trimethoxybenzene as internal standard.

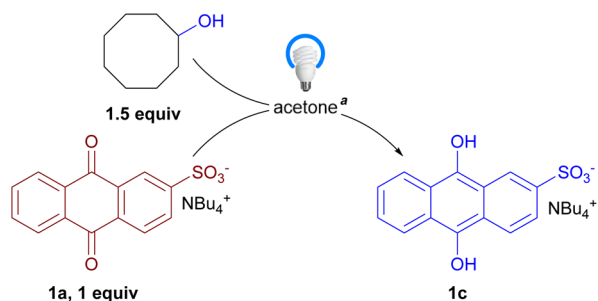


Fig. 2 Photochemical stoichiometric reaction of **1a** and cyclooctanol. ^a 0.4 mmol **1a** and 0.6 mmol cyclooctanol in 6 mL acetone, under argon atmosphere, irradiated by one 25 W 400–410 nm LEDs lamp for 16 h.

under a more catalytically relevant condition in order to address the following mechanistic questions:

(1) Are **1a** and alcohols cleanly converted to **1c** and ketones, respectively, under a catalytically relevant condition?

(2) If **1c** is formed, can **1c** be cleanly oxidized to **1a** by ambient air?

We anticipated that a qualitative test that could detect characteristic features of **1c** and a quantitative test that correlated the amount of **1c** and ketone formed over a range of reaction conversion would unambiguously address question 1. Specifically, a high fidelity of **1a**-to-**1c** and alcohol-to-ketone conversion under catalytically relevant condition would predict a 1 : 1 ratio of **1c** and ketone formed over the course of the photo-oxidation under inert atmosphere.

Indeed, upon irradiating a 0.2 M acetone-d₆ solution of cyclooctanol and 10 mol% **1a** (Fig. 3A) under Ar and taking ¹H NMR of the resultant mixture at indicated time points (Fig. 3B–D), a set of new signals in the aromatic region appeared that were consistent with the structural assignment of **1c**.²⁴ Also, relative intensity between peaks in this set of signals were

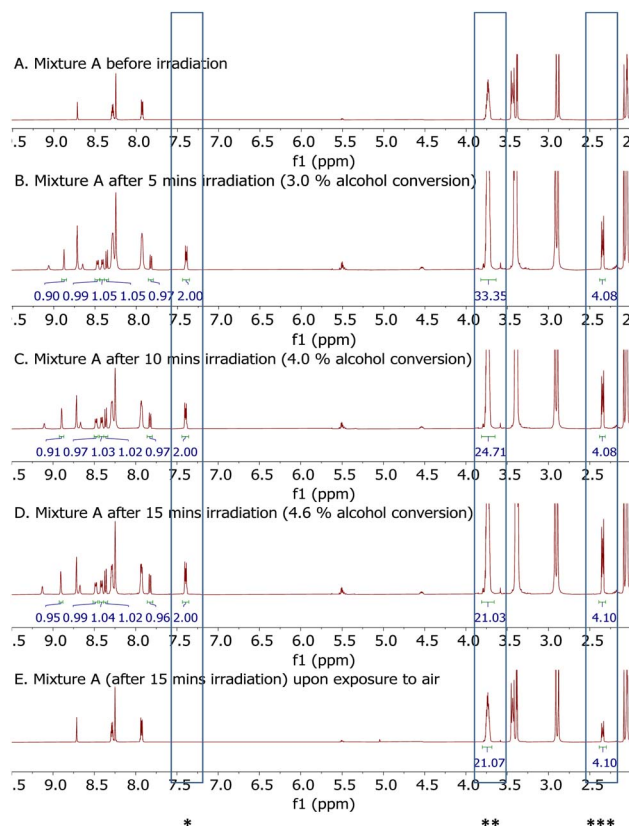


Fig. 3 NMR study of a photochemical reaction between **1a** and cyclooctanol. Condition: 0.016 mmol **1a** (10 mol%) and 0.16 mmol cyclooctanol in 0.8 mL acetone-d₆ (mixture A) in a NMR tube under argon atmosphere, irradiated by one 25 W 400–410 nm LEDs lamp (see ESI†). ***1c**; **cyclooctanol (CH(OH)); ***cyclooctanone (CH₂-CO).

