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Oxidase catalysis via aerobically generated hypervalent iodine intermediates

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The development of sustainable oxidation chemistry demands strategies to harness O_2 as a terminal oxidant. Oxidase catalysis, in which O_2 serves as a chemical oxidant without necessitating incorporation of oxygen into reaction products, would allow diverse substrate functionalization chemistry to be coupled to O_2 reduction. Direct O_2 utilization suffers from 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. This is achieved by intercepting reactive intermediates of aldehyde autoxidation to aerobically generate hypervalent iodine reagents for a broad array of substrate oxidation reactions. The use of aryl iodides as mediators of aerobic oxidation underpins an oxidase catalysis platform that couples substrate oxidation directly to O_2 reduction. We anticipate that aerobically generated hypervalent iodine reagents will expand the scope of aerobic oxidation chemistry in chemical synthesis.

O_2 is a readily available, environmentally benign, thermodynamically strong oxidant. The development of chemical strategies to couple O_2 reduction directly to substrate oxidation would enable sustainable synthetic methods[1–3]. However, selective and efficient utilization of O_2 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 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 (Fig. 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]. The application of available mediators, however, is currently limited by either the generation of weak oxidants or limited substrate scope.

In the absence of broadly applicable strategies for O_2 utilization, synthetic chemists have developed myriad 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 the 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]. The current liabilities of hypervalent iodine reagents include the frequent need for stoichiometric quantities of these compounds and the synthesis of these reagents from wasteful metal-based oxidants such as $KMnO_4$, $NaIO_4$ and oxone, or organic peracids such as *m*-chloroperbenzoic acid[11–13,16]. There are no methods available for the direct synthesis of hypervalent iodine compounds from O_2. (Liu and co-workers have suggested O_2-coupled generation of I(V) intermediates during aerobic alcohol oxidation[17], but the active oxidant in this chemistry has subsequently been reassigned as Br_2; ref. 18.) 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 O_2 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 O_2, is among the earliest reactions of O_2 with organic molecules to be characterized[19]. In 1832, Wöhler and Liebig reported the autoxidation of benzaldehyde to benzoic acid[20]. Bäckström advanced the now-accepted radical chain mechanism for aldehyde autoxidation in 1927 (Fig. 2), which involves hydrogen-atom abstraction (HAA) from aldehyde **A** to generate acyl radical **B**, reaction of **B** with O_2 to generate acyl peroxy radical **C**, and HAA to generate an equivalent of peracid **D** and the acyl radical chain carrier **B**[21]. Subsequent Baeyer–Villiger reaction via intermediate E generates two equivalents of acid **F**[22]. The synthetic utility of autoxidation intermediates in reaction development has been realized[23–27]. 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 chemistry[28–32].

We initiated our investigation of aerobic oxidation of aryl iodides by examining the viability of the oxidation of PhI with O_2 in the presence of a variety of simple aldehydes in 1,2-dichloroethane (DCE) at 23 °C (Table 1). We found that, although benzaldehyde was ineffective in promoting the oxidation of iodobenzene (Table 1, entry 1), isobutyraldehyde and butyraldehyde led to the observation of 2% and 6% yield of I(III) bis-esters, respectively

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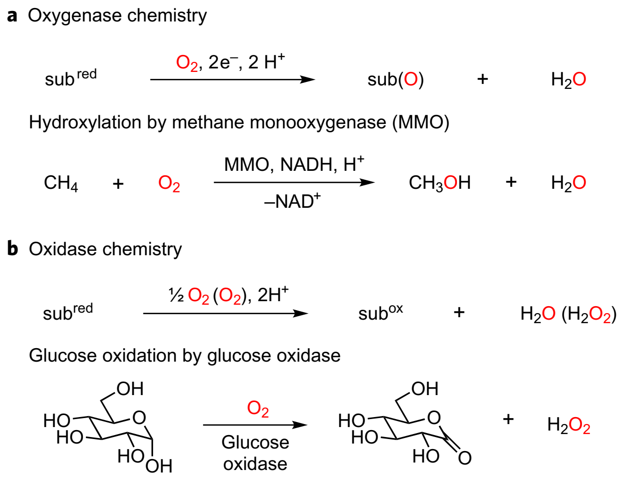


Figure 1 | Oxygenase versus oxidase aerobic oxidation chemistry. **a**, In oxygenase chemistry, O_2 functions both as the electron acceptor as well as the source of oxygen content during substrate functionalization. For example, in the hydroxylation of methane by methane monooxygenase (MMO), the oxygen content in methanol is derived from O_2. **b**, In oxidase chemistry, O_2 functions only as a proton and electron acceptor and is not incorporated into the oxidized substrate. An example of biological oxidase chemistry is the aerobic oxidation of glucose by glucose oxidase. For synthetic chemistry, oxidase strategies are attractive because they allow a broad range of substrate functionalization modes to be coupled to O_2 as the terminal oxidant.

