Sustainable Methods in Hypervalent Iodine Chemistry

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Abstract

Hypervalent iodine compounds are a widely used class of metal-free oxidants that find application in organic synthesis. Due to the homology between the reactivity of hypervalent iodine and many transition metals — oxidative addition, ligand exchange, and reductive elimination can be facile for both — hypervalent iodine species find application in a variety of synthetically important organic transformations. Major limitations of these reagents include the frequent need for (super)stoichiometric loading and the intrinsically poor atom economy that results from the generation of stoichiometric quantities of iodoarene byproducts. In addition, hypervalent iodine reagents are often synthesized using metal-based terminal oxidants, which compound the resulting waste stream. Recently, substantial progress has been made to address these limitations. Here, we discuss progress towards sustainable synthetic methods for the preparation of hypervalent iodine compounds and application of those methods in the context of hypervalent iodine catalysis. The discussion is organized according to the active oxygen content, and thus atom economy, of the terminal oxidant employed. Hypervalent iodine electrochemistry and the development of recyclable iodoarenes are also discussed.

A. Introduction

Oxidation reactions, in which electron equivalents are removed from a substrate, are often critical steps in the synthesis of functional organic molecules. By definition, oxidation reactions require the use of an electron acceptor (i.e., terminal oxidant). Because the reduced byproducts generated from the terminal oxidant are often lost as chemical waste, the chemical structure of the terminal oxidant dictates the sustainability of the oxidation reaction. Biological oxidation chemistry often utilizes dioxygen (O₂) as the terminal oxidant and generates water as the ultimate byproduct [1, 2]. As such, these enzymatic oxidation reactions are nearly ideal from the perspective of sustainability. Analogous utilization of O₂ as a terminal oxidant in synthetic chemistry remains a significant challenge because 1) the triplet ground state of O₂ imposes kinetic barriers to O₂ utilization [3], 2) O₂ often engages in poorly selective radical chain reactions [4], 3) the electron inventories of O₂ reduction (four-electron) and substrate oxidation (two electrons) are mismatched [5, 6]; and, 4) O₂ utilization can present safety concerns depending on the specific reaction conditions employed [7]. The challenges associated with direct O₂ utilization as a terminal oxidant in selective synthesis have stimulated the development of alternative chemical oxidants for application in specific synthetic contexts.

Implicit in the use of designer chemical oxidants is an increase in the waste associated with oxidation chemistry and in turn reduced sustainability.

The principles of green chemistry articulated by Anastas et al. [8, 9] codify the concept of atom economy and the impact of the nature of waste on the efficiency of a chemical process. Active oxygen content, which is defined as the percent weight ratio of the oxygen transferred to

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product divided by the formula weight of the reagent, can be used as a guiding parameter for evaluating the sustainability of oxidants [10]. Table 1 lists the active oxygen content and associated waste products generated from a variety of commonly encountered terminal oxidants.

Table 1. List of general oxidants in order of their respective active oxygen content [10].

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Active Oxygen Content (wt %)</th>
<th>Waste Generated</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂ or O₂/ reductant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 (50)</td>
<td>None (H₂O)</td>
</tr>
<tr>
<td>H₂O₂</td>
<td>47</td>
<td>H₂O</td>
</tr>
<tr>
<td>KMnO₄</td>
<td>30.4</td>
<td>Mn(II) salt</td>
</tr>
<tr>
<td>NaOCl</td>
<td>21.6</td>
<td>NaCl</td>
</tr>
<tr>
<td>O₂ / CH₃CHO</td>
<td>21.1</td>
<td>CH₃CO₂H</td>
</tr>
<tr>
<td>CH₃CO₃H</td>
<td>21.1</td>
<td>CH₃CO₂H</td>
</tr>
<tr>
<td>tBuOOH</td>
<td>17.8</td>
<td>tBuOH</td>
</tr>
<tr>
<td>H₂O₂-Urea</td>
<td>17.0</td>
<td>H₂O-Urea</td>
</tr>
<tr>
<td>KH₂SO₅</td>
<td>10.5</td>
<td>KH₂SO₄</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>9.3</td>
<td>m-CBA</td>
</tr>
<tr>
<td>NaIO₄</td>
<td>7.5</td>
<td>NaIO₃</td>
</tr>
<tr>
<td>PhIO</td>
<td>7.3</td>
<td>PhI</td>
</tr>
<tr>
<td>NaBO₃·4H₂O</td>
<td>7.2</td>
<td>NaBO₂</td>
</tr>
<tr>
<td>Oxone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.6</td>
<td>K₂S₂O₅·KH₂SO₄·K₂SO₄</td>
</tr>
</tbody>
</table>

<sup>a</sup>This analysis assumes the reduced byproduct is H₂O. If chemical reductants are employed (i.e., H₂, NADH, CH₃CHO, etc.) the active oxygen content will be lower depending on the mass of the generated byproducts.

<sup>b</sup>(2KH₂SO₅·KH₂SO₄·K₂SO₄).

