

Visible-Light-Induced Deep Aerobic Oxidation of Alkyl Aromatics

Chang-Cheng Wang¹, Guo-Xiang Zhang², Zhi-Wei Zuo^{3*}, Rong Zeng², Dan-Dan Zhai¹, Feng Liu^{1*} and Zhang-Jie Shi^{1,3*}.

¹Department of Chemistry, Fudan University, Shanghai, 200438, China.

²Department of Chemistry, School of Science, Xi'an Key Laboratory of Sustainable Energy Materials Chemistry, Xi'an Jiaotong University, Xi'an, Shaanxi 710049, China.

³State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China.

⁴State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai, 200032, China.

ABSTRACT: Oxidation is a major chemical process to produce oxygenated chemicals in both nature and the chemical industry. Currently, industrial deep oxidation processes from polyalkyl benzene are primary routes to produce benzoic acids and benzene polycarboxylic acids (BPCAs), while to some extent suffering from the energy-intensive and potentially hazardous drawbacks and the sluggish separation issues. In this report, visible-light-induced deep aerobic oxidation of (poly)alkyl benzene to benzene (poly)carboxylic acids was developed. CeCl₃ was proved to be an efficient HAT (Hydrogen Atom Transfer)catalyst in the presence of alcohol as both hydrogen and electron shuttle. Dioxygen (O₂) was found as a sole terminal oxidant. In most cases, pure products were easily isolated by simple filtration, showing the advantages of scaling up. The reaction provides an ideal way to form valuable fine chemicals from abundant petroleum feedstocks.

Benzene polycarboxylic acids (BPCAs) are key intermediates in the preparations of resins, plasticizers, pharmaceutical acids, food preservatives, as well as the modulator in the synthesis of Metal-Organic Frameworks (MOF) ¹⁻⁶. Terephthalic acid (TPA), for example, be 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 tons⁷. Benzoic acid, with million tons annually production, is commonly used as a pH adjustor, food preservation, and valuable starting material in the chemical industry⁸. Functionalized benzoic acids are also widely spread in drug discovery, material chemistry, agrochemicals as starting materials and critical ingredients. Salicylic acid itself is a druggable molecule and is mostly used in personal care, food & preservatives. Mefenamic acid is known as a nonsteroidal anti-inflammatory drug (NSAID), which has been used for short-term pain relief treatment and blood loss from menstrual periods (Fig.1a).

BPCAs are chemically synthesized through a series of oxidation reactions from the corresponding alkyl aromatics. The most notable commercial process, known as the Amoco process⁹, employs liquid-phase aerobic oxidation with homogeneous Co-Mn-Br catalyst system in acetic acid medium⁹⁻¹¹. These processes

commonly accompany high energy consumption at high temperatures (175-225 °C) and high dioxygen pressure (15-30 atm). The use of transition metal bromides¹² leads to a potential hazard to the environment and stratospheric ozone. Indeed, several severe safety accidents were caused by this point in the past few years, which has triggered public panic and protest (Fig.1b)¹³. Other developed approaches in direct oxidations of alkyl aromatics include the following ways: i) stoichiometric oxidation by using highly reactive inorganic and/or organic oxidants (KMnO₄, iodine^V species, *t*-BuOOH, *m*-CPBA, H₂O₂, NHPI, etc.)¹⁴⁻²⁰; ii) catalytic aerobic oxidation catalyzed by heterogeneous catalysts (e.g., polymer- or montmorillonite clay-supported catalysts, Pd, Au, or Co nanoparticles) (Fig.1b)^{10,21-24}. The former processes suffered from the requirement of stoichiometric amounts of harmful or unsafe oxidants. The drawbacks of the latter protocols can be ascribed to some common disadvantages of heterogeneous catalysts, including the leaching problems of catalysts, limited oxidation efficiency and/or selectivity. Chemists never stop searching for a clean and efficient way for the catalytic oxidation of alkyl aromatics to BCPAs, to meet the green and sustainable requirements in industry.