(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 sub-stoichiometric amount of various metal salts (1 mol%) that have been demonstrated to initiate autoxidation (entries 5–7)[33,34] led to identification of $CoCl_2{\cdot}6H_2O$ as a highly effective autoxidation initiator, leading to $PhI(OAc)_2$ in 99% yield. AcOH is the only by-product 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 Supplementary Fig. 1 for the 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*).

With conditions in hand for the aerobic oxidation of PhI, we examined the O_2-coupled synthesis of a family of hypervalent iodine reagents that have been applied in synthetic chemistry (Table 2). 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[35,36]. Addition of TsOH to the oxidation of PhI affords Koser's reagent (**3**)[37], 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. Benziodoxole-based hypervalent iodine reagents, in which the *ortho*-substituent chelates to the oxidized iodine centre (that is, **4**–**6**), are widely utilized in atom- and group-transfer chemistry[14]. The developed conditions also provide access to bis-I(III) compound **7**[38], 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 its substantially increased solubility versus unsubstituted iodosyl benzene[39]. 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 probably 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 by-product of autoxidation, resulted in the immediate disproportionation to I(I) and I(V) derivatives (see Supplementary Fig. 2 for ^1H NMR of disproportionation).

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 (Fig. 3). For each of the transformations illustrated in Fig. 3, 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[40], illustrated by the conversion of 4-fluorostyrene (**9**) to bis-acetate **10** in 88% yield, can be accomplished via a one-pot procedure (Fig. 3a). In the specific case of styrene functionalization, a one-pot, two-step protocol, in which $PhI(OAc)_2$ is prepared prior to styrene addition, was necessary. The incompatibility of 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-

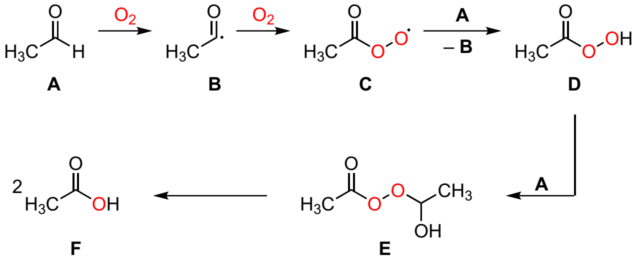
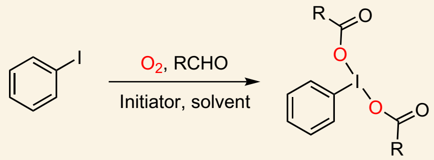


Figure 2 | Radical-chain mechanism for aldehyde autoxidation. Aldehyde autoxidation is among the oldest characterized aerobic oxidation reactions in organic chemistry. Autoxidation of aldehydes to carboxylic acids proceeds via initial hydrogen-atom abstraction (HAA) from an aldehyde **A** to generate acyl radical **B**. Subsequent reaction between **B** and O_2 generates acyl peroxy radical **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 (**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.

Table 1 | Optimization of aerobic oxidation of iodobenzene.



	RCHO	Solvent	Initiator	Yield (%)
1	PhCHO	DCE	None	0
2	*i*-PrCHO	DCE	None	2
3	*n*-PrCHO	DCE	None	6
4	CH_3CHO	DCE	None	42–91
5	CH_3CHO	DCE	$Cu(OAc)_2{\cdot}H_2O$	48
6	CH_3CHO	DCE	$Mn(OAc)_2{\cdot}4H_20$	75
7	**CH_3CHO**	**DCE**	**$CoCl_2{\cdot}6H_2O$**	**99**
8	CH_3CHO	CH_3CN	$CoCl_2{\cdot}6H_20$	73
9	CH_3CHO	AcOH	$CoCl_2{\cdot}6H_20$	98
10	CH_3CHO	THF	$CoCl_2{\cdot}6H_20$	0

Aerobic oxidation was optimized by examining the impact of experimental variables on the oxidation of iodobenzene to iodobenzene diacetate. For optimization experiments, yields were determined by ^{1}H NMR spectroscopy. DCE, 1,2-dichloroethane; AcOH, acetic acid; THF, tetrahydrofuran.