essentially constant over the course of reaction (Fig. 3B–D) which confirmed that this set of signals indeed belonged to a single molecule and did not appear by chance. This set of signals co-evolved with a characteristic signal of cyclooctanone at $\delta = 2.34$ ppm across reaction conversion and a 2 : 1 ratio of intensity between signals at $\delta = 2.34$ ppm of cyclooctanone and $\delta = 7.40$ ppm of **1c** were maintained over the same set of experiments (Fig. 3B–D). This corresponded to 1 : 1 ratio of **1c** and cyclooctanone formed across different reaction conversions. This observation supported a clean conversion of **1a** to **1c** that is concomitant with alcohol oxidation to ketones upon irradiation. Therefore, at least under argon atmosphere, photoirradiation of a mixture of **1a** and alcohols resulted in a clean putative transfer of 2 hydrogen atoms from alcohols to AQ core to form ketone products and H₂AQ core. A quick comparison of NMR data of the final reaction mixture upon exposure to air (Fig. 3E) and that of the initial mixture (Fig. 3A) confirmed a clean oxidation of **1c** to **1a** by ambient air.²⁵ Overall, these observations supported one possible mechanistic pathway for alcohol oxidation in which **1a** functions as an alcohol-activating photocatalyst and **1c**, the reduced form of **1a**, acts as a mediator for O₂ activation (Fig. 4A and B). Based on these, we proposed a detailed mechanistic pathway that reflect both potential

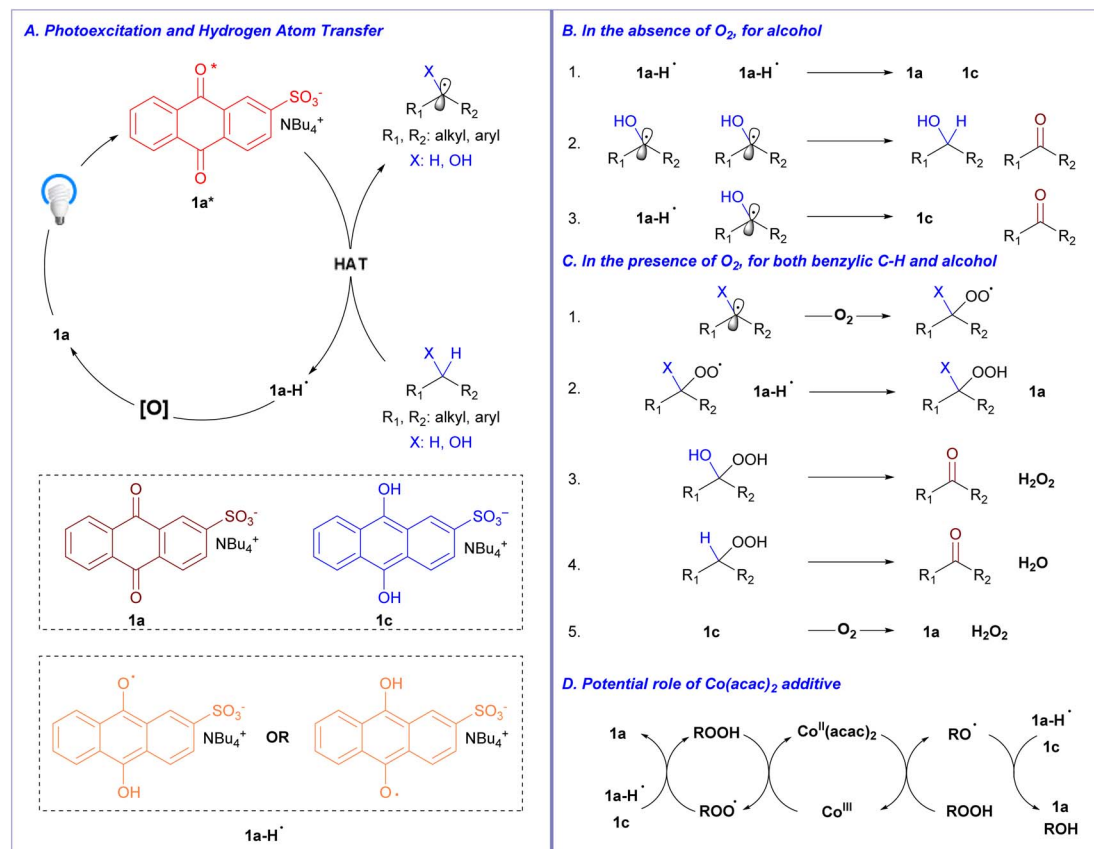


Fig. 4 Proposed mechanism of aerobic C–H bond oxidation of alcohols and alkylbenzenes.

validity of the aforementioned mechanistic pathways and explanatory function of previously proposed mechanisms for aerobic C–H bond oxidation of both alcohols and alkylbenzenes with anthraquinone derivatives (Fig. 4).²⁶