While O₂ is an attractive oxidant based on its active oxygen content, chemical strategies that utilize both oxygen atoms for substrate functionalization (i.e., dioxygenase reactivity) are rare [11]. More typically, O₂ utilization is accomplished in the presence of an appropriate reductant, which addresses the incongruous electron inventory of O₂ reduction and substrate functionalization. Consequently only 50% of active oxygen content of O₂ is utilized and the other 50% is lost as waste (ideally H₂O). Hydrogen peroxide (H₂O₂) is also considered a green oxidant, and has 47% active oxygen content when utilized in direct substrate oxidation chemistry with attendant generation of H₂O as the byproduct. Utilization of H₂O₂ as an oxidant in hypervalent iodine chemistry often requires acetic anhydride, to generate peracetic acid in situ, or the use of urea-hydrogen peroxide (UHP) adduct, both of which reduce the active oxygen content of the reagent. Other commonly encountered chemical oxidants, such as NaOCl, CH₃CO₂H, m-CPBA, NaIO₄, NaBO₃·4H₂O, and Oxone display significantly lower active oxygen contents. The recent renaissance of organic electrochemistry offers an alternative strategy to sustainable oxidation chemistry: Anodic substrate oxidation provides the opportunity to avoid stoichiometric redox reagents and the associated waste streams [12]. The frequent requirement for high concentrations of supporting electrolyte can reduce the chemical efficiency of electrochemical approaches.

Hypervalent iodine compounds are a class of metal-free oxidants based on three-centered-four-electron I–L bonds [13, 14] that have emerged as important reagents in the functionalization of unsaturated hydrocarbons, transition metal-catalyzed chemistry, alcohol and amine oxidation,
and group transfer chemistry [15-21]. The reactivity of hypervalent iodine compounds bears some similarities to that of transition metal species — namely the accessibility of multiple stable redox states, the facility of ligand exchange steps, and the participation in bond-forming processes [15-18, 22]. Both I(III) and I(V) compounds are important oxidation states in hypervalent iodine chemistry due to their complementary reactivities. Although hypervalent iodine compounds are attractive oxidants due to the abundance of iodoarene starting materials and lower toxicity compared to transition metal catalysts, when employed as terminal oxidants hypervalent iodine reagents display poor atom economy. For example, when reduced, iodosylbenzene (PhIO) generates a stoichiometric quantity of iodobenzene and only features 7.3% active oxygen content. In addition, hypervalent iodine species are typically prepared with stoichiometric metal-based oxidants (KMnO₄, Oxone, NaIO₄, etc.) or organic peracids (m-CPBA, CH₃CO₃H) which amplifies the overall chemical inefficiency of using these reagents in synthesis.

The development of either 1) methods to synthesize hypervalent iodine compounds using higher active-oxygen-content reagents, or 2) methods to employ hypervalent iodine species as catalysts in tandem with oxygen-dense oxidants could provide a platform for sustainable oxidation methods for wide variety of reactions. Here, we summarize progress towards sustainable synthesis and use of hypervalent iodine compounds. We first discuss progress towards greener methods to prepare hypervalent iodine compounds and this discussion is organized by the active oxygen content of the terminal oxidant employed. Catalytic application of hypervalent iodine compounds as a way to reduce waste generation and increase energy efficiency is discussed. Electrochemistry as an alternate sustainable method for synthesis of hypervalent iodine compounds is described in the context of both synthesis of hypervalent iodine compounds and their utilization in electrocatalysis. Polymer-supported hypervalent iodine reagents and fluorous hypervalent iodine compounds, which have been developed to support reagent recycling, are also discussed. Only organic hypervalent iodine chemistry is presented; utilization of tetrabutylammonium iodide and other inorganic iodide sources will not be described.

B. Chemical Synthesis of Hypervalent Iodine Reagents

B.1. Synthesis of Hypervalent Iodine Reagents Using O₂

In concept, if hypervalent iodine reagents were generated using O₂ as the terminal oxidant, the array of chemistry that is available to these reagents could be achieved aerobically. Iodoarenes do not react directly with O₂ to afford hypervalent iodine compounds, and thus the development of aerobic methods of hypervalent iodine chemistry requires identification of an appropriate reductant to enable aerobic oxidation to be realized.

B.1.1. Synthesis of Hypervalent Iodine(III) Reagents with O₂

In 2018, Powers et al. reported the synthesis of hypervalent iodine reagents by intercepting reactive oxidants generated during acetaldehyde autoxidation [23]. Initial studies of the oxidation of iodobenzene (1) in the presence of acetaldehyde and O₂ afforded variable yields of (diacetoxyiodo)benzene (2, 42-91% yield), presumably due to inconsistent initiation of the aldehyde autoxidation chain reaction. Co(II) additives, which have been previously used as initiators of aldehyde autoxidation chemistry [24, 25], were found to be critical in achieving reproducible chemical yields. The developed aerobic oxidation protocol provided ready access to a wide variety of hypervalent iodine reagents (Figure 1): Oxidation of 4-substituted
iodoarenes provided access to hypervalent iodine species bearing both electron-donating and -withdrawing groups (3-8). Oxidation of 2-substituted iodoarenes afforded the corresponding cyclic iodanes (9-12) in high yields, which are an important class of reagents for hypervalent iodine mediated group transfer chemistry. Addition of external acids provided direct entry to acid-exchanged I(III) products (13-15) instead of the corresponding (diacetoxyiodo)benzene derivatives; for example, addition of TsOH, benzoic acid (BzOH), and trifluoroacetic acid (TFA) led to the formation of Koser’s reagent (13), PhI(OBz)2 (14), and PhI(TFA)2 (15) in 84%, 48%, and 52% yields, respectively.

