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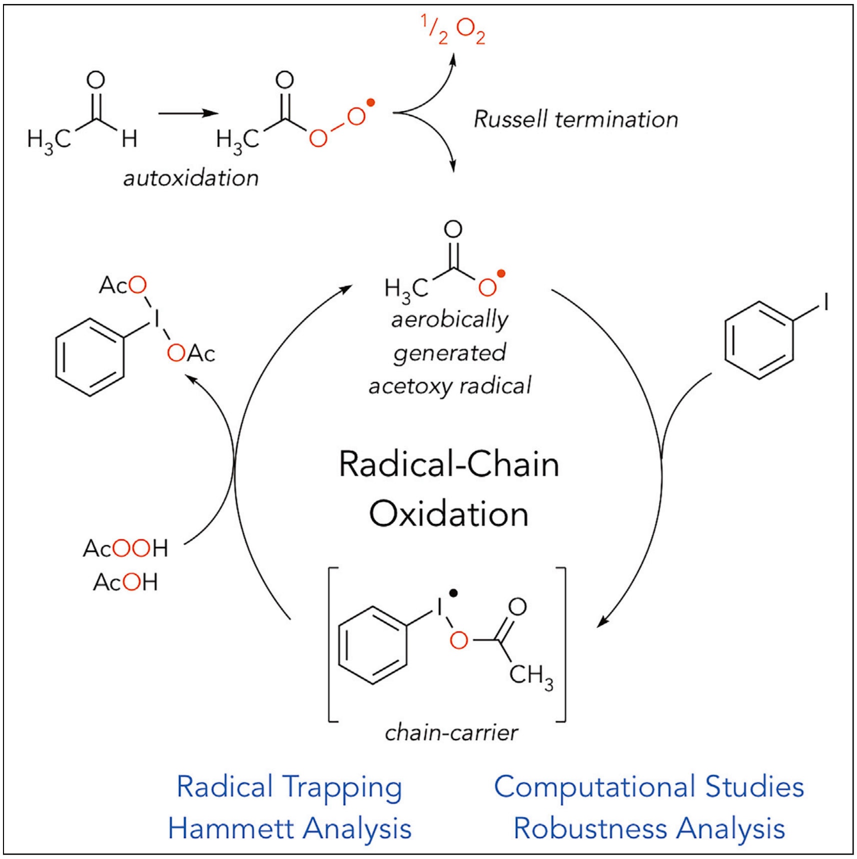
The Role of Iodanyl Radicals as Critical Chain Carriers in Aerobic Hypervalent Iodine Chemistry



Aerobic hypervalent iodine chemistry provides a strategy for coupling the one-electron chemistry of O_2 with two-electron processes typical of organic synthesis. We show that in contrast to the canonical two-electron oxidation of aryl iodides, aerobic synthesis proceeds by a radical chain process initiated by the addition of aerobically generated acetoxy radicals to aryliodides to generate iodanyl radicals. Robustness analysis reveals that the developed aerobic oxidation chemistry displays substrate tolerance similar to that observed in peracid-based methods and thus holds promise as a sustainable synthetic method.

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HIGHLIGHTS

Aerobic hypervalent iodine reagent synthesis via one-electron radical mechanism

Common autoxidation mechanism to main-group and transition-metal complexes

The demonstration of iodanyl radical during the oxidation of aryl iodides

Functional-group tolerance similar to that with oxidation by peracids

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The Role of Iodanyl Radicals as Critical Chain Carriers in Aerobic Hypervalent Iodine Chemistry

Sung-Min Hyun,[1] Mingbin Yuan,[2] Asim Maity,[1] Osvaldo Gutierrez,[2,*] and David C. Powers[1,3,*]

SUMMARY

Selective O_2 utilization remains a substantial challenge in synthetic chemistry. Biological small-molecule oxidation reactions often utilize aerobically generated high-valent catalyst intermediates to effect substrate oxidation. Available synthetic methods for aerobic oxidation catalysis are largely limited to substrate functionalization chemistry by low-valent catalyst intermediates (i.e., aerobically generated Pd(II) intermediates). Motivated by the need for new chemical platforms for aerobic oxidation catalysis, we recently developed aerobic hypervalent iodine chemistry. Here, we report that in contrast to the canonical two-electron oxidation mechanisms for the oxidation of organoiodides, the developed aerobic hypervalent iodine chemistry proceeds via a radical chain mechanism initiated by the addition of aerobically generated acetoxy radicals to aryl iodides. Despite the radical chain mechanism, aerobic hypervalent iodine chemistry displays substrate tolerance similar to that observed with traditional terminal oxidants, such as peracids. We anticipate that these insights will enable new sustainable oxidation chemistry via hypervalent iodine intermediates.

INTRODUCTION

O_2 is an attractive oxidant for use in synthetic chemistry because it is readily available, generates environmentally benign byproducts, and displays substantial reduction potential. Radical chain autoxidation—the spontaneous oxidation of organic compounds upon exposure to O_2—is a ubiquitous process in organic chemistry that can affect most organic functional groups.[1–4] Autoxidation chain reactions arise because of spin conservative reactions of the triplet ground state of O_2 (i.e., $^3O_2$) with singlet organic molecules (Figure 1A). On the commodity scale, autoxidation of cumene and *p*-xylene produce phenol[5] and terephthalic acid,[6] respectively (Figure 1B). In fine-chemical synthesis, acyl radical intermediates generated during aldehyde autoxidation (Figure 2A) have been diverted toward olefin addition chemistry (Figure 2B),[7,8] alkyl radical intermediates generated by decarbonylation of acyl radicals have been harnessed for alkylation of *N*-heterocycles (Figure 2C),[9] and peroxy radicals and peroxide intermediates have been diverted toward oxygen-atom transfer (OAT) chemistry to olefins (i.e., Mukaiyama reaction)[10–12] and to transition-metal complexes (Figures 2D and 2E).[13–15] Although these examples highlight the potential of autoxidation in specific synthetic applications, reliance on only those reactive intermediates generated in autoxidation chemistry substantially limits the diversity of substrate functionalization reactions that can be coupled to O_2.

Motivated by the desire to couple diverse substrate oxidation mechanisms to the reduction of O_2, researchers have developed a wide variety of aerobic oxidation

The Bigger Picture

O_2 is routinely utilized in biological catalysis to generate high-valent catalyst intermediates that engage in substrate oxidation chemistry. Analogous synthetic chemistry via aerobically generated high-valent intermediates would enable new sustainable synthetic methods but is largely unknown because of the challenges in selective O_2 utilization. We have developed aerobic hypervalent iodine chemistry as a platform for coupling O_2 reduction with a diverse set of substrate functionalization mechanisms. Many of the synthetic applications of hypervalent iodine reagents rely on selective two-electron oxidation-reduction chemistry. Here, we report that one-electron oxidation reactions pathways via iodanyl radical intermediates are critical in aerobic hypervalent iodine chemistry. The new appreciation for the critical role that iodanyl radicals can play in the synthesis of hypervalent iodine compounds will provide new opportunities in sustainable oxidation catalysis.

