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Arene Oxidation with Malonoyl Peroxides

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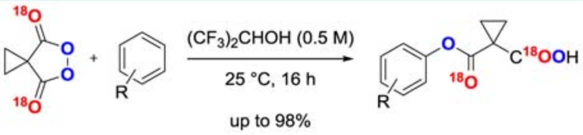
Ⓢ *Supporting Information*

ABSTRACT: Malonoyl peroxide **7**, prepared in a single step from the commercially available diacid, is an effective reagent for the oxidation of aromatics. Reaction of an arene with peroxide **7** at room temperature leads to the corresponding protected phenol which can be unmasked by aminolysis. An ionic mechanism consistent with the experimental findings and supported by isotopic labeling, Hammett analysis, EPR investigations, and reactivity profile studies is proposed.

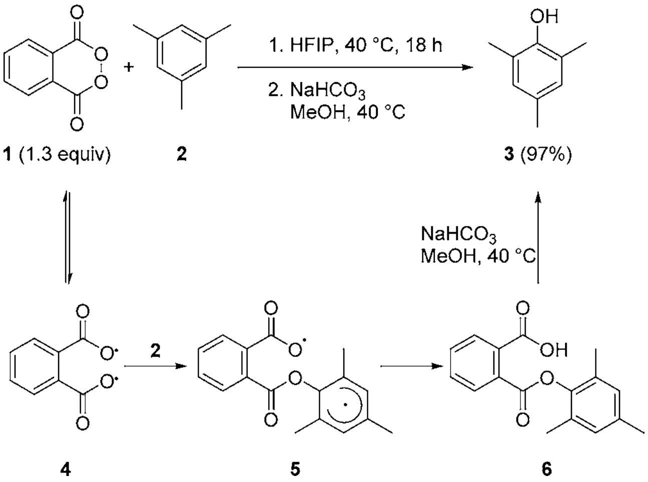


The oxidation and functionalization of hydrocarbons is a central facet of the chemical industry for the production of high-tonnage commodities and the preparation of high-value pharmaceuticals, agrochemicals, and fine chemicals. Therefore, methods for selective oxidation of C−H bonds are of great importance.[1] Phenols represent a key class of oxidized hydrocarbon.[2] While there are a small number of reports in which arenes are oxidized to the respective phenols using peroxides and strong acids as additives,[3] the oxidation of aromatic C−H bonds still presents a synthetic challenge specifically with respect to avoiding overoxidation.

A recent report from the laboratories of Houk and Siegel described a metal-free oxidation of aromatic carbon−hydrogen bonds which was proposed to proceed through an intriguing reverse-rebound mechanism (Scheme 1).[4] Reaction of mesitylene **2** with 1.3 equiv of phthaloyl peroxide **1** in hexafluoroisopropanol (HFIP) followed by basic solvolysis gave the phenol **3** (97%).

The method outlined in Scheme 1 represents a significant advance in arene oxidation. The proposed mechanistic pathway for the transformation suggested homolytic fission of the weak oxygen—oxygen bond leading to diradical **4**. Addition of this radical to the arene gives **5** which through H atom abstraction provides the observed product **6**. Ester hydrolysis leads to the phenol **3** (97%, two steps). The procedure has wide functional group tolerance, and arene overoxidation did not prove problematic. We believed two fundamental opportunities existed for development of this procedure: First, phthaloyl peroxide **1** is known to be very shock sensitive and explodes violently when heated, representing a significant hazard.[5,6] Second, the proposed reverse-rebound mechanism leading to **6** was based upon theoretical studies. Provision of experimental evidence to support this pathway would be of great importance to the understanding and development of this procedure.