![Figure 1](image)

Figure 1. Aldehyde-promoted aerobic oxidation of iodoarenes provides access to a family of hypervalent iodine(III) reagents. DCE as solvent, \(^a\)in presence of TsOH×H2O, \(^b\)in presence of BzOH, and \(^d\)in presence of CF3CO2H.

A detailed investigation of the mechanism of aerobic oxidation revealed that iodoarene oxidation proceeds via a one-electron radical chain mechanism, which differs from the commonly observed two-electron oxidation / reduction reactions of these reagents [26]. The proposed mechanism was formulated based on 1) EPR spectroscopy of spin-trapped acetoxy radicals, 2) comparative Hammett analyses of aerobic oxidation and peracetic acid oxidation, 3) kinetic competition experiments, and 4) computational analysis. These data indicated that aerobic oxidation of iodobenzene (1) in presence of acetaldehyde and O2 proceeds via addition of aerobically generated acetoxy radicals (16) to iodoarenes to generate transient iodonitroxy radicals (17) (Figure 2). Subsequent chain propagation by reaction with peracetic acid (18, an intermediate from aldehyde autoxidation) affords I(III) product (19) and regenerates the acetoxy radical chain carrier (16). Chain termination via either combination of 17 with acetoxy radical or via iodonitroxy radical disproportionation leads to (diacetoxyiodo)benzene (2).
Aldehyde-promoted aerobic oxidation proceeds by addition of an aerobically generated acetoxy radical to iodobenzene to generate a transient iodanyl radical, which is a chain carrier in the synthesis of I(III) compounds.

B.1.2. Synthesis of Hypervalent Iodine(V) Reagents with O₂

The first aerobic synthesis of iodylbenzene ($\text{20}$) was reported by Jorissen $et$ $al.$ in 1938 [27], who demonstrated that an aerated acetaldehyde solution of iodobenzene ($\text{1}$) produced white crystals over the course of three weeks (Figure 3). These crystals were identified as iodylbenzene by iodometry.

![Figure 3](image-url) Upon standing for several weeks, an aerated solution of iodobenzene ($\text{1}$) in acetaldehyde resulted in the formation of crystalline iodylbenzene ($\text{20}$).

In 2018, Powers and co-workers described a strategy for the aerobic synthesis of I(V) reagents by coupling aldehyde-promoted aerobic oxidation of iodoarenes with disproportionation of the initially generated I(III) species [28]. Aerobic oxidation of iodoarenes with weakly chelating ortho-substituents like sulfonyl, nitro, or pyridyl were found to furnish the corresponding I(V) compounds $\text{21-23}$ in good yield (Figure 4) [22, 29].

![Figure 4](image-url) Aerobic synthesis of hypervalent iodine(V) reagents was achieved by coupling aldehyde-promoted aerobic oxidation iodoarenes with subsequent $\text{in situ}$ disproportionation.
B.2. Synthesis of Hypervalent Iodine Reagents with H$_2$O$_2$ or UHP

H$_2$O$_2$ is considered to be an environmentally benign oxidant due to its 47% active oxygen content and the potential generation of water as the byproduct. H$_2$O$_2$ is produced via the Riedl–Pfleiderer process where 2-alkylantraquinone is first reduced to 2-alkylhydroantraquinone by hydrogenation and again oxidized aerobically to regenerate 2-alkylantraquinone and H$_2$O$_2$ [30]. In spite of many advantages, decomposition of H$_2$O$_2$ to H$_2$O and O$_2$ is exothermic (–94.6 kJ/mol) [31], and the use of concentrated solutions presents significant safety hazards. Hence, H$_2$O$_2$ is typically employed as ≤30% aqueous solution. An alternative way to safely deliver H$_2$O$_2$ into the reaction is by using urea adduct of hydrogen peroxide (UHP), which is an odorless, water-soluble, crystalline solid that has an active oxygen content of 17% [32].

B.2.1. Synthesis of Hypervalent Iodine(III) Reagents with H$_2$O$_2$ or UHP

There are no examples of direct oxidation of iodoarenes with H$_2$O$_2$ alone, which may be due to the spontaneous decomposition of H$_2$O$_2$ by I(III) compounds to form singlet oxygen (1$^\text{O}_2$) and reduced I(I) (Figure 5) [33]. H$_2$O$_2$ is often employed as an oxidant in combination with acid anhydrides and hydrohalic acids, which promote the in situ generation of peracids and hypohalous acids, respectively. Here, we organize presentation of H$_2$O$_2$-based methods by the type of hypervalent iodine compounds generated.

![Figure 5. Hydrogen peroxide reacts with (ditrifluoroacetoxy)iodobenzene to form singlet oxygen (1$^\text{O}_2$) and iodobenzene (1).](image)

Peracid-based oxidation of iodoarenes was first reported by Boeseken and Schneider in 1931 who synthesized (diacetoxyiodo)benzene by treatment of iodobenzene in chloroform with 55% peracetic acid [34]. In 1953, Pausacker reported a modified synthesis in which 30% H$_2$O$_2$ and acetic anhydride were stirred together at 40 $^\circ$C to generate peracetic acid followed by addition of iodobenzene (1) to the resulting solution (Figure 6) [35]. This method avoids the use of highly concentrated peracetic acid solution and was the earliest example with H$_2$O$_2$ as the terminal oxidant for the synthesis of I(III) compounds. To date, this method is among the most widely used for the synthesis of PhI(OAc)$_2$ (2).