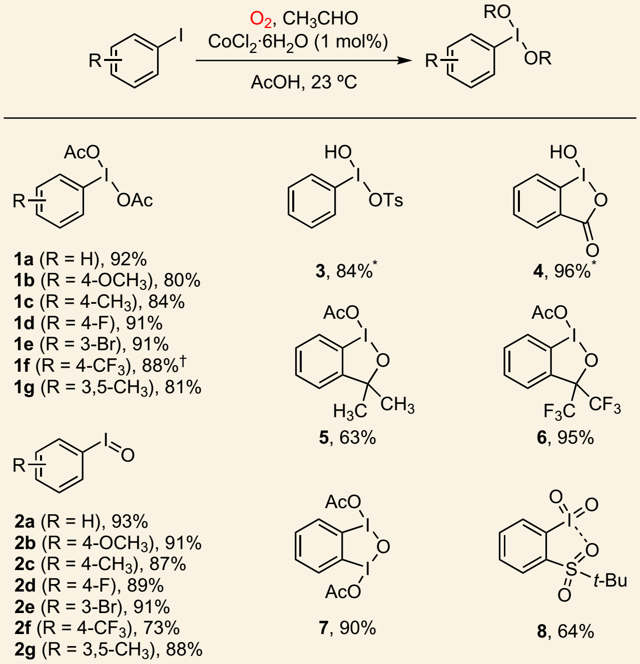
tosylation[41] to afford oxygenated compound **12** in 74% yield by the action of standard autoxidation conditions with the addition of *para*-toluene sulfonic acid (*p*-TSA) (Fig. 3b). Similarly, β-ketoester **13** is readily tosylated to afford α-oxygenate **14** in 61% yield (Fig. 3c). Use of 20 mol% PhI in the α-tosylation of acetophenone led to the observation of 33% yield of compound **12**, which provided a 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.

Application of aerobic oxidation of aryl iodides 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 the reaction products. For example, in the α-oxidation of β-ketoester **13**, replacing *p*-TSA with tetrabutylammonium bromide ([TBA]Br) results in aerobic bromination to afford compound **15** (57% yield, see Supplementary page 14), not the α-oxygenation product **14** as demonstrated above. Unlike the oxygenation reactions pictured in Fig. 3a–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 (Fig. 3d). PhI is also a competent catalyst for bromination, but superior yields are obtained with 1,2-diiodobenzene as catalyst.

We have extended aryl-iodide-catalysed aerobic oxidation to oxidative dearomatization chemistry and C–H amination chemistry. Using 20 mol% 1,2-diiodobenzene, Weinreb amide **16** (ref. 42) undergoes aerobic dearomatization to afford lactam **17** in 77% yield (Fig. 3e). 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 benzene[43] to afford phenylsulfonamide **19** in 78% yield. In each of the reactions pictured in Fig. 3d–f, aerobic oxidation is accomplished with AcOH as the only stoichiometric by-product.

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 (that is, 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 followed the kinetics of PhI consumption and $PhI(OAc)_2$ evolution by ^{1}H NMR spectroscopy in $CDCl_3$ (Fig. 4; additional data are summarized in Supplementary Figs 3 and 4). In the absence of $CoCl_2{\cdot}6H_2O$, an induction period is observed and evolution of $PhI(OAc)_2$ displays sigmoidal growth consistent with a radical chain process. In the presence of $CoCl_2{\cdot}6H_2O$, $PhI(OAc)_2$ 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 (Supplementary Figs 5 and 6) and for the oxidation of PhI in AcOH-d_4 (Supplementary Figs 7 and 8). During these ^{1}H NMR experiments, we did not observe ^{1}H 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 in a 1:3:3 ratio (Supplementary Fig. 9). We attribute these signals to Baeyer–Villiger intermediate **E** (Fig. 2)[44]. Consistent with this assignment, high-resolution mass spectrometry of the oxidation reaction reveals the presence of a signal at $m/z = 143.0318$ ($M+Na^+$ for **E**) (Supplementary Fig. 10). 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 CH_3CHO, 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 timescale of PhI oxidation (Supplementary Fig. 11). At this time, we cannot differentiate between aerobically generated

Table 2 | Application of aerobic oxidation chemistry to the synthesis of a family of hypervalent iodine reagents.



