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Computational and Experimental Studies of Phthaloyl Peroxide-Mediated Hydroxylation of Arenes Yield a More Reactive Derivative, 4,5-Dichlorophthaloyl Peroxide

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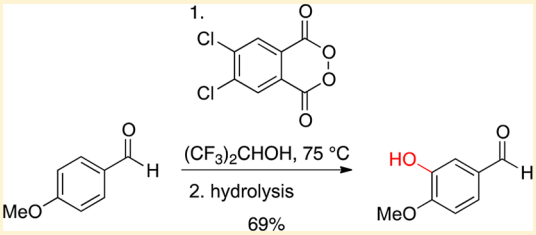
Supporting Information

ABSTRACT: The oxidation of arenes by the reagent phthaloyl peroxide provides a new method for the synthesis of phenols. A new, more reactive arene oxidizing reagent, 4,5-dichlorophthaloyl peroxide, computationally predicted and experimentally determined to possess enhanced reactivity, has expanded the scope of the reaction while maintaining a high level of tolerance for diverse functional groups. The reaction proceeds through a novel "reverse-rebound" mechanism with diradical intermediates. Mechanistic insight was achieved through isolation and characterization of minor byproducts, determination of linear free energy correlations, and computational analysis of substituent effects of arenes, each of which provided additional support for the reaction proceeding through the diradical pathway.



INTRODUCTION

The incorporation of oxygen into organic molecules in place of hydrogen is a fundamental transformation in organic synthesis. These transformations provide functional groups that can be readily manipulated, as well as atoms required in the final compounds. While significant efforts and advancements have been made in this area, there is no broadly applicable methodology for the straightforward conversion of arenes to phenols. One of the major challenges in developing hydroxylation reactions of aromatic compounds is that the products of the reactions are, under most conditions, more reactive than the starting material, and as a result overoxidation is a competitive process.[1,2] Peroxides have been extensively used as reagents to effect oxidation, and early hydroxylation reactions employing peroxides have had partial success generating monohydroxylated products. However, significant limitations remain, largely due to the restricted scope of oxidation reactions employing simple unfunctionalized arenes, frequently used in excess.[3−14] Additionally, the use of super acids to activate the oxidant and subsequently deactivate the products through protonation of the new phenolic oxygen was subsequently investigated, thereby circumventing the need for excess starting material usage.[15−18] This approach, however, cannot be broadly applied due to the requirement of exceptionally strong Brønsted acids and, under some conditions, concentrated (95%) hydrogen peroxide solutions.[19] This combination reduces functional group tolerance to only those that can withstand both strongly acidic and powerful oxidizing conditions. As a result, broadly applicable methods for phenol synthesis from arenes remain a challenge.

Using phthaloyl peroxide (**1**), a reagent extensively studied by Greene et al. in the 1950s,[20−25] we have developed a new synthetic method for arene hydroxylation. Phthaloyl peroxide, in the absence of other reagents, enables the selective oxidation of arenes with a variety of pendant functional groups.[26] The reaction can be conducted in commercial-grade fluorinated alcohols with no need for special exclusion of air or water. The oxidation reaction proceeds only once and an excess of reagent can be employed, if needed, without overoxidation becoming a competitive process. The controlled oxidation is enabled by the intermediate phthaloyl ester acid **2**, which deactivates the arene product toward a second oxidation (indicative of a radical process, vida infra). A typical transformation is shown for the reaction of mesitylene and phthaloyl peroxide (**1**) in Scheme 1. Following the reaction of phthaloyl peroxide and arene, the intermediate phthaloyl group is cleaved under neutral to slightly basic conditions, liberating the phenolic product mesitol (**3**).

Quantum mechanical calculations[26] have shown that the reaction of phthaloyl peroxide (**1**) with arenes proceeds through a "reverse-rebound" mechanism (Figure 1), as opposed

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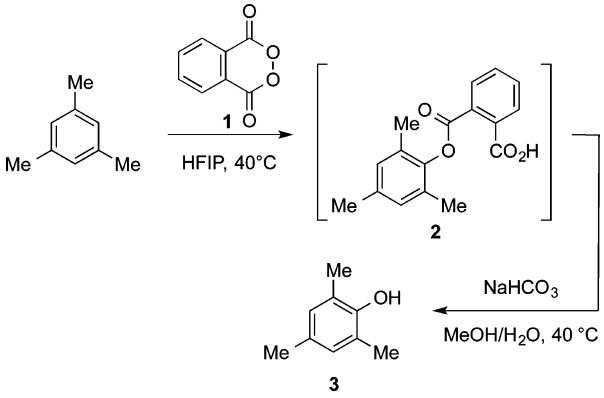
Scheme 1. Reaction of Phthaloyl Peroxide (1) with Mesitylene, Generating an Intermediate, Aryl Phthaloyl Monoester 2, Which Is Hydrolyzed To Generate Mesitol (3)



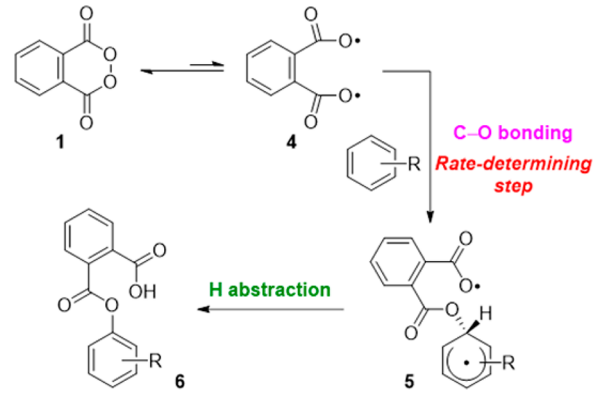


Figure 1. Reverse-rebound mechanism for phthaloyl peroxide oxidation of arenes.

to the rebound mechanism[27,28] observed with metal-oxo and dioxirane oxidants. Homolysis of the peroxide generates a diradical **4** that is in equilibrium with the parent peroxide **1**. Addition of the diradical **4** to the arene generates an intermediate diradical **5** that undergoes aromatization to provide the phthaloyl ester acid **6**. Within this mechanism there is the possibility of a molecule-assisted homolysis, wherein the arene and peroxide react directly to generate the same diradical intermediate **5**. Through these mechanistic considerations, a new arene hydroxylation reagent, 4,5-dichlorophthaloyl peroxide, was conceived and subsequently developed, and the scope of the reaction was expanded. Additional mechanistic insight was also gained through determination of linear free energy relationships, byproduct characterization, and calculations of substituent effects of arenes in both radical and ionic processes. Insights obtained through these experiments and calculations further support the diradical "reverse-rebound" mechanism. The key feature of this mechanism is that the hydrogen abstraction comes last, instead of first, as in the "oxygen rebound" mechanism.

RESULTS AND DISCUSSION

Subsequent to reporting on the ability of phthaloyl peroxide to hydroxylate functionalized arenes, we sought to improve the scope of the reaction by developing more reactive conditions and/or alternative cyclic peroxide-based reagents. The major limitations of phthaloyl peroxide as a reagent is that arenes with the electronics of anisaldehyde and those more electron deficient fail to react, returning unchanged starting material. A computational study demonstrated that the rate-determining step of the reaction was the carbon–oxygen bond formation (Figure 1). Frontier molecular orbital (FMO) analysis shows that the interaction between the highest occupied molecular orbital (HOMO) of arene and the singly occupied molecular orbital (SOMO) of diradical **4** is dominant in the carbon–oxygen bonding transition state. Elevating the HOMO energy of the arene can increase the favorable interaction in the transition state, lowering the barrier for oxidation. Alternatively, lowering the SOMO energy of the diradical generated from cyclic peroxide will also increase the favorable interaction, improving the reactivity. Further FMO analysis indicates that the 4,5-dichloro substitution decreases the SOMO energy by 0.3 eV (Figure 2a), suggesting that 4,5-dichlorophthaloyl peroxide (**7**), previously prepared,[29] would have improved reactivity relative to the parent phthaloyl peroxide (**1**) (Figure 2a).

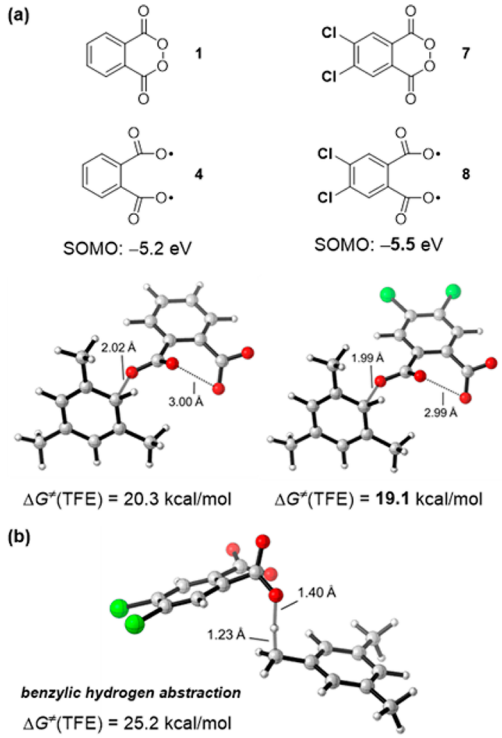


Figure 2. (a) Structures of phthaloyl peroxide and 4,5-dichlorophthaloyl peroxide, SOMO energies of the corresponding diradicals, and computed barriers for the reactions with mesitylene in trifluoroethanol (TFE). (b) Computed barrier for competing benzylic hydrogen abstraction of mesitylene by the diradical generated from 4,5-dichlorophthaloyl peroxide.

The barriers for reactions of 4,5-dichlorophthaloyl peroxide (**7**) with different arenes are calculated to be lowered by 1–2 kcal/mol relative to those for phthaloyl peroxide (**1**) in trifluoroethanol (for mesitylene, 19.1 versus 20.3 kcal/mol, Figure 2a; for others, see Supporting Information). In addition, calculations show that the competing benzylic hydrogen abstraction (Figure 2b) has a much higher barrier than the desired aryl oxidation, indicating that 4,5-dichlorophthaloyl peroxide will be selective for aromatic carbon–hydrogen bonds.