![Figure 6. The combination of hydrogen peroxide and acetic anhydride generate peracetic acid in situ, which is responsible for oxidation of iodobenzene (1) to (diacetoxyiodo)benzene (2).](image)

[Bis(trifluoroacetoxy)iodo]arenes are stronger oxidants than PhI(OAc)$_2$ due to the more electron withdraying trifluoroacetoxy groups on the iodine center [36]. Zhdankin et al. reported a direct synthetic route to [bis(trifluoroacetoxy)iodo]arenes using trifluoroperacetic acid, generated in situ by combination of 80% H$_2$O$_2$ with trifluoroacetic anhydride [37]. Although the described procedure was more efficient than previous synthetic methods based on ligand exchange reactions of hypervalent iodine(III) compounds with trifluoroacetic acid [38, 39], silver trifluoroacetate [40], or trimethylsilyl trifluoroacetate [41], the use of such high concentration of H$_2$O$_2$ poses serious safety hazards. In 2006, Wirth et al. described a
modification of the procedure using UHP as the terminal oxidant, which enabled in situ formation of trifluoroperacetic acid, leading to efficient formation of [bis(trifluoroacetoxy)iodo]benzene (15), [bis(trifluoroacetoxy)iodo]toluenes (24, 25), [bis(trifluoroacetoxy)iodo]arenes with electron-withdrawing substituents (26-29), and chiral I(III) product 30 (Figure 7) [42].

![Chemical structures](image1)

Figure 7. In situ generation of trifluoroperacetic acid from UHP and trifluoroacetic anhydride provides access to [bis(trifluoroacetoxy)iodo]arenes from the corresponding iodoarenes.

(Dichloroiodo)arenes, ArICl₂, are widely used reagents for the chlorination of unsaturated hydrocarbons and also as terminal oxidants for transition metal catalysis [43]. Historically, (dichloroiodo)benzene (31) has been synthesized by bubbling chlorine gas into a solution of iodobenzene (1) at a low temperature. Use of toxic and corrosive chlorine gas can be avoided using hydrochloric acid in combination with oxidants like KClO₃ [44], KMnO₄ [45], concentrated HNO₃ [45], Na₂S₂O₈ [46], CrO₃ [47], NaClO₂, or NaClO [48]. These methods suffer from (super)stoichiometric use of terminal oxidants and poor substrate scope with respect to electron withdrawing substituents on the iodoarenes. Jarnej and co-workers reported an alternative route for the synthesis of (dichloroiodo)arenes from a mixture of HCl/H₂O₂ (30% aqueous solution) in 1,1,1-trifluororethanol (TFE) which acts both as a solvent and activator for H₂O₂ (Figure 9) [49]. In this protocol, hypochlorous acid (HOCl) is generated in situ and acts as the active oxidant and chlorinating agent. This method tolerates alkyl substituents (32, 33) as well as electron-withdrawing groups such as carboxyl-, nitro-, and chloro substituents (34-37). In case of 4,4′-diiodo-1,1′-biphenyl, both the iodine centers are chlorinated to generate 38. In the presence of electron donating groups like dimethyl, trimethyl or methoxy substituents, the corresponding (dichloro)iodoarenes (39-41) decompose to the chlorinated arene products.

![Chemical structures](image2)

Figure 9. H₂O₂ was combined with concentrated HCl to form hypochlorous acid (HOCl) in situ, the active chlorinating reagent for the synthesis of (dichloroiodo)arenes from iodoarenes.
Diaryliodonium salts are typically synthesized via a two-step process involving iodoarene oxidation followed by arylation of the I(III) with a suitable arene; thus, catalysis is often limited and sustainable synthesis of these reagents is important to decrease the environmental impact. Building on the demonstration of UHP in the synthesis of iodine(III) reagents, Olofsson et al. developed a UHP-based synthesis of diaryliodonium triflates [50]. The authors utilized the in situ formation of triflic peroxide using UHP and triflic anhydride (Tf₂O) to oxidize the iodoarenes in presence of suitable arenes to furnish diaryliodonium triflates in a single step. The developed methodology was effective in synthesizing both symmetric (42) and unsymmetric iodonium (43-51) salts in good yield (42-86%) but, use of oxidatively labile substrate like anisole or pyridine led to undesired side-products or pyridine-N-oxides, respectively without any desired product formation (52, 53) (Figure 8).

Figure 8. Diaryliodonium triflates were synthesized using urea adduct of hydrogen peroxide in a sustainable method leading to symmetric and unsymmetric iodonium salts.

