

Oxidase Catalysis via Aerobically Generated Hypervalent Iodine Intermediates

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Development of sustainable oxidation chemistry demands strategies to harness O₂ as a terminal oxidant. In particular, oxidase catalysis, in which O₂ serves as a chemical oxidant without necessitating oxygen incorporation into reaction products, would allow diverse substrate functionalization chemistry to be coupled to O₂ reduction. Direct O₂ utilization must overcome the intrinsic challenges imposed by the triplet ground state of O₂ and the disparate electron inventories of four-electron O₂ reduction and two-electron substrate oxidation. Here, we generate hypervalent iodine reagents, a broadly useful class of selective two-electron oxidants, from O₂. Synthesis of these oxidants is achieved by intercepting reactive intermediates of aldehyde autoxidation. The use of aryl iodides as mediators of aerobic oxidation underpins an oxidase catalysis platform that couples a broad array of substrate oxidations to O₂ reduction, including olefin functionalization chemistry, carbonyl α-oxidation, oxidative dearomatization, and aerobic C–H amination chemistry.

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Oxidase Catalysis via Aerobically Generated Hypervalent Iodine Intermediates

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Abstract Development of sustainable oxidation chemistry demands strategies to harness O_2 as a terminal oxidant. In particular, oxidase catalysis, in which O_2 serves as a chemical oxidant without necessitating oxygen incorporation into reaction products, would allow diverse substrate functionalization chemistry to be coupled to O_2 reduction. Direct O_2 utilization must overcome the intrinsic challenges imposed by the triplet ground state of O_2 and the disparate electron inventories of four-electron O_2 reduction and two-electron substrate oxidation. Here, we generate hypervalent iodine reagents, a broadly useful class of selective two-electron oxidants, from O_2 . Synthesis of these oxidants is achieved by intercepting reactive intermediates of aldehyde autoxidation. The use of aryl iodides as mediators of aerobic oxidation underpins an oxidase catalysis platform that couples a broad array of substrate oxidations to O_2 reduction, including olefin functionalization chemistry, carbonyl α -oxidation, oxidative dearomatization, and aerobic C–H amination chemistry.

Introduction

O_2 is a readily available, environmentally benign, thermodynamically strong oxidant. Development of chemical strategies to couple O_2 reduction directly to substrate oxidation would enable sustainable synthetic methods.^{1–3} Selective and efficient utilization of O_2 , however, is challenging due to the triplet ground state of O_2 , which imposes substantial kinetic barriers to O_2 reduction and gives rise to poorly selective radical chemistry,^{4,5} and due to the disparity between the electron inventories of four-electron O_2 reduction and two-electron substrate oxidation.^{6,7} Broadly, there are two approaches to O_2 utilization: (1) oxygenase chemistry, in which O_2 serves as both an oxidant and the source of oxygen content in the organic reaction products, and (2) oxidase chemistry, in which O_2 serves as a proton and electron acceptor but is not incorporated into the organic reaction products (Figure 1).⁸ Oxidase chemistry is synthetically attractive because many desirable oxidation reactions do not require substrate oxygenation. To achieve oxidase chemistry, small molecule mediators that participate in facile redox chemistry with O_2 to generate two-electron oxidants, such as hydroquinone oxidation to benzoquinone, have been utilized.^{9,10} Application of available mediators, however, is currently limited by either the generation of weak oxidants or limited substrate scope.

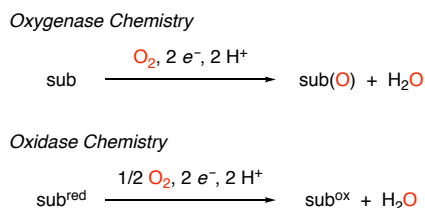


Figure 1. Oxygenase versus oxidase aerobic oxidation chemistry. In oxygenase chemistry, O₂ functions both as the electron acceptor as well as the source of oxygen content during substrate functionalization. In oxidase chemistry, O₂ functions only as a proton and electron acceptor and is not incorporated in the oxidized substrate. Oxidase strategies are conceptually more broadly applicable to synthetic chemistry, as they allow a variety of substrate functionalization modes to be coupled to O₂ as the terminal oxidant.