Preliminary safety testing of 4,5-dichlorophthaloyl peroxide achieved by thermogravimetric analysis (TGA) demonstrated

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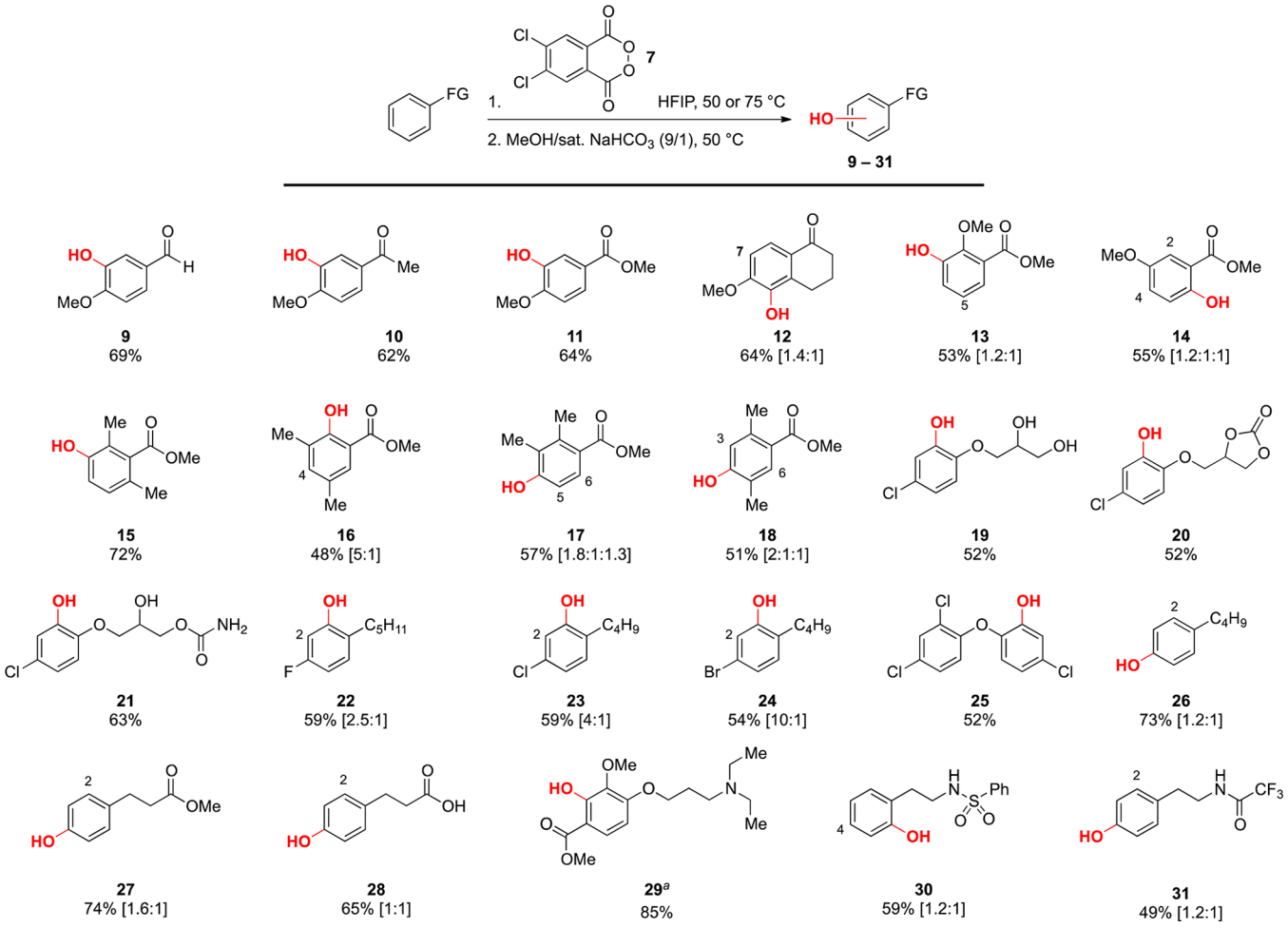

Figure 3. Arene hydroxylation mediated by 4,5-dichlorophthaloyl peroxide. Minor regioisomer(s) are labeled with the respective carbon number, if three regioisomers are produced, the ratios are given as (major product):(lowest carbon number isomer):(highest carbon number isomer). [a]1.0 equiv of *p*-toluenesulfonic acid monohydrate added.

improved thermal stability relative to the parent compound (phthaloyl peroxide has been found to decompose at 125 °C), with 4,5-dichlorophthaloyl peroxide undergoing exothermic decomposition at 135 °C (see Supporting Information). For safety consideration, reactions were conducted below the threshold for thermal decomposition and, as described herein, using a maximal oil bath temperature of 75 °C.

This new reagent allows arenes to be converted to phenols that were not previously reactive toward phthaloyl peroxide, including *p*-anisaldehyde, which reacts regioselectively with 4,5-dichlorophthaloyl peroxide to generate phenol **9** (Figure 3). Arenes with strong electron-withdrawing groups can react with the new reagent. Phenols **10**–**18** were prepared from corresponding arenes conjugated to ketones and esters. When the groups on the arene are cooperative, the reaction is highly regioselective. Importantly, the new reagent maintains broad tolerance to a variety of functional groups. Successfully transformed substrates are shown to include diols, carbonates, and carbamates, as demonstrated by the reaction of a series of chlorphenesin derivatives that formed the phenolic products **19**, **20**, and **21**. Testing the regioselectivity of the reaction with a series of halogenated alkylbenzene derivatives showed the influence of substituents relative to alkanes on the site of reaction, providing phenols **22**, **23**, and **24** with increasing levels of selectivity. The reaction was also used for the synthesis of triclosan (**25**) directly from 2,4,4′-trichlorodiphenyl ether, resulting in an improvement on the existing methods.[30,31] Triclosan is an antibacterial/antifungal agent that is included in many commonly used household products and is currently being reinvestigated by the FDA. The hydroxylation of monoalkylbenzenes was improved by using the new reagent, generating the hydroxylated products **26**, **27**, and **28** in improved yields relative to those obtained with phthaloyl peroxide (yields for **26** and **27** obtained by reactions with phthaloyl peroxide were 49% and 36%, respectively). Basic distal amines are tolerated if they are first reacted with toluenesulfonic acid monohydrate, as was observed for amine **29**. Sulfonamide phenol **30** and trifluoroacetamide phenol **31** were also successfully generated from the corresponding arenes.

The second step in the reaction sequence, hydrolysis of the intermediate phthaloyl ester acid to liberate the phenol, was initially reported by use of a warmed mixture of methanol and saturated aqueous sodium bicarbonate solution. This allowed rapid hydrolysis of the intermediate esters. However, the intermediate esters are highly labile and have been dubbed "self immolative".[32,33] If needed, exceedingly mild hydrolysis is possible under neutral conditions (pH = 7.0) at 23 °C with prolonged reaction times (Figure 4). Dichlorophthaloyl esters **30** and **31** hydrolyze faster than phthaloyl adduct **2** and, as the cleavage reaction is intramolecular, hindered esters hydrolyze at

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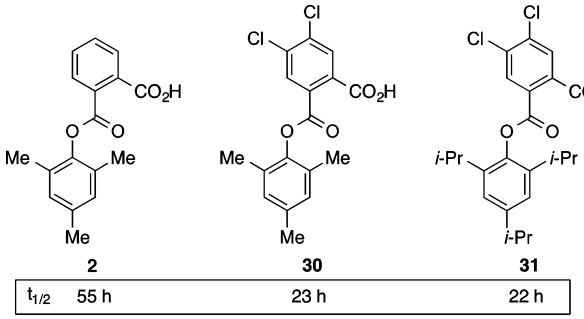

Figure 4. Half-lives for hydrolysis of phthaloyl esters at 23 °C in a 1:1 solution of pH 7.0 aqueous phosphate buffer and tetrahydrofuran (THF).

approximately the same rate as less bulky esters (**30** versus **31**, Figure 4).

Coproduct analysis of the remnants of the reaction from hydroxylation of mesitylene with either phthaloyl peroxide (**1**) or 4,5-dichlorophthaloyl peroxide (**7**) revealed benzylic functionalized products at low levels of approximately 1% (Figure 5). To permit full characterization, reactions for both

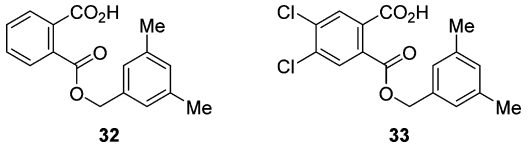

Figure 5. Structures of minor coproducts of benzylic oxidation esters **32** and **33** derived from, respectively, reactions of phthaloyl peroxide (**1**) or 4,5-dichlorophthaloyl peroxide (**7**) with mesitylene.

peroxide reagents were scaled up to produce sufficient amounts of the benzylic functionalized products **32** and **33**. The formation of these products, derived by replacing benzlic hydrogens with phthaloyl esters, is highly suggestive of radicals. These esters are significantly more stable than the corresponding aryl phthaloyl esters.

The improved reactivity of 4,5-dichlorophthaloyl peroxide enables the hydroxylation of benzene and chlorobenzene. By using substituted arenes and evaluating linear free energy relationships, investigation into the reaction mechanism was possible. Reaction rates for monosubstituted benzenes in comparison to benzene were obtained through direct competition reactions. Experiments were conducted with an excess of benzene and an excess of the appropriate substituted benzene with 1 equiv of 4,5-dichlorophthaloyl peroxide (Figure 6). Comparison of the ratios of the para- and ortho-phthaloylated substituted benzene adducts (**36** and **37**), versus the peroxide adduct with benzene **35**, provided relative rates of reaction. Hammett plots of either σ or σ+ values were then constructed, and in a notable departure from electrophilic aromatic substitution, the data fit σ values (R^2 = 0.92) better than σ+ values (R^2 = 0.78). In addition, the ρ value generated (−3.9) is notably less than those obtained for electrophilic aromatic substitution reactions where the stability of the cationic charge in the ring is strongly influenced by contributions of substituents (e.g., ρ value for arene bromination with Br_2 in acetic acid is −13).[34]

The stronger correlation with σ values as opposed to σ+ values also provides insight into the reaction's propensity to only undergo one oxidation reaction. By using phenyl benzoate (**39**), which has known σ and σ+ values,[35] as a surrogate for phthaloylated benzene **38**, the σ value of 0.13 predicts the phthaloylated benzene to be less reactive than benzene (Figure 7). Therefore, after the first addition, the ring becomes deactivated and overoxidation does not occur. Indeed, the reaction of benzene (1 equiv) with 4,5-dichlorophthaloyl peroxide (2 equiv) in HFIP provides only the mono-oxidized product **35** (40% yield) with no evidence of double addition. However, if resonance contributions were important for the reaction, as is the case for electrophilic aromatic substitution (EAS), the σ+ value (−0.07 for phenyl benzoate) would predict that phthaloylated benzene would be more reactive than benzene. As a consequence, the products of the reaction, if it were similar to EAS, would be expected to be more reactive than the starting material and undergo subsequent oxidation reactions. That stated, in reactions where phthaloyl peroxide-based reagents are used in excess, overoxidation is not a competitive process.