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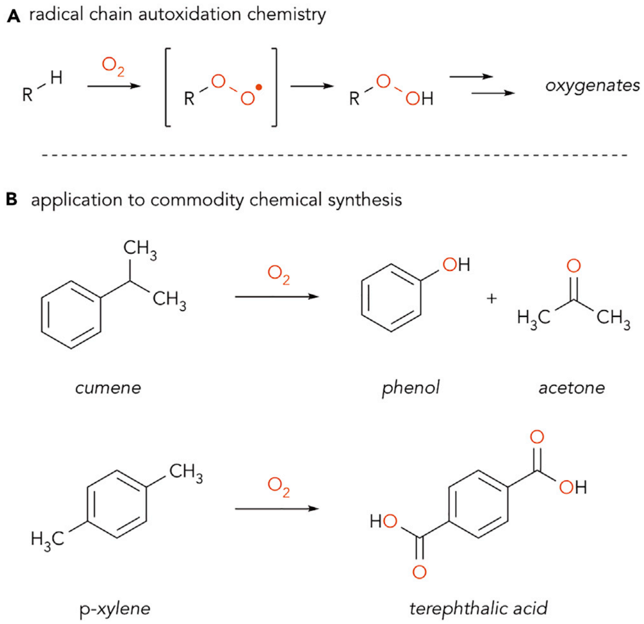

Figure 1. Radical Chain Autoxidation

(A) Autoxidation reactions proceed via peroxy radical and hydroperoxide intermediates.

(B) Autoxidation chemistry is utilized on the commodity scale to produce phenol, acetone, and terephthalic acid.

methods. Among the most well developed is palladium (Pd) oxidase chemistry, in which the diverse substrate functionalization mechanisms available to Pd(II) are coupled to aerobic re-oxidation of Pd(0) intermediates.[16–21] Pd oxidase catalysis has been leveraged for a wide variety of substrate functionalization reactions: alcohol[22–24] and olefin oxidation, Aza-Wacker chemistry,[25] arene oxidation,[26,27] oxidative Heck reactions,[28–31] and allylic oxidation.[32,33] From a mechanistic perspective, available methods are limited to those that can be achieved by low-valent Pd catalysis (i.e., Pd(0)/Pd(II) cycles). General strategies that facilitate access to high-oxidation-state catalytic cycles with O_2 are largely unavailable.[34–39]

In the absence of aerobically generated two-electron oxidants capable of mediating substrate functionalization chemistry via high-valent intermediates, an array of designer synthetic oxidants have been developed. Hypervalent iodine compounds have emerged as a particularly useful class of reagents that find application in mechanistically diverse oxidation reactions including α-oxidation of carbonyl compounds, alcohol and amine dehydrogenations, oxidative dearomatization chemistry, olefin functionalization, group transfer chemistry, and transition-metal catalysis.[40–46] The utility of these reagents derives from (1) the substantial reduction potential of many of these reagents, (2) the often-observed two-electron oxidation-reduction chemistry,[47–57] and (3) the facility of ligand exchange reactions at hypervalent iodine centers. Drawbacks of hypervalent iodine reagents include the common requirement for (super)stoichiometric loading of these reagents and the generation of substantial chemical waste during both preparation and utilization of these species. If aerobic hypervalent iodine chemistry were realized as a general platform, it would be complementary to existing methodologies by providing entry to high-oxidation-state catalytic cycles with O_2.

In 2018, we accomplished the aerobic synthesis of hypervalent iodine reagents by diverting reactive aldehyde-autoxidation intermediates and utilized the aerobically

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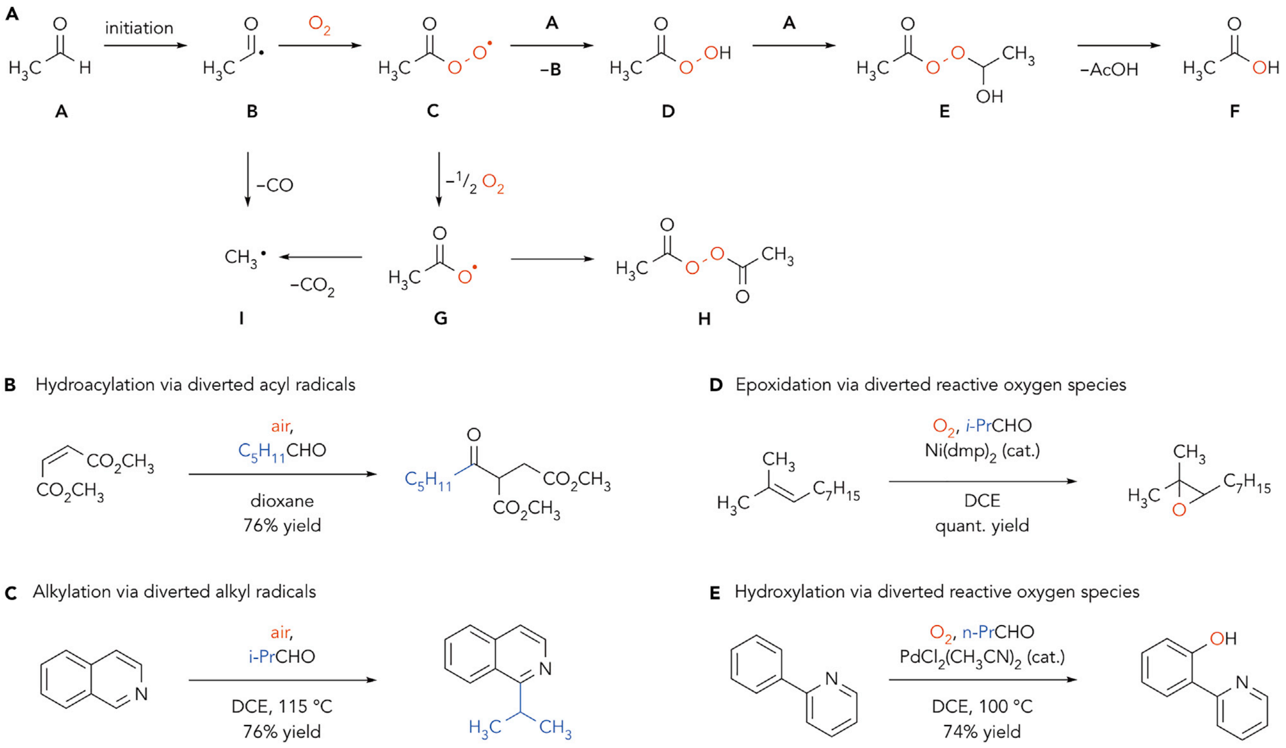

Figure 2. Aldehyde Autoxidation in Synthesis

(A) The manifold of reaction chemistry that is available during the autoxidation of acetaldehyde.