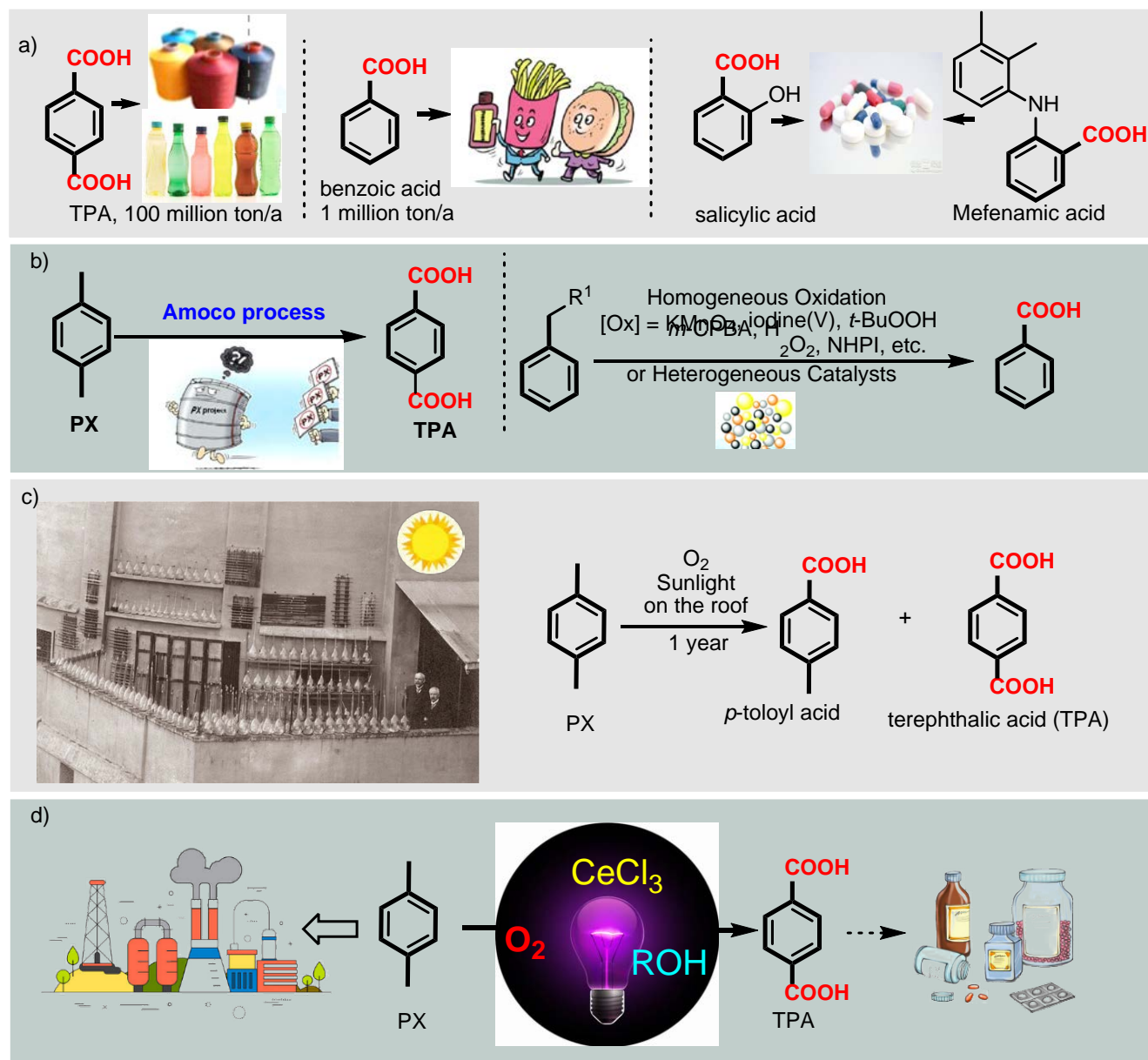


Fig.1| The nature of benzene (poly)carboxylic acids. **a**, Aromatic (poly)carboxylic acid-related products in daily life. **b**, Traditional oxidation of alkylbenzene. **c**, Photochemistry on the roof: The first oxidation of alkyl aromatics with molecular oxygen explored by Ciamician and Silber 100 years ago. **d**, Visible-light-induced deep aerobic oxidation of (poly)alkyl aromatics to aromatic (poly)carboxylic acids.