To better understand the "reverse-rebound" mechanism and the substituent effects of arenes on reaction rates, we conducted the following density functional theory (DFT) calculations. First, we located the carbon−oxygen bonding transition states via a radical or ionic process for the reaction of 4,5-dichlorophthaloyl peroxide and benzene (Figure 8a). Computational results showed that the radical addition pathway requires an activation free energy of 26.2 kcal/mol in trifluoroethanol, which is 5.7 kcal/mol lower than that for the electrophilic aromatic substitution (an ionic mechanism). The possibility of "rebound" mechanism initiated by the aromatic hydrogen abstraction was evaluated. As shown in Figure 8b, the barrier for this process is close to 40 kcal/mol, which is significantly higher than those calculated for the radical (26.2 kcal/mol) and ionic (31.9 kcal/mol) processes.

The use of fluorinated alcohol solvents under optimized oxidation conditions is suggestive of the need for stabilization of polar species. Charge analysis indicates that the diradical transition state is highly polarized (Figure 8a), which charge separation is only slightly smaller than that of the zwitterionic electrophilic aromatic substitution transition state. Therefore, the most accurate description is that the reaction involves a polarized diradical, which is not unusual in radical chemistry involving electronegative radicals.[36] Tomkinson and co-workers[37] have recently proposed an ionic mechanism for the related arene oxidation by a spirocyclopropyl malonyl peroxide, but the data presented in that work are fully consistent with the polarized diradical mechanism proposed here.

We computed activation free energies in trifluoroethanol for radical additions and electrophilic aromatic substitutions with 4,5-dichlorophthaloyl peroxide. As shown in Table 1, while they have similar reactivity trends for the substituted benzenes, the calculated barriers for electrophilic aromatic substitution are higher by 2−6 kcal/mol. In addition, computational data predict that electrophilic aromatic substitution is more sensitive to the electronics of arenes, with an activation free energy difference of approximately 9 kcal/mol for anisole and benzene (22.7 versus 31.9 kcal/mol, Table 1). The corresponding activation free energy difference for radical addition is predicted to be about 5 kcal/mol (20.8 versus 26.2 kcal/mol, Table 1). The reduced influence of groups on reaction rates in the diradical mechanism matches the experimental study of linear free energy correlations (Figure 6). Furthermore, the electrophilic aromatic substitution mechanism would predict a high para/ortho ratio for anisole on the basis of the energy

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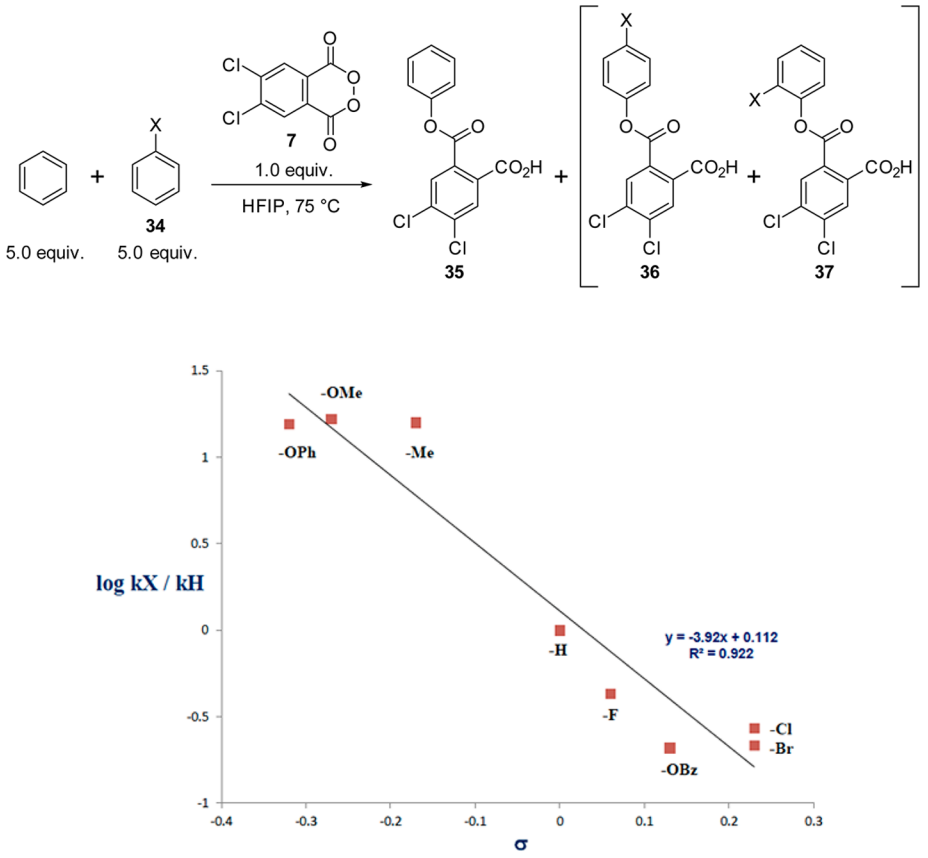

Figure 6. Linear free energy correlations derived for reactions of 4,5-dichlorophthaloyl peroxide and arenes.

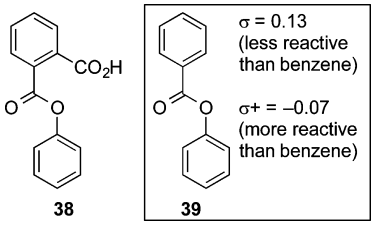

Figure 7. Phenyl benzoate σ and $\sigma+$ values.

difference of 2.3 kcal/mol. However, poor regioselectivity (the reaction of 4,5-dichlorophthaloyl peroxide with anisole provided a 1.2:1 ortho:para ratio of products) was observed, thus supporting the computational prediction based on the radical addition mechanism. More importantly, for the benzoate substitution, calculations show that it is a deactivated group, as compared to hydrogen only in the diradical mechanism. This is in conformity with the experimental observation of no overoxidation.

CONCLUSIONS

The new reagent 4,5-dichlorophthaloyl peroxide for hydroxylation of arenes, predicted to possess enhanced reactivity relative to the parent oxidant phthaloyl peroxide, has expanded the scope of the arene hydroxylation reaction. The heightened reactivity of this peroxide enables mechanistic inquiry and allows the determination of linear free energy relationships. Both experiment and theory support the reverse-rebound mechanism.

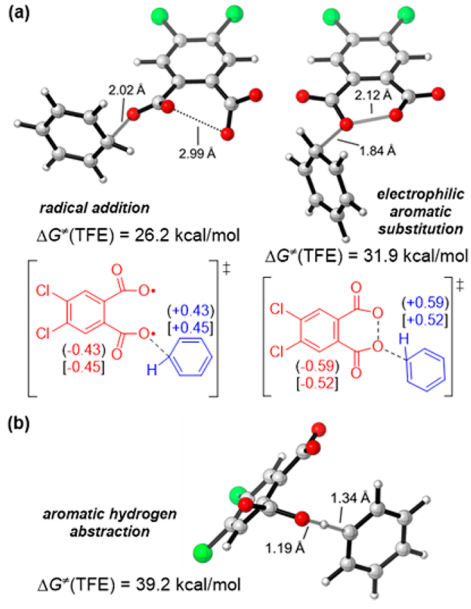

Figure 8. (a) Computed barriers for radical addition and electrophilic aromatic substitution processes for reaction of 4,5-dichlorophthaloyl peroxide and benzene, and charge analysis of the corresponding transition states (natural bond orbital or NBO charges in parentheses, Mulliken charges in brackets). (b) Computed barrier for aromatic hydrogen abstraction of benzene by the diradical generated from 4,5-dichlorophthaloyl peroxide.

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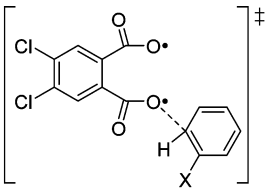
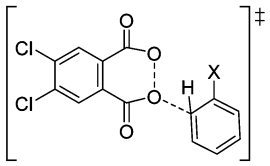
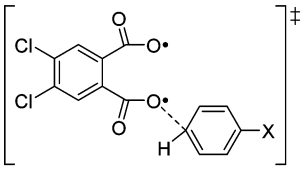
Table 1. Computed Activation Free Energies for Radical Addition and Electrophilic Aromatic Substitution Reactions with 4,5-Dichlorophthaloyl Peroxide[a]



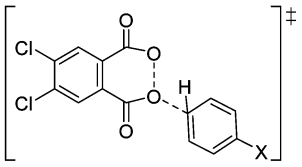
TS-R-*o*-X



TS-I-*o*-X



TS-R-*p*-X



TS-I-*p*-X

	ΔG‡(TFE), kcal/mol			
X	TS-R-*o*-X	TS-R-*p*-X	TS-I-*o*-X	TS-I-*p*-X
OMe	21.7	20.8	25.0	22.7
Me	23.5	24.1	28.5	28.1
H	26.2		31.9	
F	27.4	26.6	33.3	31.8
OBz	27.9	27.3	32.9	31.8
Cl	27.1	27.0	33.0	32.8

[a]Computed at CPCM(CF_3CH_2OH)-(U)B3LYP-D3/6-31+G(d)//(U)B3LYP/6-31+G(d).

EXPERIMENTAL SECTION

Safety Information. Research entailing the use of peroxides requires that the proper precautions be taken, and knowledgeable and experienced practitioners of organic synthesis should carry out the following procedures. At 135 °C there is a rapid loss of mass. Earlier work with phthaloyl peroxide describes the stability and proper handling of these compounds.[29,38]

General Information. Commercial reagents were purchased at the highest purity available and used without further purification. While reactions with 4,5-dichlorophthaloyl peroxide were performed without exclusion of air, other reactions were conducted under an atmosphere of N_2 unless otherwise indicated. Solvents (CH_2Cl_2 and Et_2O) were purified on a Pure-Solv MD-5 solvent purification system (Innovative Technology). Hexafluoro-2-propanol (HFIP) and trifluoroethanol (TFE) were purchased from Oakwood Products and used without purification. Analytical thin-layer chromatography (TLC) was carried out on 0.2 mm commercial glass-coated silica gel plates (silica gel 60, F254, EMD Chemical). TLC plates were visualized by exposure to ultraviolet light and/or exposure to iodine, an acidic solution of ceric ammonium molybdate, or a basic solution of potassium permanganate followed by heating on a hot plate. Chromatographic purification of products was achieved by silica gel chromatography with positive N_2 pressure as described. Infrared spectra were recorded via neat thin-film technique. High-resolution mass spectra (HRMS) were obtained via time-of-flight and quadrupole and are reported as *m*/*z* (relative intensity). Accurate masses are reported for the molecular ions $[M + Na]^+$, $[M + H]^+$, $[M]^-$, or $[M]^+$. Nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded as follows: ^1H at 400 MHz, ^{13}C at 100 and 500 MHz, ^1H at 500 MHz, ^{13}C at 125 MHz, ^1H at 600 MHz, and ^{13}C at 150 MHz. For $CDCl_3$, C_6D_6, CD_3OD, and C_3D_6O solutions, chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent: $CHCl_3$ δ 7.26 ppm, $CDCl_3$ δ 77.00 ppm, C_6D_5H δ 7.15 ppm, C_6D_6 δ 128.00 ppm, CD_2HOD δ 3.31 ppm, CD_3OD δ 47.60 ppm, C_3D_5HO δ 2.05 ppm, and C_3D_6O δ 29.00 ppm. Coupling constants are reported in hertz (Hz). Data for ^1H NMR spectra are reported as follows: chemical shift (ppm, referenced to protium), br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, tt = triplet of triplets, tq = triplet of quartets, qt = quartet of triplets, m = multiplet, integration, and coupling constant (Hz). Melting points were measured on a MEL-TEMP device with calibration by benzoic acid (mp = 122 °C) as the standard.

