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Metal-Free Aerobic Oxidation of Nitro-Substituted Alkylarenes to Carboxylic Acids or Benzyl Alcohols Promoted by NaOH

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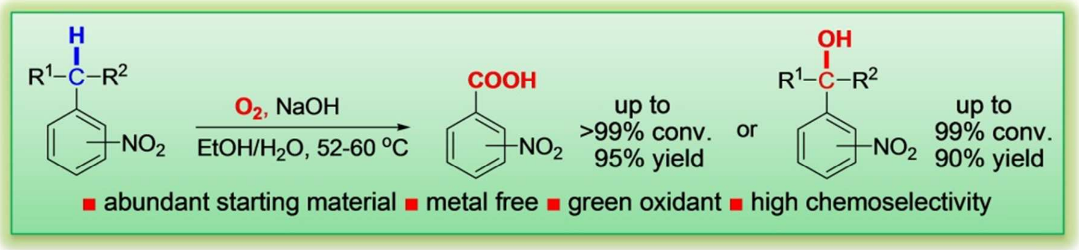


Efficient and selective aerobic oxidation of nitro-substituted alkylarenes to functional compounds is a fundamental process that remains a challenge. Here, we report a metal-free, efficient and practical approach for the direct and selective aerobic oxidation of nitro-substituted alkylarenes to carboxylic acids or benzyl alcohols. This sustainable system uses O_2 as clean oxidant in a cheap and green NaOH/EtOH mixture. The position and type of substituent critically affect the products. In addition, this sustainable protocol enabled gram-scale preparation of carboxylic acid and benzyl alcohol derivatives with high chemoselectivities. Finally, the reactions can be conducted in a pressure reactor, which can conserve oxygen and prevent solvent loss. The approach was conducive to environmental protection and potential industrial application.

INTRODUCTION

Aerobic oxidation of hydrocarbons is one of the most fundamental and critical processes in the manufacture of functional compounds, such as carboxylic acids and benzyl alcohols, which are essential materials for pharmaceutical, agricultural, dyestuff, and flavor industries (Figure 1).[1,2] Traditionally, stoichiometric amounts of hazardous oxidants, such as $KMnO_4$[3], $Na_2Cr_2O_7$[4], PdO_2[5], and HNO_3[6], or noble metal catalysts[7,8] are required for the carboxylic acids production; meanwhile, metalloporphyrin catalysts[9–11] are used in the synthesis of benzyl alcohols. The use of these chemicals limit the applications of the methods because of substantial waste, high toxicity, intense corrosion, economic problems, or poor chemoselectivities. Thus, development of environmentally friendly, mild, and cheap approaches for the oxidation of hydrocarbons by using clean oxidants is highly desired and is the focus of green chemistry.

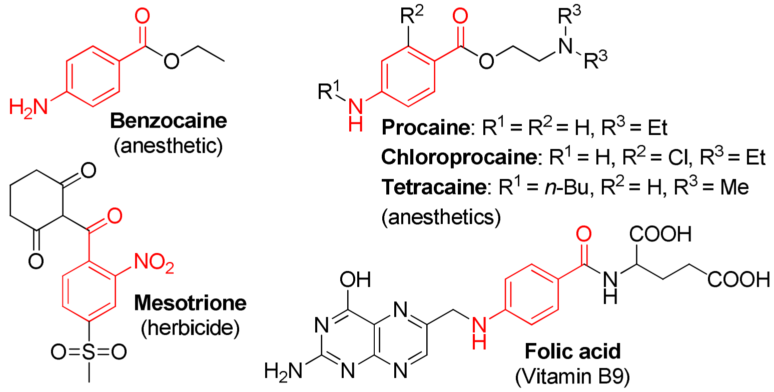
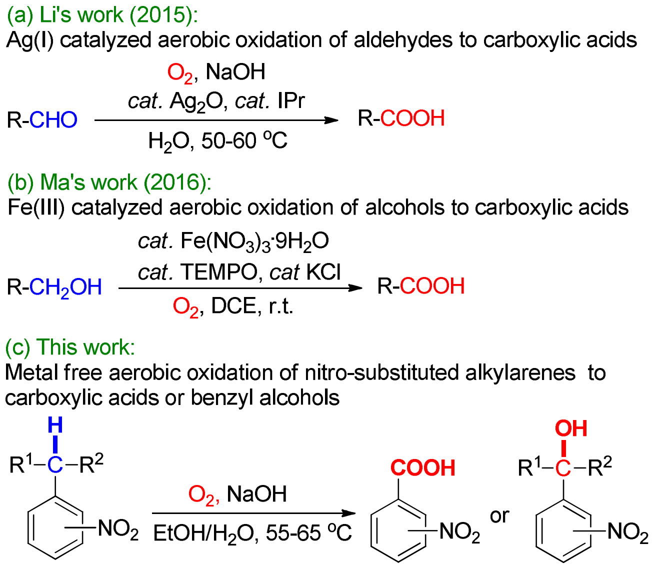


Figure 1. Selected pharmaceutical and pesticide molecules containing the nitro-benzoyl or amino-benzoyl motifs.

Several oxidants[12-17], such as H_2O_2[12], *tert*-butyl hydroperoxide[13], oxone[14], 2,6-dichloropyridine *N*-oxide[15], and 2,6-dimethylbenzoquinone[16], have been investigated for the oxidation of hydrocarbons. Among oxidants, O_2 is ubiquitous, clean, and atom-economical; thus this oxidant has attracted considerable attention in past years and gained notable progress[18-27]. Ishii's group developed a series of efficient mothods for the aerobic oxidation of eubstituted toluenes to aldehydes or carboxylic acids in the presence of carboxylic acids *N*-hydroxyphthalimide (NHPI) or its derivatives and transition metal catalysts, like Co(II), Mn(II).[19] In 2015, Li's group reported an efficient homogeneous Ag(I)-catalyzed aerobic oxidation of aldehydes to carboxylic acids in water by using IPr as ligand (Scheme 1a).[25a] In 2016, Ma's group developed a practical and efficient aerobic oxidation protocol of alcohols to carboxylic acids catalyzed by $Fe(NO_3)_3{\cdot}9H_2O$ (Scheme 1b).[26a] Recently, Pappo's group successfully developed an efficient approach for the highly selective aerobic oxidation of methylarenes to benzaldehydes using NHPI and $Co(OAc)_2$ as catalysts and hexafluoropropan-2-ol as solvent, and up to 98% conversion with 99% selectivity could be achieved.[27] However, direct, selective aerobic oxidation of aromatic alkyl groups remain challenging because of the chemical inert of the C–H bonds and the poor chemoselectivity of alcohol, aldehyde, ketone, and carboxylic acid products.[7d,9,22,28] Here, we aim to report a metal-free, efficient and practical approach for the direct and selective aerobic oxidation of nitro-substituted alkylarenes to carboxylic acids or benzyl alcohols promoted by NaOH with O_2 as clean oxidant.

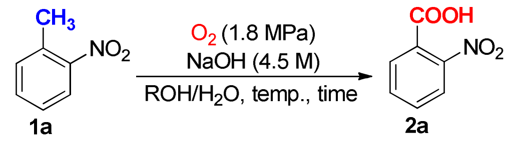
Scheme 1. Aerobic Oxidation of Aldehydes, Alcohols and Nitro-Substituted alkylarenes to Carboxylic Acids.



RESULTS AND DISCUSSION

In the investigation of aerobic oxidation of 2-nitrotoluene (**1a**) in a NaOH/MeOH system with O_2 as oxidant, we unexpectedly found that, without catalyst, 2-nitrobenzoic acid (**2a**) can be obtained in 13% yield with 68% conversion yield of **1a** at room temperature (Table 1, entry 1). This result motivated us to further explore the reaction in detail. Given the potential industrial application and environmental protection issues, a pressure reactor was utilized for the reaction to conserve O_2 and prevent solvent loss. Initially, we investigated the reaction at different temperature (entries 2–4) and found that 67% yield of **2a** can be obtained with a 90% conversion yield of **1a** in MeOH at 52 °C for 24 h (entry 3). Moreover, the addition of water to MeOH was unfavorable for the conversion (entries 5, 6). However, the isolated yield of **2a** can be improved with 80%EtOH as solvent (entry 7). Furthermore, conversions and isolated yields can be increased by prolonging the reaction time (entries 8–10). Anhydrous EtOH and ^{i}PrOH can also serve as the solvents for the aerobic oxidation (entries 11–15); **2a** can be separated in 76% yield with a 91% conversion yield of **1a** in EtOH at 60 °C for 24 h (entry 12) and 72% yield with 90% conversion if ^{i}PrOH is used as solvent at a low temperature (entry 15). A blank experimant was also carried out with the absence of NaOH, and no conversion of **1a** was observed, indicating NaOH played a critical role in the raection.