Scheme 1. C−H Oxidation Using Phthaloyl Peroxide[2]



In recent years we have been interested in the chemistry of cyclic diacylperoxides and have shown that malonoyl peroxide **7**,[7] and related derivatives,[8] are effective for the *syn*-dihydroxylation of alkenes.[9] This reagent provides significant advantages over phthaloyl peroxide **1** within the *syn*-dihydroxylation reaction in terms of yield, selectivity, reaction rate, substrate scope, and operating temperature.[10,11] Given our experience in understanding the mechanism of reactions involving the peroxide **7**,[12] together with the specific advantages provided in alkene dihydroxylation, we elected to investigate the reactivity of **7** in the oxidation of arenes. Within this report we show that **7** reacts with arenes in the presence of a hydrogen bond donor to give the corresponding functionalized aromatic and present data consistent with the arene and peroxide reacting through an ionic pathway.

As a starting point to our investigations we reacted mesitylene **2** with malonoyl peroxide **7** under the conditions

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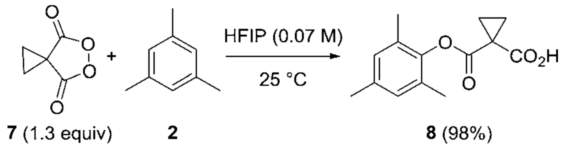
reported by Houk and Siegel (0.07 M, 40 °C).[2] Reaction of mesitylene **2** with 1.3 equiv of peroxide **7** in HFIP gave the adduct **8** (94%, 20 h). More conveniently, this reaction could be performed at room temperature (25 °C) rather than 40 °C without compromise in yield (**8**, 98%) (Scheme 2). Cleavage of the ester (MeNH$_2$, EtOH, 25 °C, 1 h) gave the corresponding phenol **3** (92% over two steps). Delighted by these excellent preliminary results and given the distinct advantages of malonoyl peroxide **7** over phthaloyl peroxide **1** outlined above, we examined this transformation further.

Scheme 2. Malonoyl Peroxide Mediated Oxidation of Mesitylene



Brief optimization of the reaction conditions showed that transformations could be performed at room temperature and considerably higher concentration (0.5 M) than those reported previously (0.07 M) (see Supporting Information).

Houk and Siegel showed their transformation to have broad functional group tolerance, describing the oxidation of over 50 substrates.[2] Direct comparison of the reaction using malonoyl peroxide **7** to those obtained for phthaloyl peroxide **1** on a selection of these substrates showed the transformation to proceed with similar yield and selectivity (Figure 1). Functional group tolerance mirrored that obtained with phthaloyl peroxide, which bodes well for further reaction development. We therefore believe that malonoyl peroxide **7** represents an effective alternative to the explosive phthaloyl peroxide **1** in the oxidation of arenes.

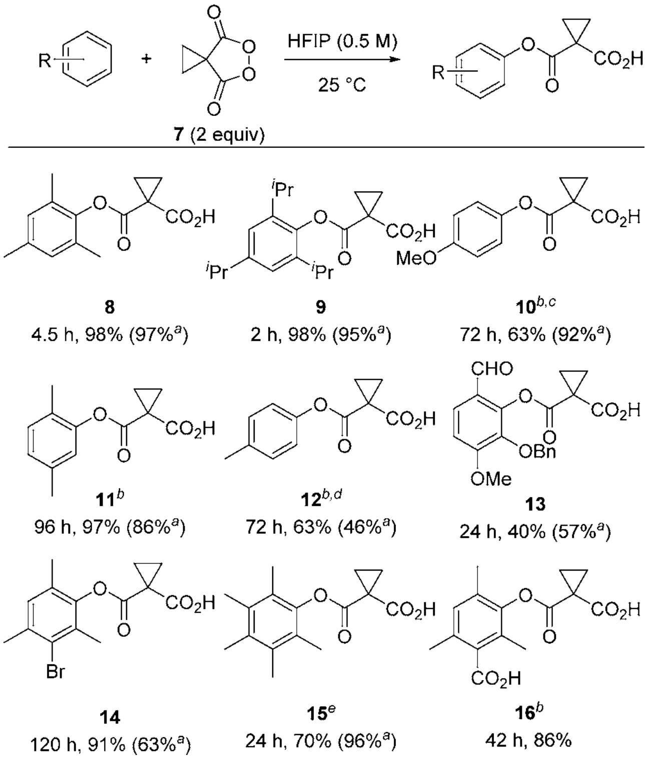
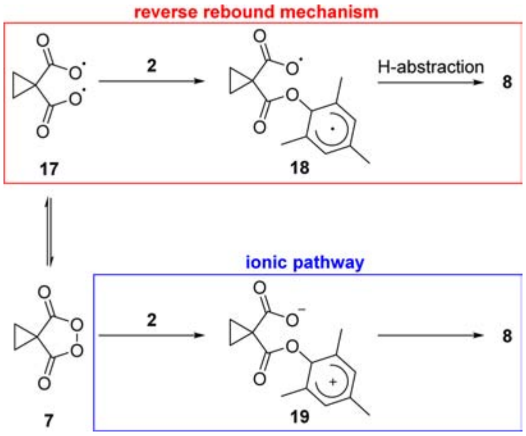