4,5-Dichlorophthaloyl Peroxide (7). Solid 4,5-dichlorophthalic acid (50.0 g, 213 mmol, 1.0 equiv) and solid phosphorus pentachloride (89.0 g, 427 mmol, 2.0 equiv) were added to a flame-dried flask equipped with a stir bar. The reaction vessel was placed under a continuous flow of N_2 and equipped with an outport leading to a saturated aqueous $NaHCO_3$ mixture. The solid mixture was then placed in an oil bath heated to 160 °C and stirred (600 rpm). Caution: a copious amount of HCl is evolved during this procedure. After 4.5 h, the reaction vessel was equipped with a fractional distillation apparatus and the resulting dark gray liquid was purified by distillation in vacuo (bp = 155−160 °C at 1.0 mbar) to provide the 4,5-dichlorophthaloyl chloride (55.1 g, 192 mmol, 90% yield, 95% pure) as a clear colorless oil that solidified upon cooling to 23 °C. The spectral and physical properties matched those reported for 4,5-dichlorophthaloyl chloride.[39] ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 2H); mp = 34 °C.

A mixture of solid 4,5-dichlorophthaloyl chloride (25.5 g, 94 mmol, 1.0 equiv) and solid sodium percarbonate (16.2 g, 103 mmol, 1.1 equiv) were covered with reagent-grade (not anhydrous) CH_2Cl_2 (470 mL). The white heterogeneous mixture was placed under an atmosphere of N_2 and stirred vigorously (1000 rpm). After 24 h, the mixture was filtered through a pad of Celite and carefully concentrated by rotary evaporation at 23 °C to provide a pale yellow solid. This solid was dissolved in benzene (110 mL) and then pentane (220 mL) was slowly added, initiating the precipitation of a white solid. The mixture was placed in an ice water cooling bath for 1 h and then filtered while cold to provide peroxide **7** as a white flaky solid (9.3 g, 40 mmol, 43% yield, 86% purity with 14% 4,5-dichlorophthalic anhydride). A second precipitation after partial (half the volume) concentration in vacuo of the filtrate solution provided a pale yellow solid peroxide **7** (2.7 g, 12 mmol, 13% yield, 86% purity with 14% 4,5-dichlorophthalic anhydride). Further concentration of the solution provided the starting 4,5-dichlorophthaloyl dichloride (5.7 g, 21 mmol, 22% yield). The spectral data for **7** match those reported for 4,5-dichlorophthaloyl peroxide.[29] This preparation afforded material of 86−99% purity, with the remainder of the material being 4,5-dichlorophthalic anhydride. We have tested the addition of 4,5-dichlorophthalic anhydride to the oxidation reaction and found that it does not affect the outcome of the reaction. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 142.4, 131.8, 122.6; IR (neat film, cm^{-1}) 1748, 906 cm^{-1}.

General Procedure A. To a flame-dried borosilicate flask equipped with a magnetic stir bar was added the corresponding arene, followed by syringe addition of HFIP to provide a clear homogeneous solution, diluting the substrate to a final concentration of 0.1 M. In some cases, when noted, $CHCl_3$ was added to make the solution homogeneous. Solid 4,5-dichlorophthaloyl peroxide was then added in one portion. After stirring at a rate of 500 rpm at 23 °C for 1 min, the peroxide was fully dissolved. The reaction vessel was capped with a polyethylene stopper, placed in an oil bath heated to 50 °C, and stirred at a rate of 500 rpm. After 24 or 48 h, the reaction was removed from the oil bath and allowed to cool to 23 °C. The solvent was evaporated by a continuous flow of N_2 to provide a crude yellow, orange, or deep red solid. The crude mixture was then placed under an atmosphere of N_2, and a deoxygenated mixture of MeOH/saturated aqueous $NaHCO_3$ solution (9/1) was added by syringe under N_2 to provide an overall reaction concentration of 0.1 M relative to the starting substrate. The heterogeneous mixture was then placed in an oil bath heated to 50 °C and stirred at a rate of 500 rpm. After 1 h the methanol was removed by a continuous flow of N_2, and to the mixture was added Et_2O or EtOAc (10 mL) and aqueous phosphate buffer (10 mL, 0.2 M, pH = 7). The mixture was vigorously stirred (800 rpm) at 23 °C for 2 min to form a biphasic solution, which was poured into a separatory funnel and partitioned. The organic layer was washed with

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aqueous phosphate buffer (4 × 30 mL, 0.2 M, pH = 7) or with an aqueous saturated solution of $NaHCO_3$ and brine (3 × 30 mL). The residual aqueous extracts were back-extracted with Et_2O (3 × 25 mL) or EtOAc (3 × 25 mL), combined with the first extract, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography with the noted solvent mixture to provide the phenolic products.

General Procedure B. To a flame-dried borosilicate flask equipped with a magnetic stir bar was added the starting arene, followed by syringe addition of HFIP to provide a clear homogeneous solution, diluting the substrate to a final concentration of 0.1 M. In some cases, when noted, $CHCl_3$ was added to make the solution homogeneous. Solid 4,5-dichlorophthaloyl peroxide was added in one portion. After the mixture was stirred at a rate of 500 rpm at 23 °C for 1 min, the peroxide dissolved. The reaction vessel was capped with a polyethylene stopper, placed in an oil bath heated to 75 °C, and stirred at a rate of 500 rpm. After 36 or 48 h, the reaction was removed from the oil bath and allowed to cool to 23 °C. The solvent was evaporated by a flow of N_2 to provide a yellow, orange, or deep red solid. The crude mixture was placed under an atmosphere of N_2, and a deoxygenated mixture of MeOH/saturated aqueous $NaHCO_3$ (9/1) solution was added via syringe under N_2 to provide 0.1 M solution relative to the amount of starting substrate. The heterogeneous mixture was placed in an oil bath heated to 50 °C and stirred at a rate of 500 rpm. After 1 h the methanol was removed by a continuous flow of N_2, and to the mixture Et_2O or EtOAc (10 mL) was added and an aqueous phosphate buffer (10 mL, 0.2 M, pH = 7). The mixture was vigorously stirred (800 rpm) at 23 °C for 2 min to provide a biphasic solution, which was poured into a separatory funnel and partitioned. The organic layer was collected and washed with an aqueous phosphate buffer (4 × 30 mL, 0.2 M, pH = 7) or with the combination of an aqueous saturated $NaHCO_3$ solution and brine (3 × 30 mL). The aqueous extracts were back-extracted with Et_2O (3 × 25 mL) or EtOAc (3 × 25 mL), combined with the initial extracts, dried over Na_2SO_4, filtered, and concentrated. The crude material was then purified by silica gel chromatography with the noted solvent mixture to provide the phenolic products.

General Procedure C. To a flame-dried borosilicate flask equipped with a magnetic stir bar was added the starting arene neat, followed by syringe addition of HFIP to provide a clear homogeneous solution with the substrate diluted to a final concentration of 0.1 M. Solid 4,5-dichlorophthaloyl peroxide was then added in one portion. After stirring at a rate of 500 rpm at 23 °C for 1 min, a homogeneous solution formed. The reaction vessel was capped with a polyethylene stopper, placed in an oil bath heated to 75 °C, and stirred at a rate of 500 rpm. After 36 h the reaction was removed from the oil bath and allowed to cool to 23 °C. The solvent was evaporated to dryness by a continuous flow of N_2 to provide a yellow solid. The crude mixture was then dissolved in a methanol/benzene (2/7) solution providing an overall substrate concentration of 0.1 M, and the clear yellow homogeneous solution was stirred at a rate of 500 rpm. $TMSCHN_2$ solution (5.0 equiv, 0.2 M in Et_2O) was added dropwise over 1 min with gas evolution. After 30 min the yellow−orange solution was evaporated by a continuous flow of N_2 to provide a yellow−orange viscous oil, which was purified by silica gel chromatography with the noted solvent mixture, yielding the mixed phthalate ester products.

*3-Hydroxy-4-methoxybenzaldehyde (**9**).* Prepared following General Procedure B with anisaldehyde (30.0 mg, 0.22 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [239 mg, 0.88 mmol, 4.0 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (2.2 mL) at 75 °C for 36 h. The crude brown viscous oil was purified by silica gel chromatography with 1−10% Et_2O in CH_2Cl_2/hexanes (1/1) to provide aldehyde **9** (23.0 mg, 0.15 mmol, 69%) as a deep yellow solid. The spectrum of the phenol matched that reported for **9**.[40] ^1H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.45−7.43 (m, 2H), 6.98 (d, J = 8.9 Hz, 1H), 6.72 (s, 1H), 3.99 (s, 3H).

*1-(3-Hydroxy-4-methoxyphenyl)ethan-1-one (**10**).* Prepared following General Procedure B with 4-methoxyacetophenone (100 mg, 0.67 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [446 mg, 1.67 mmol, 2.5 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (6.7 mL) at 75 °C for 36 h. The crude brown viscous oil was purified by silica gel chromatography with 1−10% Et_2O in CH_2Cl_2/hexanes (1/1) to provide ketone **10** (68.5 mg, 0.41 mmol, 62%) as a yellow solid and the starting acetophenone (18.8 mg, 0.13 mmol, 19%) as a white solid. The spectrum of the phenol matched that reported for **10**.[41] ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.52 (m, 2H), 6.89 (d, J = 8.2 Hz, 1H), 5.64 (br s, 1H), 3.97 (s, 3H), 2.55 (s, 3H).

*Methyl 3-Hydroxy-4-methoxybenzoate (**11**).* Prepared following General Procedure B with methyl 4-methoxybenzoate (100 mg, 0.60 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [408 mg, 1.50 mmol, 2.5 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (6.0 mL) at 75 °C for 36 h. The crude brown viscous oil was purified by silica gel chromatographywith 1−20% Et_2O in CH_2Cl_2/hexanes (1/1) to provide phenol **11** (70.0 mg, 0.39 mmol, 64%) as a yellow solid and the starting benzoate (5.0 mg, 0.03 mmol, 5%) as a white solid. The spectrum of the phenol matched that reported for **11**.[42] ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 2.0, 8.6 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 5.61 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H).