Table 1. Metal-Free Aerobic Oxidation of 2-Nitrotoluene Using O_2 as Oxidant Under Different Conditions[a]

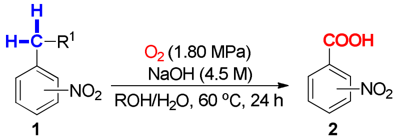


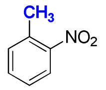
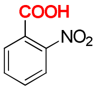
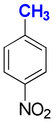
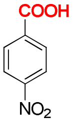
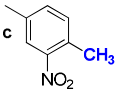
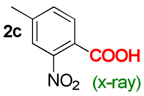
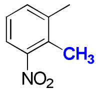
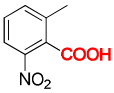
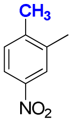
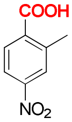
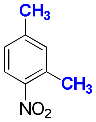
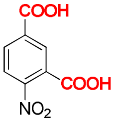
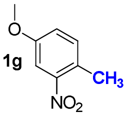
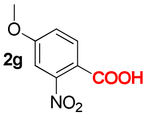
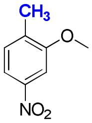
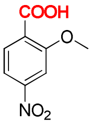
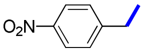
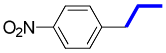
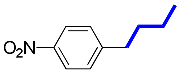
Entry	Solvent	Temp.[b]	Time	Conv.[c]/Yield[d]
1	MeOH	25 °C	24 h	68% / 13%
2	MeOH	38 °C	24 h	83% / 40%
3	MeOH	52 °C	24 h	90% / 67%
4	MeOH	60 °C	24 h	81% / 45%
5	80%MeOH	52 °C	24 h	73% / 57%
6	50%MeOH	60 °C	24 h	49% / 33%
7	80%EtOH	52 °C	24 h	87% / 69%
8	80%EtOH	52 °C	36 h	84% / 75%
9	80%EtOH	52 °C	48 h	90% / 80%
10	80%EtOH	52 °C	72 h	93% / 83%
11	EtOH	52 °C	24 h	80% / 71%
12	EtOH	60 °C	24 h	91% / 76%
13	EtOH	65 °C	24 h	90% / 71%
14	EtOH	77 °C	24 h	87% / 67%
15	^{i}PrOH	52 °C	24 h	90% / 72%
16[e]	EtOH	60 °C	12 h	0% / 0%

[a]Reaction was carried out in a pressure reactor on a 6.0 mmol scale in 10 mL of ROH/H_2O. [b]Internal temperature. [c]Conversion yield was based on the recovery yield of the starting material **1a**. [d]Isolated yield. [e]Without NaOH.

By employing the optimized conditions, a series of nitro-substituted alkylarenes were used to investigate the substrate scope of the above aerobic reaction in pressure reactor, and the comparison of various reaction conditions is shown in Table 2. The oxidation of 4-nitrotoluene (**1b**) can proceed smoothly with a conversion yield nearly quantitative in various solvents (entries 6–11), and 50%EtOH was demonstrated to be a superior solvent for obtaining a 95% yield of **2b** (entry 11), however, if this reaction was carried out in glass bottle using oxygen balloon either under light or in dark, just obtained a litter desired product and a plenty of tarry product, which was insoluble in normal solvents. Then, the substrates bearing two methyl groups on the phenyl ring (**1c**–**1f**) were investigated (entries 12–20). Notably, the methyl groups on the *ortho* or *para* positions of the nitro group can be oxidized selectively to yield corresponding carboxylic acids (**2c**–**2e**) in a moderate to good yield under various conditions, because of their stronge acidity; however, the methyl groups on the *meta* positions remained unchanged (entries 12–18). Moreover, the molecular structure of **2c** was confirmed by single-crystal X-ray diffraction analysis (see Figure S9). As expected, both methyl groups on the 2,4-dimethylnitrobenzene (**1f**) can be converted into carboxyl groups with a conversion yield of up to 97%, but the 4-nitrobenzene-1,3-dioic acid (**2f**) was separated in a low yield owing to a large amount of oily tar formed (entry 20). The substrates containing methoxyl group (**1g**, **1h**) also yielded efficient results (entries 21–23). Unexpectedly, the nitrobenzene substrates bearing the linear alkyl group on the para position (**1i**–**1k**) can be smoothly oxidized involving C–C δ-bond cleavage to generate the sole product **2b** in 93%, 75%, and 91% yields (entries 24, 27, 29). Moreover, mixture of nitro-substituted alkylarenes can easily produce **2b**, indicating that a crude raw material can be used for the reaction and also keep reasonable yield (entries 30, 31). We also tried to some substrates with other electron-withdrawing group, like -Cl, -Br, -F, or cyano group, only no reactions or hydrolysate were observed (see Scheme S1). The reactions were very messy if 2-chloro-1-methyl-4-nitrobenzene, 2-chloro-1-methyl-4-nitrobenzene, 2-methyl-1-nitronaphthalene or 1-methyl-4-(methylsulfonyl)-2-nitrobenzene were used as substrates (see Scheme S1), owing to the possible side reactions, like nucleophilic substitution, Aldol condensation, oxidation of naphthalene ring et. al.

Table 2. Aerobic Oxidation of Nitro-Substituted Alkylarenes to Carboxylic Acids.[a]



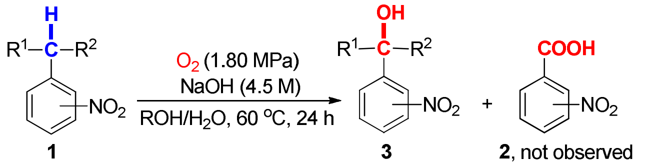
Entry	Substrate	Product	Solvent	Conv.[b]/Yield[c]
1[d]	**1a** 	**2a** 	MeOH	90% / 67%
2[d]			EtOH	80% / 71%
3[d,e]			80%EtOH	93% / 83%
4			EtOH	91% / 76%
5[d]			^{i}PrOH	90% / 72%
6[d]	**1b** 	**2b** 	MeOH	96% / 72%
7[d]			80%MeOH	>99% / 77%
8[d]			50%MeOH	>99% / 92%
9[d]			EtOH	>99% / 70%
10[d]			80%EtOH	>99% / 87%
11[d]			50%EtOH	>99% / 95%
12	**1c** 	**2c** 	80%MeOH	77% / 65%
13			80%EtOH	86% / 75%
14	**1d** 	**2d** 	80%EtOH	69% / 46%
15			EtOH	90% / 64%
16	**1e** 	**2e** 	50%MeOH	92% / 62%
17			50%EtOH	>99% / 53%
18			80%EtOH	>99% / 58%
19	**1f** 	**2f** 	50%EtOH	60% / 18%
20			80%EtOH	97% / 28%
21	**1g** 	**2g** 	80%EtOH	>99% / 75%
22			EtOH	>99% / 57%
23[d]	**1h** 	**2h** 	50%EtOH	>99% / 55%
24	**1i** 	**2b**	50%EtOH	98% / 93%
25			80%EtOH	97% / 80%
26	**1j** 	**2b**	80%EtOH	>99% / 41%
27			EtOH	98% / 75%
28	**1k** 	**2b**	80%EtOH	>99% / 51%
29			EtOH	98% / 91%
30[f]	**1b+1i** (1:1)	**2b**	50%EtOH	— / 89%
31	**1j+1k** (1:1)	**2b**	EtOH	— / 65%

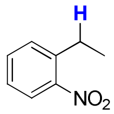
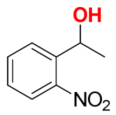
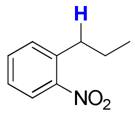
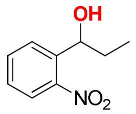
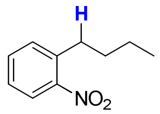
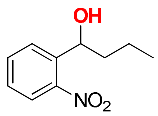
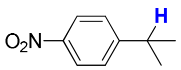
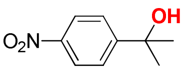
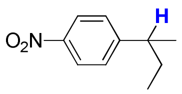
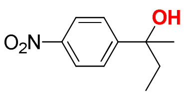
[a] All reactions were carried out in pressure reactors at concentrations of 0.6 M for the substrates unless noted, and internal temperature was reported. [b] Conversion yield was based on the recovery yield of the starting material. [c] Isolated yield. [d] At 52 °C. [e] 72 h. [f] At 55 °C.