In the absence of broadly applicable strategies for O₂ utilization, synthetic chemists have developed a myriad of reagents that participate in selective two-electron oxidation chemistry. For example, hypervalent iodine reagents are a broadly useful class of selective two-electron chemical oxidants based on 3-centered, 4-electron (3c-4e) iodine–ligand bonds.^{11–13} These reagents find application in diverse chemical settings, including C–H hydroxylation and amination, olefin functionalization, oxidative dearomatization, and as group-transfer reagents in catalysis. The broad utility of hypervalent iodine reagents derives from facile ligand exchange chemistry available at iodine. Ligand exchange reactions allow hypervalent iodine reagents to be utilized in oxidative oxygen-, nitrogen-, halogen-, and hydrocarbyl-transfer chemistry.^{11,14,15} Current liabilities of hypervalent iodine reagents include the frequent need for stoichiometric reagent loading and the synthesis of these reagents from wasteful metal-based oxidants, such as KMnO₄, NaIO₄, and oxone, or organic peracids, such as *m*-CPBA.^{11–13,16} No methods are available for the direct synthesis of hypervalent iodine compounds from O₂.¹⁷ We were attracted to aerobic oxidation of aryl iodides based on the hypothesis that the resulting hypervalent iodine reagents, in conjunction with ligand exchange at iodine, could provide a new platform for oxidase chemistry. Here we intercept aldehyde autoxidation intermediates to prepare a family of hypervalent iodine reagents using O₂ as the terminal oxidant, and demonstrate the utility of aerobic oxidation of aryl iodides in oxidase catalysis to functionalize a variety of substrate classes.

Results and Discussion

Intercepting Aldehyde Autoxidation for Aerobic Oxidation of Aryl Iodides. Aldehyde autoxidation chemistry, which converts aldehydes to carboxylic acids under the action of O₂, is among the earliest reactions of O₂ with organic molecules to be characterized.²⁰ In 1832, Wöhler and Liebig reported the autoxidation of benzaldehyde to benzoic acid.²¹ Bäckström advanced the now-accepted radical chain mechanism for aldehyde autoxidation in 1927 (Figure 2), which involves hydrogen-atom abstraction (HAA) from aldehyde **A** to generate acyl radical **B**, reaction of **B** with O₂ to generate acyl superoxo **C**, and HAA to generate an equivalent of peracid **D** and the acyl radical chain carrier **B**.²² Subsequent Baeyer-Villiger reaction via intermediate **E** generates two equivalents of acid **F**.²³ The synthetic utility of autoxidation intermediates in reaction development has been

realized.²⁴⁻²⁸ For example, aerobically generated acyl radical intermediates have been intercepted for olefin addition chemistry and aerobically generated peracids have been utilized for oxygen-atom transfer (OAT) chemistry.²⁹⁻³³

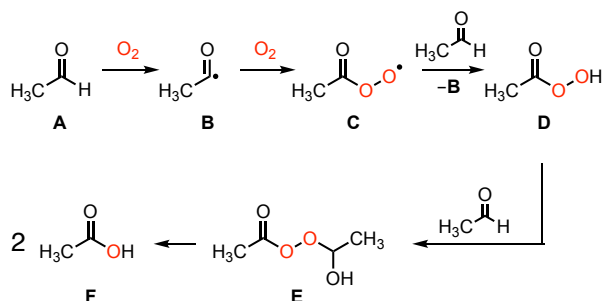


Figure 2. Radical-chain mechanism for aldehyde autoxidation. Aldehyde autoxidation is among the oldest characterized aerobic oxidation reactions in organic chemistry. Autoxidation of aldehydes to carboxylic acids proceeds via initial hydrogen-atom abstraction (HAA) from an aldehyde (**A**) to generate an acyl radical (**B**). Subsequent reaction between **B** and O_2 generates acyl superoxo **C**. HAA from a second equivalent of **A** generates peracid **D** and chain carrier **B**. Conversion of peracid **D** to carboxylic acids is accomplished by a Baeyer-Villiger reaction via intermediate **E**. Here, we intercept reactive oxidants generated during autoxidation (*i.e.* **D** and **E**) to access hypervalent iodine reagents. Coupling O_2 reduction to the synthesis of hypervalent iodine compounds provides a platform for oxidase chemistry.