Ciamician and Silber reported the first photo-induced oxidation of alkyl aromatics with molecular oxygen in 1912²⁵. Authors exposed toluene, o-xylene, m-xylene, p-xylene, and p-cymene to oxygen and sunlight for about a year without any photosensitizer. The corresponding monocarboxylic acids were obtained as major products. Besides *m*- and *p*-toluyl acids, iso and terephthalic acids were also formed from *m*- and *p*-xylenes, respectively (Fig.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. This typical application was proved as a safe and green synthesis protocol in organic synthesis²⁶⁻³³. Several elegant aerobic C-H bond photo-oxidation protocols were developed towards the synthesis of alcohol, aldehyde, and ketones in the past few decades³⁴⁻³⁹. Cerium salts were proved as efficient and favored photo-catalysts due to the relatively high abundance and excellent photo-catalytic performance. Zuo and co-workers developed sophisticated chemistry for the activation of C(sp³)-H bond through the synergistic utilization of hydrogen atom transfer (HAT) and ligand-to-metal charge

transfer process (LMCT) with Ce catalysts⁴⁰⁻⁴¹. By the analysis of recent developments, we envisioned that via a photo-induced, Ce-promoted benzylic C(sp³)-H bond activation, the toluene derivatives could be deeply oxidized to carboxylic acids in the presence of molecular oxygen as terminal oxidant through the radical pathway (Fig.1d). This approach might present novel, green and sustainable oxidation in both fundamental sciences and chemical industry toward valuable fine chemical productions from abundant feedstocks.

Results

Reaction development. 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 CeCl₃ (5 mol%) as a HAT catalyst in the presence of CCl₃CH₂OH (20 mol% for mono-methyl benzenes, 1.0 equiv. for polymethyl benzenes), irradiated by LED light under O₂ (1 atm) in CH₃CN for 24 h (see the supporting information for details.). The substrate scope was explored by oxidation of toluene and its derivatives. Benzoic acid **2a** was obtained with 84% yield from toluene under standard conditions. The three xylenes **1b-1d** were then irradiated with 40 w Kessil PR160L-390 nm light to give the corresponding phthalic acids in good yields. As to the oxidation of orthoxylene **1b**, the *in-situ* formed phthalic acid will be spontaneously dehydrated to *o*-phthalic anhydride **2b**. While trimethyl-, tetramethyl-, pentamethyl-, and even hexamethyl- benzenes (**1e-1l**) were introduced to the

developed catalytic photo-oxidation system, we were happy to find that all of these methyl groups were fully converted to benzene polycarboxylic acids (BPCAs, **2e-2l**). By a simple work-up, all of these conversions were in good to excellent yields, showing the power of this oxidation protocol (Fig.2a). Due to the importance of BPCAs and the long-standing environmental and safety problems in their syntheses, this methodology provides a sustainable way to produce those basic chemicals that benefit for the human's livelihood and national economy.

We then proceeded to test the scope of substituted toluene derivatives to extend the applications (Fig.2b). The oxidation of 2-methoxy- and 4-methoxy toluene underwent smoothly to give the corresponding benzoic acids **4a** and **4b** in 65% and 78% yield. A variety of *para*-substituted toluene substrates were then examined. Phenolic ester skeletons have recurred in many pharmaceutical molecules and natural products. The method makes it possible to proceed with the late-stage structure modification of those important molecules (**4c-4e**). Both electron-donating groups, like *tert*-butyl (**4f**), phenyl (**4n**), and electron-withdrawing groups CF₃ (**4g**), NO₂ (**4h**), COOEt (**4l**), CN (**4m**), as well as halogens (**4i-4k**) could tolerate this oxidation well, leaving useful synthetic functionalities for further derivatization. *Meta*-substituted toluene derivatives were oxidized to various benzoic acids (**4o-4q**), and slightly higher yields were given compared to their corresponding *ortho*- or *para*-isomers. Moreover, multi-substituted toluene derivatives were investigated, and all the oxidations worked well, showing good functional groups tolerance and synthetic diversity (**4s-4x**).