*5-Hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**12a**) and 7-Hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**12b**).* Prepared following General Procedure B with 6-methoxytetralone (100 mg, 0.57 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [367 mg, 1.42 mmol, 2.5 equiv (material of 90% purity with 10% 4,5-dichlorophthalic anhydride)], and HFIP (5.7 mL) at 75 °C for 36 h. The crude brown viscous oil was purified by silica gel chromatography with 1−20% Et_2O in CH_2Cl_2/hexanes (1/1) to provide phenols **12a** (41.0 mg, 0.21 mmol, 38%) and **12b** (29.0 mg, 0.15 mmol, 48%) as yellow solids and the starting tetralone (13.0 mg, 0.07 mmol, 13%) as a pale yellow solid. The spectra of the phenols match those reported for **12a** and **12b**.[43,44] Major isomer (**12a**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 5.71 (br s, 1H), 3.96 (s, 3H), 2.93 (t, J = 6.2 Hz, 2H), 2.60 (t, J = 6.2 Hz, 2H), 2.11 (tt, J = 6.2, 6.2 Hz, 2H). Minor isomer (**12b**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.66 (s, 1H), 5.52 (br s, 1H), 3.95 (s, 3H), 2.88 (t, J = 6.2 Hz, 2H), 2.59 (t, J = 6.8 Hz, 2H), 2.10 (tt, J = 6.2, 6.8 Hz, 2H).

*Methyl 3-Hydroxy-2-methoxybenzoate (**13a**) and Methyl 5-Hydroxy-2-methoxybenzoate (**13b**).* Prepared following General Procedure A with methyl salicylate (100 mg, 0.60 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [212 mg, 0.78 mmol, 1.3 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (6.0 mL) at 50 °C for 24 h. The crude brown viscous oil was purified by silica gel chromatography with 1−20% Et_2O in CH_2Cl_2/hexanes (1/1) to provide phenols **13a** (31.0 mg, 0.17 mmol, 28%) and **13b** (27.2 mg, 0.15 mmol, 25%) as yellow solids and the starting salicylate (25.6 mg, 0.15 mmol, 26%) as a clear colorless oil. The spectra of the phenols match those reported for **13a** and **13b**.[45,46] Major isomer (**13a**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 1.7, 7.9 Hz, 1H), 7.15 (dd, J = 1.7, 8.2 Hz, 1H), 7.05 (dd, J = 7.9, 8.2 Hz, 1H), 5.91 (br s, 1H), 3.93 (s, 3H), 3.92 (s, 3H). Minor isomer (**13b**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 3.4 Hz, 1H), 6.97 (dd, J = 3.1, 8.9 Hz, 1H), 6.88 (d, J = 9.2 Hz, 1H), 4.52 (br s, 1H), 3.89 (s, 3H), 3.86 (s, 3H).

*Methyl 4-Hydroxy-3-methoxybenzoate (**14a**), Methyl 2-Hydroxy-3-methoxybenzoate (**14b**), and Methyl 2-Hydroxy-5-methoxybenzoate (**14c**).* Prepared following General Procedure A with methyl 3-methoxybenzoate (100 mg, 0.60 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [212 mg, 0.78 mmol, 1.3 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (6.0 mL) at 50 °C for 24 h. The crude brown viscous oil was purified by silica gel chromatography with 1−20% Et_2O in CH_2Cl_2/hexanes (1/1) to provide phenols **14a** (22.1 mg, 0.12 mmol, 20%), **14b** (19.7 mg, 0.11 mmol, 18%), and **14c** (18.8 mg, 0.10 mmol, 17%) as pale yellow solids and the starting benzoate (20.9 mg, 0.13 mmol, 21%) as a clear colorless oil. The spectra of the phenols match those reported for **14a**, **14b**, and **14c**.[40,47,48] Major isomer (**14a**): ^1H NMR (400 MHz, $CDCl_3$) δ 10.37 (br s, 1H), 7.29 (d, J = 3.2 Hz, 1H), 7.08 (dd, J = 3.1, 8.9 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.78 (s, 3H).

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Minor isomer (**14b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (br s, 1H), 7.43 (dd, J = 1.5, 8.2 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.83 (dd, J = 8.2, 7.9 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H). Minor isomer (**14c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 2.1, 8.2 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 5.97 (br s, 1H), 3.95 (s, 3H), 3.89 (s, 3H).

*Methyl 3-Hydroxy-2,6-dimethylbenzoate (**15**).* Prepared following General Procedure B with methyl 2,6-dimethylbenzoate (100.0 mg, 0.61 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** (422.0 mg, 1.52 mmol, 2.5 equiv, 84%), and HFIP (6.1 mL) at 75 °C for 48 h. The crude orange foam was purified by silica gel chromatography with pentane and then hexane → 15% acetone in hexane to afford the phenol **15** as a pale yellow amorphous oil (63.0 mg, 0.35 mmol, 58%). R_f = 0.46 (50% Et_2O in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 4.64 (br s, 1H), 3.91 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 151.8, 135.1, 128.3, 126.5, 121.1, 116.1, 52.1, 18.9, 12.9; IR (neat film, cm $^{-1}$) 3399, 2360, 2341, 1706, 1293, 1047; HRMS (EC−CI) calcd for $C_{10}H_{12}O_3$ [M] 180.0786, found 180.0787.

*Methyl 5-Hydroxy-2,4-dimethylbenzoate (**16a**) and Methyl 3-Hydroxy-2,4-dimethylbenzoate (**16b**).* Prepared following General Procedure B with methyl 2,4-dimethylbenzoate (150.0 mg, 0.91 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** (649.0 mg, 2.28 mmol, 2.5 equiv, 82%), and HFIP (9.1 mL) at 75 °C for 48 h. The crude orange foam was purified by silica gel chromatography with pentane and then hexane → 30% EtOAc in hexane to afford phenol **16a** as a pale yellow amorphous oil (63.2 mg, 0.35 mmol, 38%) and phenol **16b** as a pale yellow oil (57.4 mg, 0.22 mmol, 35%). The spectral data for the title compound match those of phenol **16a**.[44] Major isomer (**16a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.99 (s, 1H), 3.86 (s, 3H), 2.48 (s, 3H), 2.25 (s, 3H). Minor isomer (**16b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 4.91 (br s, 1H), 3.87 (s, 3H), 2.48 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 152.6, 133.0, 129.1, 127.6, 124.7, 122.5, 51.9, 16.4, 12.6; IR (neat film, cm^{-1}) 3477, 2952, 1702, 1435, 1273, 1054; HRMS (EC−CI) calcd for $C_{10}H_{13}O_3$ $[M + H]^+$ 181.0865, found 181.0865.

*Methyl 4-Hydroxy-2,3-dimethylbenzoate (**17a**), Methyl 6-Hydroxy-2,3-dimethylbenzoate (**17b**), and Methyl 5-Hydroxy-2,3-dimethylbenzoate (**17c**).* Prepared following General Procedure B with methyl 2,3-dimethylbenzoate (100.0 mg, 0.61 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** (422.0 mg, 1.52 mmol, 2.5 equiv, 84%), and HFIP (6.1 mL) at 75 °C for 48 h. The crude orange foam was purified by silica gel chromatography with 1−5% Et_2O in hexane/CH_2Cl_2 (1:1) to afford the phenols **17a** as a pale yellow amorphous oil (25.9 mg, 0.14 mmol, 24%), **17b** as a pale yellow amorphous oil (21.8 mg, 0.12 mmol, 20%), and **17c** as a pale yellow foam (14.9 mg, 0.08 mmol, 14%). The spectral data for the title compounds match those for phenols **17a** and **17b**.[44,47] Major isomer (**17a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 3.85 (s, 3H), 2.51 (s, 3H), 2.20 (s, 3H). Minor isomer (**17b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (br s, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 3.88 (s, 3H), 2.45 (s, 3H), 2.32 (s, 3H). Minor isomer (**17c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 2.7 Hz, 1H), 6.80 (d, J = 2.7 Hz, 1H), 5.25 (br s, 1H), 3.87 (s, 3H), 2.35 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 152.6, 139.7, 131.7, 129.8, 120.4, 114.1, 52.0, 20.7, 15.8; IR (neat film, cm^{-1}) 3398, 1718, 1436, 1225; HRMS (EC−CI) calcd for $C_{10}H_{12}O_3$ [M] 180.0786, found 180.0785.

*Methyl 3-Hydroxy-2,5-dimethylbenzoate (**18a**), Methyl 4-Hydroxy-2,5-dimethylbenzoate (**18b**), and Methyl 2-Hydroxy-3,6-dimethylbenzoate (**18c**).* Prepared following General Procedure B with methyl 2,5-dimethylbenzoate (100.0 mg, 0.61 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** (422.0 mg, 1.52 mmol, 2.5 equiv, 84%), and HFIP (6.1 mL) at 75 °C for 48 h. The crude orange foam was purified by silica gel chromatography with pentane and then hexane → 15% acetone in hexane to afford the phenols **18a** (27.7 mg, 0.15 mmol, 25%) and **18b** (14.5 mg, 0.08 mmol, 13%) as pale yellow foams and **18c** (13.9 mg, 0.08 mmol, 13%) as a pale yellow solid. The spectral data for the title compounds match those for phenols **18a**, **18b**, and **18c**.[49,50] Major isomer (**18a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.77 (s, 1H), 5.22 (br s, 1H), 3.88 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H). Minor isomer (**18b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 6.62 (s, 1H), 5.57 (br s, 1H), 3.85 (s, 3H), 2.52 (s, 3H), 2.22 (s, 3H). Minor isomer (**18c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (br s, 1H), 7.15 (d J = 7.5 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 2.50 (s, 3H), 2.22 (s, 3H).

*3-(4-Chloro-2-hydroxyphenoxy)propane-1,2-diol (**19**).* Prepared following General Procedure A with chlorphenesin (95 mg, 0.47 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [165 mg, 0.61 mmol, 1.3 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (4.7 mL) at 50 °C for 24 h. After removal of HFIP by continuous positive flow of N_2, the mixed phthalate acid was placed under an atmosphere of N_2 and a deoxygenated mixture of methanol/saturated aqueous $NaHCO_3$ (9/1, 4.7 mL) was added via syringe under N_2. The resulting red-orange suspension was placed in an oil bath heated to 50 °C and stirred (700 rpm). After 1 h the methanol was removed by a continuous flow of N_2 from the red solution and diluted with EtOAc (15 mL), and an aqueous phosphate buffer (5 mL, 0.2 M, pH = 7), and brine (5 mL) were added. The biphasic mixture was stirred (700 rpm) for 5 min and then poured into a separatory funnel containing brine (10 mL) and aqueous phosphate buffer (10 mL, 0.2 M, pH = 7). After the layers were partitioned, the organic layer was collected and washed with a saturated aqueous mixture of $NaHCO_3$ and brine (1:1, 3 × 30 mL). The aqueous layers were back-extracted with EtOAc (4 × 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to provide a brown solid, which was purified by silica gel chromatography with 5−50% acetone in hexanes to provide triol **19** (53.0 mg, 0.24 mmol, 52%) as a pale yellow viscous oil and chlorphenesin (11.0 mg, 0.05 mmol, 12%) as a white solid. R_f = 0.47 (50% acetone in hexanes); ^{1}H NMR (400 MHz, C_3D_6O) δ 8.21 (br s, 1H), 6.98 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 2.7, 8.6 Hz, 1H), 4.39 (br s, 1H), 4.14 (m, 1H), 4.01 (m, 2H), 3.84 (m, 1H), 3.67 (t, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, C_3D_6O) δ 148.2, 145.9, 125.8, 119.1, 115.5, 114.6, 71.4, 70.4, 62.9; IR (neat film, cm^{-1}) 3410, 2935, 1634, 1592, 1504, 1268, 1215; HRMS (EC−ESI) calcd for $C_9H_{11}ClNaO_4$ $[M + Na]^+$ 241.0238, found 241.0234.