We initiated our investigation of aerobic oxidation of aryl iodides by examining the viability of oxidation of PhI with O_2 in the presence of a variety of simple aldehydes in 1,2-dichloroethane (DCE) at 23 °C (Figure 3). We found that while benzaldehyde was ineffective in promoting oxidation of iodobenzene (Figure 3, Entry 1), isobutyraldehyde and butyraldehyde led to the observation of 2% and 6% yield of I(III) *bis*-esters, respectively (Entries 2 and 3). Use of acetaldehyde afforded PhI(OAc)₂ (**1a**) in 42-91% yield (yields obtained from five identical reactions, Entry 4). We speculated that the variability of oxidation efficiency was due to inconsistent initiation of radical autoxidation chemistry. Addition of a catalytic amount of various metal salts (1 mol%) that have been demonstrated initiate autoxidation (entries 5-7)^{34,35} led to identification of $CoCl_2 \cdot 6H_2O$ as a highly effective catalytic autoxidation initiator, leading to PhI(OAc)₂ in 99% yield. AcOH is the only byproduct of aldehyde-promoted PhI oxidation, and PhI(OAc)₂ can be isolated as a pure compound following a simple aqueous extraction to remove Co salts (see Figure S1 for crude 1H NMR spectrum). Using $CoCl_2 \cdot 6H_2O$ as radical chain initiator, PhI oxidation can be accomplished with air as the O_2 source (63% yield). Aerobic oxidation of PhI to generate PhI(OAc)₂ could be carried out on gram scale (97% yield, 1.59 g isolated product). The developed aerobic oxidation is compatible with a broad range of organic solvents; in addition to DCE, high yields are obtained in coordinating solvents, such as CH_3CN (Entry 8), and protic solvents, such as AcOH (Entry 9). In contrast, PhI oxidation does not proceed in THF, which we hypothesize is due to inhibition of autoxidation by the presence of relatively weak C-H bonds (*vide infra*).

Entry	RCHO	Solvent	Initiator	Yield
1	PhCHO	DCE	none	0%
2	<i>i</i> -PrCHO	DCE	none	2%
3	<i>n</i> -PrCHO	DCE	none	6%
4	CH ₃ CHO	DCE	none	42-91%
5	CH ₃ CHO	DCE	Cu(OAc) ₂ · H ₂ O	48%
6	CH ₃ CHO	DCE	Mn(OAc) ₂ · 4H ₂ O	75%
7	CH₃CHO	DCE	CoCl₂ · 6H₂O	99%
8	CH ₃ CHO	CH ₃ CN	CoCl ₂ · 6H ₂ O	73%
9	CH ₃ CHO	AcOH	CoCl ₂ · 6H ₂ O	98%
10	CH ₃ CHO	THF	CoCl ₂ · 6H ₂ O	0%

Figure 3. Optimization of aerobic oxidation of iodobenzene. Aerobic oxidation was optimized by examining the impact of experimental variables on the oxidation of iodobenzene to iodobenzene diacetate. Optimization of aerobic oxidation of iodobenzene to generate iodobenzene diacetate. Consistent with oxidation of PhI by autoxidation intermediates, the addition of autoxidation initiators is required to achieve consistent high yields of PhI oxidation. For optimization experiments, yields were determined by ¹H NMR spectroscopy.

With conditions in hand for the aerobic oxidation of PhI, we have examined the O₂-coupled synthesis of a family of hypervalent iodine reagents that have been applied in synthetic chemistry (Figure 4). Aerobic oxidation is tolerant to a range of electron-donating and -withdrawing substituents on the aryl iodide (compounds **1**) and hydrolysis of the initially formed I(III) diacetates provides ready access to iodosyl benzene derivatives (**2**) in uniformly high yield. Substitution of the aromatic ring has been demonstrated to provide a synthetic handle to tune both the activity and the aggregation state of aryl I(III) reagents.^{36,37} Addition of TsOH to the oxidation of PhI affords Koser's reagent (**3**),³⁸ an acid-activated iodosylbenzene derivative, in 84% yield. Similarly, addition of carboxylic acids to the reaction mixture directly affords the corresponding I(III) esters: oxidation in the presence of trifluoroacetic acid (TFA) and benzoic acid results in PhI(TFA)₂ and PhI(OBz)₂ in 52% and 48% yields, respectively. Aldehyde-promoted oxidation of 2-iodobenzoic acid, 2-(2-iodophenyl)propan-2-ol, and 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol affords I(III) compounds **4**, **5**, and **6**, respectively. Benziiodoxole-based hypervalent iodine reagents, in which the *ortho*-substituent chelates to the oxidized iodine center (*i.e.* **4–6**), are widely utilized in atom- and group-transfer chemistry.¹⁴ The developed conditions also provide access to *bis*-I(III) compound **7**,³⁹ by four-electron oxidation of 1,2-diiodobenzene, in 90% yield. Finally, we examined oxidation of 2-*tert*-butylsulfonyliodobenzene to access 2-*tert*-butylsulfonyliodosylbenzene, a hypervalent iodine derivative that has found application in hydroxylation catalysis due to substantially increased solubility versus unsubstituted iodosyl benzene.⁴⁰ Unlike the aforementioned oxidation reactions, which generate I(III) derivatives in high yield, oxidation of 2-*tert*-butylsulfonyliodobenzene affords I(V) derivative **8**. The unanticipated overoxidation in this case is likely due to disproportionation of an initially formed I(III) derivative. Consistent with this hypothesis, treatment of independently prepared 2-*tert*-butylsulfonyliodosylbenzene with AcOH,

