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Dearomatization Reactions Using Phthaloyl Peroxide

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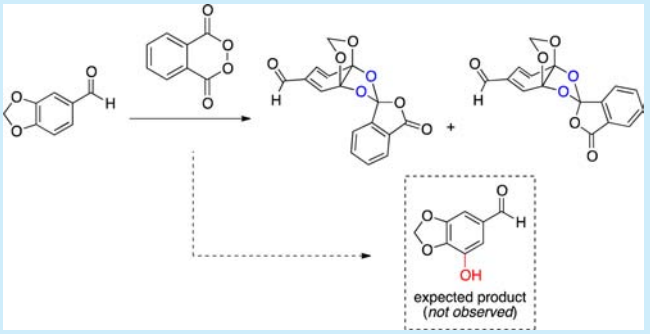
Supporting Information

ABSTRACT: A new oxidative dearomatization reaction has been developed using phthaloyl peroxide to chemoselectively install two oxygen−carbon bonds into aromatic precursors. The oxidation reaction proceeds only once; addition of superstoichiometric equivalents of phthaloyl peroxide does not react further with the newly generated 1,3-cyclohexadiene. The reaction has been challenged by the addition of different functional groups and shown to maintain chemoselectivity. Due to the broad reactivity with 1,2-methylenedioxybenzene derivatives, linear free energy correlations were determined and support a mechanism proceeding through diradicals analogous to arene-hydroxylation reactions using phthaloyl peroxide.



Nature has evolved a diverse set of enzymes to transform aromatic compounds with a key reaction involving the insertion of oxygen into arenes, thereby disrupting aromatic stabilization and allowing further enzymatic digestion of the newly formed 1,3-cyclohexadiene system.[1] These enzymes, oxygenases, are divided based upon whether one or both atoms of dioxygen are incorporated into the aromatic precursor (Figure 1).[2] The enzymes can use an iron heme cofactor as the

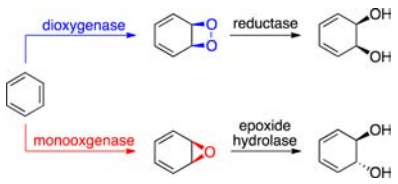


Figure 1. Metabolism of benzene. Two oxidative metabolic pathways for benzene include dioxygenation and monooxygenation.

reactive center with the catalytically active state being either an iron(V)−oxo or iron(III)−peroxo complex.[3] The resulting epoxide or 1,2-dioxetane is degraded further through hydrolytic or reductive steps.

From a chemical reactivity standpoint, the lack of over-oxidation in these enzymatic systems is noteworthy as the first oxidation step overcomes the barrier of aromaticity and generates a product that is more easily oxidized. The analogous reaction in chemical synthesis has not been possible as the products are more reactive than the starting material. The majority of reagents fail to react with arenes, and if the reagents do possess sufficient reactivity the newly generated products are typically consumed in preference to the starting material. Herein, we report that the reagent phthaloyl peroxide alone can oxidatively dearomatize benzodioxole and dihydrobenzofuran derivatives forming oxygenated 1,3-cyclohexadienes without over oxidation.

Oxidative dearomatization has proven to be an effective tool in synthesis, rapidly converting commercial and easily prepared arenes into highly functionalized cyclohexadienes and cyclohexadienone derivatives.[4−6] These products undergo subsequent functionalization, including carbon−carbon bond formation, annulation, and hydrogenation. This strategy increases structural complexity and aligns well with synthetic targets identified from natural sources and enables the syntheses of chemically diverse compound collections derived from privileged core structures. Recently, the Njardarson group utilized hypervalent iodine to perform an oxidative dearomatization followed by Diels−Alder reaction to assemble the core of vinigrol.[7] Relatedly, Pettus and co-workers utilized oxidative dearomatization to convert (−)-sophoracarpan A into (±)-kushecarpin A.[8] Dearomatization also enables access to privileged molecular scaffolds, demonstrated by Doyle,[9] Tan,[10] Hergenrother,[11] and Porco.[12]