Chlorphenesin Carbonate. The solid mixture of chlorphenesin (0.40 g, 1.97 mmol, 1.0 equiv), 1,1′-carbonyldiimidazole (0.48 g, 3.0 mmol, 1.5 equiv), and 4-(*N*,*N*′-dimethylamino)pyridine (0.01 g, 0.10 mmol, 0.05 equiv) was added under N_2 into a flame-dried reaction vessel. Purified CH_2Cl_2 (19.7 mL) was added under N_2, followed by the addition of freshly distilled Et_3N (1.0 g, 1.39 mL, 9.87 mmol, 5.0 equiv). The homogeneous, clear pale yellow solution was allowed to stir (300 rpm) for 18 h at 23 °C and then diluted with Et_2O (30 mL), and an aqueous phosphate buffer (50 mL, 0.2 M, pH = 7) was added. The mixture was poured into a separatory funnel and the layers were separated. The organic layer was removed and the residual organics were back-extracted from the aqueous layer with Et_2O (4 × 20 mL), dried over Na_2SO_4, filtered, and concentrated to provide an off-white solid, which was purified by column chromatography with 5−25% acetone in hexanes to provide the carbonate as a white solid (0.30 g, 1.31 mmol, 67%). The spectrum of the carbonate matches that reported.[51] R_f = 0.56 (40% acetone in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 5.02 (m, 1H), 4.62 (dd, J = 7.6, 8.6 Hz, 1H), 4.52 (dd, J = 5.81, 8.5 Hz, 1H), 4.22 (dd, J = 4.1, 10.6 Hz, 1H), 4.12 (dd, J = 3.4, 10.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 154.5, 129.6, 127.0, 115.9, 73.9, 67.3, 66.1; IR (neat film, cm^{-1}) 1790, 1492, 1243, 1169.

*4-[(4-Chloro-2-hydroxyphenoxy)methyl]-1,3-dioxolan-2-one (**20**).* Prepared following General Procedure A with carbonate (50 mg, 0.22 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [138 mg, 0.51 mmol, 2.5 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (2.0 mL) at 50 °C for 24 h. The crude brown viscous oil was purified by silica gel chromatography with 5−30% acetone in hexanes to provide the carbonate **20** (28.0 mg, 0.11 mmol, 52%) as a pale orange solid. R_f = 0.46 (40% acetone in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 2.4, 8.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 5.48 (br s, 1H), 5.07 (m, 1H),

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4.66 (dd, J = 8.2, 8.9 Hz, 1H), 4.47 (dd, J = 5.8, 8.9 Hz, 1H), 4.30 (dd, J = 3.4, 10.9 Hz, 1H), 4.20 (dd, J = 4.4, 10.9 Hz, 1H); ^{1}H NMR (400 MHz, C_3D_6O) δ 8.39 (br s, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 2.6 Hz, 1H), 6.80 (dd, J = 2.5, 8.5 Hz, 1H), 5.20 (m, 1H), 4.71 (t, J = 8.5 Hz, 1H), 4.56 (dd, J = 6.9, 8.5 Hz, 1H), 4.39 (dd, J = 3.4, 11.2 Hz, 1H), 4.33 (dd, J = 4.7, 11.2 Hz, 1H); ^{13}C NMR (150 MHz, C_3D_6O) δ 155.5, 148.9, 146.3, 127.2, 120.0, 116.8, 115.8, 75.7, 69.5, 66.7; IR (neat film, cm^{-1}) 3400, 2922, 1783, 1634; HRMS (EC−CI) calcd for $C_{10}H_9ClO_5$ $[M - H]^+$ 244.0139, found 244.0141; mp = 122−125 °C.

*3-(4-Chloro-2-hydroxyphenoxy)-2-hydroxypropyl Carbamate (**21**).* Prepared following General Procedure A with chlorphenesin carbamate (85 mg, 0.35 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [122 mg, 0.45 mmol, 1.3 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (3.5 mL) at 50 °C for 24 h. After removal of the HFIP by continuous positive flow of N_2, the intermediate phthalate ester acid was placed under an atmosphere of N_2, and a deoxygenated mixture of methanol/saturated aqueous $NaHCO_3$ (9/1, 3.5 mL) was added via syringe under N_2. The resulting red-orange suspension was placed in an oil bath heated to 50 °C and stirred vigorously (500 rpm). After 1 h the methanol was removed by a continuous flow of N_2 and diluted with EtOAc (15 mL), and an aqueous phosphate buffer (5 mL, 0.2 M, pH = 7) and brine (5 mL) were added. The biphasic mixture was stirred vigorously (700 rpm) for 5 min and then poured into a separatory funnel containing additional brine (10 mL) and aqueous phosphate buffer (10 mL, 0.2 M, pH = 7). After the layers were separated, the organics were washed with a saturated aqueous mixture of $NaHCO_3$ and brine (1:1, 3 × 30 mL). The residual organics were back-extracted from the aqueous layer repeatedly with EtOAc (4 × 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to provide a brown solid, which was purified by silica gel chromatography with 5−35% acetone in hexanes to yield the carbamate **21** (57.0 mg, 0.22 mmol, 63%) as an off-white solid. R_f = 0.45 (50% acetone in hexanes); ^{1}H NMR (400 MHz, CD_3OD) δ 6.88 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 2.7 Hz, 1H), 6.74 (dd, J = 2.4, 8.6 Hz, 1H), 4.16 (m, 3H), 4.06 (m, 1H), 3.98 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.3, 147.6, 145.6, 126.0, 118.9, 115.5, 113.8, 70.0, 68.1, 64.9; IR (neat film, cm^{-1}) 3369, 1706, 1501; HRMS (EC−ESI) calcd for $C_{10}H_{12}ClNNaO_5$ $[M + Na]^+$ 284.0296, found 284.0293; mp = 124−127 °C.

*5-Fluoro-2-pentylphenol (**22a**) and 2-Fluoro-5-pentylphenol (**22b**).* Prepared following General Procedure B with 4-pentylfluorobenzene (100 mg, 0.60 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [403 mg, 1.50 mmol, 2.5 equiv (material of 87% purity with 13% 4,5-dichlorophthalic anhydride)], and HFIP (6.0 mL) at 75 °C for 36 h. The crude brown viscous oil was purified by silica gel chromatography with 1% Et_2O in CH_2Cl_2/hexanes (1/1) to provide fluorophenols **22a** and **22b** (64.3 mg, 0.35 mmol, 59%, **22a**:**22b** = 2.5:1) as a yellow oil. The spectra of phenols matched that reported for **22b**.[52] R_f = 0.57 (3% Et_2O in 49% hexanes and 48% CH_2Cl_2). Major isomer (**22a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, J = 6.8, 8.6 Hz, 1H), 6.57 (ddd, J = 5.8, 8.2, 10.0 Hz, 1H), 6.52 (dd, J = 2.4, 9.9 Hz, 1H), 4.82 (br s, 1H), 2.53 (t, J = 8.2 Hz, 2H), 1.58 (m, 2H), 1.35 (m, 4H), 0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ161.4 (d, J_{CF} = 243.4 Hz), 154.2 (d, J_{CF} = 10.7 Hz), 130.7 (d, J_{CF} = 9.9 Hz), 124.2 (d, J_{CF} = 3.8 Hz), 107.5, 103.0, 31.6, 29.5, 29.3, 22.5, 14.0; IR (neat film, cm^{-1}) 3391, 2929, 1609, 1514, 1279, 1112; HRMS (EC−CI) calcd for $C_{11}H_{15}OF$ $[M + H]^+$ 182.1107, found 182.1106. Minor isomer (**22b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dd, J = 8.2, 10.3 Hz, 1H), 6.84 (dd, J = 2.1, 8.6 Hz, 1H), 6.66−6.63 (m, 1H), 5.01 (br s, 1H), 2.53 (t, J = 8.2 Hz, 2H), 1.58 (m, 2H), 1.35 (m, 4H), 0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3 (d, J_{CF} = 234.2 Hz), 142.9 (d, J_{CF} = 14.5 Hz), 139.9 (d, J_{CF} = 3.1 Hz), 120.5 (d, J_{CF} = 6.1 Hz), 117.0 (d, J_{CF} = 1.5 Hz), 115.0 (d, J_{CF} = 1.6 Hz), 35.3, 31.4, 31.1, 22.5, 14.0; IR (neat film, cm^{-1}) 3391, 2929, 1609, 1514, 1279, 1112; HRMS (EC−CI) calcd for $C_{11}H_{15}OF$ $[M + H]^+$ 182.1107, found 182.1106.

*2-Butyl-5-chlorophenol (**23a**) and 5-Butyl-2-chlorophenol (**23b**).* Prepared following General Procedure B with 4-butylchlorobenzene (100 mg, 0.59 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [406 mg, 1.48 mmol, 2.5 equiv (material of 85% purity with 15% 4,5-dichlorophthalic anhydride)], and HFIP (5.9 mL) at 75 °C for 36 h. The crude brown viscous oil was purified by silica gel chromatography with 1% Et_2O in CH_2Cl_2/hexanes (1/1) to provide chlorophenols **23a** and **23b** (64.4 mg, 0.35 mmol, 59%, **23a**:**23b** = 4:1) as a yellow oil. R_f = 0.57 (3% Et_2O in 49% hexanes and 48% CH_2Cl_2). Major isomer (**23a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 7.9 Hz, 1H), 6.5 (dd, J = 2.1, 8.2 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 4.69 (br s, 1H), 2.56 (t, J = 7.5 Hz, 2H), 1.60−1.53 (m, 2H), 1.37 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ154.2, 132.0, 131.2, 127.4, 121.1, 115.8, 32.0, 29.4, 22.7, 14.2; IR (neat film, cm^{-1}) 3412, 2957, 2930, 1603, 1588, 1413; HRMS (EC−CI) calcd for $C_{10}H_{13}OCl$ $[M + H]^+$ 184.0655, found 184.0653. Minor isomer (**23b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.2 Hz, 1H), 6.86−6.83 (m, 1H), 6.69 (dd, J = 2.1, 8.2 Hz, 1H), 5.43 (br s, 1H), 2.54 (t, J = 7.5 Hz, 2H), 1.60−1.53 (m, 2H), 1.37 (tq, J = 7.5, 7.9 Hz, 2H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 143.8, 128.5, 121.5, 116.9, 116.1, 35.1, 33.3, 22.2, 13.9; IR (neat film, cm^{-1}) 3412, 2957, 2930, 1603, 1588, 1413; HRMS (EC−CI) calcd for $C_{10}H_{13}OCl$ $[M + H]^+$ 184.0655, found 184.0653.