**B.2.1. Synthesis of Hypervalent Iodine(V) Reagents from H₂O₂ or UHP**

Zhdankin and co-workers reported a two-step, one-pot strategy to access iodylarenes using H₂O₂ as the terminal oxidant by coupling in situ generation of peracid with subsequent disproportionation chemistry catalyzed by RuCl₃ (0.8 mol%) [51]. This method was effective in furnishing iodylarenes bearing both electron-donating (54-57) and electron-withdrawing groups (58-63), but formation of 2-iodoxybenzoic acid (IBX) from 2-iodobenzoic acid was unsuccessful (Figure 10a). When independently synthesized PhI(OAc)₂ (2) was treated with RuCl₃ (0.4 mol%) in an aqueous acetonitrile solution at room temperature, immediate formation of equimolar amount of iodylbenzene (20) and iodobenzene (1) were observed, which is consistent with disproportionation being operative in the synthesis of I(V) species (Figure 10b) [52].
Figure 10. (a) RuCl₃-mediated disproportionation of initially formed hypervalent iodine(III) intermediates provided access to the corresponding iodylarenes. (b) Treatment of independently synthesized (diacetoxyiodo)benzene (2) with RuCl₃ resulted in disproportionation to equimolar amount of iodobenzene (1) and iodylbenzene (20).

C. Electrochemical Synthesis of Hypervalent Iodine Reagents

Anodic oxidation of iodoarenes represents a conceptually attractive approach to these species, in which stoichiometric oxidants are replaced by electrical potential. Electrosynthesis can broadly be classified as either ex cell, in which anodic oxidation of iodoarenes is accomplished during a first step and the resulting hypervalent iodine reagents are subsequently utilized for substrate functionalization in a separate step, or in cell, in which anodic oxidation of iodoarenes is carried out in the presence of substrate, such as is required to achieve electrocatalysis [53]. Both I(III) and I(V) reagents have been prepared electrochemically. Due to the substantial overpotential that is typically required for the anodic oxidation of iodoarenes, hypervalent iodine electrochemistry is often limited to ex cell applications (i.e., at the potential required to oxidize iodoarenes, many substrates participate in background oxidation).

C.1. Electrochemical Synthesis of Hypervalent Iodine(III) Reagents

The first example of electrochemical synthesis of hypervalent I(III) reagents was reported in 1960 by Schmidt and Meinert, who described the anodic oxidation of iodobenzene in the presence of silver fluoride (AgF), which acts as both the fluorine source and supporting electrolyte, to generate (difluoroiodo)benzene (PhIF₂, 65) [54]. Subsequent reports have described difficulty reproducing this synthesis [55]. In 1994, Fuchigami and co-workers discovered that direct electrolysis of 4-iodonitrobenzene (64) in presence of Et₃N-3HF as the supporting electrolyte and fluorine source formed 4-(difluoroiodo)nitrobenzene (66) in 53% yield (Figure 11) [56]. But, electrolysis of iodobenzene and 4-iodotoluene did not lead to the desired I(III) compounds, but instead gave rise to benzylic fluorination and diaryliodonium products, respectively.

Figure 11. Electrochemical synthesis of 4-(difluoroiodo)nitrobenzene (66) was achieved using triethyl amine adduct of hydrogen fluoride both as the source of fluoride and the supporting electrolyte under constant current electrolysis conditions.
Hara et al. later discovered that by using Et₃N·5HF as the supporting electrolyte and fluorine source resulted in the successful electrosynthesis of 4-(difluoroiodo)toluene (68) via potentiostatic electrolysis of 4-iodotoluene (67) at 1.5 V vs Ag⁺/Ag [57]. Electrochemically generated 68 has been applied to a variety of substrate functionalization reactions including fluorination of β-dicarbonyl substrates [57], fluoro cyclization of N-allylbenzamides [58], and vicinal difluorination of olefins (Figure 12) [59].

**Figure 12.** Electrochemical synthesis of 4-(difluoroiodo)toluene (67) was carried out under constant current electrolysis condition and then utilized in various ex cell fluorination reactions.

Ex cell electrochemistry of hypervalent iodine reagents provides a means to generate unstable, or dangerous reagents in situ without the need for isolation, which often leads to improved yields and safer reaction conditions [60, 61]. Nishiyama and co-workers developed anodic oxidation of iodoarenes in fluorinated solvents, such as trifluoroethanol (TFE) to afford [bis(trifluoroethoxy)iodo]benzene (72) [62-64]. Fluorinated alcohol solvents are known to help stabilize radical cation intermediates and consequently improve single electron oxidation events of iodoarenes at anode surfaces [36, 65-67]. While many of the I(III) reagents supported by fluorinated alkoxide ligands are not stable to isolation (with the exception of the p-nitro substituted derivative), these electrochemically derived reagents have been widely employed in subsequent ex cell substrate functionalization (Figure 13) [62-64, 68-72].

**Figure 13.** Fluorinated alcohol solvents such as trifluoroethanol (TFE) is used to stabilize anodically generated hypervalent iodine(III) intermediate and the resulting oxidizing solution is utilized for ex cell applications leading to various alkaloids, lactones and lactams. *Only stable in solution, not isolable.