(B–E) Reactive intermediates in aldehyde autoxidation have been redirected to accomplish (B) olefin addition chemistry, (C) alkylation reactions, (D) oxygen-atom transfer (OAT), and (E) transition-metal-catalyzed hydroxylation.

generated hypervalent iodine species as intermediates in a variety of synthetic chemistries (Figure 3).[58–60] This approach couples strongly oxidizing intermediates generated during aldehyde autoxidation with disparate substrate oxidation mechanisms. This strategy has provided a platform for coupling O_2 reduction with the broad classes of substrate functionalization chemistry that are available to hypervalent iodine reagents, such as α-carbonyl oxidation, oxidative dearomative cyclization, C–H/N–H coupling, and alcohol dehydrogenation chemistry. Given the frequency with which peracids are used in the synthesis of hypervalent iodine reagents,[61–65] our initial investigations were predicated on the hypothesis that aerobically generated peracetic acid **D** could be diverted toward the oxidation of PhI. Here, we report a detailed experimental and theoretical investigation of aldehyde-promoted oxidation of aryl iodides. A combination of *in situ* spectroscopy, kinetic studies, and computational investigations supports a mechanism in which aldehyde-promoted aerobic oxidation of aryl iodides proceeds via one-electron oxidation at iodine to generate iodanyl radicals, which subsequently generate the observed I(III) products via a radical chain mechanism. The results of these studies provide evidence for the critical role of single-electron chemistry and open-shell intermediates in hypervalent iodine chemistry and substantially enrich the mechanistic landscape available for the synthesis of these important reagents.

RESULTS AND DISCUSSION

Figure 2A illustrates the manifold of reactions operative during the autoxidation of acetaldehyde.[66,67] Hydrogen-atom abstraction (HAA) from acetaldehyde **A** generates acyl radical **B**, which rapidly reacts with O_2 to generate peroxy radical **C**.[68]

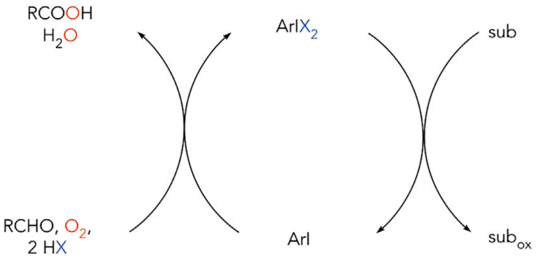

Figure 3. Aerobic Hypervalent Iodine Catalysis

Aerobically generated hypervalent iodine intermediates present a strategy for accomplishing aerobic oxidation catalysis via strongly oxidizing intermediates.

HAA from a second equivalent of acetaldehyde affords radical chain carrier **B** and an equivalent of peracetic acid **D**. Baeyer-Villiger reaction of **D** with **A** affords acetic acid via the intermediacy of peroxide **E**. In addition, dimerization of peroxy radical **C** generates $^1O_2$ and 2.0 equiv of acetoxy radical **G** via the fragmentation of a transient tetroxide intermediate (i.e., Russell termination; see Figure S1 for additional discussion of this reaction step).[69–73] Dimerization of acetoxy radicals **G** generates diacetyl peroxide **H**.[66] Methyl radical **I** can arise by decarboxylation of **G** or by decarbonylation of **B**.[66,67] A number of the species illustrated in Figure 2A—oxygen-centered radicals **C** and **G**, peroxides **E** and **H**, and peracetic acid—are potential oxidants of aryl iodides during aldehyde-promoted aerobic oxidation.

Identification of Potential Oxidants

Previously, we observed initial formation and subsequent consumption of peroxide **E** during acetaldehyde-promoted oxidation of iodobenzene (PhI) by *in situ* ^1H NMR spectroscopy.[58] A ^1H NMR magnetization transfer experiment demonstrated that **E** equilibrates with acetaldehyde and peracetic acid rapidly relative to PhI oxidation. To evaluate the presence of open-shell intermediates during the aerobic oxidation of PhI, we carried out a series of electron paramagnetic resonance (EPR) measurements by using *N*-*tert*-butyl-α-phenylnitrone (PBN, **1**) as a radical spin trap (Figure 4).[74] Figure 4A illustrates the X-band EPR spectrum obtained after the addition of PBN to the reaction mixture of PhI, acetaldehyde, O_2, and $CoCl_2$. The spectrum can be fit as the admixture of a triplet of doublets (a_H = 2.14 G, a_N = 14.06 G) and a triplet (a_N = 7.86 G). The triplet of doublets is attributed to PBN-trapped acetoxy radical (**2**; Figure 4B),[75,76] and the triplet is attributed to a radical arising from single-electron oxidation of PBN (**3**, Figure 4C).[77] The formation of PBN-trapped acetoxy radical **2** was confirmed by electrospray ionization-mass spectrometry (ESI-MS) analysis (*m/z* = 258.1100, $[M+Na]^+$; Figure S2). Addition of PBN to the acetaldehyde-promoted oxidation of PhI in 1,2-dichloroethane (DCE) and CH_2Cl_2 also displayed spectral features arising from compounds **2** and **3** (Figure S3). The presence of open-shell intermediates was further implicated by analysis of the headspace of a reaction in which PhI was oxidized under the dual action of acetaldehyde and O_2, which revealed that in addition to acetaldehyde, trace CO_2 and CO were observed (Figure S4). These observations implicate the generation of acyl radical intermediates during aldehyde autoxidation.

Evaluation of the Oxidation of PhI by Potential Closed-Shell Oxidants

We pursued the following experiments to evaluate the chemical competence of peracetic acid, Baeyer-Villiger peroxide **E**, diacetyl peroxide, and $Co(OAc)_3$ as primary oxidants in the aldehyde-promoted aerobic oxidation of aryl iodides.

Peracetic Acid

Peracetic acid **D** is often employed as the terminal oxidant in the synthesis of hypervalent iodine reagents. In our hands, treatment of PhI with a commercially obtained

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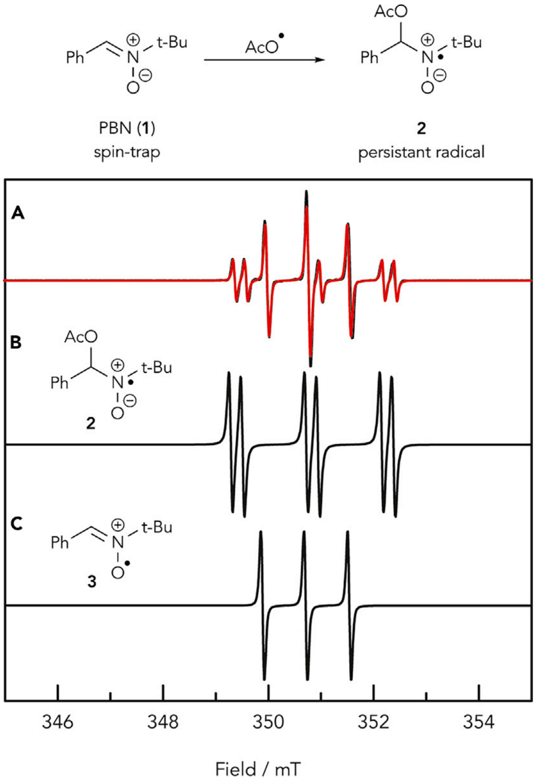

Figure 4. Spin-Trapped EPR Spectroscopy of Open-Shell Oxidants

(A) X-band EPR spectrum obtained after the addition of PBN (**1**) to the oxidation of PhI in AcOH; experimental data (black trace) and fitting (red trace) are also shown. The obtained spectrum displays features of both **2** and **3**.

(B) Simulated spectrum of acetoxy radical adduct **2**.

(C) Simulated spectrum of one-electron oxidation product **3**.

32 wt % peracetic acid (5 equiv) in AcOH afforded $PhI(OAc)_2$ in 92% yield, which confirmed the chemical competence of peracetic acid as an oxidant of PhI.