Phthaloyl peroxide was first reported by Russell in 1955[13] and extensively studied by Greene for the ability to add to alkenes or alkynes with pendant aryl groups.[14] Recently, 4,5-dichlorophthaloyl peroxide was demonstrated to be a more reactive oxidant than the parent phthaloyl peroxide.[15] The first

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demonstration of arene-selective reactivity enabling the conversion of arenes to phenols followed.[16] The mechanism of the reaction of arenes with phthaloyl peroxide was explored computationally and shown to proceed via a reverse-rebound mechanism in contrast to the established rebound mechanism.[17]

In a marked divergence in the reactivity previously observed with phthaloyl peroxide (**2**), the reaction with 1,3-benzodioxole (**1**) provides a diastereomeric mixture of cyclohexadiene bisketals (**3a** and **3b**) shown in Figure 2. This unprecedented

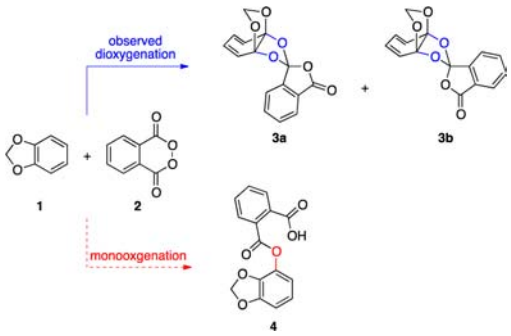


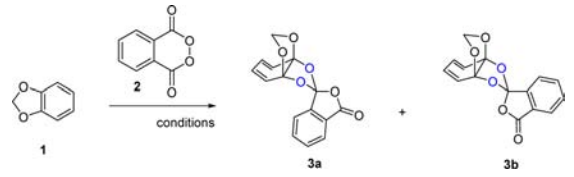
Figure 2. Reaction of 1,3-benzodioxole (**1**) with phthaloyl peroxide (**2**).

reactivity establishes two carbon−oxygen bonds, dearomatizing the arene, and forms a 1,3-cyclohexadiene. Full NMR and single-crystal X-ray diffraction analysis confirms these types of structures.

The reaction is proposed to be driven by the strain associated with the ring fusion and reactivity directed by oxygen. To estimate the strain energy present in (methylenedioxy)benzene, the difference in the calculated ΔH_f° (using the Benson group increment method) and that found experimentally was determined.[18] Benson group additivity parameters suggest that benzodioxole substrates possess significant Baeyer (angle) strain, calculated to be 17.6 kcal mol^{-1} in the liquid state.[19] Double *ipso*-addition at the ring junction alleviates this strain through rehybridization at the carbons, from sp^2 to sp^3, providing an energetic driving force for this reaction. The *ipso* reactivity is in turn driven by oxygen *ortho* to the carbon reacting. It is worth noting that heating the adducts does not lead to the formation of related phenolic products.

The effects of equivalents of phthaloyl peroxide (**2**), temperature, and solvent on the outcome of the reaction were examined in an effort to optimize the reaction (Table 1). While the use of slightly greater than 1 equiv of phthaloyl peroxide led to the isolation of unreacted starting material (variant 1), increasing the peroxide to 3 equiv (variant 2) did not positively affect the yields. Notably, no overoxidized products were identified in these reactions, even in the presence of multiple equivalents of peroxide. Running the reaction at 0 °C resulted in incomplete conversion of starting material (variant 3). Reaction above ambient temperature (variant 4) did not improve the outcome and for operational simplicity heating was not used. Analogous to the hydroxylation reaction, we found the fluorinated alcohol solvents (commercial grade) trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP) were superior for arenes, including those possessing electron-withdrawing substituents.[20] For electron-rich substrates, trifluorotoluene (TFT, commercial grade) proved optimal (see the Supporting Information).

