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Photo-induced deep aerobic oxidation of alkyl aromatics

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Oxidation is a major chemical process to produce oxygenated chemicals in both nature and the chemical industry. Presently, the industrial manufacture of benzoic acids and benzene polycarboxylic acids (BPCAs) is mainly based on the deep oxidation of polyalkyl benzene, which is somewhat suffering from environmentally and economically disadvantageous due to the formation of ozone-depleting MeBr and corrosion hazards of production equipment. In this report, photo-induced deep aerobic oxidation of (poly)alkyl benzene to benzene (poly)carboxylic acids was developed. $CeCl_3$ was proved to be an efficient HAT (hydrogen atom transfer) catalyst in the presence of alcohol as both hydrogen and electron shuttle. Dioxygen (O_2) was found as a sole terminal oxidant. In most cases, pure products were easily isolated by simple filtration, implying large-scale implementation advantages. The reaction provides an ideal protocol to produce valuable fine chemicals from naturally abundant petroleum feedstocks.

photo-induced, oxidation, alkyl aromatics

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Benzene polycarboxylic acids (BPCAs), one of the most important compounds made by the chemical industry, are used as key intermediates in the preparations of resins, plasticizers, pharmaceutical acids, food preservatives, and as the modulator in the synthesis of metal-organic frameworks (MOF). A vast majority of chemicals are made from BPCAs. Terephthalic acid (TPA), as an example being consumed principally as a monomer precursor in the manufacture of polyester (PET), has become one of the most in-demand chemicals with an annual output of up to a hundred million tons. Functionalized benzoic acids are extensively used in drug discovery, material chemistry, and agrochemicals as starting materials or critical ingredients. For instance, salicylic acid is a widespread druggable molecule and principally been used in personal care and food preservatives (Figure 1a). BPCAs are chemically synthesized *via* multistep oxidation reactions from the corresponding alkyl aromatics. The most notable commercial process for synthesizing BPCAs is the Amoco process [1], which employs liquid-phase aerobic oxidation with a homogeneous Co-Mn-Br catalyst system in acetic acid medium [1–3]. The importance and success of the Amoco process is beyond all doubt. This process commonly requires a harsh reaction condition, accompanied by high-risk safety accidents (Figure 1b) [4]. Furthermore, the use of transition metal bromides [5] might release a possible stratospheric ozone-depletion substance, MeBr. Other approaches in direct oxidations of alkyl aromatics including (i) stoichiometric oxidation by using highly reactive inorganic and/or organic oxidants ($KMnO_4$, iodine^V species, *t*-BuOOH, *m*-CPBA, H_2O_2, NHPI, *etc.*) [6–12]; (ii) heterogeneous catalytic aerobic oxidation (*e.g.*, polymer- or montmorillonite clay-supported catalysts, Pd,

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Au, or Co nanoparticles) (Figure 1b) [2,13–16]. Besides, several cerium catalyzed examples for the oxidation of alkylbenzenes were reported in recent years [17–19].

Ciamician and Silber [20] reported the first photo-induced oxidation of alkyl aromatics with molecular oxygen in 1912. In their pioneering work, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and *p*-cymene were directly exposed to oxygen and natural sunlight for about a year. The corresponding monocarboxylic acids were obtained as major products without any photosensitizer. Besides *m*- and *p*-toluyl acids, iso and terephthalic acids were also formed from *m*- and *p*-xylenes, respectively (Figure 1c). In recent years, photochemistry was re-announced, and photo-catalysts have been used to activate specific functional groups or substrates to complete various transformations *via* energy or electron transfer [21,22]. This typical application was proved as a "green" synthetic protocol in organic synthesis [23–28]. Scientists developed several elegant aerobic C–H bond photo-oxidation protocols towards the synthesis of alcohol, aldehyde, ketones and carboxylic acids in the past few decades [29–42]. Due to the relatively high abundance and excellent photocatalytic performance, cerium salts were widely used as efficient and promising photo-catalysts. Zuo and co-workers [43–45] utilized the synergistic effect of hydrogen atom transfer (HAT) and ligand-to-metal charge transfer (LMCT) with Ce catalysts to develop a sophisticated chemistry pathway for the activation of C(sp^3)–H bond. After taking an in-depth analysis of recent photocatalysis developments, we envisioned that through a photo-induced, Ce-promoted benzylic C(sp^3)–H bond activation, the toluene derivatives could be deeply oxidized to carboxylic acids in the presence of molecular oxygen, which acts as terminal oxidant through the radical pathway (Figure 1d). This approach might unfold green and sustainable oxidation, in both fundamental sciences and chemical industry, for valuable fine chemical productions from naturally abundant feedstocks.