Baeyer-Villiger Peroxides

Addition of a commercially available solution of peracetic acid to acetaldehyde resulted in the evolution of peroxide **E**,[78] along with 1-hydroperoxyethan-1-ol, the adduct of H_2O_2, and acetaldehyde (Figure S5). Exposure of PhI to reaction mixtures containing peroxide **E** resulted in no $PhI(OAc)_2$ after 13 h (Figure S6), which indicates that peroxide **E** is not a competent oxidant of PhI.

Diacetyl Peroxide

Diacetyl peroxide is potentially generated during acetaldehyde autoxidation by dimerization of acetoxy radicals.[66] Treatment of PhI with independently synthesized[79] diacetyl peroxide **H** in AcOH-d_4 at 23°C resulted in no reaction, as ascertained by ^1H NMR analysis for 17 h (Figures S7–S10). A potassium iodide (KI) test confirmed the presence of peroxide after the reaction.

$Co(OAc)_3$

To ensure consistent initiation of aldehyde autoxidation,[80,81] we included Co(II) salts in the optimized conditions for aldehyde-promoted PhI. In addition to functioning as an autoxidation initiator, Co(III) species can oxidize peracids to generate peroxy radicals (i.e., oxidation of **D** to generate **C**), and Co(II) species are readily oxidized to

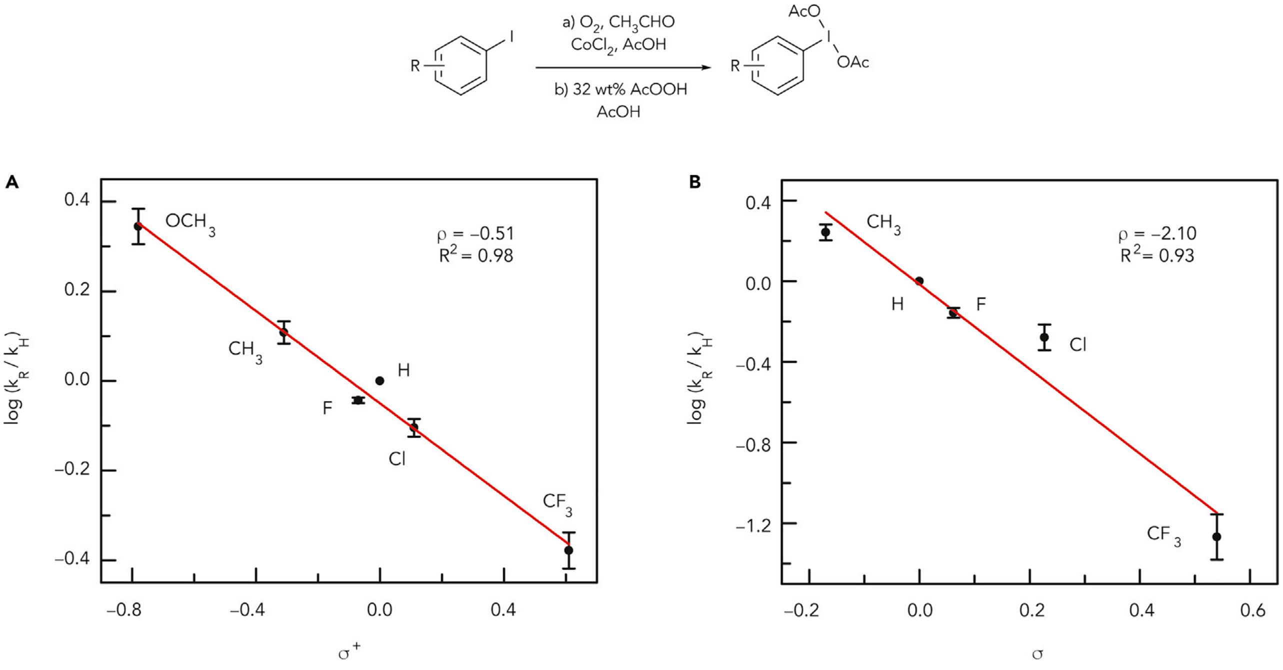

Figure 5. Hammett Analysis of Peracid and Aerobic Oxidation Conditions

Hammett plots of (A) the aldehyde-promoted aerobic oxidation of aryl iodides and (B) the peracetic acid oxidation of aryl iodides. Error bars indicate the standard deviation of triplicate measurements.

Co(III) by peracids (i.e., **D**).[82] One might also envision direct oxidation of PhI by Co(III).[82,83] The following lines of experimental evidence suggest that Co-based additives are not intimately involved in the oxidation of PhI. (1) Co-based promoters are not necessary for aldehyde-promoted aerobic oxidation of aryl iodide. Removal of these additives from aerobic oxidation reactions results in variable initiation time, but a high yield of $PhI(OAc)_2$ can still be obtained.[58] (2) Exposure of PhI to an AcOH solution of $Co(OAc)_3$,[82] which is the product of aerobic oxidation of Co(II) in AcOH, did not result in the observation of any $PhI(OAc)_2$ (Figure S11). (3) Comparison of the concentration-versus-time plots for aerobic oxidation with and without Co(II) (1 mol % $CoCl_2 \cdot 6H_2O$; Figure S12) revealed that although the length of time that is required for initiation depends intimately on the presence of Co(II), once oxidation commences, the presence of Co initiators does not affect the kinetics of oxidation.

Hammett Analysis

To probe the nature of the kinetically relevant oxidants responsible for aldehyde-promoted aerobic oxidation of aryl iodides, we evaluated the impact of aryl iodide substitution on the rate of aryl iodide oxidation for both aldehyde-promoted aerobic oxidation and peracetic-acid-mediated protocols (Figure 5). Because of the presence of a kinetic induction period during aldehyde-promoted aerobic oxidation of aryl iodides, initial rate data were obtained with a series of competition experiments in which pairs of aryl iodides were exposed to aldehyde-promoted aerobic oxidation conditions (Figure 5A; see Figures S13–S15 and Tables S1 and S2 for raw data).[84] Each competition reaction was carried out in triplicate. The resulting data for aldehyde-promoted oxidation of aryl iodides are well correlated with σ^+ parameters ($\rho = -0.51$, $R^2 = 0.98$; Figure 5A) and less well correlated with σ parameters ($R^2 = 0.93$; Figure S16). In contrast, the Hammett plot pictured in Figure 5B, which displays the initial rate data for peracetic acid oxidation of aryl iodides, is well correlated with both σ parameters ($\rho = -2.10$, $R^2 = 0.93$; Figure 5B; see Figure S17 and Tables S3 and

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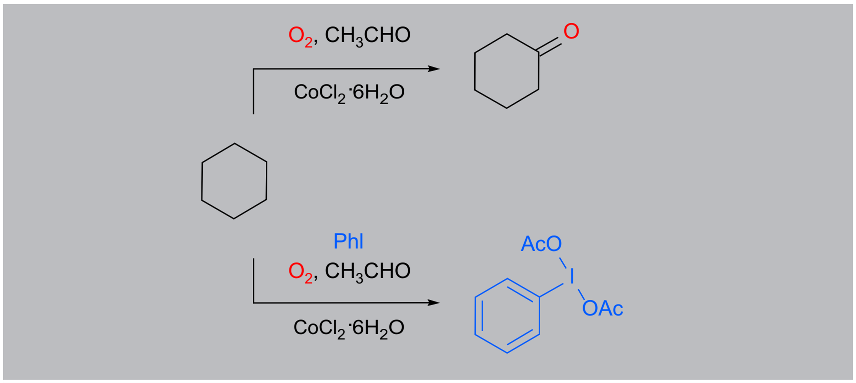
Table 1. Products from the Addition of PhI to Aldehyde Autoxidation Reactions in the Presence of Cyclohexane



Entry	PhI Loading (Equiv)	Cyclohexanone Yield (%)
1	0.00	9.5
2	1.00	2.4
3	5.00	2.0
4	10.0	0.8

S4 for raw data) and is less well correlated with σ^+ parameters (R^2 = 0.85; Figure S18).[85] The significantly different slopes of the Hammett plots pictured in Figure 5 indicate that aldehyde-promoted aerobic oxidation and peracid-mediated oxidation do not proceed via the same rate-determining transition state.