The anodic oxidation of iodoarenes can also be used to electrochemically synthesize diaryliodonium salts. In 1967, Miller and Hoffmann disclosed that potentiostatic electrolysis of iodobenzene at 1.65 V vs Ag⁺/Ag, in acetonitrile, with lithium perchlorate as the supporting electrolyte afforded (4-iodophenyl)(phenyl)iodonium perchlorate in 45% yield [73]. Similarly,
electrolysis of iodobenzene and 4-iodotoluene in the presence of benzene resulted in diphenyliodonium perchlorate (32% yield) and (4-methylphenyl)(phenyl)iodonium perchlorate (56% yield), respectively. Wendt and co-workers later investigated the mechanism of diaryliodonium formation. Because benzene does not oxidize below 1.9 V vs Ag+/Ag, they concluded that iodoarenes are oxidized at the anode surface [74].

In 2000, Peacock and Pletcher reported a method to expand the scope of diaryliodonium salts that could be prepared electrochemically [75, 76]. By using a mixture of acetic acid, acetic anhydride, and sulfuric acid as the reaction solvent, anodic synthesis of iodonium salts (75) was extended to electron rich iodoarenes and arene coupling partners (Figure 14). In addition, both symmetric and asymmetric iodonium salts were synthesized. Due to the substantial overpotential for anodic oxidation of iodoarenes, many functional groups were still found to be incompatible with the developed conditions. Electron-withdrawing substituents on the iodoarene (73) increased the onset potential beyond the solvent window and thus prevented initial anodic oxidation. Electron-donating substituents on the iodoarene, such as 4-methoxy, decreased the onset potential for iodoarene oxidation, however, gave rise to side reactions, such as anisole sulfonation by sulfuric acid. With respect to the arene coupling partner (74), electron-withdrawing substituents decreased yields due to decreased nucleophilicity and electron-rich arene coupling partners were limited due to direct anodic oxidation and subsequent radical polymerization.

Figure 14. Electrochemical synthesis of both symmetric and unsymmetric diaryliodonium bisulfates under constant current conditions.

One challenge in utilizing electrochemically derived hypervalent iodine reagents for substrate functionalization is the need to remove the iodoarene byproducts and electrolyte from the reaction product. To address this, Francke and coworkers developed low-molecular-weight, charged iodoarenes as potential ex cell mediators in which the supporting electrolyte and the iodoarene mediator were combined [77-79]. The first examples developed were quaternary ammonium substituted 4-iodoarenes. Anodic oxidation of iodoarene 76 in fluorinated solvents provided access to the corresponding hypervalent iodine compound 77, which was subsequently utilized in ex cell C–N bond forming reactions such as carbazole formation (78), N-arylation (79) [77], and oxazole syntheses (80) (Figure 15) [78].
Iodoarene (76) with tetramethylammonium moiety obviates the need to use additional supporting electrolyte and acts as a mediator for C–N bond forming reactions leading to carbazoles, N-aryl benzoxazinones and oxazoles. "Only stable in solution, not isolable.

Francke and co-workers advanced iodophenylsulfonates (83, 84) and iodo benzoates (85-87) as redox-active supporting electrolytes [79]. The ex cell reactivity of the corresponding I(III) compounds [ArI(OCH(CF₃)₂)] was evaluated by reaction with N-([1,1'-biphenyl]-2-yl)acetamide (81) to afford 1-(9H-carbazol-9-yl)ethan-1-one (82) (Figure 16). While both of the iodophenylsulfonate isomers 83 and 84 could be used as ex cell mediators for the intramolecular C–H amination reaction, iodo benzoate compounds 85-87 did not promote substrate oxidation to form carbazole 82.

Flow chemistry has also been advanced as an approach to achieve anodic synthesis of hypervalent iodine reagents and utilize them in ex cell substrate functionalization. Flow conditions offer advantages compared to mechanical stirring, such as better mixing, more efficient heat transfer, and easy scale-up [80]. Flow systems can be especially useful in industrial settings for energy conservation [81], multistep synthesis [82] or end-to-end production [83]. Wirth and co-workers have studied the synthesis and utilization of hypervalent iodine species via flow technology [84-87]. Symmetrical and unsymmetrical iodonium salts have been synthesized by Wirth and co-workers using a microreactor with two platinum electrodes separated by a thin film (250 mm) [84]. This method was later elaborated to achieve meta-selective C–H arylation of anilines in an end-to-end production [85].
More recently, Wirth and co-workers extended the scope of electrochemically derived hypervalent iodine reagents generated in flow by preparing [bis(hexafluoropropoxy)iodo]arenes and utilizing them in a wide range of substrate oxidation reactions including sulfide oxidation, oxidative heterocyclization, and α-functionalization of carbonyl compounds (Figure 17) [87].

![Figure 17](image)

Figure 17. Anodically generated bis-HFIP adduct under flow condition is used for various substrate functionalization reactions.

**C.2. Electrochemical Synthesis of Hypervalent Iodine(V) Reagents**

Anodic oxidation of 2-iodobenzoic acid (88) in 0.2 M H₂SO₄ aqueous solution with a boron-doped diamond electrode produced IBX (89) under potentiostatic electrolysis conditions [88, 89]. This system displayed potential-dependent product selectivity: Applied potentials between 1.6–1.8 V vs SCE resulted in the formation of 1-hydroxy-13-benzo[d][1,2]iodaoxol-3(1H)-one (9) while applied potentials above 1.8 V vs SCE yielded IBX (89) (Figure 18). The boron-doped diamond electrode was found to be important due to both its stability and the high overpotential for O₂ evolution at this electrode.