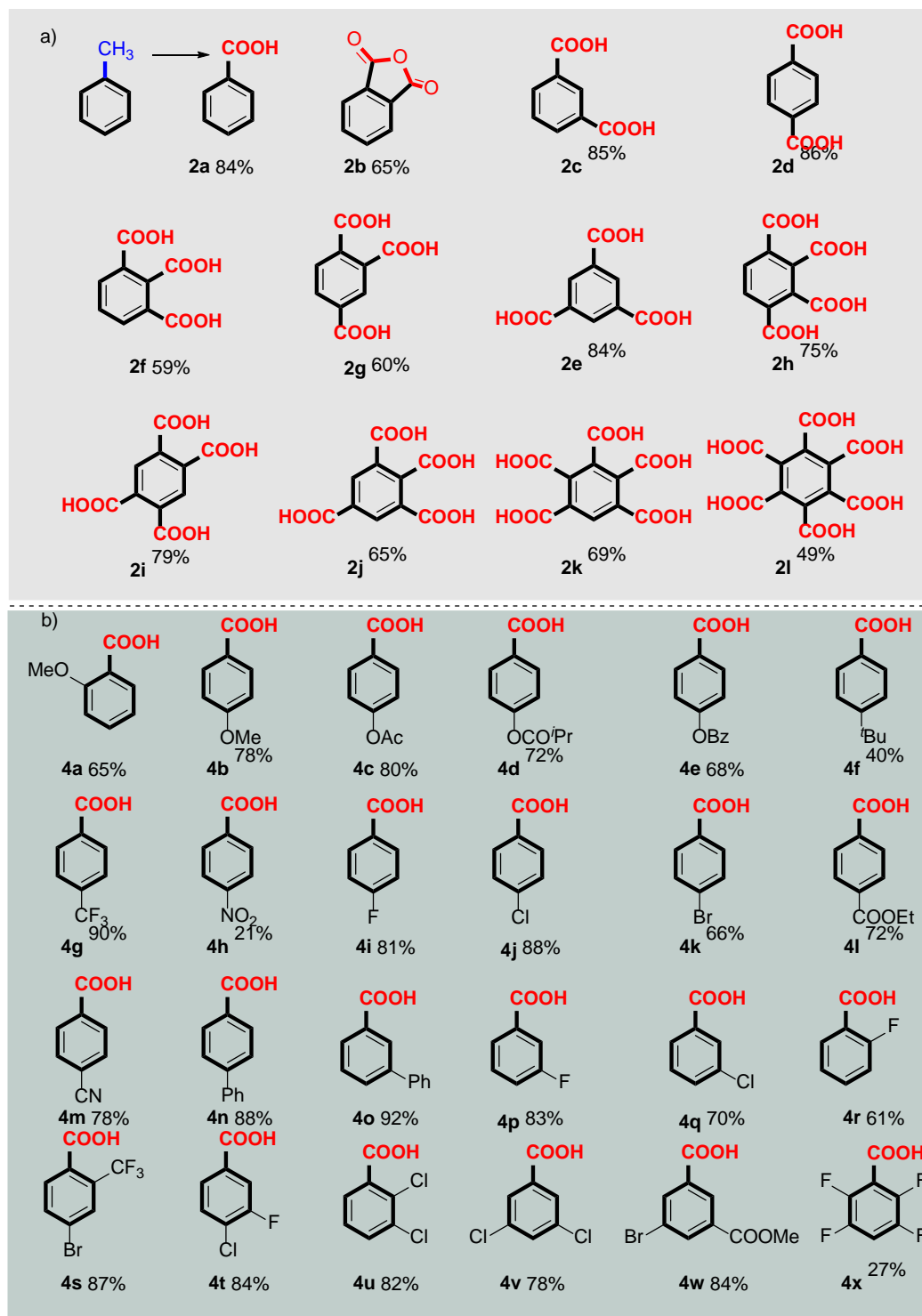


Fig.2| Deep aerobic oxidation of (poly)methylbenzene. a, Oxidation of polyalkyl benzene **1** to BPCAs **2**. **b,** Oxidation of substituted toluene **3** to substituted benzoic acids **4**. Conditions: **1** or **3** (0.1 mmol), CeCl_3 (5.0 mol%), $\text{CCl}_3\text{CH}_2\text{OH}$ (20 mol% for mono-methyl 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 Supplementary Information for details.