Table 1. Optimization of the Reaction of 1,3-Benzodioxole with Phthaloyl Peroxide



variation	equiv PPO (**2**)	temperature	solvent	yield (**3a** + **3b**)
-	1.5	23 °C	CF_3CH_2OH	74%
1.	1.2	23 °C	CF_3CH_2OH	53%
2.	3.0	23 °C	CF_3CH_2OH	72%
3.	1.5	0 °C	CF_3CH_2OH	37%
4.	1.5	40 °C	CF_3CH_2OH	68%
5.	1.5	23 °C	$(CF_3)_2CHOH$	58%
6.	1.5	23 °C	CH_3CH_2OH	45%
7.	1.5	23 °C	$C_6H_5(CF_3)$	17%
8.	1.5	23 °C	CH_2Cl_2	31%

The reaction is compatible with diverse substituents on the arene, demonstrating the reaction to be chemoselective (Figure 3). As outlined in the methods development 1,3-benzodioxole performed well under the optimized conditions providing a 74% yield of the dearomatized products (**3a** and **3b**). Electron-rich arenes (generating **5** and **6**) readily dearomatize in minutes; however, these reactive substrates necessitated the use of trifluorotoluene, as the fluorinated alcohol solvents hexafluoro-2-propanol and trifluoroethanol led to additional unproductive reactions. Halogenated arenes possessing chlorine (**10**) or bromine (**11**) reacted well and can be envisioned to provide synthetic handles for further synthetic manipulation.

Appended phenyl (**17**) and benzyl (**18**) groups were left unreacted, demonstrating the selectivity phthaloyl peroxide has for the 1,3-benzodioxole. Other functionality susceptible to oxidation including aldehydes and ketones (**19**, **20**, and **25**) remained unchanged under the reaction conditions. Substituents *ortho* to the methylenedioxy proceed with only a slight erosion in yield relative to *meta* isomers regardless of whether the substituent is electron donating (**15** and **16**) or withdrawing (**19** and **20**). Substrates with esters (**6** and **21**), amides (**22**), and carbamates (**23**) all reacted selectively on the arene. Nitriles (**13**) provided the corresponding cyano diene, albeit in low yield. The 1,3-benzodioxole core with a nitro provided the nitrodiene **12** in 57% yield. If the nitro is connected through a vinyl spacer the yields increased for the formation of **8**. Remarkably, the reaction generating the styrene derivative **7** provided the dearomatized product in 67% with phthaloyl peroxide selecting to react at the arene rather than the olefin.

Given that the reaction tolerates a wide variety of substituents on the benzodioxole aryl ring, the methylenedioxy was examined. The geminal dimethyl groups of an acetonide (as in products **24** and **25**), while providing a lower yield, do not preclude oxidative dearomatization. The importance of both oxygen atoms of the methylenedioxy was investigated, and it was found that subjecting 2,3-dihydrobenzofuran to the reaction provided the dearomatized product (**26**) in 40% yield (with recovery of 26% of starting material), indicating that while lower yields are achieved the system still reacts to provide the oxygenated cyclohexadiene product. The substrate 3-