which is generated as a byproduct of autoxidation, resulted in the immediate disproportionation to I(I) and I(V) (^1H NMR of disproportionation presented in Figure S2).

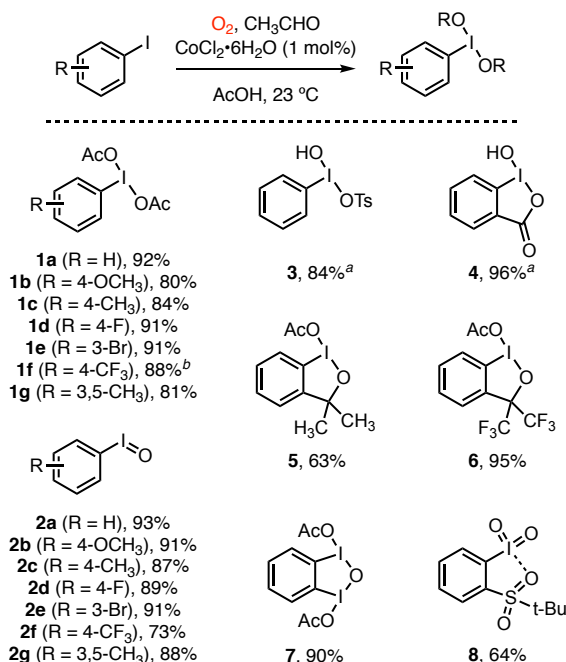


Figure 4. Application of aerobic oxidation chemistry to the synthesis of a family of hypervalent iodine reagents. Aerobic oxidation of aryl iodides provides access to a family of hypervalent iodine reagents that have been demonstrated to be useful oxidants in synthetic chemistry. ^aReaction solvent in these oxidation reactions was 1,2-dichloroethane (DCE). ^bFor this substrate, dimerization affords $(4\text{-CF}_3\text{C}_6\text{H}_4\text{I}(\text{OAc}))_2\text{O}$, see Supporting Information.

Application of Aerobic Oxidation of Aryl Iodides to Oxidase Chemistry. Access to chemical platforms for oxidase chemistry, in which O_2 is utilized as the terminal oxidant without participating in substrate oxygenation, would provide an approach to coupling diverse modes of substrate oxidation directly to O_2 reduction. Here, we demonstrate that aerobic oxidation of aryl iodides can be used to couple O_2 reduction to 1,2-difunctionalization of olefins, carbonyl α -functionalization, oxidative dearomatization chemistry, and direct C–H amination chemistry (Figure 5). For each of the transformations illustrated in Figure 5, control reactions in the absence of aryl iodides resulted in no conversion to the illustrated oxidation products.

Aerobic oxidation of aryl iodides can be utilized in substrate oxygenation. Aerobic 1,2-*bis*-acetoxylation of styrene derivatives,⁴¹ illustrated by the conversion of 4-fluorostyrene (**9**) to *bis*-acetate **10** in 88% yield, can be accomplished via a one-pot procedure (Figure 5a). In the specific case of styrene functionalization, a one-pot, two-step protocol, in which $\text{PhI}(\text{OAc})_2$ is prepared prior to styrene addition, was necessary. The incompatibility radical chain autoxidation of PhI with the presence of styrene is consistent with the facility of radical addition to styrenes. One-step aerobic carbonyl α -oxidation reactions proceed