Surprisingly, if the linear alkyl groups were on the *ortho* position of the nitro group (**1l**–**1n**), sole product benzyl alcohols (**3a**–**3c**) were obtained in 63%–89% yields under various conditions

(Table 3). These excellent chemoselectivities may be attributed to intramolecular hydrogen bonds between nitro and hydroxyl groups, preventing the benzyl alcohols from being further oxidized.[27] Notably, the reaction can proceed smoothly using an O_2 balloon and achieved 98% conversion and 85% yield (entry 4). Importantly, aerobic oxidation of nitrobenzene substrates with branched alkyl group on the *para* position of the nitro group (**1o**, **1p**) also produced the benzyl alcohol derivatives **3d** and **3e** in good yields (entries 9–12). This approach can be highly efficient for the synthesis of 2-nitrobenzylalcohols , which are difficult to prepare from direct nucleophilic addition between nitrobenzaldehydes and the corresponding Grignard or lithium reagents. Notably, the direct oxidation of the benzyl C–H bond to benzyl alcohol remains challenging because of low yields or poor chemoselectivities.[7d, 9,22, 28]

Table 3. Aerobic Oxidation of Nitro-Substituted Alkylarenes to Benzyl Alcohols[a]



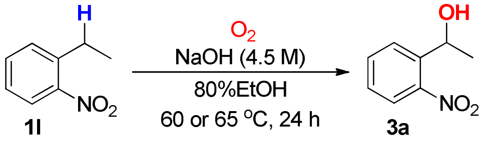
Entry	Substrate	Product	Solvent	Conv.[b]/Yield[c]
1	**1l** 	**3a** 	MeOH	97% / 63%
2			80%MeOH	97% / 63%
3			80%EtOH	95% / 88%
4[d]			80%EtOH	98% / 85%
5	**1m** 	**3b** 	80%EtOH	89% / 85%
6			EtOH	94% / 70%
7	**1n** 	**3c** 	80%EtOH	92% / 89%
8			EtOH	93% / 68%
9	**1o** 	**3d** 	80%EtOH	77% / 76%
10			EtOH	97% / 87%
11[e]	**1p** 	**3e** 	80%EtOH	71% / 68%
12[f]			80%EtOH	81% / 78%

[a] All reactions were performed in pressure reactors with concentrations of 0.6 M for the substrates unless noted, and intrnal temperature was reported. [b] Conversion yield was based on the recovery yield of the starting material. [c] Isolated yield. [d] O_2 balloon was used. [e] 48 h. [f] At 80 °C.

In addition, the effect of substrate concentration on aerobic reaction was investigated based on **1l** (Table 4). Decreased substrate concentration to 0.45 M could further increased the isolated yield to

90% compared with that at 0.60 M under O_2 balloon (entry 2). In general, increased substrate concentration resulted in the decrease in both conversion yields of **1l** and the isolated yields of **3a**. However, production efficiency is a critical parameter for potential application in industry, and the isolated yield was not significantly reduced even at 1.2 M in the pressure reactor under the O_2 balloon (entries 3,4). More than 60% yield can still be obtained even with the increase of substrate concentration to 2.25 M (entries 6,7). It should be noted that some waste water were inevitable in the treatment of the reaction, but not very much.

Table 4. Substrate Conversion at Various Concentrations



Entry	Concentration (**1l**)	O_2 (1.8 MPa) Conv.[a,c]/Yield[b]	O_2 (balloon) Conv.[a,d]/Yield[b]
1	0.30 M	--------	>99% / 84%
2	0.45 M	97% / 78%	99% / 90%
3	0.60 M	95% / 88%	98% / 85%
4	1.20 M	90% / 86%	95% / 67%
5	1.50 M	91% / 69%	93% / 60%
6	2.25 M	80% / 62%	78% / 59%
7[e]	2.25 M	89% / 63%	91% / 69%
8	3.00 M	75% / 48%	63% / 45%

[a] Conversion yield was based on the recovery yield of **1l**. [b] Isolated yield. [c] At 60 °C. [d] At 65 °C. [e] 48 h.

For understanding the reaction process, the in situ NMR experiment was performed using **1l** in NaOD/D_2O/EtOD-d_6 (Figure 2a-d). Evidently, the changes in spectral sharps that the methylene protons (2.85–3.00 ppm) was gradually deuterated. An extremely small amount of **1l** remained after 3.5 h at 65 °C under N_2 (Figure 2c), indicating the strong acidity of the methylene group and the involvement of carbon anion in the reaction.

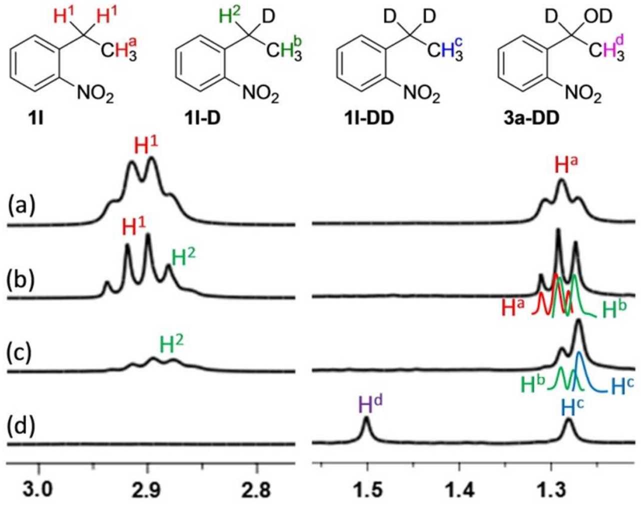
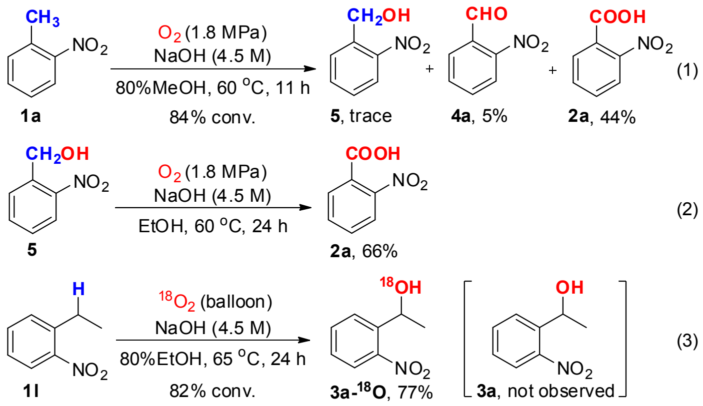


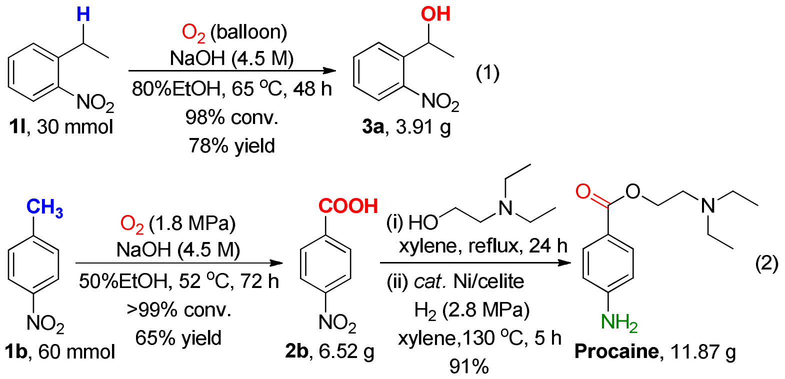
Figure 2. ^{1}H NMR spectrum of **1l** in NaOD/D_2O/EtOD-d_6 for (a), at 65 °C under N_2 for 1.0 h for (b), at 65 °C under N_2 for 3.5 h for (c), and at 65 °C under O_2 for 12.0 h for (d).

To further gain insight into the mechanism of the aerobic oxidation, the control and ^{18}O-labeling experiments were also conducted as shown in Scheme 2. The oxidation of **1a** in 80%MeOH at 60 °C for 11 h afforded 5% 2-nitrobenzaldehyde (**4a**), 44% **2a**, and a trace of 2-nitrobenzenemethanol (**5**) (Scheme 2, Eq 1). Compound **5** can be further oxidized in EtOH under similar conditions to provide **2a** in 66% yield (Eq 2). In addition, the aerobic oxidation of **1l** with the $^{18}O_2$ gas yielded a sole ^{18}O-labeled product **3a-^{18}O** (see Figure S8), indicating that the oxygen atom in the hydroxyl group exclusively originated from the molecular oxygen and not through OH$^\cdot$ from the OH$^-$ of the NaOH. Thus, the reaction was considerably different from the based-catalyzed anthranilate rearrangement in the absence of O_2.[29]

Scheme 2. Control and ^{18}O-Labeling Experiments



Scheme 3. Large-Scale Reactions and Application.