*5-Bromo-2-butylphenol (**24a**) and 2-Bromo-5-butylphenol (**24b**).* Prepared following General Procedure B with 4-butylbromobenzene (100 mg, 0.47 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [321 mg, 1.17 mmol, 2.5 equiv (material of 85% purity with 15% 4,5-dichlorophthalic anhydride)], and HFIP (4.7 mL) at 75 °C for 36 h. The crude brown viscous oil was purified by silica gel chromatography with 1% Et_2O in CH_2Cl_2/hexanes (1/1) to provide bromophenols **24a** and **24b** (58.3 mg, 0.25 mmol, 54%, **24a**:**24b** = 10:1) as a dark yellow oil. R_f = 0.57 (3% Et_2O in 49% hexanes and 48% CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 6.88 (dd, J = 2.0, 8.2 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 6.29 (s, 1H), 3.90 (br s, 1H), 2.36 (t, J = 7.9 Hz, 2H), 1.40 (tt, J = 7.5, 7.9 Hz, 2H), 1.17 (qt, J = 7.5, 7.5 Hz, 2H), 0.80 (t, J = 7.52 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 1.7 Hz, 1H), 6.97 (br s, 1H), 6.93 (d, J = 1.7 Hz, 1H), 4.72 (br s, 1H), 2.55 (t, J = 7.5 Hz, 2H), 1.60−1.53 (m, 2H), 1.42−1.33 (qt, J = 7.5, 7.5 Hz, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 131.6, 128.0, 124.0, 119.6, 118.6, 31.9, 29.5, 22.7, 14.2; IR (neat film, cm^{-1}) 3390, 2957, 2928, 1408, 1123; HRMS (EC−CI) calcd for $C_{10}H_{12}OBr$ $[M + H]^+$ 228.0150, found 228.0149.

2-Nitro-4-dichlorobenzene. Concentrated H_2SO_4 (6.7 mL, 18 M, 98%) was slowly added to fuming HNO_3 (6.7 mL, 90%) in a cold bath (0 °C). After 5 min, *p*-dichlorobenzene (2.0 g, 13.6 mmol, 1.0 equiv) was added in one portion. After 2 min the cooling bath was removed and the yellow heterogeneous mixture was stirred vigorously (700 rpm) at 23 °C. After 15 min the yellow homogeneous solution was poured into ice water (250 mL), and the resulting yellow solid was filtered. The yellow solid was dried in vacuo with heating (100 °C) for 30 min to remove excess H_2O to provide 2-nitro-4-dichlorobenzene (2.43 g, 12.7 mmol, 93%) as a pure yellow solid.[53] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.50 (m, 2H).

2-Nitro-4,4′-dichlorophenyl Ether. The solid mixture of 2-nitro-4-dichlorobenzene (2.40 g, 12.5 mmol, 1.0 equiv), KOH (0.74 g, 13.1 mmol, 1.1 equiv), and 4-chlorophenol (1.77 g, 13.8 mmol, 1.1 equiv) was suspended in water (1 mL), placed in a hot oil bath heated to 170 °C, and stirred (400 rpm). After 2.5 h the reddish-brown solution was removed from the oil bath, cooled to 23 °C, diluted with Et_2O (20 mL), and diluted with 4 N NaOH (20 mL). The biphasic mixture was then poured into a separatory funnel. Water (20 mL) and Et_2O (20 mL) were added to dissolve residual solids and, following sonication, the yellow-orange mixture was added to the separatory funnel. The layers were separated and the organic layer was washed with 4 N NaOH (3 × 20 mL) to remove excess 4-chlorophenol. The aqueous phase was extracted with Et_2O (3 × 20 mL), combined with the initial organic extract, dried over Na_2SO_4, filtered, and concentrated to provide the 2-nitro-4,4′-dichlorophenyl ether (3.43 g, 12.1 mmol, 97%) as a pure yellow-orange solid.[53] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 2.4 Hz, 1H), 7.48 (dd, J = 2.7, 8.9 Hz, 1H), 7.35 (d, J = 8.9 Hz, 2H), 6.97 (d, J = 9.2 Hz, 3H).

2-Amino-4,4′-dichlorophenyl Ether. To a suspension of the nitrophenyl ether (3.43 g, 12.1 mmol, 1.0 equiv) in ethanol (48.3 mL) and water (48.3 mL) were added solid iron powder (1.82 g, 32.6 mmol, 2.7 equiv) and solid NH_4Cl (2.91 g, 54.3 mmol, 4.5 equiv). The

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reaction vessel was equipped with a reflux condenser, purged with N_2, and the black mixture was placed in an oil bath heated to 110 °C with vigorous stirring (1000 rpm). After 12 h the black mixture was filtered over Celite and the EtOH was removed in vacuo. The resulting yellow mixture was diluted with CH_2Cl_2 (50 mL) and an aqueous phosphate buffer solution (50 mL, 0.2 M, pH = 10) and poured into a separatory funnel, and the layers were separated. The organic extract was washed with an aqueous phosphate buffer (1 × 25 mL, 0.2 M, pH = 10). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), combined with the previous organic extract, dried over Na_2SO_4, filtered, and concentrated to provide the aniline (2.96 g, 11.65 mmol, 96% pure) as a yellow solid.[53] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 9.2 Hz, 2H), 6.80 (d, J = 2.4 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 6.67 (dd, J = 2.4, 8.6 Hz, 1H), 3.86 (br s, 2H).

2,4,4′-Trichlorophenyl Ether. To the dichloroaniline (2.96 g, 11.7 mmol, 1.0 equiv) were added water (9.0 mL) and concentrated HCl (7.0 mL, 87.0 mmol, 7.5 equiv, 38%, 12.4 M). The orange mixture was placed in an ice water bath and stirred vigorously (400 rpm). After 5 min, solid $NaNO_2$ (0.88 g, 12.8 mmol, 1.1 equiv) was added in one portion and the mixture changed to a deep red-orange solution. After 25 min, CuCl (1.73 g, 17.5 mmol, 1.5 equiv) was added in one portion, followed by concentrated HCl solution (1.5 mL, 18.0 mmol, 1.6 equiv, 38%, 12.4 M). The dark red-orange solution was removed from the cooling bath and stirred vigorously (400 rpm) at 23 °C. After 30 min the dark orange biphasic mixture was diluted with Et_2O (20 mL) and poured into a separatory funnel, and the layers were partitioned. The organic layer was washed with 1 N HCl (3 × 25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL), combined with the first organic extract, dried over Na_2SO_4, filtered, and concentrated, and the crude yellow-orange solid was purified by silica gel chromatography with hexanes to provide the trichloride (1.34 g, 4.90 mmol, 42%) as a white crystalline solid. The spectrum of the trichloride matched that reported for 2,4,4′-trichlorophenyl ether.[54] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.7 Hz, 1H), 7.29 (d, J = 8.9 Hz, 2H), 7.21 (dd, J = 2.4, 8.6 Hz, 1H), 6.92 (d, J = 8.9 Hz, 1H), 6.88 (d, J = 8.9 Hz, 2H).[24]

*Triclosan (**25**).* Prepared following General Procedure A with trichloride (95 mg, 0.35 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [188 mg, 0.70 mmol, 2.0 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (3.5 mL) at 60 °C for 24 h. The crude brown viscous oil was purified by silica gel chromatography with 1−10% Et_2O in pentane to provide triclosan (**25**) (52.0 mg, 0.18 mmol, 52%) as a pale-yellow viscous oil and the starting trichloride (8.4 mg, 0.03 mmol, 9%). The spectrum of the phenol matched that reported for triclosan (**25**).[55] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 2.4, 8.6 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.81 (dd, J = 2.4, 8.9 Hz, 1H), 6.66 (d, J = 8.6 Hz, 1H), 5.63 (br s, 1H).

*4-Butylphenol (**26a**) and 2-Butylphenol (**26b**).* Prepared following General Procedure A with butylbenzene (100 mg, 0.75 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [262 mg, 0.97 mmol, 1.3 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], and HFIP (7.5 mL) at 50 °C for 24 h. The crude orange viscous oil was purified by silica gel chromatography with 1−5% Et_2O in CH_2Cl_2/hexanes (1/1) to provide phenols **26a** and **26b** (81.1 mg, 0.54 mmol, 73%, **26a**:**26b** = 1.2:1) as a pale yellow viscous oil. The spectra of phenols matched those reported for **26a** and **26b**.[26,40] Major isomer (**26a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.56 (br s, 1H), 2.54 (t, J = 7.8 Hz, 2H), 1.64−1.52 (m, 2H), 1.44−1.31 (m, 2H), 0.92 (t, J = 7.1 Hz, 3H) Minor isomer (**26b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13−7.05 (m, 2H), 6.87 (ddd, J = 1.1, 7.4, 8.6 Hz, 1H), 6.77−6.74 (m, 1H), 4.64 (br s, 1H), 2.61 (t, J = 7.9 Hz, 2H), 1.64−1.52 (m, 2H), 1.44−1.31 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H).

*Methyl 3-(4-Hydroxyphenyl)propanoate (**27a**) and Methyl 3-(2-Hydroxyphenyl)propanoate (**27b**).* Prepared following General Procedure B with hydrocinnamyl methyl ester (100 mg, 0.61 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [399 mg, 1.52 mmol, 2.5 equiv (material of 89% purity with 11% 4,5-dichlorophthalic anhydride)], and HFIP (6.1 mL) at 75 °C for 36 h. The crude brown viscous oil was purified by silica gel chromatography with 1−5% Et_2O in CH_2Cl_2/hexanes (1/1) to provide esters **27a** and **27b** (81.3 mg, 0.55 mmol, 74%, **27a**:**27b** = 1.4:1) as a pale yellow viscous oil and the starting ester (5.1 mg, 0.03 mmol, 5%) as a clear colorless oil. The spectra of the phenols match those reported for **27a** and **27b**.[50,56] Major isomer (**27a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (br s, 1H), 7.06 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 7.9 Hz, 2H), 3.69 (s, 3H), 2.91 (t, J = 6.8 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H). Minor isomer (**27b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (m, 2H), 6.75 (m, 2H), 3.66 (s, 3H), 2.88 (t, J = 7.9 Hz, 2H), 2.59 (t, J = 6.9 Hz, 2H).