Figure 1. Arene oxidation with malonoyl peroxide **7**. [a] Isolated yield of phenol using phthaloyl peroxide **1** reported in ref 2. [b] The reaction was perfomed at 50 °C. [c] 1:1.6 mixture of *o*- and *p*-isomers obtained. [d] 1:1 mixture of *o*- and *p*-isomers obtained. [e] 1.1 equiv of malonoyl peroxide **7** used.

In order to understand the reaction further a series of experiments were undertaken to probe the mechanistic course of the process. The reverse-rebound mechanism proposed for the reaction of phthaloyl peroxide **1** was based upon theoretical calculations.[2] We sought to obtain experimental data using malonoyl peroxide **7** to underpin knowledge of this transformation. An analogous reverse-rebound mechanism with peroxide **7** would involve homolytic cleavage of the peroxide bond to give the diradical species **17** which on addition to the arene would give the intermediate **18**. Rearomatization of **18** through H atom abstraction would lead to the observed product **8** (Scheme 3). In addition to this reverse-rebound mechanism we also considered an ionic pathway based on the established reactivity of **7** with alkenes.[10] Thus, nucleophilic attack of the electron-rich arene **2** on the weak peroxide bond would lead to intermediate **19**, which upon rearomatization would give **8**.

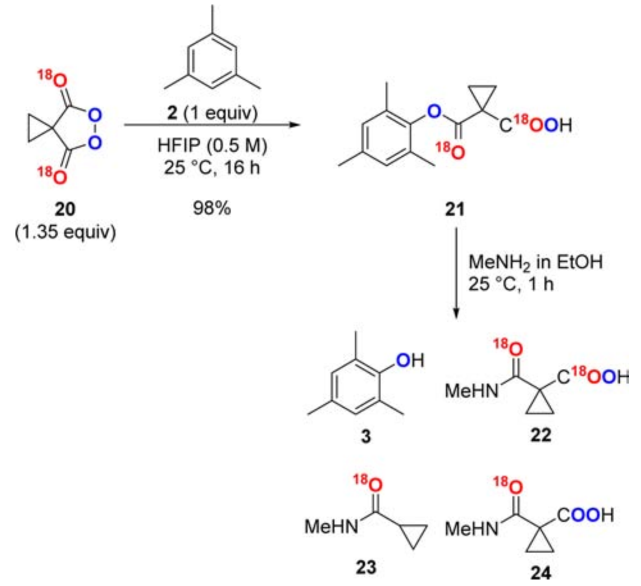
Scheme 3. Potential Mechanistic Course of Reaction