For further demonstrating the practicality of the metal-free aerobic oxidation method, large-scale reactions and application in the synthesis of **Procaine**, one of anesthetics used commonly in clinic, were conducted (Scheme 3). A 30 mmol reaction of **1l** was performed under the O_2 balloon, resulting in 3.91 g of **3a** in 78% yield (Scheme 3, Eq 1). The other gram-scale oxidation was carried out for **1b** on a 60 mmol scale, and 6.52 g of **2b** can be separated in 65% yield (Eq 2). After esterification of **2b** with 2-(diethylamino)ethanol, **Procaine** can be efficiently synthesized through the hydrogenation of the nitro group catalyzed with a recyclable Ni/celite catalyst with 91% yield by using only two environmentally friendly organic solvents. This procedure can also be utilized for synthesizing other anesthetics.

CONCLUSION

In summary, we developed an efficient, metal-free approach for the aerobic oxidation of nitro-substituted alkylarenes to carboxylic acids or benzyl alcohols with high chemoselectivities. This sustainable system can use O_2 as clean oxidant in green NaOH/EtOH mixture under mild conditions. The position and type of the alkyl substituent critically affected the product. Moreover, this cheap and green protocol is suitable for gram-scale preparation. Furthermore, the reactions conducted in the pressure reactor or under the balloon can conserve oxygen and avoid solvent loss, which are all conducive to the environmental protection problem. Further studies on the mechanism details and other potential applications are still under way in our laboratory.

EXPERIMENTAL SECTION

General Information. ^1H NMR spectra were recorded at 400 or 500 MHz, and ^{13}C NMR spectra were recorded at 100 or 126 MHz NMR instruments in $CDCl_3$ or DMSO–d_6 solutions and chemical shifts were referenced to tetramethylsilane (TMS) or residual protiated solvent. If $CDCl_3$ was used as solvent, ^1H NMR spectra were recorded with TMS (δ = 0.00 ppm) as internal reference; ^{13}C NMR spectra were recorded with $CDCl_3$ (δ = 77.00 ppm) as internal reference. If DMSO–d_6 was used as solvent, ^1H NMR spectra were recorded with TMS (δ = 0.00 ppm) or residual H_2O (δ = 3.33 ppm) as internal reference; ^{13}C NMR spectra were recorded with DMSO–d_6 (δ = 39.52 ppm) as internal reference. All of the new compounds were analyzed for HRMS on an ESI-QTOF mass spectrometer using electrospray ionization in positive ion mode. The following abbreviations (or combinations thereof) were used to explain ^1H NMR ultiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad. Mass spectra were recorded on Thermo Fisher Scientific LTQ FT Ultra mass spectrometer.

All the starting materials were purchased and used as received without further purification. The Ni/celite (Ni: 50%) catalyst was from the donation of professor Jiantai Ma (Lanzhou University).

General Experimental Procedure A: Aerobic Oxidation of Nitro-Substituted Alkylarenes to Carboxylic Acids in Pressure Reactor.

The nitro hydrocarbon, solvent (EtOH, EtOH/H_2O, MeOH or MeOH/H_2O) and NaOH were added to a 100 mL pressure reactor equipped with a magnetic stir bar. The pressure reactor was filled with oxygen (1.0 MPa), then the gas was deflated, this fill and deflation procedure was repeated another twice. After that, the pressure reactor was refilled with oxygen (1.8 MPa), sealed, then stirred at 52 or 60 ^{o}C for 24–72 h (oil bath temp. 55 or 65 ^{o}C). Then the mixture was cooled down to ambient temperature, and the excess oxygen was released slowly. The reaction mixture was transferred to a round bottom flask and neutralized with concentrated hydrochloric acid to pH = 2–3. If EtOH or MeOH as the solvent, the residue was diluted with ethyl acetate, dried over anhydrous Na_2SO_4; If EtOH/H_2O or MeOH/H_2O as the solvent, the residue was extracted with ethyl acetate three times, and the combined organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford the desired product.

General Experimental Procedure B: Aerobic Oxidation of Nitro-Substituted Alkylarenes to Benzyl Alcohols in Pressure Reactor.

The nitro hydrocarbon, solvent (EtOH, EtOH/H_2O, MeOH or MeOH/H_2O) and NaOH were added to a 100 mL pressure reactor equipped with a magnetic stir bar. The pressure reactor was filled with oxygen (1.0 MPa), then the gas was deflated, this fill and deflation procedure was repeated another twice. After that, the pressure reactor was refilled with oxygen (1.8 MPa), sealed, then stirred at 60 ^{o}C for 24–48 h(oil bath temp. 65 ^{o}C). Then the mixture was cooled down to ambient temperature, and the excess oxygen was released slowly. The reaction mixture was transferred to a round bottom flask neutralized with concentrated hydrochloric acid to pH = 6–7. If EtOH or MeOH as the solvent, the residue was diluted with ethyl acetate, dried over anhydrous Na_2SO_4; If EtOH/H_2O or MeOH/H_2O as the solvent, the residue was extracted with ethyl acetate three times, and the combined organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford the desired product.

General Experimental Procedure C: Aerobic Oxidation of Nitro-Substituted Alkylarenes to Benzyl Alcohols Under Oxygen Balloon.

The nitro hydrocarbon, solvent (EtOH/H_2O=4:1) and NaOH were added to flask equipped with a magnetic stir bar. The flask was then evacuated and backfilled with oxygen (0.1 MPa), this evacuation and backfill procedure was repeated twice. Then the flask was placed in an oil bath (65 ^{o}C) and stirred under a oxygen balloon for 24–48 h. Then the mixture was cooled down to ambient temperature. The reaction mixture was transferred to a round bottom flask neutralized with concentrated hydrochloric acid to pH=6–7. Then the organic solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate three times, and the combined organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford the desired product.

Aerobic oxidation of 2-nitrotoluene (**1a**) to 2-nitrobenzoic acid (**2a**):

Table 2, entry 1: Following the general experimental procedure A, the reaction mixture of **1a** (823 mg, 6.0 mmol), MeOH (10 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 ^{o}C (oil bath temp.: 55 ^{o}C) for 24 hours to afford **2a** (eluent: petroleum ether/ethyl acetate

= 5:1–3:1) as a slight yellow solid, 673 mg in 67% yield, wherein **1a** was recycled 99 mg in 10% yield. Mp: 141.1–141.7 °C. ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.75–7.81 (m, 2H), 7.85–7.87 (m, 1H), 7.97–7.99 (m, 1H), 13.84 (br, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 123.7, 127.3, 129.9, 132,4, 133.1, 148.4, 165.9. The NMR data was in accordance with the literature.[30] MS (DART Negative) *m/z*: 166.0 ([M–H]$^-$, 100%), 333.0 ([2M–H]$^-$, 46%). HRMS (DART Negative, LTQ FT): calcd for $C_7H_4O_4N$ [M–H]$^-$: 166.0146, found 166.0144.

Table 2, entry 2: Following the general experimental procedure A, the reaction mixture of **1a** (823 mg, 6.0 mmol), EtOH (10 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 24 hours to afford **2a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 713 mg in 71% yield, wherein **1a** was recycled 201 mg in 20% yield. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 3: Following the general experimental procedure A, the reaction mixture of **1a** (823 mg, 6.0 mmol), 80%EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 72 hours to afford **2a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 825 mg in 83% yield, wherein **1a** was recycled 62 mg in 7% yield. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 4: Following the general experimental procedure A, the reaction mixture of **1a** (823 mg, 6.0 mmol), EtOH (10 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) for 24 hours to afford **2a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 757 mg in 76% yield, wherein **1a** was recycled 73 mg in 9% yield. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 5: Following the general experimental procedure A, the reaction mixture of **1a** (823 mg, 6.0 mmol), ^{i}PrOH (10 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 24 hours to afford **2a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 724 mg in 72% yield, wherein **1a** was recycled 99 mg in 10% yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 4-nitrotoluene (**1b**) to 4-nitrobenzoic acid (**2b**):

Table 2, entry 6: Following the general experimental procedure A, the reaction mixture of **1b** (823 mg, 6.0 mmol), MeOH (10 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 719 mg in 72% yield, wherein **1b** was recycled 34 mg in 4% yield. Mp: 234.7–235.9 °C. ^{1}H NMR (500 MHz, DMSO–d_6): δ 8.16 (dt, J = 9.5, 2.0 Hz, 2H), 8.32 (dt, J = 9.0, 2.0 Hz, 2H), 13.66 (br, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 123.7, 130.7, 136.4, 150.0, 165.8. The NMR data was in accordance with the literature.[31] MS (DART Negative) *m/z*: 166.0 ([M–H]$^-$, 100%), 333.0 ([2M–H]$^-$, 12%). HRMS (DART Negative, LTQ FT): calcd for $C_7H_4O_4N$ [M–H]$^-$: 166.0146, found 166.0144.