![Figure 18](image)

Figure 18. Electrochemical oxidation of 2-iodobenzoic acid (88) leads to both 1-hydroxy-13-benzo[d][1,2]iodaoxol-3(1H)-one (9) and 2-iodoxybenzoic acid (89) under constant potential electrolysis conditions.

**D. Recyclable Hypervalent Iodine Reagents**

In addition to developing more sustainable oxidation protocols for the synthesis of hypervalent iodine compounds, significant effort has been made to improve iodoarene recyclability. Separation of iodoarene byproducts from the desired reaction products is often tedious, and thus iodoarenes are not typically reused. Strategies based on polymer-supported hypervalent iodine compounds, which facilitate recovery via simple filtration, and based on fluorous alkyl iodoarenes, which facilitate recovery via biphasic separations with fluororous solvents, have been developed to enable iodoarene recycling. Here we highlight the synthesis and application of polymer-supported and fluorous I(III) and I(V) reagents.

**D.1. Synthesis of Polymer-supported Hypervalent Iodine(III) Reagents**

Poly[4-(diacetoxyiodo)styrene] (90) was first prepared by Okawara via iodination of polystyrene followed by oxidation with peracetic acid [90, 91]. The loading of I(III) centers on
the polystryrene backbone was determined to be 1.99 mmol/g by iodometry. In other examples, polystyrenes that display high molecular weight (poly-(diacetoxyiodo)styrene, ~45,000) and low molecular weight (poly-(diacetoxyiodo)(α-methylstyrene), ~6000) have been converted to the corresponding hydroxy(tosyloxy)iodine(III) polymers (91 and 92, respectively) by treatment with p-toluenesulfonic acid monohydrate [92, 93]. Alternately, iodinated polymers derived from coupling between poly[[aminomethyl]styrene] and either p-iodobenzoic acid or p-iodophenylacetic acid, were oxidized with \textit{in situ} generated peracetic acid to afford the polymer-supported (diacetoxyiodo)arenes (93 and 94, respectively) (Figure 19) [94]. In each of these cases, iodoarene recycling was achieved by simple filtration followed by a methanol wash of the polymer. In a similar context, highly insoluble small-molecule iodoarene mediators have also been demonstrated to be recyclable [95-98].

![Figure 19. Synthesis of polymer-supported (diacetoxyiodo)arenes using H$_2$O$_2$ and acetic anhydride. These reagents participate in ligand exchange chemistry in presence of p-toluenesulfonic acid to form tosylated I(III) reagents. These reagents can be recycled by simple filtration.

D.2. Synthesis of Polymer-Supported Hypervalent Iodine(V) Reagents

IBX is poorly soluble in many organic solvents, which often necessitates the use of dimethyl sulfoxide (DMSO) as a reaction solvent. In general, it is challenging to recover the corresponding I(III) byproduct (i.e., 9) from these reaction conditions [99, 100]. To alleviate the need for DMSO as solvent, Mülbaiere and Giannis developed silica-immobilized IBX reagent 95 (0.4 mmol/g) by tethering the appropriate iodoarene via a phenoxy linker (Figure 20) [101]. Oxidation to the corresponding immobilized I(V)-based material was accomplished with Oxone. Oxidation of alcohols was achieved in good yield by 95 in THF instead of DMSO, the solvent required for IBX-mediated alcohol oxidation. Polychloromethyl styrene- [102] and multiwalled carbon nanotubes (MWCNT)-supported for I(V) reagents (96 and 97, respectively) have also been synthesized [103]. Similarly, amide linkages have been used to prepare polymer-supported I(V) reagents 98-101 [104, 105].
Yakura and co-workers reported magnetic nanoparticle-supported iodoarene 103 for the catalytic oxidation of phenols 102 to form p-quinones 104 and demonstrated recovery by application of an external magnetic field (Figure 21a) [106]. Kirsch and co-workers also reported solid-supported iodoarene catalysts 106 and 107 and for catalytic oxidation of secondary alcohols 105 to ketones 108 in the presence of Oxone and demonstrated that the recovered catalyst was catalytically active up to 5 cycles (Figure 21b) [107]. For additional discussion of iodoarene catalysis, see Section E.

Fluorous hypervalent iodine reagents have also been developed to enable extraction-based recovery of iodoarene byproducts. Since the first synthesis of hypervalent iodine reagents with fluoroalkyl substituents in 1971 [108], these reagents have proved to be useful due to their high lipophobicity and hydrophobicity. In 2003, Gladysz and co-workers developed a series of hypervalent iodine reagents with fluoroalkyl substituents 110-113, which were prepared by
oxidation with NaBO₃·H₂O [109]. This family of hypervalent iodine reagents participated in the oxidation of hydroquinones 109 to generate p-quinones 114 (Figure 22). The resulting iodoarene byproducts displayed high fluorous-phase affinity, which facilitated separation and recycling.

Figure 22. Fluorous hypervalent iodine mediated oxidation of hydroquinone led to high yield of benzoquinone. Iodoarene byproducts were recovered by fluorous-phase extraction with CF₃C₆F₁₁.