readily. Acetophenone (**11**) undergoes α -tosylation⁴² to afford oxygenated compound **12** in 74% yield by the action of the standard autoxidation conditions with the addition of *para*-toluene sulfonic acid (*p*-TSA) (Figure 5b). Similarly, β -ketoester **13** is readily tosylated to afford α -oxygenate **14** in 61% yield (Figure 5c). Use of 20 mol% PhI in the α -tosylation of acetophenone led to the observation of 33% yield of compound **12**, which demonstrated proof-of-principle that PhI could be used as a catalyst for aerobic oxidation chemistry. We hypothesize that the poor catalyst turnover observed in these reactions may be due to relatively slow α -oxygenation of carbonyl substrates by aerobically generated I(III); if substrate functionalization is slow relative to aldehyde autoxidation, insufficient I(I) will be generated to intercept reactive autoxidation intermediates.

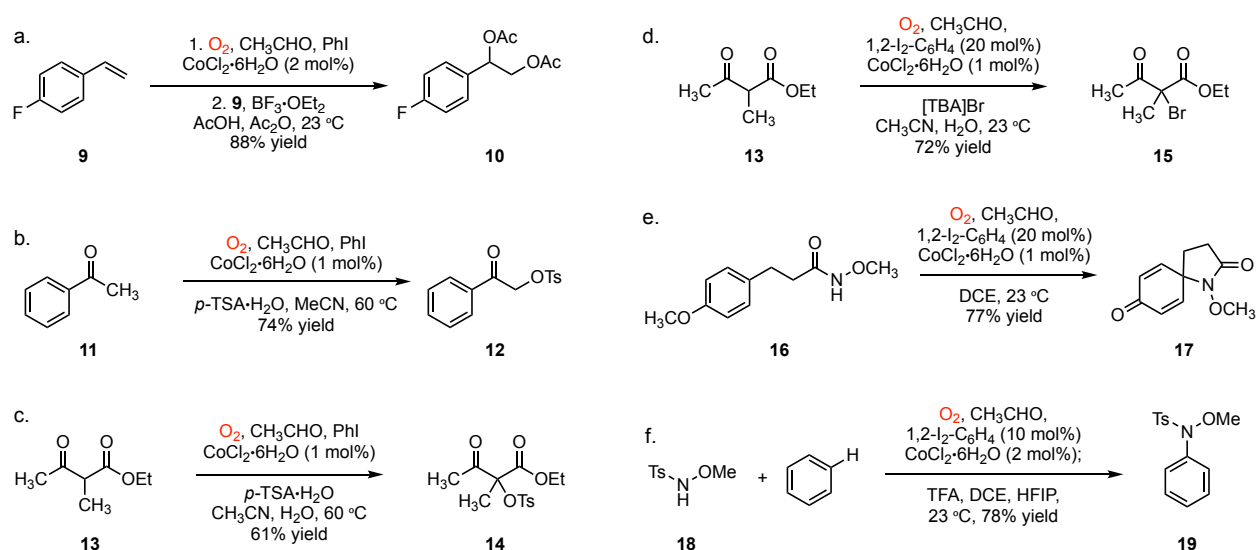


Figure 5. Aerobic oxidation of PhI provides a broad platform to directly utilize O_2 as the terminal oxidant in substrate oxidation reactions. Utilization of PhI oxidation to oxygenate substrates is highlighted by (a) 1,2-difunctionalization of olefins, (b) α -oxygenation of acetophenone, and (c) α -oxygenation of β -keto esters. Ligand exchange chemistry at hypervalent iodine reagents, and *in situ* aerobic oxidation, supports oxidase catalysis of heterofunctionalization reactions, such as: (d) aerobic bromination of β -keto esters, (e) oxidative dearomatization chemistry; and (f) direct aerobic C-H amination chemistry. *p*-TSA: *para*-toluenesulfonic acid, [TBA]Br: tetrabutylammonium bromide, DCE: 1,2-dichloroethane, TFA: trifluoroacetic acid, HFIP: 1,1,1,3,3,3-hexafluoroisopropanol.