Table 2, entry 7: Following the general experimental procedure A, the reaction mixture of **1b** (823 mg, 6.0 mmol), 80% MeOH (MeOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 767 mg in 77% yield, and **1b** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 8: Following the general experimental procedure A, the reaction mixture of **1b** (823 mg, 6.0 mmol), 50% MeOH (MeOH/H_2O=5 mL/5 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 920 mg in 92% yield, and **1b** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 9: Following the general experimental procedure A, the reaction mixture of **1b** (823 mg, 6.0 mmol), EtOH (10 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 698 mg in 70% yield, and **1b** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 10: Following the general experimental procedure A, the reaction mixture of **1b** (823 mg, 6.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 874 mg in 87% yield, and **1b** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 11: Following the general experimental procedure A, the reaction mixture of **1b** (823 mg, 6.0 mmol), 50% EtOH (EtOH/H_2O = 5 mL/5 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 52 °C (oil bath temp.: 55 °C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 947 mg in 95% yield, and **1b** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 1,4-dimethyl-2-nitrobenzene (**1c**) to 4-methyl-2-nitrobenzoic acid (**2c**):

Table 2, entry 12: Following the general experimental procedure A, the reaction mixture of **1c** (907 mg, 6.0 mmol), 80% MeOH ($MeOH/H_2O$ = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) 24 hours to afford **2c** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 707 mg in 65% yield, wherein **1c** was recycled 207 mg in 23% yield. Mp: 156.6–157.3 °C. ^{1}H NMR (500 MHz, DMSO–d_6): δ 2.43 (s, 3H), 7.59 (dd, J = 8.0, 1.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H) , 13.72 (br, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 20.6, 123.8, 123.8, 130.0, 133.1, 143.5, 148.9, 165.6. MS (DART Negative) *m/z*: 180.0 ($[M–H]^-$, 100%), 361.1 ($[2M–H]^-$, 35%). HRMS (DART Negative, LTQ FT): calcd for $C_8H_6O_4N$ $[M–H]^-$: 180.0302, found 180.0301.

Table 2, entry 13: Following the general experimental procedure A, the reaction mixture of **1c** (907 mg, 6.0 mmol), 80% EtOH ($EtOH/H_2O$ = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) for 24 hours to afford **2c** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 811 mg in 75% yield, wherein **1c** was recycled 129 mg in 14% yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 1,2-dimethyl-3-nitrobenzene (**1d**) to 2-methyl-6-nitrobenzoic acid (**2d**):

Table 2, entry 14: Following the general experimental procedure A, the reaction mixture of **1d** (455 mg, 3.0 mmol), 80% EtOH ($EtOH/H_2O$ = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) for 24 hours to afford **2d** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a yellow solid, 247 mg in 46% yield, wherein **1d** was recycled 141 mg in 31% yield. Mp: 144.4–145.1 °C. ^{1}H NMR (500 MHz, DMSO–d_6): δ 2.39 (s, 3H), 7.59 (t, J = 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 13.83 (br, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 18.7, 121.6, 129.9, 130.1, 136.3, 136.5, 145.7, 167.1. MS (DART Negative) *m/z*: 180.0 ($[M–H]^-$, 100%), 361.1 ($[2M–H]^-$, 41%). HRMS (DART Negative, LTQ FT): calcd for $C_8H_6O_4N$ $[M – H]^-$: 180.0302, found 180.0301.

Table 2, entry 15: Following the general experimental procedure A, the reaction mixture of **1d** (455 mg, 3.0 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2d** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a yellow solid, 350 mg in 64% yield, wherein **1d** was recycled 47 mg in 10% yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 1,2-dimethyl-4-nitrobenzene (**1e**) to 2-methyl-4-nitrobenzoic acid (**2e**):

Table 2, entry 16: Following the general experimental procedure A, the reaction mixture of **1e** (907 mg, 6.0 mmol), 50% MeOH (MeOH/H_2O = 5 mL/5 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2e** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 673 mg in 62% yield, wherein **1e** was recycled 72 mg in 8% yield. Mp: 140.5–141.6 ^{o}C. ^{1}H NMR (500 MHz, DMSO–d_6): δ 2.60 (s, 3H), 7.98 (d, J = 9.0 Hz, 1H), 8.09 (dd, J = 8.5, 2.5 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 13.55 (br, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 20.7, 120.8, 125.7, 131.2, 136.9, 140.7, 148.7, 167.5. MS (DART Negative) *m/z*: 180.0 ([M–H]$^-$, 100%), 361.1 ([2M–H]$^-$, 10%). HRMS (DART Negative, LTQ FT): calcd for $C_8H_6O_4N$ [M–H]$^-$: 180.0302, found 180.0300.

Table 2, entry 17: Following the general experimental procedure A, the reaction mixture of **1e** (907 mg, 6.0 mmol), 50% EtOH (EtOH/H_2O = 5 mL/5 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2e** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a red solid, 580 mg in 53% yield, and **1e** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 18: Following the general experimental procedure A, the reaction mixture of **1e** (454 mg, 3.0 mmol), 80% EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2e** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a red solid, 312 mg in 58% yield, and **1e** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 2,4-dimethyl-1-nitrobenzene (**1f**) to 4-nitrobenzene-1,3-dioic acid (**2f**):

Table 2, entry 19: Following the general experimental procedure A, the reaction mixture of **1f** (907 mg, 6.0 mmol), 50% EtOH (EtOH/H_2O = 5 mL/5 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2f** (eluent:

petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 231 mg in 18% yield, wherein **1f** was recycled 367 mg in 40% yield. Mp: 259.9–260.8 °C (literature reported: 260–263 °C)[32]. ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.77 (d, J = 8.5 Hz, 1H), 8.01 (dd, J = 8.0, 2.0 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 13.85 (br, 2H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 124.3, 126.7, 130.8, 133.5, 134.4, 151.0, 164.8, 165.1. The NMR data was in accordance with the literature.[3] MS (DART Negative) *m/z*: 166.0 ($[M\text{-}H\text{-}CO_2]^-$, 24%), 210.0 ($[M–H]^-$, 100%). HRMS (DART Negative, LTQ FT): calcd for $C_8H_4O_6N$ $[M–H]^-$: 210.0044, found 210.0042.

Table 2, entry 20: Following the general experimental procedure A, the reaction mixture of **1f** (454 mg, 3.0 mmol), 80% EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) for 24 hours to afford **2f** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 180 mg in 28% yield, wherein **1f** was recycled 16 mg in 3% yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 4-methoxy-1-methyl-2-nitrobenzene (**1g**) to 4-methoxy-2-nitrobenzoic acid (**2g**):

Table 2, entry 21: Following the general experimental procedure A, the reaction mixture of **1g** (501 mg, 3.0 mmol), 80%EtOH (EtOH/H2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) for 24 hours to afford **2g** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a white solid, 444 mg in 75% yield, and **1g** was consumed completely. Mp: 194.1–194.9 °C. ^{1}H NMR (500 MHz, DMSO–d_6): δ 3.89 (s, 3H), 7.27 (dd, J = 9.0, 2.5 Hz, 1H), 7.49 (d, J = 2.5 Hz, 1H), 7.87 (d, J = 9.0 Hz, 1H), 13.55 (br, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 56.4, 109.1, 117.0, 117.3, 132.2, 151.2, 162.2, 164.7. MS (DART Positive Ion Mode) *m/z*: 136.0 ($[M\text{-}NO_2\text{-}CH_3]^+$, 2%), 149.0 ($[M\text{-}H_2O\text{-}CH_3O\text{+}H]^+$, 4%), 180.0 ($[M\text{-}H_2O\text{+}H]^+$, 17%), 198.0 ($[M\text{+}H]^+$, 42%), 215.1 ($[M\text{+}H_2O]^+$, 100%). HRMS (DART Positive Ion Mode, LTQ FTICR): calcd for $C_8H_8O_5N$ $[M\text{+}H]^+$: 198.0397, found 198.0396.