We set out to investigate the desirable photo-induced oxidation by examining 4-methyl-1,1′-biphenyl **3n** as a prototypical substrate. After careful optimization, we established an efficient photo-oxidation protocol using $CeCl_3$ (5 mol%) as a HAT catalyst in the presence of CCl_3CH_2OH (20 mol% for mono-methyl benzenes, 1.0 equiv. for poly-methyl benzenes), irradiated by light-emitting diode (LED) light under O_2 (1 atm) in CH_3CN for 24 h (see the Supporting Information online for details.).

The substrate scope was explored by the oxidation of toluene and its derivatives. Firstly, benzoic acid **2a** was obtained with 84% yield from toluene under standard conditions. The three xylenes **1b**–**1d** were then irradiated to give the corresponding phthalic acids in good yields. The

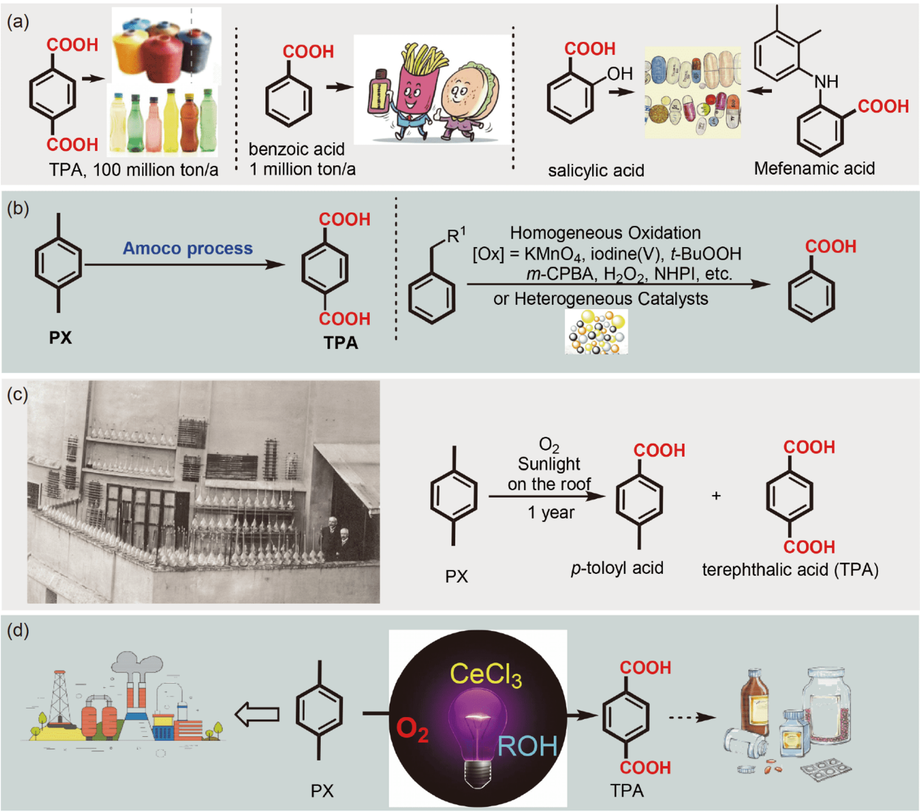

Figure 1 The nature of benzene (poly)carboxylic acids. (a) Aromatic (poly)carboxylic acid-related products in daily life. (b) Traditional oxidation of alkylbenzene. (c) Photochemistry on the roof: the first oxidation of alkyl aromatics with molecular oxygen explored by Ciamician and Silber 100 years ago [20]. (d) Photo-induced deep aerobic oxidation of (poly)alkyl aromatics to aromatic (poly)carboxylic acids (color online).

in-situ formed phthalic acid from oxidation of orthoxylene **1b**, will be spontaneously dehydrated to *o*-phthalic anhydride **2b**. We were happy to find out that trimethyl-, tetramethyl-, pentamethyl-, and hexamethyl-benzenes (**1e**–**1l**) were fully converted to benzene polycarboxylic acids (BPCAs, **2e**–**2l**) when introduced to the developed catalytic photo-oxidation system. These reactions gave good yields by simple work-up, showing industrial production and application prospect of this oxidation protocol (Figure 2a). To demonstrate the utility of this interesting method, the gram-scale reaction of **1a** is carried out in the presence of 1 mol% of $CeCl_3$ as photocatalyst. After irradiated with 390 nm Kessil light for 132 h, **2a** was formed with 63% isolated yield. The main reason for this low efficiency is that the mixture turned to be a little bit turbid, which affected the light transmittance.