Aromatic heterocyclic carboxylic acids widely existed in bio-active natural products, pharmaceutical compounds, and functional materials. Nevertheless, some could serve as multi-dentate ligands in coordination chemistry. We then introduced methyl heteroarenes to the developed oxidation system. To our delight, the oxidation reaction could proceed

smoothly, given the target aromatic heterocyclic carboxylic acids with the moderate to good yields (Fig.3a). 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 even 3-methyl-1-phenyl-1H-

pyrazole **5f** were compatible with this system, which could be converted to the heterocyclic carboxylic acid **6e-6f**, albeit the 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 (Fig.3b,3c). However, a benzylic C-H must be presented to initiate this oxidation process. It is important to note that when the mixture of toluene, ethylbenzene, cumene was introduced to this system, one sole benzoic acid product

2a was obtained with excellent yield (Fig.3d). This result illustrated that this oxidation reaction has a potent application in the separation and high-value transformation of the off-gases containing substituted benzene homologue compounds. Ultimately, this method was further applied to the late-stage modification of drugs. For example, the photocatalytic reaction of Celebrex, a non-steroidal anti-inflammatory drug, delivered the oxidized product **10** in 65% yield in one step (Fig.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.

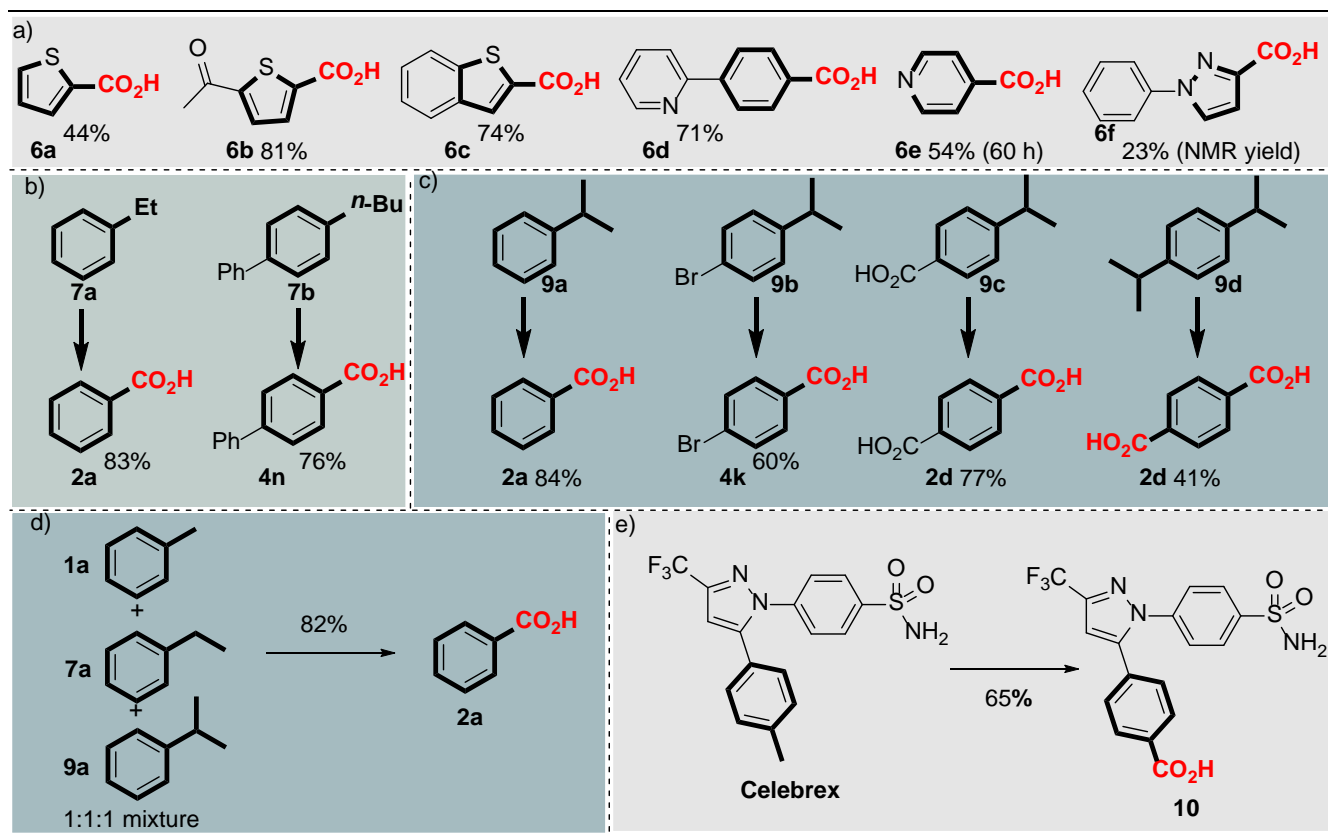


Fig. 3 | The substrate extension of the oxidation. **a**, Oxidation of the benzylic C-H bond in heterocyclic compounds. **b**, Secondary benzylic C-H oxidation to benzoic acids through sequential cleavage of C-H and C-C bonds. **c**, Tertiary benzylic C-H oxidation. **d**, Oxidation of toluene, ethylbenzene,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

To explore the mechanism of this catalytic oxidation, a series of control experiments were conducted (Fig. 4a). Firstly, a radical scavenger (TEMPO) was added under standard conditions, and no targeted product **4n** was detected, indicating a possible radical pathway for this oxidation reaction. While attempting to capture the intermediates with TEMPO in the absence of O₂, compound **11** was detected by GC-MS. This result provided reliable support of the existence of benzylic radicals, which might be the initiator of this photo-induced radical oxidative procedure. ¹⁸O₂ was then used to take the place of O₂, and undoubtedly only the

desired ¹⁸O labeled benzoic acid **4n'** was obtained with good yield, which clearly illustrated that the [O] atom in the product came from O₂. To get more insight on the reaction mechanism, we carried out the oxidation of **3n** with 1.0 eq. of CCl₃CH₂OH. The reaction was monitored by ¹H NMR spectroscopy every 15 minutes (Fig.4b). Two key intermediates were traced during the reaction. The hydroperoxide was first observed, it was further oxidized after the peak at 45 min (**12**, green volcano I). Aldehyde was produced and get to its summit at around 90 mins (**13**, red

spot). Finally, both were transferred to the desired product (**4n**, blue triangle) at 135 minutes.