Initially, **1a** absorbs light and is excited, with intersystem crossing, to a triplet excited state **1a***. The triplet excited state **1a*** might participate in a thermodynamically favorable hydrogen atom transfer with organic substrates (alcohols and alkylbenzenes) to yield the semi-anthrahydroquinone (**1a-H•**) and a C-centered organic radical (Fig. 4A).^{20,27} Based on our study of photochemical reaction of **1a** and alcohol under inert atmosphere (Fig. 3) which establish a clean 1 : 1 ratio of **1c** and ketone formed upon irradiation, we proposed elementary steps in Fig. 4B to be operative in high fidelity, at least in the absence of O₂ for oxidation of alcohols. The disproportionations of **1a-H•** (Fig. 4B1) and ketyl radical (Fig. 4B2) yield **1c** and ketone, respectively, and alternatively a second hydrogen atom transfer between **1a-H•** and ketyl radical (Fig. 4B3) can give rise to **1c** and ketone. In the presence of O₂, we hypothesize a more complex set of elementary steps to be in operation (Fig. 4C),²⁶ in addition to potentially operative elementary steps outlined in Fig. 4B. The C-centered organic radical, formed from HAT between **1a*** and organic substrate (Fig. 4A), could trap O₂ to yield organic peroxy radical (Fig. 4C1), which subsequently oxidizes the semi-anthrahydroquinone (**1a-H•**) through hydrogen atom transfer to yield organic peroxide and give back **1a** (Fig. 4C2). The decomposition of the resulting organic peroxide to ketone

product might depend on the identity of the substituent X (Fig. 4C3 and C4), with expulsion of hydrogen peroxide if X is hydroxy group^{21a} and with simple dehydration if X is hydrogen as in the case of benzylic C–H oxidation.^{21c} Lastly, **1c**, if formed when elementary steps in Fig. 4B are kinetically competitive, could be oxidized by O₂ back to **1a** and hydrogen peroxide (Fig. 4C5).

Regarding the role of Co(acac)₃, based on reported works on interaction of Co(acac)₃ with peroxides,²⁸ it is proposed that Co(acac)₃ assisted the decomposition of organic peroxides and/or hydrogen peroxide, which should be generated in higher amount in alcohol oxidation than in benzylic C–H oxidation, to produce more oxidizing equivalents that help recycle the catalyst in its oxidized form and accelerate the overall process (Fig. 4D). This might explain why the benefit of Co(acac)₃ inclusion was much more pronounced in the case of alcohol oxidation where **1c** might be formed through elementary steps of Fig. 4B and an assistance of Co(acac)₃, which utilizes *in situ* formed peroxides to recycle **1a**, might provide rate enhancement of the overall process.

Upscale oxidation

In order to evaluate the plausibility of the developed protocols for large-scale applications, we performed three experiments of gram-scale oxidations, all of which were conducted in simple batch setting using round-bottom flasks and ambient air as the



oxidant (Fig. 5). Additionally, although the production of **1a** is scalable and **1a** is non-hygroscopic and easy to handle, we chose to further simplify the reaction setup, at least in batch setting, by employing a 1 : 1 combination of sodium anthraquinone-2-sulfonate monohydrate and tetrabutylammonium chloride in place of **1a**. A 100 mmol-scale oxidation of 4-*tert*-butylcyclohexanol (commercially available as a mixture of *cis* and *trans* diastereomers) afforded 95% yield of 4-*tert*-butylcyclohexanone in less than 4 h (Fig. 5) which presented no drop in yield compared to a small scale synthesis (Table 2, entry 2, 91% yield). As an example of secondary benzylic alcohol, 1-phenylethanol could be effectively oxidized to acetophenone (Figure 5, 98% yield), at 500 mmol scale with time to completion of 11 h. It is worth mentioning that for this upscale experiment, we employed a lower catalyst/additive loading (2 mol% 2-AQ-SO₃-Na·H₂O, 2 mol% NBu₄Cl, and 0.4 mol% Co(acac)₃) and the reaction was conducted at a more concentrated mixture (500 mmol alcohol in 1 L acetone), compared to our standard condition for benzylic alcohol oxidation (Table 2, entries 14–27). Finally, xanthene could be converted to xanthone at 10 mmol scale with excellent 91% yield (Fig. 5) within 2 h, which is comparable to reaction at 1 mmol scale (Table 3, entry 41, 88% yield). Since our developed procedures could accommodate upscale oxidation for three representative examples of aliphatic/benzylic alcohols and benzylic C–H bonds in simple batch setting with ambient air, we expect few hurdles exists in adopting the protocols in large-scale production, especially when a more sophisticated reaction setup such as flow chemistry is employed.