Based upon reactivity patterns an ionic process appeared plausible: the reaction required electron-rich aromatics to proceed, with electron-donating groups directing the addition of the peroxide to the *ortho*/*para* positions. Interestingly, aromatic substrates containing electron-withdrawing groups proved unreactive within this transformation. For example, acetophenone, benzoic acid, methyl benzoate, and benzonitrile all proved to be unreactive to peroxide **7** under the optimized reaction conditions (**7** (2 equiv), HFIP 0.5 M, 25 °C). Conducting the reaction of mesitylene **2** and malonoyl peroxide **7** in HFIP (i) in the presence of light and air; (ii) exposed to light under an argon atmosphere; (iii) in the dark in an aerobic environment; and (iv) in the dark under an inert atmosphere showed no significant differences in outcome with reactions giving the product **8** (90−92% yield) after 6 h. In addition, conducting the reaction at 4 °C, in the dark under an argon atmosphere, gave the product (83% yield) after 24 h. Combined, these observations show the reaction to proceed under very mild conditions and did not rule out an ionic pathway.

Further investigations were carried out using ^{18}O isotopically labeled malonoyl peroxide **20** as a mechanistic probe, which was prepared from cyclopropane-1,1-dicarboxylic acid (see Supporting Information for full details). Treatment of mesitylene **2** with 1.35 equiv of malonoyl peroxide **20** (25 °C, 16 h) gave the ester **21** with two labels incorporated in the structure (Scheme 4). Mass spectrometric analysis was consistent with incorporation of one label in the carboxylic acid terminus of the molecule and a second label in the carbonyl oxygen atom of the ester. No labeled oxygen was observed in the newly formed carbon—oxygen bond. To corroborate this finding, a sample of **21** was treated with methylamine and the crude reaction mixture was analyzed by GCMS. The observed products were 2,4,6-trimethylphenol **3**, amides **22** and **24** containing either one or two ^{18}O labels, and amide **23** resulting from decarboxylation. These findings show that no scrambling of the ^{18}O label from the peroxide **20** is observed during the course of reaction and are consistent with addition of an arene nucleophile to the weak O−O peroxide bond.

Scheme 4. Reaction of Mesitylene with Isotopically Labelled Peroxide 20



It was possible that reversible formation of the labeled diradical **25** could proceed without scrambling, if the rate of peroxide bond formation is quicker than bond rotation (Figure 2).[13] This would mean that **26** and **27** would not be present in solution. However, the observed selectivity in C−O bond formation would require addition of the diradical **25** to the aromatic ring to occur specifically through the unlabeled oxygen atom to achieve the results observed. It is not clear how this selectivity would occur within a reverse-rebound process.

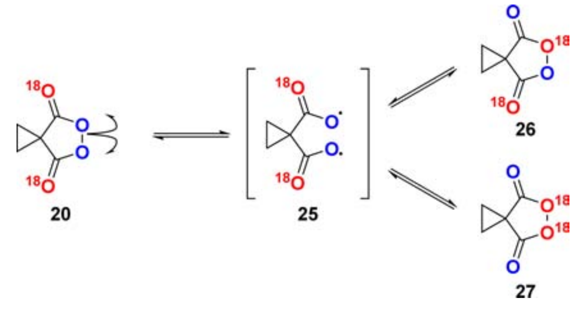


Figure 2. Potential scrambling of labels on formation of diradical.

The data assembled at this stage were consistent with an ionic interaction between the aromatic substrate and the peroxide **7**. To gain further evidence for the formation of a carbocation intermediate, a Hammett analysis was conducted on the arene oxidation. Monosubstituted mesitylene derivatives were reacted with 1 equiv of malonoyl peroxide **7** (Figure 3), and peroxide consumption was monitored against an internal standard by ^{1}H NMR spectroscopy. Determination of the initial rates provided a linear Hammett plot based on literature σ_{meta} values.[14]