Table 2, entry 22: Following the general experimental procedure A, the reaction mixture of **1g** (501 mg, 3.0 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) for 24 hours to afford **2g** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a white solid, 336 mg in 57% yield, and **1g** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 2-methoxy-1-methyl-4-nitrobenzene (**1h**) to 2-methoxy-4-nitrobenzoic acid (**2h**):

Table 2, entry 23: Following the general experimental procedure A, the reaction mixture of **1h** (1003 mg, 6.0 mmol), 50% EtOH (EtOH/H_2O = 5 mL/5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 52 ^oC (oil bath temp.: 55 ^oC) for 24 hours to afford **2h** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a red solid, 646 mg in 55% yield, and **1h** was consumed completely. Mp: 126.4.1–127.4 ^oC. ^1H NMR (500 MHz, DMSO–d_6): δ 3.95 (s, 3H), 7.82 (dd, J = 7.5, 1.0 Hz, 1H), 7.84–7.86 (m, 2H), 13.36 (br, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 56.5, 107.1, 115.1, 128.2, 130.9, 149.8, 157.9, 166.3. The NMR data was in accordance with the literature.[33] MS (DART Positive Ion Mode) *m/z*: 136.0 ($[M-NO_2-CH_3]^+$, 5%), 149.0 ($[M-H_2O-CH_3O+H]^+$, 8%), 154.0 ($[M-H_2O-CH_3]^+$, 21%), 180.0 ($[M-H_2O+H]^+$, 23%), 198.0 ($[M+H]^+$, 100%), 215.1 ($[M+H_2O]^+$, 8%), 244.1 ($[M+NO_2+H]^+$, 8%). HRMS (DART Positive Ion Mode, LTQ FTICR): calcd for $C_8H_8O_5N$ $[M + H]^+$: 198.0397, found 198.0397.

Aerobic oxidation of 1-ethyl-4-nitrobenzene (**1i**) to 4-nitrobenzoic acid (**2b**):

Table 2, entry 24: Following the general experimental procedure A, the reaction mixture of **1i** (907 mg, 6.0 mmol), 50% EtOH (EtOH/H_2O = 5 mL/5 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 929 mg in 93% yield, wherein **1i** was recycled 18 mg in 2% yield. The structure of the product was confirmed by ^1H NMR.

Table 2, entry 25: Following the general experimental procedure A, the reaction mixture of **1i** (907 mg, 6.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 798 mg in 80% yield, wherein **1i** was recycled 27 mg in 3% yield. The structure of the product was confirmed by ^1H NMR.

Aerobic oxidation of 1-nitro-4-propylbenzene (**1j**) to 4-nitrobenzoic acid (**2b**):

Table 2, entry 26: Following the general experimental procedure A, the reaction mixture of **1j** (496 mg, 3.0 mmol), 80% EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **2b** (eluent:

petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 205 mg in 41% yield, and **1j** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 27: Following the general experimental procedure A, the reaction mixture of **1j** (496 mg, 3.0 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 375 mg in 75% yield, wherein **1j** was recycled 10 mg in 2% yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 1-butyl-4-nitrotoluene (**1k**) to 4-nitrobenzoic acid (**2b**):

Table 2, entry 28: Following the general experimental procedure A, the reaction mixture of **1k** (538 mg, 3.0 mmol), 80% EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 256 mg in 51% yield, and **1k** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

Table 2, entry 29: Following the general experimental procedure A, the reaction mixture of **1k** (538 mg, 3.0 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 456 mg in 91% yield, wherein **1k** was recycled 11 mg in 2% yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of a mixture of **1b+1i** to 4-nitrobenzoic acid (**2b**):

Table 2, entry 30: Following the general experimental procedure A, the reaction mixture of **1b** (411 mg, 3.0 mmol), **1i** (453 mg, 3.0 mmol), 50%EtOH (EtOH/H_2O = 5 mL/5 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 55 ^{o}C (oil bath temp.: 60 ^{o}C) for 24 hours to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 891 mg in 89% yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of a mixture of **1j+1k** to 4-nitrobenzoic acid (**2b**):

Table 2, entry 31: Following the general experimental procedure A, the reaction mixture of **1j** (248 mg, 1.5 mmol), **1k** (269 mg, 1.5 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **2b** (eluent:

petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 325 mg in 65% yield. wherein **1j+1k** was recycled 50 mg. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 1-ethyl-2-nitrobenzene (**1l**) to 1-(2-nitrophenyl)ethanol (**3a**):

Table 3, entry 1: Following the general experimental procedure B, the reaction mixture of **1l** (907 mg, 6.0 mmol), MeOH (10 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 631 mg in 63% yield, wherein **1l** was recycled 30 mg in 3% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (d, J = 6.5 Hz, 3H), 2.34 (s, 1H), 5.42 (q, J = 6.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.90(d, J = 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.2, 65.5, 124,3, 127.5, 128.1, 133.6, 140.9, 147.8. The NMR data was in accordance with the literature.[34] HR (DART Positive, LTQ FT) *m/z*: 120.1 ($[M-NO_2-H]^+$, 2%), 150.1 ($[M-H_2O+H]^+$, 100%), 185.1 ($[M+NH_4]^+$, 15%).

Table 3, entry 2: Following the general experimental procedure B, the reaction mixture of **1l** (907 mg, 6.0 mmol), 80% MeOH ($MeOH/H_2O$ = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 629 mg in 63% yield, wherein **1l** was recycled 23 mg in 3% yield. The structure of the product was confirmed by ^{1}H NMR.

Table 3, entry 3: Following the general experimental procedure B, the reaction mixture of **1l** (907 mg, 6.0 mmol), 80 % EtOH ($EtOH/H_2O$ = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 878 mg in 88% yield, wherein **1l** was recycled 47 mg in 5% yield. The structure of the product was confirmed by ^{1}H NMR.

Table 3, entry 4: Following the general experimental procedure C, the reaction mixture of **1l** (907 mg, 6.0 mmol), 80% EtOH ($EtOH/H_2O$ = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) under an oxygen balloon was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 856 mg in 85% yield, wherein **1l** was recycled 17 mg in 2 % yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 1-nitro-2-propylbenzene (**1m**) to 1-(2-nitrophenyl)propan-1-ol (**3b**):

Table 3, entry 5: Following the general experimental procedure B, the reaction mixture of **1m** (496 mg, 3.0 mmol), 80% EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **3b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow liquid, 464 mg in 85% yield, wherein **1m** was recycled 57 mg in 11 % yield. ^1H NMR (500 MHz, DMSO–d_6): δ 0.92 (t, J = 7.5 Hz, 3H), 1.51–1.60 (m, 1H), 1.64–1.72 (m, 1H), 4.86–4.89 (m, 1H), 5.51 (d, J = 4.5 Hz, 1H), 7.47–7.50 (m, 1H), 7.72 (td, J = 7.5, 2.0 Hz, 1H), 7.78 (dd, J = 7.5, 2.0 Hz, 1H), 7.87 (dd, J = 8.5, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 10.5, 31.5, 68.8, 123.6, 127.9, 128.2, 133.1, 140.7, 147.7. HRMS (EI, TOF): calcd for $C_7H_6NO_3$ $[M-C_2H_5]^+$: 152.0348, found 152.0346.

Table 3, entry 6: Following the general experimental procedure B, the reaction mixture of **1m** (496 mg, 3.0 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **3b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 382 mg in 70% yield, wherein **1m** was recycled 30 mg in 6 % yield. The structure of the product was confirmed by ^1H NMR.

Aerobic oxidation of1-butyl-2-nitrobenzene (**1n**) to 1-(2-nitrophenyl)butan-1-ol (**3c**):

Table 3, entry 7: Following the general experimental procedure B, the reaction mixture of **1n** (538 mg, 3.0 mmol), 80% EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **3c** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow liquid, 522 mg in 89% yield, wherein **1n** was recycled 43 mg in 8 % yield. ^1H NMR (500 MHz, DMSO–d_6): δ 0.88 (t, J = 7.5 Hz, 3H), 1.35–1.40 (m, 1H), 1.44–1.50 (m, 1H), 1.51–1.59 (m, 2H), 4.94–4.98 (m, 1H), 5.49 (d, J = 5.0 Hz, 1H), 7.47–7.50 (m, 1H), 7.71(td, J = 7.5, 1.0 Hz, 1H), 7.79 (dd, J = 8.0, 1.0 Hz, 1H), 7.87 (dd, J = 8.0, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 13.6, 18.8, 40.7, 67.0, 123.6, 127.9, 128.1, 133.1, 141.1, 147.6. HRMS (EI, TOF): calcd for $C_7H_6NO_3$ $[M-C_3H_7]^+$: 152.0348, found 152.0358.