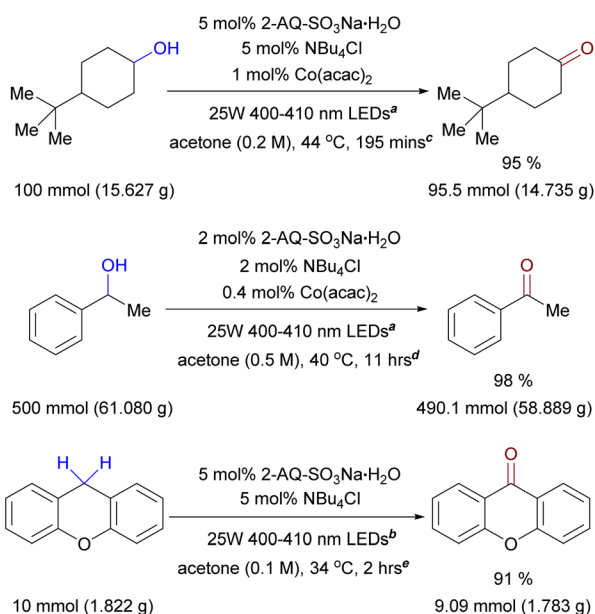


Fig. 5 Representative upscale C–H bond oxidation of aliphatic alcohol, benzylic alcohol, and benzylic C–H. ^a With four 25 W 400–410 nm LEDs lamps; ^b with two 25 W 400–410 nm LEDs lamps; ^c in a 1 L round-bottom flask, open to air; ^d in a 2 L round-bottom flask, open to air; ^e in a 500 mL round-bottom flask, open to air; all yields values are yields of the isolated compounds.

Conclusion

We described herein organo-photocatalytic protocols for aerobic C–H bond oxidation of alcohols and alkylbenzenes to corresponding ketones with ambient air as the source of oxidant. The protocols employed an easy-to-separate organic photocatalyst and were readily scalable even in simple batch setting with round-bottom flasks and ambient air. A preliminary investigation was conducted to study the role of the organic photocatalyst – tetrabutylammonium anthraquinone-2-sulfonate – in aerobic C–H bond oxidation. From this study, we found experimental evidences that support plausibility of one mechanistic pathway for alcohol oxidation in which the aromatic core of the catalyst cycles back and forth between anthraquinone form and anthrahydroquinone form, in addition to previously proposed mechanisms. The anthraquinone form acts as the substrate-activating photocatalyst and the anthrahydroquinone form activates O₂. Combined together with previously reported mechanisms, a detailed mechanism was proposed to rationalize the formation of ketones from activation of both alcohol and benzylic C–H bond. We anticipate that the devised protocols will provide compelling alternatives to traditional methods for C–H bond oxidation of alcohols and alkylbenzenes. Furthermore, we expect anthraquinone derivatives will serve as a fruitful catalyst platform for other C–H functionalization procedures.

Author contributions

K. V. N. conceived of the project, developed the idea, designed and performed experiments, and wrote the manuscript. V. T. N. and H. M. T. assisted with substrates preparation. P. V. P. acquired funding, supervised the project, and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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S. Isayama, S. Inoki, K. Kato, T. Yamada and T. Takai, *Chem. Lett.*, 1989, **18**, 449–452; (c) K. Kato, T. Yamada, T. Takai, S. Inoki and S. Isayama, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 179–186; (d) M. S. Alam, B. S. M. Rao and E. Janata, *Radiat. Phys. Chem.*, 2003, **67**, 723–728; (e) T. Matsue, M. Fujihira and T. Osa, *J. Electrochem. Soc.*, 1981, **128**, 2565–2569. Additionally, regarding the great works of Prof. Mukaiyama (ref. 28b) and Prof. Yamada (ref. 28c) where $\text{Co}(\text{acac})_2$ was also believed to activate O_2 to eventually form $\text{Co}(\text{acac})_2\text{-OOH}$, we believe that this specific process might be less relevant for our alcohol activation because our chemistry proceeded well under lower temperature than the condition (75 °C) reported in the aforementioned two references. Moreover, as demonstrated in our manuscript, **1c** (and the semi-anthrahydroquinone radical) can activate O_2 , this might be the dominant O_2 activation pathway; and in entry 3 of Table 4, a 0% yield and 0% conversion showed that under our condition, a $\text{Co}(\text{acac})_2$ -initiated-oxidation with O_2 of alcohol might not contribute to the success of the alcohol oxidation protocol.