Application of Aryl Iodide Oxidation to Oxidase Catalysis. The ability to accomplish ligand exchange chemistry in hypervalent iodine compounds allows the developed aerobic oxidation of aryl iodides to be applied to substrate oxidation chemistry that does not involve incorporation of oxygen in reaction products. For example, in the α -oxidation of β -ketoester **13**, replacing *p*-TSA with [TBA]Br results in aerobic bromination to afford compound **15** (57% yield, see Supporting Information), not the α -oxygenation product **14** as demonstrated above. Unlike the oxygenation reactions pictured in Figure 5a–c, which require stoichiometric aryl iodide to access synthetically useful oxidation yields,

bromination could be achieved with a catalytic amount of aryl iodide. With 20 mol% 1,2-diiodobenzene, bromination proceeds in 72% yield (Figure 5d). PhI is also a competent catalyst for bromination, but superior yields are obtained with 1,2-diiodobenzene as catalyst.

We have extended aryl-iodide catalyzed aerobic oxidation to oxidative dearomatization chemistry and C–H amination chemistry. Using 20 mol% 1,2-diiodobenzene, Weinreb⁴³ amide **16** undergoes aerobic dearomatization to afford lactam **17** in 77% yield (Figure 5e). Dehydrogenative N–H / C–H coupling to arylate amines with unfunctionalized aromatics can also be accomplished by the action of aryl iodide catalysis. With 10 mol% 1,2-diiodobenzene, amine **18** undergoes arylation with benzene⁴⁴ to afford phenylsulfonamide **19** in 78% yield. In each of the reactions pictured in Figure 5d–f, aerobic oxidation is accomplished with AcOH as the only stoichiometric byproduct.

Aerobic Oxidation Mechanism. Aldehyde-promoted aerobic oxidation of aryl iodides was developed based on the hypothesis that strongly oxidizing intermediates in aldehyde autoxidation chemistry could be coopted for the oxidation of aryl iodides. Consistent with this hypothesis, the use of reaction solvents with relatively weak C–H bonds (*i.e.* THF) or the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT), a common radical inhibitor, suppressed the formation of hypervalent iodine products. To further probe the mechanism of PhI oxidation, we have followed the kinetics of PhI consumption and PhI(OAc)₂ evolution by ¹H NMR spectroscopy in CDCl₃ (Figure 6, additional data is summarized in Figures S3 and S4). In the absence of CoCl₂·6H₂O, a substantial induction period is observed and evolution of PhI(OAc)₂ displays sigmoidal growth consistent with a radical chain process. In the presence of CoCl₂·6H₂O, PhI(OAc)₂ evolution still displays sigmoidal growth, but the induction period for PhI oxidation to PhI(OAc)₂ is substantially shortened, which is consistent with more rapid initiation of a radical chain process. Similar kinetic profiles were measured for the oxidation of 4-iodotoluene (Figure S5 and S6) and for the oxidation of PhI in AcOH-*d*₄ (Figures S7 and S8). During these ¹H NMR experiments, we did not observe ¹H NMR resonances of peracetic acid, but we did note the initial evolution and subsequent disappearance of a quartet at 5.41 ppm, a singlet at 2.01 ppm, and a doublet at 1.35 ppm, which integrate as a 1:3:3 ratio (Figure S9). We attribute these signals to Baeyer-Villiger intermediate **E** (Figure 2).⁴⁵ Consistent with this assignment, high-resolution mass spectrometry of the oxidation reaction which reveals the presence of a signal at *m/z* = 143.0318 (M+Na⁺ for **E**) (Figure S10). Intermediate **E** is also observed when PhI oxidation is carried out in AcOH-*d*₄. Observation of **E**, which is the adduct of a molecule of aerobically generated AcOOH and a molecule of CH₃CHO, confirms that aldehyde autoxidation is operative during aerobic oxidation of aryl iodides. Magnetization transfer experiments demonstrate that compound **E** is in equilibrium with acetaldehyde and peracetic acid on the time scale of PhI oxidation (Figure S11). At this time, we cannot differentiate between aerobically generated AcOOH or compound **E**, the adduct of AcOOH with CH₃CHO, as the active oxidant in PhI oxidation.