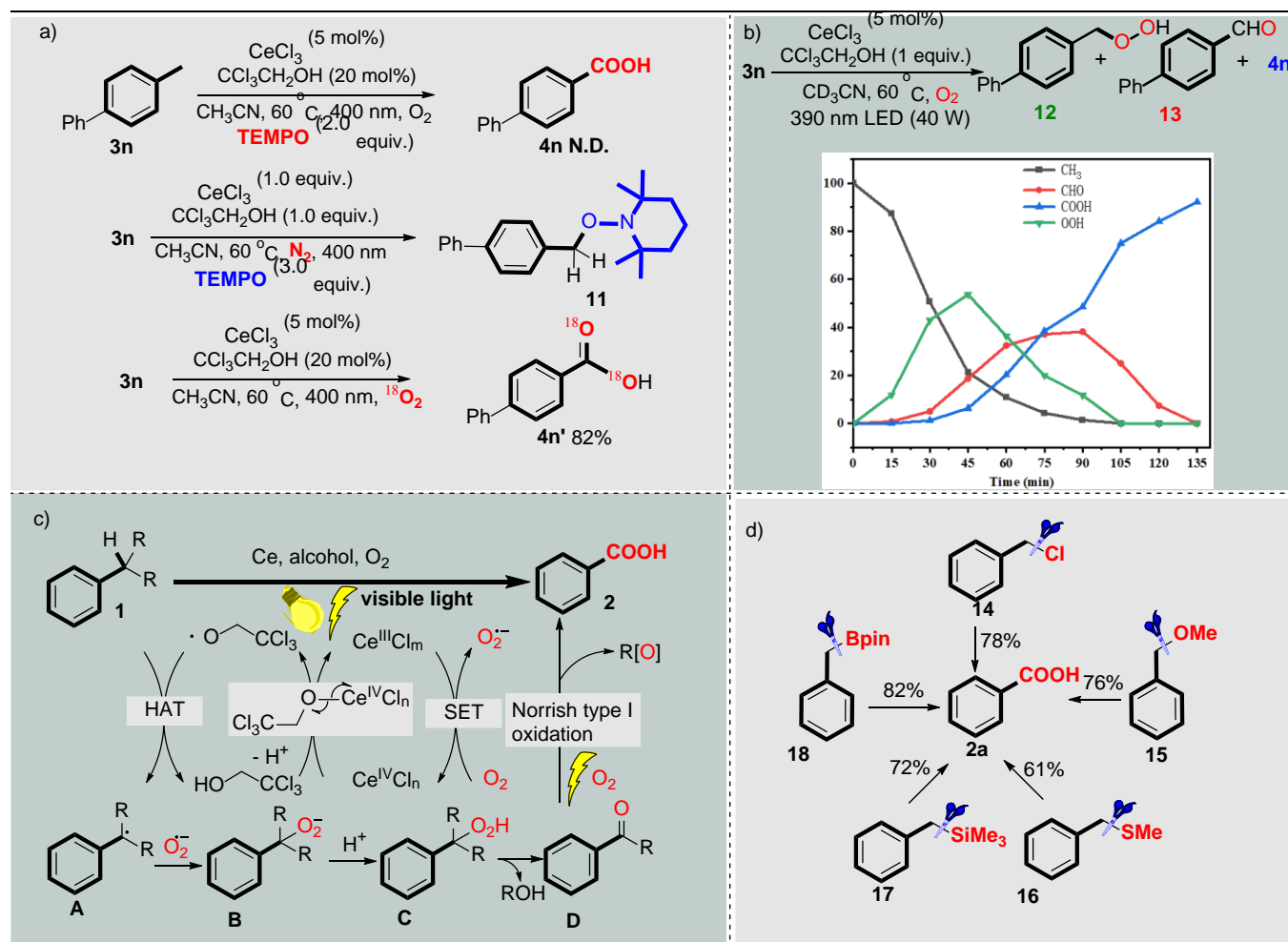


Fig.4| Mechanistic investigations. **a**, Control experiments. **b**, Kinetic experiments. **c**, Plausible mechanism for the oxidation from toluene to benzoic acids. **d**, The deep oxidation of benzyl derivatives with heteroatom group substituents.

Based on the observations and previous studies, a plausible mechanism was proposed in Fig.4c. First, electrophilic alkoxy radical was generated from alcohol *via* Ce (IV)-alkoxide intermediate participated photo-induced LMCT process. Alkoxy radical then abstracted the hydrogen from benzylic C-H bond to form benzyl radical **A**; Subsequently, a single electron transfer occurred between molecular dioxygen (O₂) and Ce(III) to form superoxide radical; The *in-situ* formed superoxide radical was involved in the reaction and oxidized the alkyl radicals to hydroperoxide **B**. After protonation and ROH released, **D** was obtained, which further accelerated the Norrish type I oxidation process to produce carboxylic acids **2** under illumination and heating conditions⁴². Under these reaction conditions, we further proved that

both benzaldehyde and acetophenone could be further oxidized.

Understanding the feature of herein developed deep oxidation of toluene derivatives, we envisioned that different substituents at a benzylic position would not affect such oxidation. Therefore, we further investigated the oxidation reaction of benzyl derivatives with different functionalities (Fig.4d). To our delight, all tested heteroatom substituted