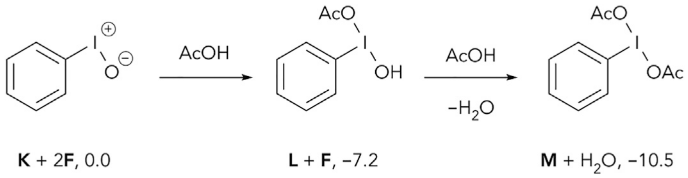
The sensitivity of aldehyde-promoted oxidation (ρ = –0.51) indicates the buildup of positive charge during the rate-determining transition state of aldehyde-promoted aerobic oxidation, but substantially less than was observed during peracid oxidation (ρ = –2.10). The ρ-value for aldehyde-promoted oxidation is similar to ρ-values that have been reported for the radical autoxidation of cumene derivatives (ρ = –0.41)[86] and for the epoxidation of stilbene derivatives under aldehyde-autoxidation conditions (ρ = –0.73)[87] (a reaction proposed to proceed via initial addition of an aerobically generated acyl peroxy radical to the olefin). These results (1) demonstrate that peracetic acid is not kinetically competent as the oxidant during aldehyde-promoted aerobic oxidation and (2) suggest that open-shell species may serve as critical oxidants during aldehyde-promoted aerobic oxidation.

Evaluation of the Oxidation of PhI by Potential Open-Shell Oxidants

On the basis of the observation of oxygen-centered radicals by spin-trapped EPR and the results of Hammett analysis, we pursued a series of experiments to evaluate the competence of these species as oxidants for PhI.

Kinetic Competition Experiments

Reactive oxidants generated during the autoxidation of aldehydes have previously been demonstrated to be competent oxidants toward aliphatic C–H bonds.[88,89] In our study, exposure of a solution of cyclohexane and acetaldehyde to O_2 afforded cyclohexanone in 9.5% yield (Table 1, entry 1). Using a mixture of d_{12}- and H_{12}-cyclohexane, we measured the kinetic isotope effect (KIE) for cyclohexane oxidation under these conditions to be 4.8(4), which suggests that HAA from cyclohexane is the rate-determining step in the generation of cyclohexanone. Using dispersion-corrected DFT (UB3LYP-D3/def2-TZVPP-SMD(DCE)//UB3LYP/def2-TZVPP-SMD(DCE)), we identified the barriers for HAA from cyclohexane by acetoxy radical **G** to be



Scheme 1. Conversion of Iodosylbenzene to (Diacetoxyiodo)benzene

10.8 kcal/mol (computed k_H/k_D = 3.6) and by peroxy radical **C** to be 17.3 kcal/mol (computed k_H/k_D = 6.1) (Figure S19). Previous measurements of the KIEs for HAA by peroxy radicals have reported large values (k_H/k_D = 9–19).[71,86,90] The observation of acetoxy radicals by PBN-trapped EPR spectroscopy, in combination with the measured KIE, suggests that cyclohexane oxidation most likely proceeds via initial HAA from cyclohexane by acetoxy radical **G**.

To evaluate the kinetic competence of acetoxy radical **G** for oxidation of PhI, we examined the aldehyde-promoted oxidation of hydrocarbon substrates in the presence of added PhI. We reasoned that if the reactive oxygen–centered radicals responsible for C–H oxidation of cyclohexane (i.e., **G**) were also responsible for PhI oxidation, PhI would be a competitive inhibitor of cyclohexane oxidation. Consistent with this hypothesis, addition of an increasing amount of PhI to aldehyde-promoted cyclohexane oxidation reactions resulted in the suppression of cyclohexanone evolution (Table 1, entries 2–4). Similarly, exposure of adamantane to acetaldehyde autoxidation reaction mixtures resulted in 1-adamantanol in 47% yield,[91] which was reduced to 14% upon the addition of 1.0 equiv of PhI, and exposure of ethylbenzene to acetaldehyde autoxidation reaction mixtures resulted in acetophenone in 30% yield, which was reduced to 9% upon addition of PhI. The yields for C–H oxidation and iodobenzene oxidation are anti-correlated: for example, during oxidation of ethylbenzene, in the presence of 1.0 equiv of PhI, acetophenone was generated in 9% yield and $PhI(OAc)_2$ was generated in 53% yield; in the presence of 5.0 equiv of PhI, acetophenone was generated in 5% yield, and $PhI(OAc)_2$ was generated in 100% yield (based on ethylbenzene). These data indicate that PhI is a kinetic inhibitor of C–H oxidation and thus implicates open-shell oxidants in the oxidation of PhI (Tables S5–S7).

Computational Results

In this section, we evaluate pathways that would generate either iodosylbenzene **K**[92] or (diacetoxyiodo)benzene **M** because under the reaction conditions we examined (i.e., in the presence of AcOH), iodosylbenzene was readily converted to (diacetoxyiodo)benzene via the intermediacy of hydroxy iodinane **L** (Scheme 1).[93] See Figures S20–S28 for computational details.

Pathways via Initial Two-Electron Oxidation

We initiated our computational investigation by evaluating potential two-electron OAT reactions from peracetic acid, peroxy radical **C**, and acetoxy radical **G** to afford iodosylbenzene (Figure 6).[94] The lowest-energy transition state located for oxygenation of PhI by peracetic acid was $\mathbf{TS_{DJ\text{-}FK}}$ (22.2 kcal/mol versus PhI and **D**), in which OAT was activated by internal hydrogen bonding of the peracid proton to the carbonyl group (Figure 6A). The located transition state is analogous to the butterfly transition states invoked for olefin epoxidation with peracids.[95] Potential ionic mechanisms via initial hydroxylation of PhI followed by recombination with acetate anions were not found to be lower in energy (Figure S22). We also evaluated OAT from peroxy radical **C** and acetoxy radical **G**, reactions steps that have been suggested to be

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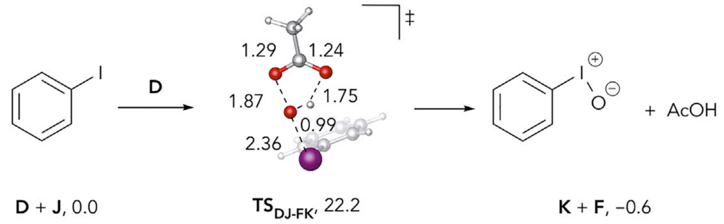

Figure 6. Analysis of Two-Electron Pathways

Evaluation of OAT from peracetic acid to PhI. Free energies (kcal/mol) were computed at the UB3LYP-D3/def2-TZVPP-SMD(DCE)//UB3LYP/def2-TZVPP-SMD(DCE) level of theory.

operative in the autoxidation of phosphorous(III) compounds.[96–102] Both processes are substantially endergonic—OAT from **C** to generate iodosylbenzene **K** and acetoxy radical **G** is +12.1 kcal/mol, and OAT from **G** to generate iodosylbenzene **K** and acyl radical **B** is +67.3 kcal/mol—and thus we will not consider these pathways further (Figure S23).