We further proceeded with this reaction on various substituted toluene derivatives to extend the application scope (Figure 2b). 2-Methoxy- and 4-methoxy toluene underwent this oxidation smoothly and gave the corresponding benzoic acids **4a** and **4b** in 65% and 78% yield. A variety of *para*-substituted toluene substrates were also examined. Phenolic ester skeletons have ocurred in many pharmaceutical molecules and natural products [46–48]. The result indicates that our method enables the structure modification of those important molecules (**4c**–**4e**). Both electron-donating groups, like *tert*-butyl (**4f**), phenyl (**4n**), and electron-withdrawing groups CF_3 (**4g**), COOEt (**4l**), CN (**4m**), as well as halogens (**4i**–**4k**) could tolerate this oxidation well, leaving useful synthetic functionalities for further derivatization. The reaction yield of 1-methyl-4-nitrobenzene (**3h**) is low, maybe because of the strong electron-withdrawing effect of $–NO_2$. *Meta*-substituted toluene derivatives were oxidized to various benzoic acids (**4o**–**4q**), and slightly higher yields were achieved than that of their corresponding *ortho*- or *para*-isomers. In addition, oxidations of multi-substituted toluene derivatives were investigated, showing good functional group tolerance and synthetic diversity (**4s**–**4x**).

Aromatic heterocyclic carboxylic acids are widespread in

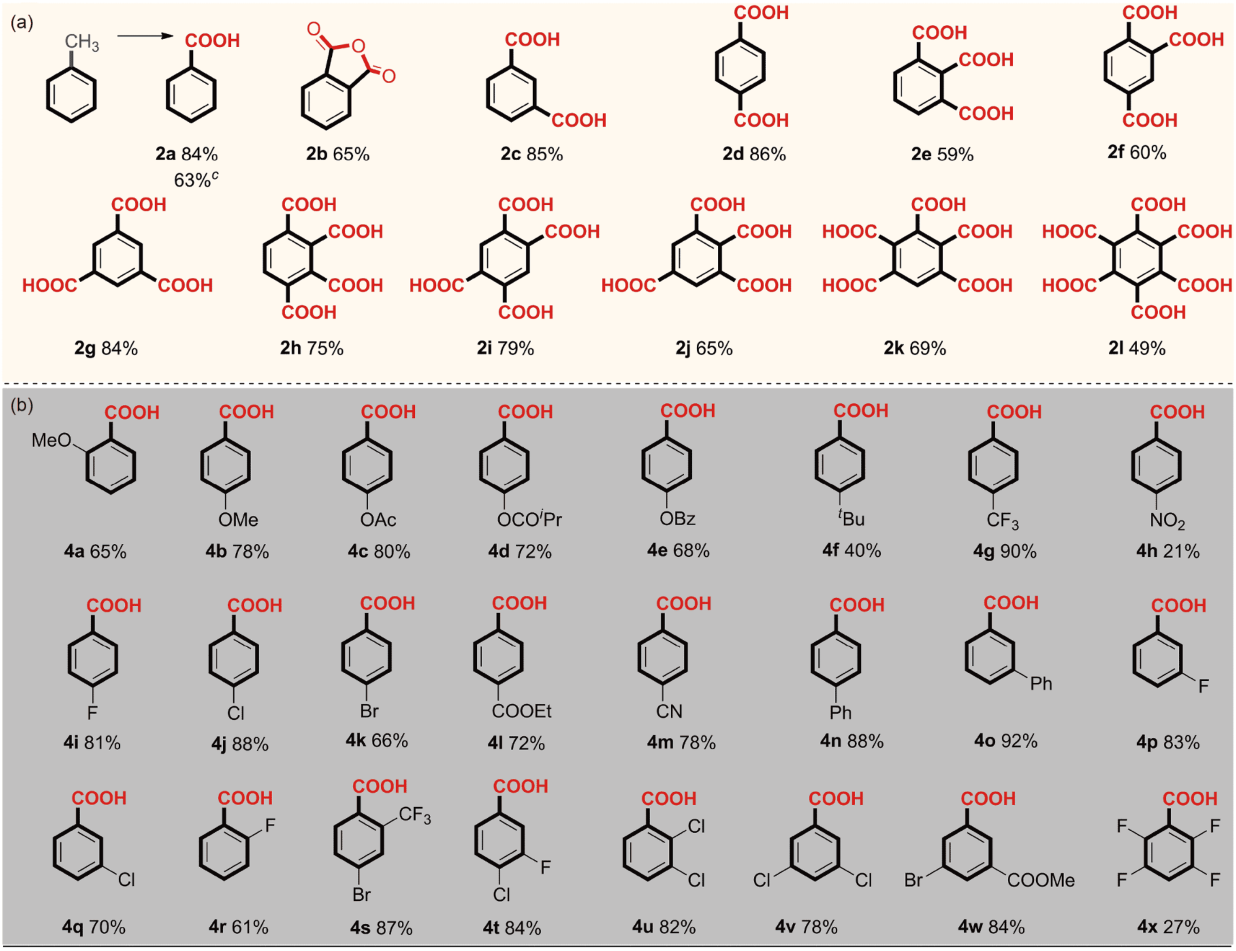

Figure 2 Deep areobic oxidation of (poly)methylbenzene. (a) Oxidation of polyalkyl benzene **1** to BPCAs **2**. (b) Oxidation of substituted toluene **3** to substituted benzoic acids **4**. Conditions: **1** or **3** (0.1 mmol), $CeCl_3$ (5.0 mol%), CCl_3CH_2OH (20 mol% for mono-methyl benzenes, 1.0 equiv. for polymethyl benzenes) in CH_3CN (2 mL) under 1 atm O_2 atmosphere at 60 °C, and irradiated with a 400 nm/390 nm LED lamp for 24–72 h. See Supporting Information online for details. (c) In a 10 mmol scale reaction, a 500 mL round bottom flask was charged with a stiring bar, and added with reagent **1a** (10 mmol), $CeCl_3$ (1 mol%), CCl_3CH_2OH (20 mol%), CH_3CN (100 mL) under O_2 atmosphere. The mixture was stirred under the irradiation of 390 nm LEDs for 132 h (color online).