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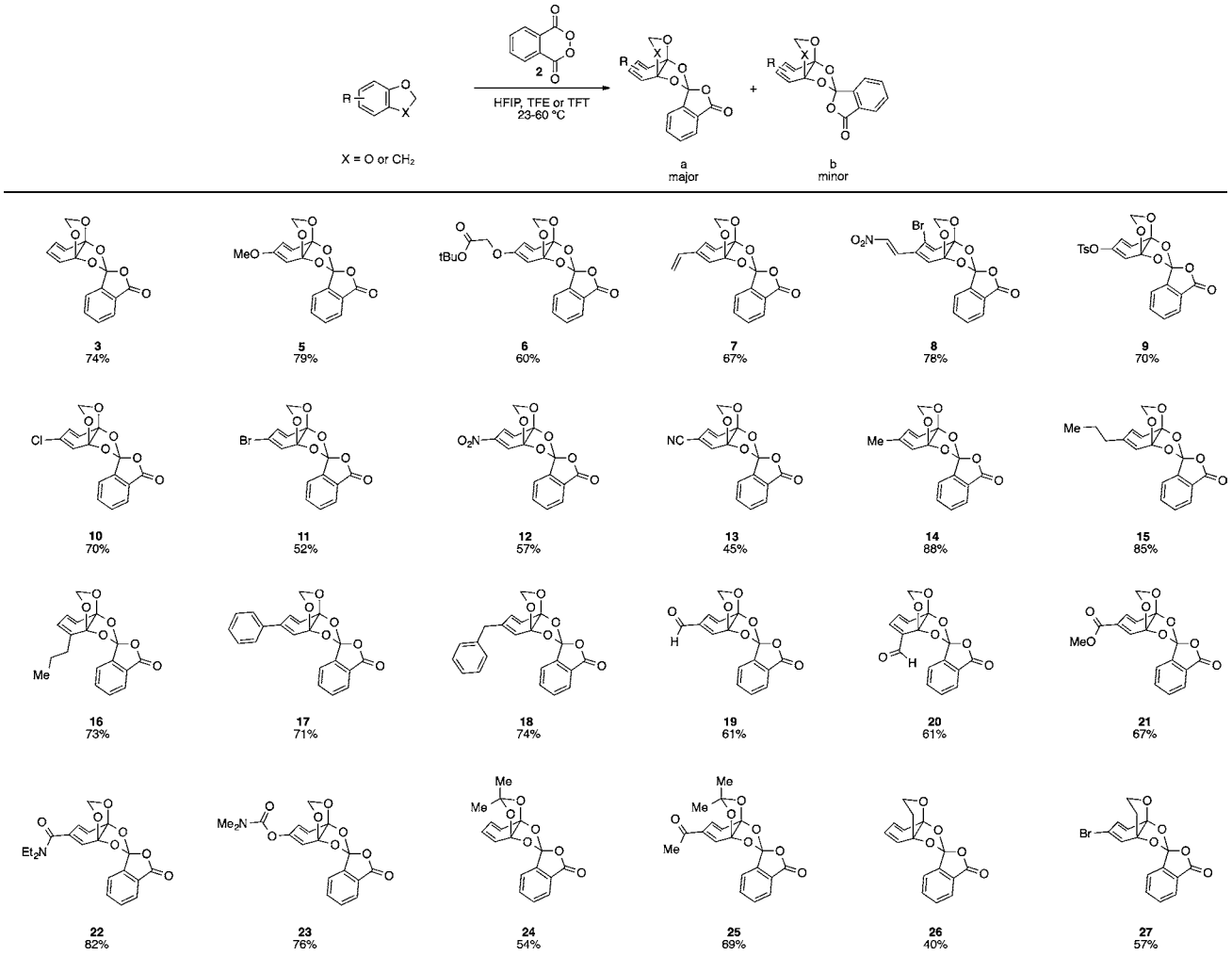

Figure 3. Phthaloyl peroxide mediated dearomatization. Isolated yields are indicated below each entry for both isomers with the major isomer shown (yields following silica gel flash chromatography). See the Supporting Information for experimental details and diastereomeric selectivity. Ts: *p*-toluenesulfonyl.

bromodihydrobenzofuran reacted to provide **27** in a yield comparable to that for the (bromomethylene)dioxy product **11**. Indan, lacking oxygen direction, provides the phenolic product.[16a]

The major diastereomers generated possess the aryl ring of the phthalate projecting away from the methylenedioxy bridge. For most products of the oxidation reaction, the major and minor isomers can be separated by silica gel column chromatography, if desired, and isolated in pure form. Warming either of the pure diastereomers in HFIP leads to the formation of the same starting mixture of isomers.