Pathways via Initial One-Electron Oxidation

On the basis of Hammett analyses and PhI-mediated inhibition of C–H oxidation chemistry, we examined one-electron oxidation pathways for the reaction of reactive intermediates generated during aldehyde autoxidation (e.g., acetoxy radical **G**) with PhI.[103] Addition of acetoxy radical to form iodanyl radical **N** was uphill by 3.9 kcal/mol and was accessed via $\mathbf{TS_{GJ\text{-}N}}$, which was 8.9 kcal/mol above the separated reactants (Figure 7). Iodanyl radical **N** displayed a bent geometry at the hypervalent iodine center (C–I–O: 97.6°) and a long I–O bond (2.63 Å; for comparison, I–O in **M**: 2.19 Å [computed], 2.16 Å [experimental][104]). Iodanyl radical **N** resembled intermediates proposed during alkylation reactions accomplished by photoredox catalysis.[105,106] Evaluation of the spin density of **N** indicates substantial spin on the iodine center with delocalization to the oxygen atoms of the acetate ligand (see Table S8 for detailed analysis of the spin density of **N**). An I(II) compound resulting from the addition of peroxy radical **C** to PhI could not be located as a stationary point; all attempts resulted in evolution of iodosylbenzene with extrusion of the acetoxy radical.

Reaction of I(II) intermediates (i.e., **N**) with peroxides present in solution would result in radical chain propagation. On the basis of the relative facility of acetoxy versus peroxy radical addition to PhI, we evaluated a variety of potential reaction pathways for reactions of iodanyl radical **N** (Figure 8). Addition of peracetic acid to iodanyl radical **N** to generate hydroxy iodinane **L** and acetoxy radical was downhill by 11.7 kcal/mol and proceeded via transition state $\mathbf{TS_{DN\text{-}GL}}$, which was calculated to be 17.2 kcal/mol above the separated reactants. Reaction of iodanyl radical **N** with either diacetyl peroxide **H** or peroxide **E**, which would generate I(III) products and regenerate chain-carrying acetoxy radicals, was thermodynamically favored and proceeded via transition states of similar, yet higher, energy (Figure S26). Chain-propagating addition of peracetic acid to iodanyl radical **N** was found to be the highest barrier along the computed pathway from PhI to $PhI(OAc)_2$.[107]

Reaction of transiently generated iodanyl radicals with open-shell species in solution would result in chain termination. We considered several potential termination pathways (Figure 9). Disproportionation of 2.0 equiv of iodanyl radical **N** to generate (diacetoxyiodo)benzene and iodobenzene was thermodynamically favored (–30.3 kcal/mol); we were unable to locate a transition state for this process (Figure 9A). The addition of

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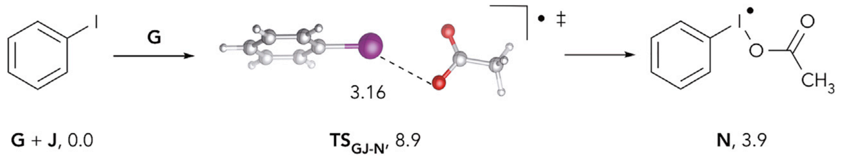

Figure 7. Analysis of Radical Chain Initiation

Computed pathways for initiation steps in which oxygen-centered radicals are added to PhI. Free energies (kcal/mol) were computed at the UB3LYP-D3/def2-TZVPP-SMD(DCE)//UB3LYP/def2-TZVPP-SMD(DCE) level of theory.

acetoxy radical **G** to iodanyl radical **N** proceeded without barrier (Figure 9B), as determined by a scan about the O–I bond, leading to (diacetoxyiodo)benzene (–26.4 kcal/mol). In addition to productive termination steps leading to the production of $PhI(OAc)_2$, unproductive termination, such as loss of acetoxy radical followed by radical coupling to generate diacetyl peroxide, was also downhill (Figure 9C).

Summary of Mechanistic Data

Figure 10 summarizes the radical chain process that is consistent with the available experimental and computational results. Russell termination of 2.0 equiv of peroxy radical **C** generated $^1O_2$ and 2.0 equiv of acetoxy radical **G**. Addition of acetoxy radical **G** to PhI generated iodanyl radical **N**. Reaction of **N** with peracetic acid generated hydroxy iodinane **L**, which reacted spontaneously with AcOH to afford the observed $PhI(OAc)_2$, and regenerated acetoxy radical **G**. Radical chain termination was accomplished either by combination of iodanyl radical **N** with acetoxy radical **G** or by disproportionation of iodanyl radical **N**. In this chain reaction, both iodanyl radical **N** and acetoxy radical **G** were chain carriers. The oxidation mechanism that emerged from these studies shares common features with autoxidation reactions of some main-group species and transition-metal complexes, which—unlike simple organics—can access expanded valences. For example, the radical autoxidation of phosphorous(III) derivatives to generate phosphorous(V) oxides has been extensively studied (Figure 10B).[96–102] On the basis of both kinetic data and EPR spectroscopy, four-coordinate phosphanyl radicals, generated by the addition of peroxy and alkoxy radicals to P(III) derivatives, have been implicated as autoxidation intermediates. Similarly, during the aerobic oxidation of dimethyl Pd(II) complexes, transient peroxo Pd(III) intermediates generated by the addition of oxygen-centered radicals have been implicated (Figure 10C).[108]

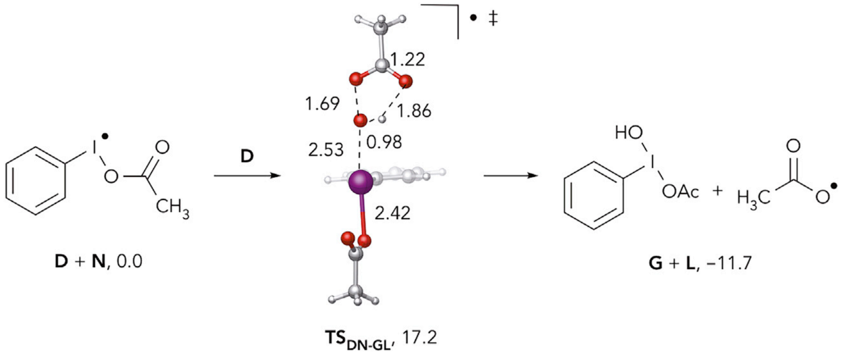

Figure 8. Analysis of Radical Chain Propagation

Computed pathways for radical chain propagation by reaction of iodanyl radical **N** with peracetic acid **D**. Free energies (kcal/mol) were computed at the UB3LYP-D3/def2-TZVPP-SMD(DCE)//UB3LYP/def2-TZVPP-SMD(DCE) level of theory.