bio-active natural products, pharmaceutical compounds, and functional materials. Not only that, some could also serve as multi-dentate ligands in coordination chemistry. We then introduced methyl heteroarenes to this oxidation system. To our delight, the oxidation reaction proceeds smoothly, giving the target aromatic heterocyclic carboxylic acids with moderate to good yields (Figure 3a). For example, thiophene-2-carboxylic acid **6a**, 5-acetyl thiophene-2-carboxylic acid **6b** and benzo[*b*]thiophene-2-carboxylic acid **6c** were obtained from the corresponding methyl-substrates **5a**–**5c**. 4-Methyl pyridine **5e** and 3-methyl-1-phenyl-1*H*-pyrazole **5f** were also compatible with this system, converted to the heterocyclic carboxylic acid **6e**–**6f**, albeit latter with a lower efficacy.

Substances with linear and branched alkyl substituents were then examined. We found that both benzylic C–H oxidation and C–C bond cleavage took place subsequently, delivering the corresponding carboxylic acid products in moderate yields (Figure 3b, c). However, a benzylic C–H must be presented to initiate this oxidation process. It is important to note that when the mixture of toluene **1a**, ethylbenzene **7a**, and cumene **9a** was introduced to this system, **2a** was obtained as the only product with high yield (Figure 3d). This result indicated a potent application of this oxidation reaction in the high-value transformation of the off-gases containing substituted benzene homolog compounds. Ultimately, this method was further applied to the late-stage modification of Celebrex, a non-steroidal anti-inflammatory drug, delivering the oxidized product **10** in 65% yield in one step (Figure 3e). Considering the importance of this kind of medicinal agent, we expect this methodology to be useful for drug modification by introducing hydrophilic carboxylic acid groups at a very late stage.