Table 3, entry 8: Following the general experimental procedure B, the reaction mixture of **1n** (538 mg, 3.0 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **3c** (eluent: petroleum ether/ethyl acetate = 5:1-3:1) as a slight yellow liquid, 396 mg in 68% yield, wherein **1n** was recycled 76 mg in 7 % yield.The structure of the product was confirmed by ^1H NMR.

Aerobic oxidation of 1-isopropyl-4-nitrobenzene (**1o**) to 2-(4-nitrophenyl)propan-2-ol (**3d**):

Table 3, entry 9: Following the general experimental procedure B, the reaction mixture of **1o** (496 mg, 3.0 mmol), 80 %EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **3d** (eluent: petroleum ether/ethyl acetate = 5:1-3:1) as a brown liquid, 411 mg in 76% yield, wherein **1o** was recycled 115 mg in 23 % yield. ^{1}H NMR (500 MHz, DMSO–d_6): δ 1.46 (s, 6H), 5.36 (s, 1H), 7.23–7.76 (m, 2H), 8.16–8.18 (m, 2H). ^{13}C NMR (126 MHz, DMSO–d_6): δ 31.2, 70.8, 123.0, 125.9, 145.9, 158.4. HRMS (EI): calcd for $C_8H_8NO_3$ $[M-CH_3]^+$: 166.0504, found 166.0512.

Table 3, entry 10: Following the general experimental procedure B, the reaction mixture of **1o** (496 mg, 3.0 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **3d** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 474 mg in 87% yield, wherein **1o** was recycled 17 mg in 3 % yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 1-*sec*-butyl-4-nitrobenzene (**1p**) to 2-(4-nitrophenyl)butan-2-ol (**3e**):

Table 3, entry 11: Following the general experimental procedure B, the reaction mixture of **1p** (538 mg, 3.0 mmol), 80 %EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 48 hours to afford **3e** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow liquid, 398 mg in 68% yield, wherein **1p** was recycled 118 mg in 29 % yield. ^{1}H NMR (400 MHz, DMSO–d_6): δ 0.67 (t, J = 9.0 Hz, 3H), 1.43 (s, 3H), 1.66–1.80 (m, 2H), 5.17 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO–d_6): δ 8.1, 29.5, 36.1, 73.2, 122.9, 126.5, 145.8, 157.1. HRMS (EI, TOF): calcd for $C_{10}H_{11}NO_2$ $[M–H_2O]^+$: 177.0790, found 177.0797.

Table 3, entry 12: Following the general experimental procedure B, the reaction mixture of **1p** (538 mg, 3.0 mmol), 80% EtOH (EtOH/H_2O = 4 mL/1 mL) and NaOH (900 mg, 22.5 mmol) in the pressure reactor was stirred at 73 ^{o}C (oil bath temp.: 80 ^{o}C) for 24 hours to afford **3e** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow liquid, 459 mg in 78% yield, wherein **1p** was recycled 102 mg in 19 % yield. The structure of the product was confirmed by ^{1}H NMR.

Aerobic oxidation of 1-ethyl-2-nitrobenzene (**1l**) to 1-(2-nitrophenyl)ethanol (**3a**) at different concentrations:

Table 4, entry 1: Following the general experimental procedure C, the reaction mixture of **1l** (454 mg, 3.0 mmol), 80 %EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) under an oxygen balloon was placed in an oil bath (65 ^oC) and was stirred for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1-3:1) as a brown liquid, 419 mg in 84% yield, and **1l** was consumed completely. The structure of the product was confirmed by ^1H NMR.

Table 4, entry 2: Following the general experimental procedure B, the reaction mixture of **1l** (680 mg, 4.5 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 590 mg in 78% yield, wherein **1l** was recycled 18 mg in 3 % yield. The structure of the product was confirmed by ^1H NMR.

Following the general experimental procedure C, the reaction mixture of **1l** (680 mg, 4.5 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) under an oxygen balloon was placed in an oil bath (65 ^oC) and was stirred for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 669 mg in 90% yield, wherein **1l** was recycled 7 mg in 1 % yield. The structure of the product was confirmed by ^1H NMR.

Table 4, entry 3: Following the general experimental procedure B, the reaction mixture of **1l** (907 mg, 6.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 878 mg in 88% yield, wherein **1l** was recycled 47 mg in 5 % yield. The structure of the product was confirmed by ^1H NMR.

Following the general experimental procedure C, the reaction mixture of **1l** (907 mg, 6.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) under an oxygen balloon was placed in an oil bath (65 ^oC) and was stirred for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 856 mg in 85% yield, wherein **1l** was recycled 17 mg in 2 % yield. The structure of the product was confirmed by ^1H NMR.

Table 4, entry 4: Following the general experimental procedure B, the reaction mixture of **1l** (1814 mg, 12.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^oC (oil bath temp.: 65 ^oC) for 24 hours to afford **3a** (eluent:

petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 1733 mg in 86% yield, wherein **1l** was recycled 190 mg in 10 % yield. The structure of the product was confirmed by ^{1}H NMR.

Following the general experimental procedure C, the reaction mixture of **1l** (1814 mg, 12.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) under an oxygen balloon was placed in an oil bath (65 ^{o}C) and was stirred for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 1339 mg in 67% yield, wherein **1l** was recycled 99 mg in 5 % yield. The structure of the product was confirmed by ^{1}H NMR.

Table 4, entry 5: Following the general experimental procedure B, the reaction mixture of **1l** (2268 mg, 15.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 1734 mg in 69% yield, wherein **1l** was recycled 211 mg in 9 % yield. The structure of the product was confirmed by ^{1}H NMR.

Following the general experimental procedure C, the reaction mixture of **1l** (2268 mg, 15.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) under an oxygen balloon was placed in an oil bath (65 ^{o}C) and was stirred for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 1494 mg in 60% yield, wherein **1l** was recycled 183 mg in 7 % yield. The structure of the product was confirmed by ^{1}H NMR.

Table 4, entry 6: Following the general experimental procedure B, the reaction mixture of **1l** (3401 mg, 22.5 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 ^{o}C (oil bath temp.: 65 ^{o}C) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 2334 mg in 62% yield, wherein **1l** was recycled 673 mg in 20 % yield. The structure of the product was confirmed by ^{1}H NMR.

Following the general experimental procedure C, the reaction mixture of **1l** (3401 mg, 22.5 mmol), 80%EtOH (EtOH/H_2O=8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) under an oxygen balloon was placed in an oil bath (65 ^{o}C) and was stirred for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 2216 mg in 59% yield, wherein **1l** was recycled 765 mg in 22% yield. The structure of the product was confirmed by ^{1}H NMR.

Table 4, entry 7: Following the general experimental procedure B, the reaction mixture of **1l** (3401 mg, 22.5 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) for 48 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 2368 mg in 63% yield, wherein **1l** was recycled 391 mg in 11 % yield. The structure of the product was confirmed by ^{1}H NMR.

Following the general experimental procedure C, the reaction mixture of **1l** (3401 mg, 22.5 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) under an oxygen balloon was placed in an oil bath (65 °C) and was stirred for 48 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 2595 mg in 69% yield, wherein **1l** was recycled 291 mg in 9 % yield. The structure of the product was confirmed by ^{1}H NMR.

Table 4, entry 8: Following the general experimental procedure B, the reaction mixture of **1l** (4535 mg, 30.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in the pressure reactor was stirred at 60 °C (oil bath temp.: 65 °C) for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 2398 mg in 48% yield, wherein **1l** was recycled 1251 mg in 25 % yield. The structure of the product was confirmed by ^{1}H NMR.

Following the general experimental procedure C, the reaction mixture of **1l** (4535 mg, 30.0 mmol), 80% EtOH (EtOH/H_2O = 8 mL/2 mL) and NaOH (1800 mg, 45.0 mmol) in under an oxygen balloon was placed in an oil bath (65 °C) and was stirred for 24 hours to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 2272 mg in 45% yield, wherein **1l** was recycled 1687 mg in 37 % yield. The structure of the product was confirmed by ^{1}H NMR.

Control Experiments.