1a (R = H), 92%
1b (R = 4-OCH_3), 80%
1c (R = 4-CH_3), 84%
1d (R = 4-F), 91%
1e (R = 3-Br), 91%
1f (R = 4-CF_3), 88%†
1g (R = 3,5-CH_3), 81%

3, 84%*

4, 96%*

5, 63%

6, 95%

2a (R = H), 93%
2b (R = 4-OCH_3), 91%
2c (R = 4-CH_3), 87%
2d (R = 4-F), 89%
2e (R = 3-Br), 91%
2f (R = 4-CF_3), 73%
2g (R = 3,5-CH_3), 88%

7, 90%

8, 64%

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. AcOH, acetic acid; OTs, tosylate. *Reaction solvent in these oxidation reactions: 1,2-dichloroethane (DCE). †For this substrate, dimerization affords $(4\text{-}CF_3C_6H_4I(OAc))_2O$, see Supplementary page 7.

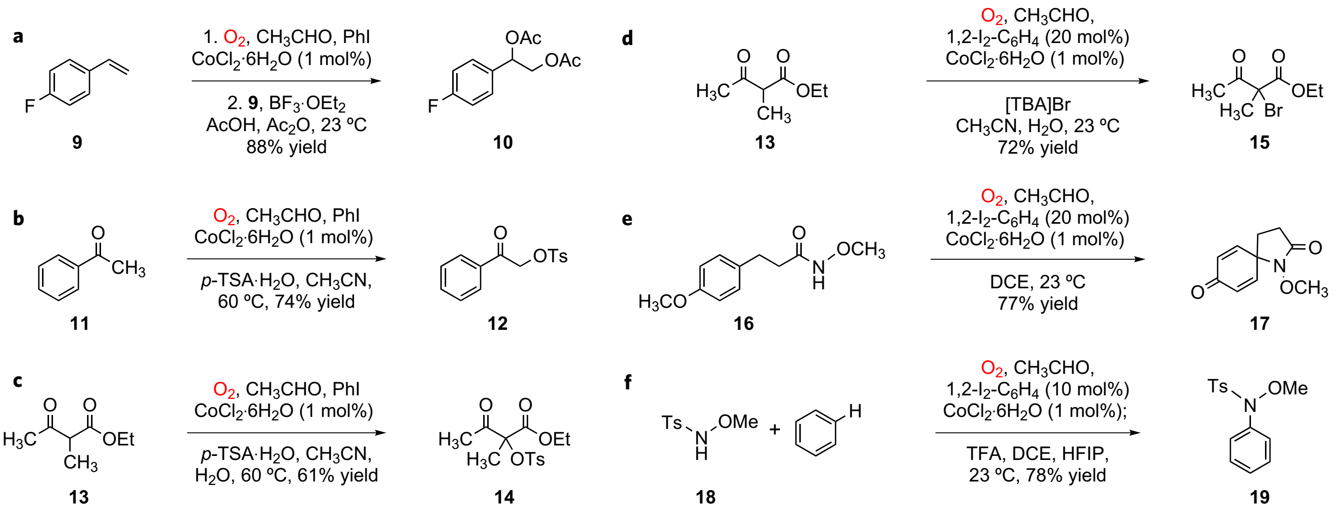


Figure 3 | Aerobic oxidation of PhI provides a broad platform to directly utilize O_2 as the terminal oxidant in substrate oxidation reactions. a–c, Utilization of PhI oxidation to oxygenate substrates is highlighted by 1,2-difunctionalization of olefins (**a**), α-oxygenation of acetophenone (**b**)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