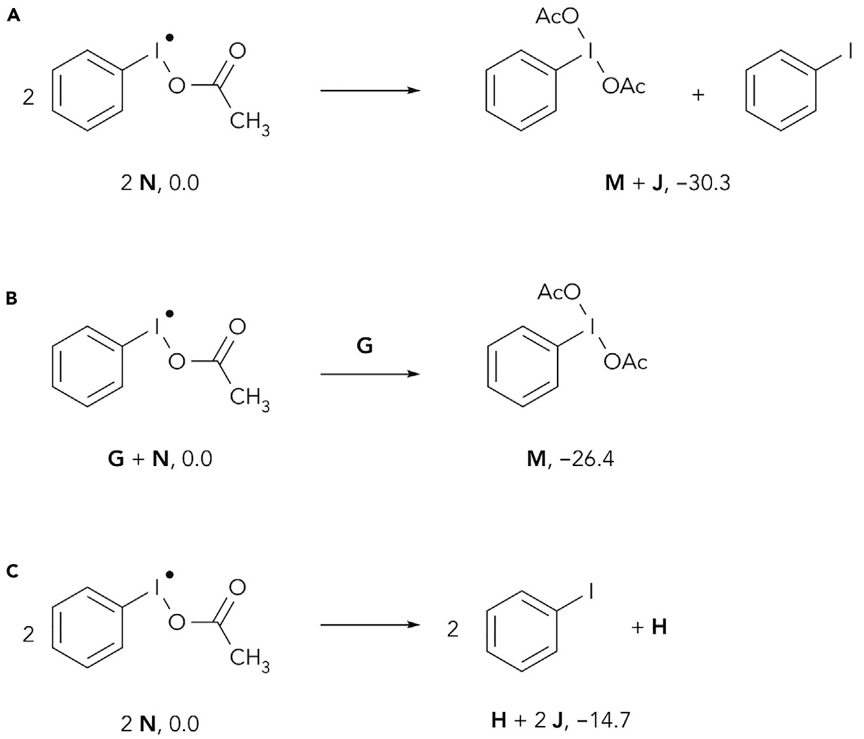

Figure 9. Analysis of Radical Chain Termination

Reaction pathways for (A) disproportionation of 2.0 equiv of iodanyl radical **N**, (B) addition of acetoxy radical **G** to iodanyl radical **N**, and (C) loss of diacyl peroxide **H** from 2.0 equiv of iodanyl radical **N**. Free energies (kcal/mol) were computed at the UB3LYP-D3/def2-TZVPP-SMD(DCE)//UB3LYP/def2-TZVPP-SMD(DCE) level of theory.

Analysis of the free-energy surface for two-electron oxidation of PhI by peracetic acid versus the radical chain mechanism advanced for aldehyde-promoted aerobic oxidation rationalizes the observation that although peracetic acid is a chemically competent oxidant for PhI, it is not kinetically competent during aldehyde-promoted aerobic oxidation. Addition of acetoxy radical to PhI proceeded with a barrier of 8.9 kcal/mol. The barrier to oxidation of PhI by peracetic acid was computed to be 22.2 kcal/mol, whereas the highest barrier calculated along the radical chain mechanism depicted in Figure 10 was oxidation of iodanyl radical **N** by peracetic acid at 21.1 kcal/mol. These relative barrier heights are consistent with a Curtin-Hammett scenario, in which rapid reversible addition of acetoxy radical to PhI proceeds to generate **N**, and selectivity for one- and two-electron oxidation is governed by the relative barrier heights for reaction of peracetic acid with **N** and PhI, respectively.

Impact on Synthetic Chemistry

Interest in understanding the mechanism(s) relevant to aerobic hypervalent iodine chemistry is in part motivated by the desire to enable aerobic oxidation catalysis via hypervalent iodine intermediates. A serious challenge to achieving hypervalent iodine catalysis is the relative rates of iodine-centered oxidation and direct substrate oxidation by the terminal oxidant. Recently, substantial progress has been made toward realizing hypervalent iodine catalysis using *m*-CPBA and other peracids as terminal oxidants. To evaluate the functional-group tolerance of the radical chain aerobic oxidation of PhI, we carried out robustness analyses[109] for PhI oxidation by our aerobic protocol and for *m*-CPBA oxidation (Figure 11). In this experiment, small molecules featuring a variety of functional groups were added to a reaction,

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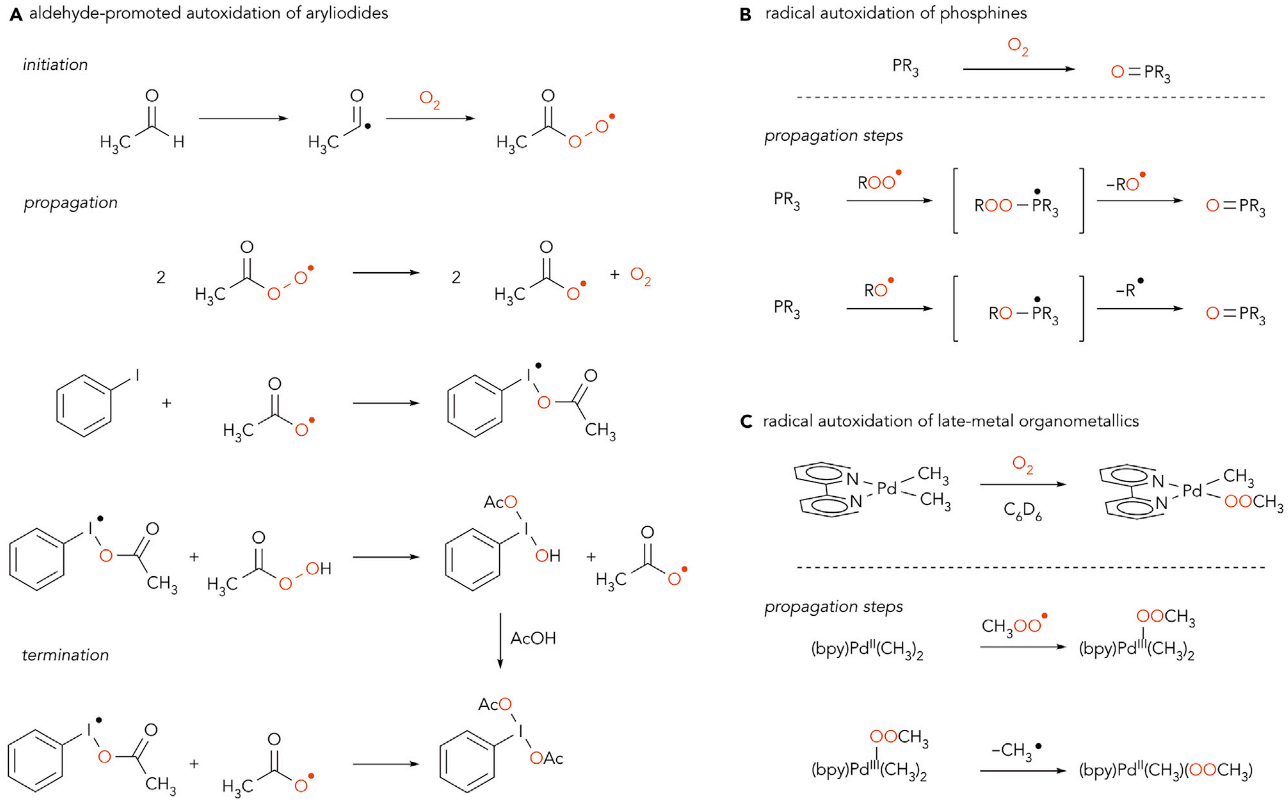

Figure 10. Valence Expansion and Open-Shell Intermediates during Autoxidation Chain Reactions

(A) Summary of the reaction steps involved in aldehyde-promoted aerobic oxidation of aryl iodides.