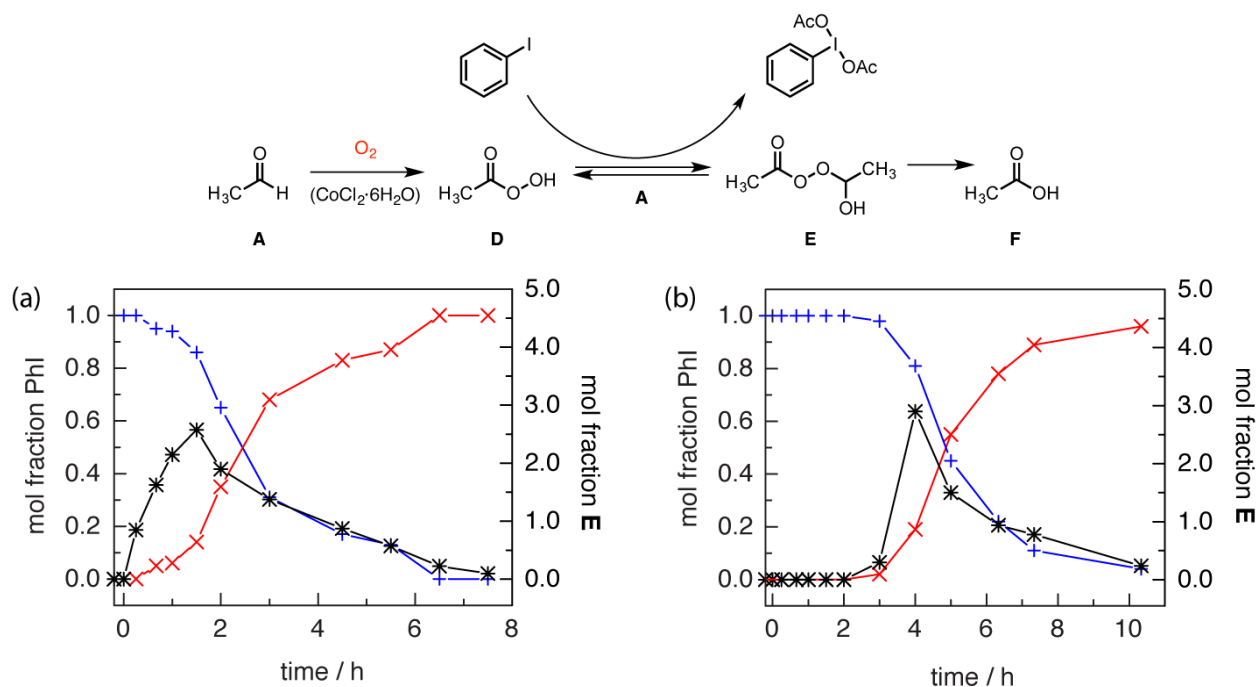


Figure 6. Aerobic oxidation of aryl iodides is accomplished by intercepting the oxidizing intermediates of aldehyde autoxidation chemistry. Monitoring the kinetics of consumption of PhI (+) and evolution of PhI(OAc)₂ (x) by ¹H NMR in the presence (a) or absence (b) of Co₂Cl₂·6H₂O, added as a radical initiator, indicates that Co(II) catalyzes the oxidation of PhI by initiating autoxidation. At intermediate times during PhI oxidation, peroxo intermediate E (*) is observed (by both ¹H NMR and mass spectrometry) which confirms that autoxidation is operative during aryl iodide oxidation. We can not currently differentiate between D or E as the active oxidant for aryl iodides.

Concluding Remarks

Development of a broadly applicable platform for oxidase catalysis, which utilizes O₂ as the terminal oxidant without necessitating the incorporation of oxygen during substrate functionalization, would provide new opportunities to utilize O₂ as a sustainable oxidant in chemical synthesis. Aldehyde autoxidation chemistry, in which an aldehyde is converted to a carboxylic acid under the action of O₂, is among the earliest examples of aerobic oxidation in organic chemistry and proceeds via reactive peroxo radicals and peracids. Here, we redirect the reactive two-electron oxidants that are generated during aldehyde autoxidation to provide access to a family of hypervalent iodine reagents. The synthesis strategy leverages the intrinsic proclivity of O₂ to participate in radical chain chemistry (*i.e.* autoxidation) to prepare selective two-electron oxidants for use in synthesis. The importance of generating hypervalent iodine-based oxidants, and not utilizing aldehyde autoxidation intermediates directly for substrate oxidation, is highlighted by the diversity of oxidative substrate functionalization chemistry that can be coupled to O₂ reduction using aryl iodides. We have demonstrated aryl iodide supported oxidase chemistry and catalysis can be leveraged for aerobic olefin functionalization, carbonyl α-oxidation to introduce both oxygen and halogen functionality, oxidative dearomatization reactions, and aerobic C–

H amination chemistry. We anticipate that aryl-iodide catalyzed aerobic oxidation chemistry will provide new opportunities and strategies to directly utilize O₂ in sustainable chemical synthesis.