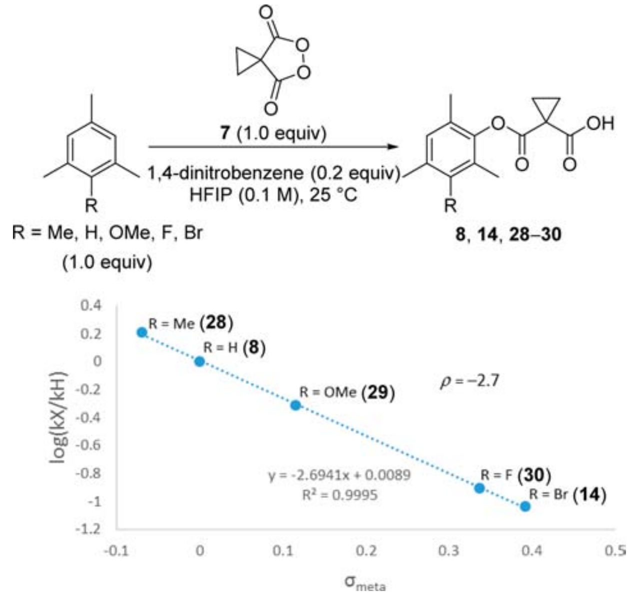


Figure 3. Hammett analysis of arene oxidation with peroxide **7**.

The Hammett plot (Figure 3) showed an excellent linear relationship for both electron-withdrawing and -donating substituents in the *meta*-position indicating that the same mechanism is in operation with each substrate examined. The gradient of the line, ρ, gave a moderate negative value of −2.7 indicating a considerable buildup of positive charge during the transition state of the reaction, consistent with an aryl carbocation intermediate (e.g., **19**). As expected, reactions of substrates with a *meta*-electron-donating substituent (e.g., **28**) proceeded at a significantly faster rate than those containing a *meta*-electron-withdrawing group (e.g., **14** and **30**).

To probe further the possibility of the reaction proceeding through the diradical intermediate **17**, we examined the homolytic bond cleavage of peroxide **7** through DFT calculations ((U)B3LYP/6-31+G(d)). Of importance was the use of trifluoroethanol as the solvent in a CPCM, providing a more accurate reflection of the reaction medium when compared to the previous approaches to modeling this class of transformation.[2] A transition state **TS1** (29.7 kcal mol^{-1}) to form the diradical species **17** (24.8 kcal mol^{-1}) from peroxide **7** was found (Figure 4), a particularly high barrier for a reaction that proceeds readily at 4 °C.

The potential of **17** being present within the reaction mixture was also examined using electron paramagnetic resonance (EPR) spectroscopy experiments using 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), a spin trap used in EPR spectroscopy for the detection of oxygen based radicals.[15] DMPO was inert

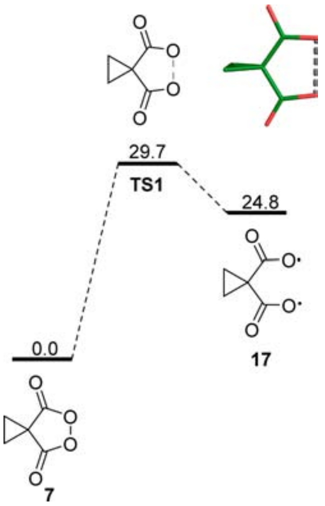


Figure 4. Peroxide homolytic cleavage (kcal mol^{-1}).

to the peroxide **7** in HFIP, as shown by control experiments. Mixtures of mesitylene **2** and malonoyl peroxide **7** in both the presence and absence of DMPO were analyzed by EPR spectroscopy. In each of these experiments no radicals were detected providing further important evidence in support of an ionic pathway.

In summary, reaction of an arene with malonoyl peroxide **7** at room temperature in the presence of a hydrogen bond donor leads to the corresponding functionalized aromatic. Experimental findings supported by isotopic labeling, Hammett analysis, EPR studies, and reactivity profile studies support an ionic reaction pathway. The importance of the phenol functional group in imparting unique structural, physical, and electronic properties within molecules suggests this simple, effective, and high yielding method for the oxidation of aromatics will provide a useful route for the late stage aromatic functionalization. Given the specific advantages of malonoyl peroxide **7** over phthaloyl peroxide **1**, it is expected that this methodology will be of great use in the introduction of the phenol functionality.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Analytical data, experimental procedures, and NMR spectra for all compounds reported. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00953.

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Notes

The authors declare no competing financial interest.

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