(B and C) Valence expansion during radical chain autoxidation has also been implicated during (B) the autoxidation of P(III) compounds and (C) the autoxidation of late-metal complexes.

and both the impact on the reaction yield and the amount of recovered additive were recorded. The results of these experiments revealed that despite the radical chain mechanism, the functional-group tolerance of the two conditions is remarkably similar. Challenges to both sets of conditions include electron-rich aromatic substrates (i.e., phenol and aniline) and C–C multiply bonded substrates. Similar analysis of the aryliodide-catalyzed cross-coupling of benzene with *N*-methoxy-4-methylbenzenesulfonamide is detailed in Figure S29.

Conclusions

Development of new strategies for coupling O_2 reduction with oxidative substrate functionalization chemistry is required for realizing sustainable synthetic chemistry. In furtherance of this goal, we developed new strategies for accessing hypervalent iodine compounds from O_2 by intercepting reactive oxidants generated during aldehyde-autoxidation chemistry. Here, we utilized experiment and theory to demonstrate that hypervalent iodine reagents are accessed by a radical chain reaction initiated by aerobically generated acetoxy radicals. Aerobically generated acetoxy radicals and the iodanyl radicals resulting from their addition to aryl iodides are critical chain carriers during aerobic oxidation. This report represents the first demonstration of the important role of I(II) species during the oxidation of aryl iodides. These observations are striking given that application of hypervalent iodine reagents in synthesis is largely predicated on the well-behaved two-electron oxidation-reduction chemistry characteristic of these species.

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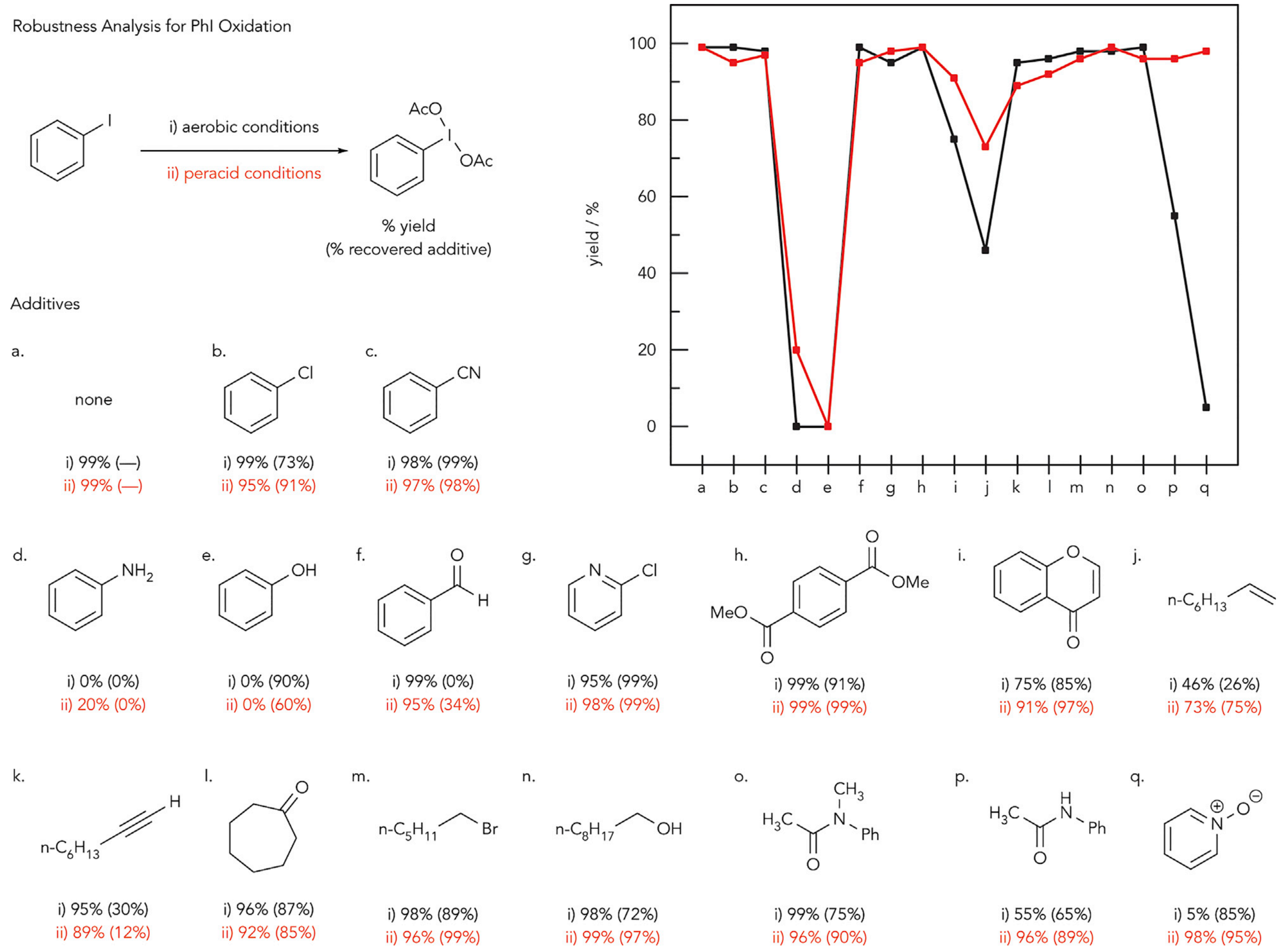

Figure 11. Robustness Analysis for Aerobic Oxidation of Aryl Iodides

Robustness analysis for oxidation of PhI in the presence of a variety of small-molecule additives (a–q). The functional-group tolerance for aerobic oxidation (black) is similar to that of *m*-CPBA oxidation (red).

A continuing challenge for the development of sustainable oxidation chemistry is the need to identify chemical strategies that provide access to strong chemical oxidants, such as hypervalent iodine compounds, under sufficiently mild conditions to be compatible with broad families of substrates. Robustness analysis reveals that the developed aerobic oxidation chemistry displays substrate tolerance similar to that of more commonly employed peracid-based methods, but oxidatively labile substrates, such as olefins, remain a challenge. We anticipate that the demonstration of the critical role of one-electron processes and iodanyl radical intermediates in the preparation of hypervalent iodine reagents will provide the mechanistic basis for the development of strategies to achieve sustainable substrate oxidation under mild reaction conditions.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2019.06.006.

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AUTHOR CONTRIBUTIONS

O.G. and D.C.P. conceived the study. S.-M.H. and A.M. carried out experimental work, and M.Y. carried out computational studies. All authors contributed to interpreting the data and writing the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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