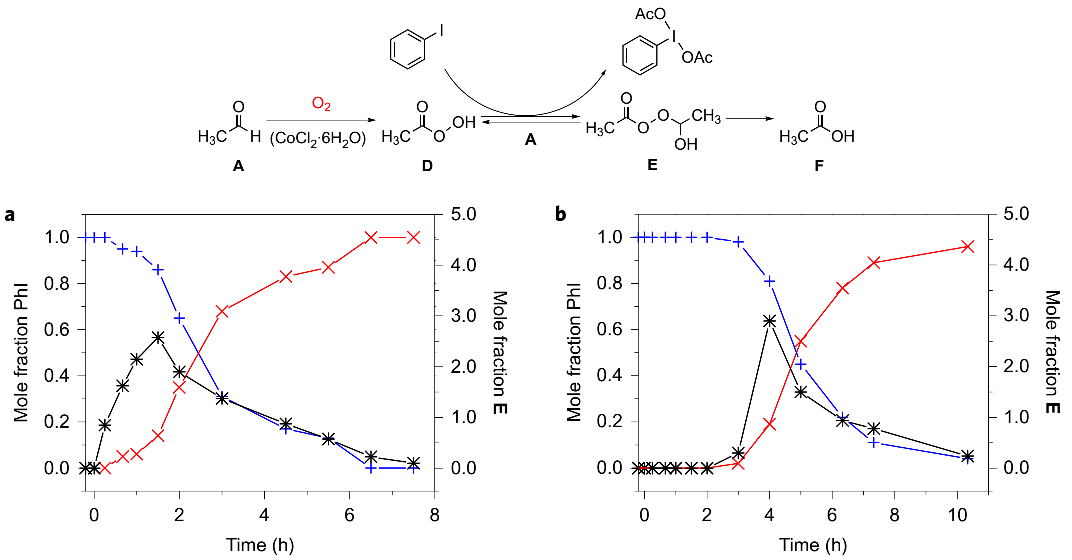


Figure 4 | Aerobic oxidation of aryl iodides is accomplished by intercepting the oxidizing intermediates of aldehyde autoxidation chemistry. **a**,**b**, Monitoring the kinetics of consumption of PhI (blue plus symbols) and evolution of $PhI(OAc)_2$ (red crosses) by ^1H NMR in the presence (**a**) or absence (**b**) of $Co_2Cl_2·6H_2O$, added as a radical initiator, indicates that Co(II) initiates autoxidation of PhI. At intermediate times during PhI oxidation, peroxo intermediate **E** (black asterisks) is observed (by both ^1H NMR and mass spectrometry), which confirms that autoxidation is operative during aryl iodide oxidation. We cannot currently differentiate between **D** and **E** as the active oxidant for aryl iodides.

AcOOH or compound E, the adduct of AcOOH with CH_3CHO, as the active oxidant in PhI oxidation.

Conclusions

Development of a broadly applicable platform for oxidase catalysis, which utilizes O_2 as the terminal oxidant without necessitating the incorporation of oxygen during substrate functionalization, would provide new opportunities to utilize O_2 as a sustainable oxidant in chemical synthesis. Aldehyde autoxidation chemistry, in which an aldehyde is converted to a carboxylic acid under the action of O_2, is among the earliest examples of aerobic oxidation in organic chemistry and proceeds via reactive peroxy 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 O_2 to participate in radical chain chemistry (that is, 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 O_2 reduction using aryl iodides. We have demonstrated that 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-catalysed aerobic oxidation chemistry will provide new opportunities and strategies to directly utilize O_2 in sustainable chemical synthesis.

Note added in proof: After acceptance of our paper, we became aware of a related manuscript (ref. 45) discussing aldehyde-promoted aerobic oxidation of aryl iodides.

Methods

General method for the oxidation of iodoarenes. In a typical experiment, a 20 ml scintillation vial was charged with glacial AcOH (2 ml), iodoarene (0.401 mmol) and $CoCl_2{\cdot}6H_2O$ (0.004 mmol, 1 mol%) and was fitted with a rubber septum. The reaction vessel was purged with O_2 for 5 min before acetaldehyde (4.07 mmol, 10.2 equiv.) was added in one portion. The reaction mixture was stirred under 1 atm O_2, delivered by inflated balloon at 23 °C for 5 h. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2. The organic layer was washed with distilled water and extracted with CH_2Cl_2 (3×7 ml). The organic layer was dried over $MgSO_4$ and solvent was removed *in vacuo* to afford the corresponding iodobenzene diacetate. The isolated compounds were characterized by ^1H and ^{13}C NMR spectroscopies.

Data availability. The characterization data and experimental protocol that are described in this paper are available within the paper and its Supplementary Information, or from the corresponding authors upon request.

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Author contributions

A.M. and D.C.P. conceived of the project. A.M. and S.-M.H. carried out the experimental work. A.M., S.-M.H. and D.C.P. analysed the data and wrote the manuscript.

Additional information

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Competing financial interests

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