The broad array of functional groups tolerated by the dearomative reaction provided an opportunity to investigate the mechanism of the transformation through the determination of linear free energy relationships (Figure 4). A comparison of the rates of reaction between the parent compound, 1,3-benzodioxole, and substituted derivatives were obtained through direct competition reactions using a 5-fold excess of each arene relative to phthaloyl peroxide. Comparison of the ratio of adducts formed was achieved from crude reaction NMR analysis; k_X/k_H was determined for each competition reaction. Hammett plots were constructed using σ_p or σ_p^+. The reaction fits σ_p values (R^2 = 0.95) more closely than σ_p^+ (R^2 = 0.91), a divergence from electrophilic aromatic substitution reactions

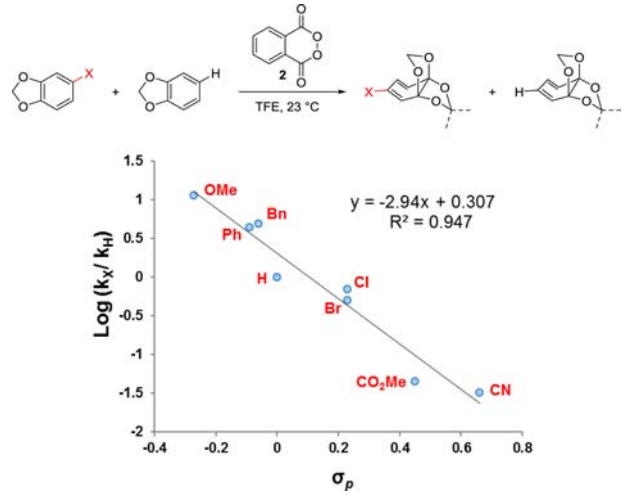

Figure 4. Linear free energy diagram using σ_p values. Ratios were determined by NMR integration.

(EAS) which correlate strongly with σ_p^+.[20] Linear regression analysis provides a correlation (ρ) of the linear free energy diagram and provides insight into the reaction mechanism. A ρ value of −2.94 suggests the reaction is mildly influenced by the

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stabilization of polar intermediates but is not predicted to be ionic as EAS reactions possess larger negative ρ values.[21] It is important to note that diradicals, differing from radicals, do possess polarity.

The diradical-based intermediates present in the rate-determining step are analogous to what was found computationally for the phthaloyl peroxide mediated arene hydroxylation reaction.[16a] A mechanistic pathway that is in agreement is depicted in Figure 5. Carbon−oxygen bond formation yields

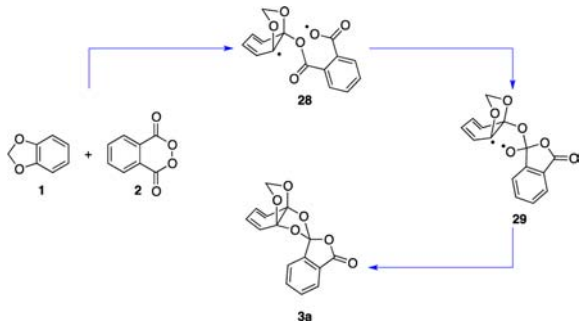

Figure 5. Proposed mechanism of dearomatization reaction.

a cyclohexadienyl radical **28**. The carboxyl radical adds into the ester carbonyl generating radical **29**. Combination of the two radicals forms the lactonic orthoester **3a**.

A new dearomatative oxidation reaction has been developed using phthaloyl peroxide. High levels of chemoselectivity allow the reaction to be run with predictability with benzodioxole and dihydrobenzofuran derivatives reacting on the arene in preference to other functional groups. Additionally, the reaction is convientiently run in commercial grade solvents and, in most cases, at ambient temperature. The determination of linear free energy correlations fitting to σ_p with a ρ value of −2.93 supports previously proposed diradical intermediates. With an absence of overoxidation of the resulting 1,3-cyclohexadiene the reaction provides a key advancement in the development of synthetic methods that can achieve aromatic dihydroxylation reactions in a manner similar to Nature's dioxygenases.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02008.

Experimental procedures, characterization data, and spectral reproductions for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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