*3-(4-Hydroxyphenyl)propanoic Acid (**28a**) and 3-(2-Hydroxyphenyl)propanoic Acid (**28b**).* Prepared following General Procedure B with hydrocinnamic acid (100 mg, 0.67 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** [451 mg, 1.67 mmol, 2.5 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)], $CHCl_3$ (1.7 mL), and HFIP (5.0 mL) at 75 °C for 48 h. After removal of the HFIP and $CHCl_3$ by continuous positive flow of N_2, the mixed phthalate acid ester was placed under an atmosphere of N_2, suspended in 1,4-dioxane (6.0 mL) and then a saturated aqueous solution of $NaHCO_3$ (0.7 mL) was added. The red-orange suspension was placed in an oil bath heated to 50 °C and stirred (700 rpm). After 1 h the red solution was removed from the oil bath, acidified to pH = 2 by use of 1 N HCl (3 mL), diluted with EtOAc (20 mL), and poured into a separatory funnel containing brine (20 mL), and the layers were separated. The organic extract was washed with an aqueous phosphate buffer (2 × 20 mL, 0.2 M, pH = 4) and the aqueous layer was combined with the brine and back-extracted with EtOAc (4 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to provide an orange solid. The orange solid was suspended in CH_2Cl_2 (30 mL), heated for 5 min, and sonicated for 1 min. The residual orange mixture was filtered to remove the insoluble 4,5-dichlorophthalic acid. The orange filtrate solution was concentrated to provide an orange solid, which was purified by silica gel chromatography with 1% CH_3OH + 1% AcOH in CH_2Cl_2 to provide acids **28a** and **28b** (71.8 mg, 0.43 mmol, 65%, **28a**:**28b** = 1:1) as an orange solid. The starting acid (12.0 mg, 0.08 mmol, 12%) was isolated as a white solid. The spectra of the phenols match those reported for **28a** and **28b**.[57,58] Isomer **28a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 2.90 (t, J = 8.2 Hz, 2H), 2.65 (t, J = 7.9 Hz, 2H). Isomer **28b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (m, 2H), 6.82−6.89 (m, 2H), 2.92 (t, J = 6.5 Hz, 2H), 2.78 (t, J = 6.5 Hz, 2H).

Methyl 4-[2-(Diethylamino)ethoxy]-3-methoxybenzoate. To a stirred solution of known methyl 4-(3-chloropropoxy)-3-methoxybenzoate[26] (1.37 g, 5.3 mmol, 1.0 equiv) in dimethylformamide (28.5 mL) were added NaI (1.59 g, 10.6 mmol, 2.0 equiv) and diethylamine (1.64 mL, 15.9 mmol, 3.0 equiv). The flask was purged with N_2 and placed in an oil bath heated to 80 °C. After 24 h the solution was removed from the oil bath and allowed to cool to 23 °C, poured into a separatory funnel containing 3 N LiCl (150 mL), and extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with 3 N LiCl (1 × 50 mL) to remove residual dimethylformamide, washed with brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo, and the crude mixture was purified by silica gel chromatography with 1% CH_3OH and 1% Et_3N in CH_2Cl_2 to provide the amine as an amber oil (1.25 g, 80%). R_f = 0.40 (2% CH_3OH + 2% Et_3N in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 2.0, 8.6 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 4.12 (t, J = 6.6 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.61 (t, J = 7.1 Hz, 2H), 2.54 (q, J = 7.4 Hz, 4H), 1.99 (m, 2H), 1.01 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 152.5, 148.8, 123.5, 122.4, 112.3, 111.5, 67.4, 56.0, 51.9, 49.1, 46.9, 26.6, 11.7; IR (neat film, cm $^{-1}$) 2967, 2809, 1717, 1293; HRMS (EC−CI) $[M + Na]^+$ calcd for $C_{16}H_{25}NO_4Na$ 318.16758, found 318.16729.

*Methyl 4-[2-(Diethylamino)ethoxy]-2-hydroxy-3-methoxybenzoate (**29**).* To a stirred (500 rpm) solution of amine (75.0 mg, 0.25 mmol, 1.0 equiv) in HFIP (2.5 mL) at 23 °C was added *p*-toluenesulfonic acid (43.7 mg, 0.25 mmol, 1.0 equiv), and then 4,5-dichlorophthaloyl peroxide **7** [89.0 mg, 0.33 mmol, 1.3 equiv (material of 86% purity with 14% 4,5-dichlorophthalic anhydride)] was added.

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After 4 h, the solvent was removed by a continuous flow of N_2, providing the mixed phthalate ester acid as a red solid. The crude solid was placed under an atmosphere of N_2, suspended in a deoxygenated mixture of methanol and saturated aqueous $NaHCO_3$ (9/1, 2.5 mL), and placed in an oil bath heated to 50 °C. After 1 h the reaction was poured into an aqueous phosphate buffer solution (5 mL, 0.2 M, pH = 10) and then into a separatory funnel, and the layers were separated. The residual organics were back-extracted from the aqueous layer with EtOAc (3 × 5 mL). The combined organic layers were washed with an aqueous phosphate buffer (1 × 5 mL, 0.2 M, pH = 10) and with brine (1 × 5 mL), dried over Na_2SO_4, and concentrated. The crude mixture was purified by silica gel chromatography with 1% methanol and 1% triethylamine in CH_2Cl_2, providing phenol **29** as a clear colorless oil (67.7 mg, 0.22 mmol, 86%). R_f = 0.40 (2% methanol and 2% triethylamine in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.79 (s, 1 H), 7.55 (d, J = 9.0 Hz, 1H), 6.48 (d, J = 9.0 Hz, 1H), 4.12 (m, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 2.65 (t, J = 7.0 Hz, 2H), 2.57 (q, J = 7.0 Hz, 4H), 1.99 (t, J = 7.4 Hz, 2H), 1.04 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 157.3, 155.7, 136.4, 125.3, 106.5, 103.9, 66.8, 60.3, 51.8, 48.9, 46.7, 26.4, 11.2; IR (neat film, cm^{-1}) 3369, 2966, 2917, 1720, 1240; HRMS (EC−CI) $[M + H]^+$ calcd for $C_{16}H_{26}NO_5$ 312.1806, found 312.1800.

*N-(2-Hydroxyphenethyl)benzenesulfonamide (**30a**) and N-(4-Hydroxyphenethyl)benzenesulfonamide (**30b**).* Prepared following General Procedure B with sulfonamide (100.0 mg, 0.38 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** (265.0 mg, 0.96 mmol, 2.5 equiv, 84%), and HFIP (3.8 mL) at 75 °C for 72 h. The crude orange foam was purified by silica gel chromatography with hexane → 25% acetone in hexane to provide the sulfonamide **30a** (34.8 mg, 0.13 mmol, 33%) as a yellow amorphous foam and **30b** (27.8 mg, 0.10 mmol, 26%) as a white solid. Major isomer (**30a**): R_f = 0.40 (35% acetone in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 7.9 Hz, 1H), 7.45 (dt, J = 7.2, 7.9 Hz, 2H), 7.08 (t, 7.9 Hz, 1H), 6.97 (dd, J = 1.4, 7.5 Hz, 1H), 6.81 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 5.62 (br s, 1H), 4.99 (br s, 1H), 3.23 (m, 2H), 2.79 (t, J = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 139.5, 132.8, 132.6, 130.9, 129.1, 128.2, 127.0, 126.4, 124.4, 121.0, 115.6, 43.6, 30.4; IR (neat film, cm^{-1}) 3274, 1457, 1447, 1322, 1157, 1093, 755; HRMS (EC−CI) calcd for $C_{14}H_{15}NO_3S$ [M] 277.0773, found 277.0779. Minor isomer (**30b**): R_f = 0.33 (35% acetone in hexane); ^{1}H NMR (400 MHz, C_3D_6O) δ 8.14 (br s, 1H), 7.85 (m, 2H), 7.60 (m, 3H), 6.97 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 6.45 (br s, 1H), 3.09 (m, 2H), 2.67 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 142.0, 133.1, 130.5, 130.2, 129.9, 127.7, 116.0, 45.7, 35.9; IR (neat film, cm^{-1}) 3391, 3019, 2924, 1215, 757; HRMS (EC−CI) calcd for $C_{14}H_{15}NO_3S$ [M] 277.0773, found 277.0776; mp 116−121 °C.

*2,2,2-Trifluoro-N-(2-hydroxyphenethyl)acetamide (**31a**) and 2,2,2-Trifluoro-N-(4-hydroxyphenethyl)acetamide (**31b**).* Prepared following General Procedure B with the starting trifluoroacetamide (100.0 mg, 0.46 mmol, 1.0 equiv), 4,5-dichlorophthaloyl peroxide **7** (523.0 mg, 1.84 mmol, 4.0 equiv, 82%), and HFIP (4.6 mL) at 75 °C for 72 h. After removal of HFIP by continuous positive flow of nitrogen, the mixed phthalate ester acid was placed under an atmosphere of N_2, tetrahydrofuran (THF) (2.3 mL) was added via syringe, and an aqueous phosphate buffer (2.3 mL, pH = 7, 0.2 M) was added via syringe. The yellow biphasic solution was stirred vigorously (1000 rpm) at 23 °C. After 24 h the solution was diluted with EtOAc (20 mL) and poured into a separatory funnel containing aqueous phosphate buffer (10 mL, pH = 7, 0.2 M), and the layers were partitioned. The organics were washed with an aqueous phosphate buffer (4 × 20 mL, 0.2 M, pH = 7) and the residual organics were extracted from the aqueous layer with EtOAc (4 × 30 mL). The combined organics were dried over solid Na_2SO_4, decanted, and concentrated. The crude brown foam was purified by silica gel chromatography with hexane → 25% acetone in hexane to provide the amides **31a** (28.8 mg, 0.12 mmol, 27%) and **31b** (23.6 mg, 0.10 mmol, 22%) as pale yellow foams.[59] Major isomer (**31a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.10 (m, 2H), 7.05 (br s, 1H), 6.91 (dt, J = 1.0, 7.5 Hz, 1H), 6.80 (d, 8.2 Hz, 1H), 3.60 (q, J = 6.5 Hz, 2H), 2.93 (t, J = 6.5 Hz, 2H). Minor isomer (**31b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.2 Hz, 2H), 6.25 (br s, 1H), 3.58 (q, J = 6.5 Hz, 2H), 2.81 (t, J = 6.5 Hz, 2H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01079.

Thermogravimetric analysis, ^{1}H and ^{13}C spectra, computational details, and coordinates and energies of stationary points (PDF)

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Notes

The authors declare no competing financial interest.

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