Scheme 2, eq 1 : The 1-methyl-2-nitrobenzene **1a** (1646 mg, 12.0 mmol), 80% MeOH (MeOH/H_2O = 16 mL/4 mL) and NaOH (3600 mg, 90.0 mmol) were added to a pressure reactor equipped with a magnetic stir bar. The pressure reactor was filled with oxygen (1.0 MPa), then the gas was deflated, this fill and deflation procedure was repeated another twice. After that, the pressure reactor was refilled with oxygen (1.8 MPa), sealed, then the mixture was stirred at 60 °C (oil bath temp.: 65 °C) for 11 h, cooled down to ambient temperature, and the excess oxygen was released slowly. The reaction mixture was transferred to a round bottom flask and the organic solvent was removed under reduced pressure. The residue was extracted with ethyl acetate three times, and the combined organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified through column chromatography on silica gel using petroleum ether/ethyl acetate = 5:1-3:1 as eluent to afford **4a** as a slight yellow solid, 91 mg in 5% yield; and a trace of (2-nitrophenyl)methanol **5** was also observed; **2a** as a slight yellow solid, 873 mg in 44% yield, wherein **1a** was recycled 262 mg in 16% yield. The structure of the product **2a** was confirmed by ^{1}H NMR. **4a:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75–7.82 (m, 2H), 7.96 (dd, J = 7.5, 1.5 Hz, 1H), 8.13 (dd, J = 8.0, 1.0 Hz, 1H), 10.43 (s, 1H).

Scheme 2, eq 2: The (2-nitrophenyl)methanol **5** (367 mg, 3.0 mmol), EtOH (5 mL) and NaOH (900 mg, 22.5 mmol) were added to a pressure reactor equipped with a magnetic stir bar. The pressure reactor was filled with oxygen (1.0 MPa), then the gas was deflated, this fill and deflation procedure was repeated another twice. After that, the pressure reactor was refilled with oxygen (1.8 MPa), sealed. The mixture was stirred at 60 °C (oil bath temp.: 65 °C) for 24 h, cooled down to ambient temperature, the excess oxygen was released slowly. The reaction mixture was transferred to a round bottom flask, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through column chromatography on silica gel to afford **2a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a slight yellow solid, 268 mg in 66% yield, and **1a** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

^{18}O-labeling Experiment.

Scheme 2, eq 3: The 1-ethyl-2-nitrobenzene **1l** (181 mg, 1.2 mmol), and NaOH (360 mg, 9.0 mmol) were added to a 10 mL round bottom flask equipped with a magnetic stir bar. The flask was evacuated and backfilled with $^{18}O_2$ gas (balloon). Then EtOH (1.6 mL) and H_2O (0.4 mL) were added through a syringe. The mixture was stirred under $^{18}O_2$ gas balloon in an oil bath at 65 °C for 24 h, cooled down to ambient temperature and neutralized with concentrated hydrochloric acid to pH = 6–7. The reaction mixture was diluted with ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through column chromatography on silica gel to afford **3a-^{18}O** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 153 mg in 77% yield, wherein **1l** was recycled 33 mg in 18% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (d, J = 6.5 Hz, 3H), 2.30 (d, J = 3.5 Hz, 1H), 5.43 (qd, J = 6.5, 3.0 Hz 1H), 7.41–7.44 (m, 1H), 7.66 (td, J = 8.0, 1.0 Hz, 1H), 7.85 (dd, J = 8.0, 1.5 Hz, 1H), 7.91 (dd, J = 8.5, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.2, 65.5, 124.3, 127.5, 128.1, 133.6, 140.9, 147.8. HR (DART Positive) *m/z*:

150.1 ($[M-H_2O+H]^+$, 100%), 185.1 ($[M+NH_4]^+$, 4%). HRMS (DART Positive, LTQ FT): calcd for $C_8H_9NO_2{}^{18}O$ $[M+NH_4]^+$ 187.0963, found 187.0963. The **3a** was not observed from the mass spectrum of the product (**Figure S8**, bottom), see the spectra comparison in **Figure S8**.

Large-scale Reactions.

Scheme 3, eq 1: The 1-ethyl-2-nitrobenzene **1l** (4535 mg, 12.0 mmol) and NaOH (9000 mg, 225 mmol) were added to a flask equipped with a magnetic stir bar. The flask was evacuated and backfilled with O_2 gas (balloon). This evacuation and backfill procedure were repeated for twice. Then EtOH (40 mL) and H_2O (10 mL) were added through a syringe. Then the flask was stirred under a oxygen balloon in an oil bath at 65 °C under a oxygen balloon for 48 h. Then the reaction mixture was cooled down to ambient temperature and neutralized with concentrated hydrochloric acid to pH = 6–7. Then the organic solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate three times, and the combined organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through column chromatography on silica gel to afford **3a** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a brown liquid, 3928 mg in 78% yield, wherein **1l** was recycled 91 mg in 2% yield. The structure of the product was confirmed by ^1H NMR.

Application of the Aerobic Oxidation in the Synthesis of Procaine.

Scheme 3, eq 2: The 1-methyl-4-nitrobenzene **1b** (8.23 g, 60 mmol), 50% EtOH ($EtOH/H_2O$ = 50 mL/50 mL) and NaOH (18.00 g, 450 mmol) were added to a pressure reactor equipped with a magnetic stir bar. The pressure reactor was filled with oxygen (1.0 MPa), then the gas was deflated, this fill and deflation procedure was repeated another twice. After that, the pressure reactor was refilled with oxygen (1.8 MPa), sealed, then the mixture was stirred at 52 °C (oil bath: 55 °C) for 72 h, cooled down to ambient temperature, and the excess oxygen was released slowly. The reaction mixture was transferred to a round bottom flask and the organic solvent was removed under reduced pressure. The residue was extracted with ethyl acetate three times, and the combined organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified through column chromatography on silica gel to afford **2b** (eluent: petroleum ether/ethyl acetate = 5:1–3:1) as a yellow solid, 6.52 g in 65% yield, and **1b** was consumed completely. The structure of the product was confirmed by ^{1}H NMR.

The 4-nitrobenzoic acid **2b** (10.11g, 60.5 mmol), *N*,*N*-diethyletholamine (6.65 g, 55.0 mmol), HCOOH (95 mg, 2.1 mmol) and xylene (45 mL) were added to a 100 mL three-necked flask equipped with a magnetic stir bar, a water separator and a condenser. The mixture was stirred at refluxed temperature for 24 h until about 1.0 mL water was separated. The reaction mixture was then cooled down to ambient temperature, and diluted with xylene (40 ml), and then transferred into a 250ml separating funnel, washed with 5%wt NaOH solution (50ml), dried with anhydrous sodium sulfate, filtered and concentrated until 40–50ml xylene left in a glass bottle. The obtained solution was then transferred into a 250 mL pressure reactor equipped with a magnetic stir bar, the glass bottle washed with xylene (50 mL) and the mixture was also transferred into the pressure reactor. Then catalyst Ni/celite (825 mg) was added. The pressure reactor was filled with hydrogen (1.0 MPa), then the gas was deflated, this fill and deflation procedure was repeated another twice. After that, the pressure reactor was refilled with hydrogen (2.8 MPa), sealed, then the mixture was stirred at 130 ^{o}C (oil bath: 160 ^{o}C) for 4 h until the pressure of the reactor was no longer down, then kept at that temperature for another 1 h.[35] The mixture was cooled down to ambient temperature, and the excess hydrogen was released slowly. The mixture was filtered and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel, which was pretreated with petroleum ether/Et_3N = 100:0.5, to afford **Procaine** (eluent: petroleum ether/ethyl acetate = 5:1, then petroleum ether/ethyl acetate/MeOH = 75:25:10) as a slight yellow liquid, 11.87 g in 91% total yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07 (t, J = 7.5 Hz, 6H), 2.63 (q, J = 7.0 Hz, 4H), 2.84 (t, J = 6.5 Hz, 2H), 4.04 (brs, 2H), 4.34 (t, J = 6.5 Hz, 2H), 6.64 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 12.0, 47.8, 51.1, 62.7, 113.8, 119.9, 131.6, 150.8, 166.6. The NMR data was in accordance with the literature.[36] HRMS (EI, TOF): calcd for $C_{12}H_{17}N_2O_2$ $[M-CH_3]^+$ 221.1285, found 221.1295.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Details of condition optimization of aerobic oxidation of **1a**, **1b**, **1l**; In situ NMR experiment for **1l**; Stepwise synthesis of Procaine; X-ray molecular structure of **2c** and the crystal data (CCDC 1553779); NMR and HRMS spectra of new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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