A series of control experiments were conducted to explore the mechanism of this catalytic oxidation (Figure 4a). Firstly, a radical scavenger (TEMPO) was added under standard conditions. The targeted product **4n** was not detected, indicating a possible radical pathway for this oxidation reaction. While we attempted to capture the intermediates with TEMPO in the absence of O_2, compound **11** was detected by gas chromatograph-mass spectrometer (GC-MS). This result provided reliable support for the existence of benzylic radicals, which might be the initiator of this photo-induced radical oxidative procedure. $^{18}O_2$ then replaced O_2. Only ^{18}O labeled benzoic acid **4n′** was obtained with good yield, which proved that the [O] atom in the product came from O_2. For a deep insight into the reaction mechanism, we traced the oxidation of **3n** under standard conditions and monitored it by ^1H nuclear magnetic resonance (^1H NMR) spectroscopy every 2 h (Figure 4b). Hydroperoxide **12** (red dot) was first observed but was further oxidized after the peak at 4 h. Aldehyde **13** (blue spot) has been detected and reaches its summit at around 10 h. Both the above two intermediates were converted to the desired final product **4n** (green triangle) at 24 h. Based on the observations and previous studies, a plausible mechanism was proposed in Figure 4c. First, electrophilic alkoxy radical was generated from alcohol *via* Ce (IV)-alkoxide intermediate participating in photo-induced LMCT process. It then abstracted hydrogen from

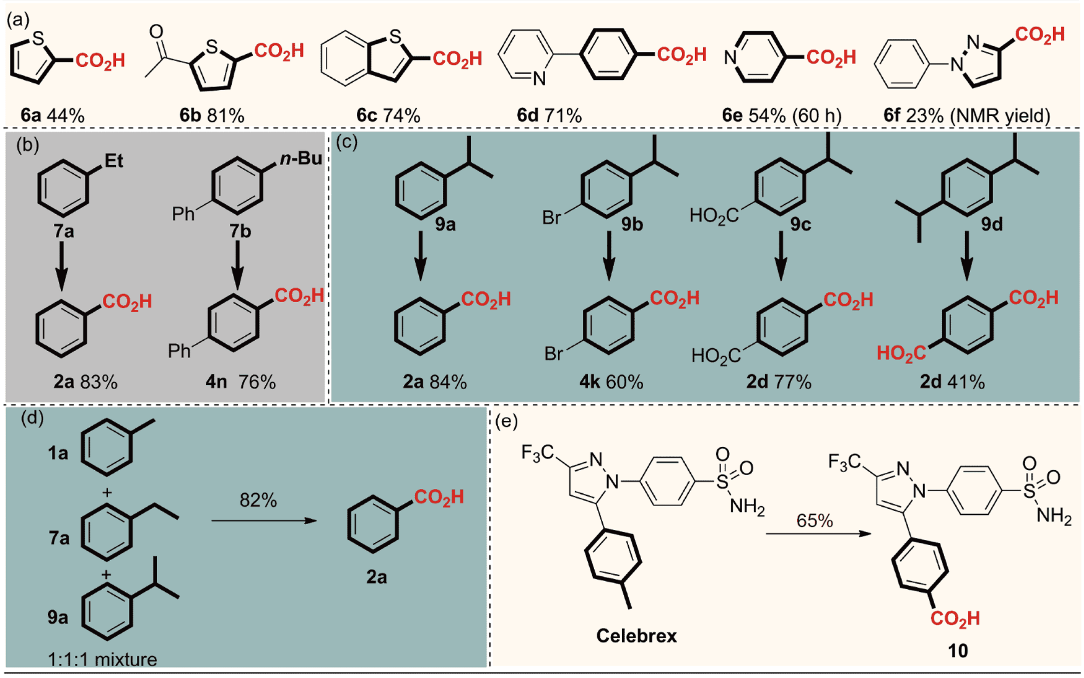

Figure 3 The substrate extension of the oxidation. (a) Oxidation of the benzylic C–H bond in heterocyclic compounds. (b) Secondary benzylic C–H oxidation to benzoic acids through sequential cleavage of C–H and C–C bonds. (c) Tertiary benzylic C–H oxidation. (d) Oxidation of toluene, ethylbenzene, cumene mixture. (e) Late-stage diversification of medicinal reagent under standard reaction conditions (color online).