Methods

Aerobic Oxidation of Aryl Iodides

Synthesis of iodobenzene diacetate (1a) and iodosylbenzene (2a)

A 20-mL scintillation vial was charged with glacial AcOH (2 mL), iodobenzene (82.2 mg, 0.401 mmol, 1.00 equiv), and CoCl₂·6H₂O (0.9 mg, 0.004 mmol, 1 mol%) and was fitted with a rubber septum. The reaction vessel was purged with O₂ for 5 min before acetaldehyde (224 µL, 4.07 mmol, 10.2 equiv) was added in one portion. The reaction mixture was stirred under 1 atm O₂, delivered by inflated balloon, at 23 °C for 5 h. The solvent was removed *in vacuo* and residue was dissolved in CH₂Cl₂. The organic layer was washed with distilled water and extracted with CH₂Cl₂ (3 × 7 mL). The organic layer was dried over MgSO₄ and solvent was removed *in vacuo* to afford 119 mg of iodobenzene diacetate (**1a**) as white solid (92% yield). Characterization of **1a**: ¹H NMR (δ, 23 °C, CDCl₃): 8.09 (d, *J* = 7.3 Hz, 2H), 7.63–7.47 (m, 3H), 2.01 (s, 6H). ¹³C NMR (δ, 23 °C, CDCl₃): 176.5, 135.0, 131.8, 131.0, 121.7, 20.5.

A 20-mL scintillation vial was charged with iodobenzene diacetate (**1a**) (97.1 mg, 0.301 mmol, 1.00 equiv) and 3 M NaOH (5 mL) and stirred for 3 h at 23 °C. The resulting suspension was then filtered to afford 62 mg of iodosylbenzene (**1b**) as yellow solid (93 % yield). Characterization of **2a**: ¹H NMR (δ, 23 °C, CD₃OD): 8.04 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.60–7.56 (m, 3H). HRMS (ESI⁺): Calcd. for C₆H₆IO [M+H]⁺ *m/z* 220.9463. Found: 220.9453.

Aerobic Amination Chemistry

Synthesis of N-Methoxy-4-methyl-N-phenylbenzenesulfonamide (19)

A 20-mL vial was charged with DCE (0.25 mL), 1,1,1,3,3,3-hexafluoro-2-propanol (0.25 mL), 1,2-diiodobenzene (5.0 mg, 0.015 mmol, 10 mol%), CoCl₂·6H₂O (0.4 mg, 3 µmol, 2 mol%), compound **18** (30.2 mg, 0.150 mmol, 1.00 equiv), benzene (160 µL, 1.79 mmol, 12.0 equiv), and trifluoroacetic acid (57.4 µL, 0.750 mmol, 5 equiv) and was fitted with a rubber septum. The reaction vial was purged with O₂ for 5 min and then acetaldehyde (11 µL, 0.20 mmol, 1.3 equiv) was added to the reaction mixture. The reaction mixture was stirred for 3 h at 23 °C under 1 atm O₂ (supplied via a balloon). An additional portion of acetaldehyde (11 µL, 0.20 mmol, 1.3 equiv.) was added and the reaction mixture was stirred for 12 h at 23 °C under 1 atm O₂. Solvent was removed *in vacuo*. The residue was dissolved in CH₂Cl₂ (5 mL), excess solid NaHCO₃ was added, the mixture was filtered, and solvent was removed *in vacuo*. The residue was purified by column chromatography on SiO₂ using a hexane/EtOAc (96/4, v/v) eluent to afford 32.4 mg of the title compound (78% yield). ¹H NMR (δ, 23 °C, CDCl₃): 7.43–7.41 (m, 2H), 7.27–7.26 (m, 3H), 7.22–7.21 (m, 2H), 7.13–7.11 (m, 2H), 3.89 (s, 3H), 2.42 (s, 3H). ¹³C NMR (δ, 23 °C, CDCl₃): 144.7, 140.9, 130.0, 129.6, 129.0, 128.3, 127.5, 123.5, 64.2, 21.7.

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Author Contributions

AM and DCP conceived of the project. AM and SMH executed the experimental work. AM, SMH, and DCP analyzed the data and wrote the manuscript.

Competing Financial Interests

A provisional patent has been filed on aerobic oxidation of aryl iodides.

Materials & Correspondence

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