toluene derivatives, including benzylic chloride **14**, benzyloxy methane **15**, benzyl(methyl)sulfane **16**, benzyl-trimethyl silane **17**, and benzylic borolane **18** was oxidized in this system as expected, and all gave benzoic acid **2a** as the same sole product. These results detailed that both the C-H oxidation and the C-X bond cleavage taken place under standard conditions.

In conclusion, we have successfully developed a general and practical photocatalytic protocol for deep aerobic oxidation of (poly)alkylbenzene. To use the inexpensive and earth-abundant CeCl_3 as the catalyst, $\text{CCl}_3\text{CH}_2\text{OH}$ 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 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 this chemistry. Not only does this development provides 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 feedbacks of petroleum chemistry.

AUTHOR INFORMATION

Corresponding Author

zjshi@fudan.edu.cn, liufeng@fudan.edu.cn,
zuozhw@shanghaitech.edu.cn

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AUTHOR CONTRIBUTIONS

S.Z.-J. and L.F. directed the research and developed the concept of the reaction with W.C.-C., who also performed the experiments and characterized all the products. Z.G.-X., Z.Z.-W., Z.R., and Z.D.-D. gave some helpful suggestions for the reaction and analyze the results. S.Z.-J. and L.F. wrote the manuscript with contributions from the other authors.

COMPETING INTERESTS

The authors declare no competing interests.

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