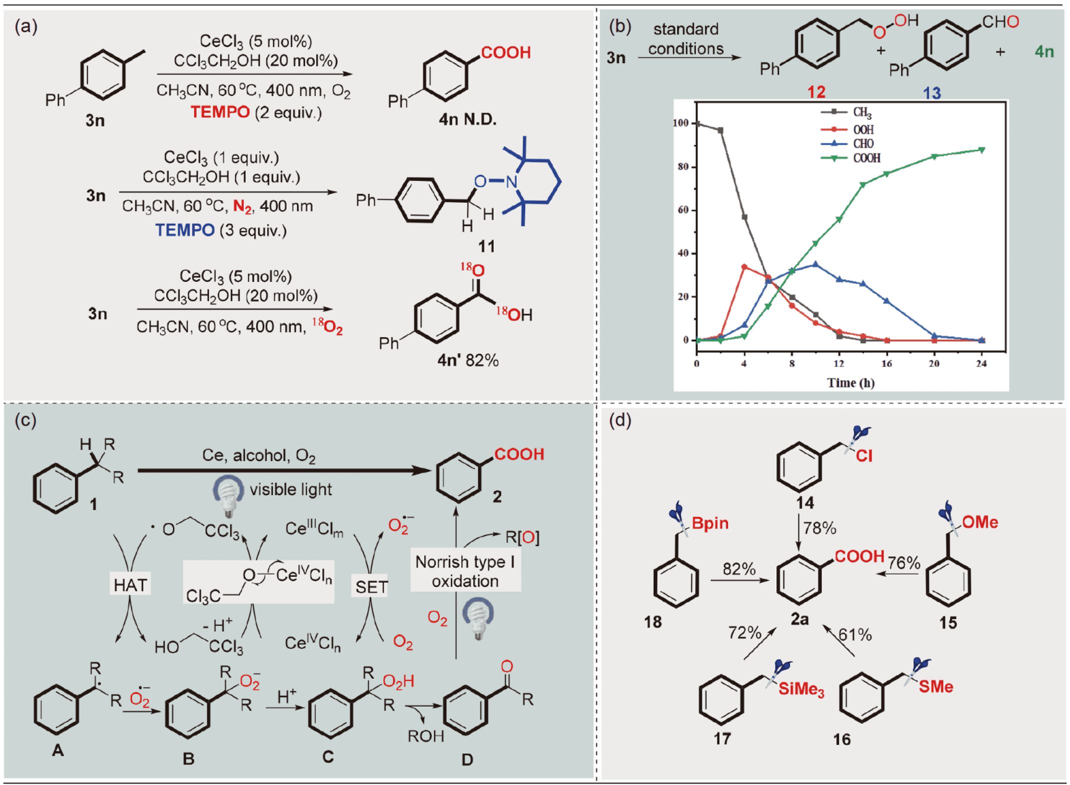

Figure 4 Mechanistic investigations. (a) Control experiments. (b) Kinetic experiments. (c) Plausible mechanism for the oxidation from toluene to benzoic acids. (d) The deep oxidation of benzyl derivatives with heteroatom group substituents (color online).

benzylic C–H bond to form benzyl radical **A**; subsequently, single electron transfer occurred between molecular dioxygen (O_2) and Ce(III) to form superoxide radical; this *in-situ* formed superoxide radical was involved in the reaction as an oxidizer of alkyl radicals to generate hydroperoxide **B**. After protonation and ROH release, **D** was obtained, which further accelerated the Norrish type I oxidation process to produce carboxylic acids **2** under illumination and heating conditions [49]. We have proved that both benzaldehyde and acetophenone could be further oxidized under these specific reaction conditions.

By understanding the feature of herein-developed deep oxidation of toluene derivatives, we anticipated that the benzylic position of substituents did not affect such oxidation. Therefore, we further investigated the oxidation reaction of benzyl derivatives with different functionalities (Figure 4d). To our delight, all of the tested hetero-atom-substituted toluene derivatives, including benzylic chloride **14**, benzyloxy methane **15**, benzyl(methyl)-sulfane **16**, benzyl-trimethyl silane **17**, and benzylic borolane **18**, could be oxidized, and with a 100% selectivity towards benzoic acid **2a** in this system. These results detailed that both C–H oxidation and C–X bond cleavage took place under standard conditions.

In conclusion, we have successfully developed a moderate and practical photocatalytic protocol for the deep aerobic oxidation of (poly)alkylbenzene. This protocol uses inexpensive and earth-abundant $CeCl_3$ as catalyst and CCl_3CH_2OH as HAT reagent. Benzyl C–H, C–C bond, C–X bonds were cleaved and finally oxidized to benzoic acid when irradiated with LED light under O_2 atmosphere. The chemistry here showed good functional group tolerance and could be used as an efficient strategy in the late-stage modification in druggable molecules. Mechanistic studies unveiled that the oxidation initiated from the hydrogen abstraction at the benzylic position. Thus the presence of benzyl C–H bond was the critical requirement to proceed with this chemistry. Not only does this development provide a green and efficient protocol to produce the valuable substituted benzoic acids, heteroaromatic carboxylic acids and benzene polycarboxylic acids (BPCAs), but it offers new thinking to oxidize the aliphatic C–H bonds to oxygenated products from feedstocks of petroleum chemistry.

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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