In 2006 Gladysz and co-workers reported a family of hypervalent iodine reagents (115) derived from fluorous alkyliodides and applied them in alcohol oxidation chemistry (Figure 23a) [110]. Fluorous extraction enabled repeated use and recovery; three cycles achieved with high recovery of alkyliodides. More recently, polyfluorinated hypervalent iodine reagents have been utilized towards the synthesis of sulfoximines from sulfides under mild conditions [111, 112]. Wirth and co-workers developed oxidation of sulfides (116) with hypervalent iodine compound 117, catalyzed by Fe(acac)₃ in acetonitrile, to afford N-substituted sulfoximines (118) (Figure 23b) [111]. Using the (diacetoxyiodo)arene 119 and TPGS-750-M as a surfactant allowed for formation of N–H sulfoximines (120) from 116 in aqueous media (Figure 23c) [112].

Figure 23. Fluorous hypervalent iodine compounds can be utilized for the oxidation of (a) alcohols to ketones, (b) sulfides to N-substituted sulfoximines, and (c) sulfides to N–H sulfoximines.

E. Catalytic Application of Hypervalent Iodine Compounds

Hypervalent iodine catalysis utilizes selective in situ oxidation of substoichiometric amounts of iodoarenes to accomplish hypervalent iodine mediated substrate functionalization chemistry. Catalysis inherently reduces the iodoarene waste that is generated by hypervalent iodine reagents. The central challenge in achieving hypervalent iodine catalysis is the selective oxidation of the iodoarene catalyst in the presence of oxidatively labile substrates. Here we highlight recent progress in hypervalent iodine catalysis, and as above, organize the presentation by the nature of the terminal oxidant employed. The examples presented are not
exhaustive, but have been selected to highlight different approaches to achieving hypervalent iodine catalysis.

E.1.1 Catalytic Hypervalent Iodine(III) Reactions Using O₂

Miyamoto and co-workers developed iodoarene-catalyzed aerobic glycol cleavage and Hofmann rearrangement chemistry under isobutyraldehyde autoxidation conditions [113]. Using pentamethyliodobenzene (122) as catalyst, oxidative C–C cleavage of various diols (121) was achieved forming ketones 123 (Figure 24a). Notably, this aerobic oxidation condition was effective for glycol scission of cyclic trans-diols, which can be difficult to achieve using common oxidants like NaIO₄. The authors also carried out Hofmann rearrangement of carboxamides 124 to form carbamates 125 using the same catalysis conditions (Figure 24b). This was an improvement over existing protocols that use m-CPBA as the terminal oxidant because aromatic amides undergo background oxidation with m-CPBA to form N-oxides [114]. The reported hypervalent iodine catalysis can also be performed using air, in place of O₂, without significant decrease in yield.

Contemporaneously, Powers et al. utilized aerobically generated I(III) reagents (Figure 1) derived from acetaldehyde autoxidation in catalytic C–H amination, carbonyl α-functionalization, and spirocyclization reactions [23]. C–H amination was achieved using catalytic amount of 1,2-diiodobenzene (127) [115] with O₂ as the terminal oxidant to furnish N-methoxy-4-methyl-N-phenylbenzenesulfonamide (128) from benzene and amine 126 (Figure 25a). Similar reaction conditions resulted in aerobic bromination of ethyl acetoacetate (129) and aerobic spirocyclization of N-methoxy-3-(4-methoxyphenyl)propenamide (131) to form 130 and 132 respectively (Figure 25b-c). Control reactions in the absence of iodoarene did not furnish products in any of the reactions in Figure 25, which demonstrates that reactive intermediates from aldehyde autoxidation are not directly involved in substrate functionalization.
Utilization of aerobically generated hypervalent iodine(III) reagents are exemplified in the context of (a) C–H amination, (b) aerobic halogenation, and (c) spirocyclization using O₂ as terminal oxidant.

Similar aldehyde-promoted aerobic oxidation catalysis was reported by Sen and co-workers, who demonstrated the synthesis of substituted 1,3,4-oxadiazole 135 from N°-anilidene acetohydrazines 133 using 4-iodoanisole (134) as catalyst (Figure 26) [116].

E.1.2 Catalytic Hypervalent Iodine(V) Reactions Using O₂

In 2018, Powers and co-workers utilized in situ aerobic synthesis of (2-tert-butylsulfonyl)iodyln- benzene (21, Figure 4) from (2-tert-butylsulfonyl)iodobenzene (136) to accomplish hypervalent-iodine-catalyzed alcohol oxidation [28]. Secondary alcohols were oxidized to ketones, whereas primary alcohols were oxidized to carboxylic acids because initially generated aldehydes were further oxidized under aldehyde autoxidation conditions (Figure 27a). Oxidative C–C cleavage was observed for 1,2-diols, which is characteristic of the reactivity of Dess-Martin Periodinane (DMP) (Figure 27b).

E.2 Catalytic Hypervalent Iodine Reactions Using Peracid Oxidants

Peracid oxidants are among the most utilized terminal oxidants in hypervalent iodine catalysis. Use of peracetic acid as a terminal oxidant generates acetic acid as the only byproduct. While less oxygen dense, m-CPBA has also become a popular terminal oxidant in hypervalent iodine catalysis. Because 1) similar reactions have been accomplished using peracetic acid and m-
CPBA as terminal oxidants, and 2) the chemical structures of these reagents are similar, hypervalent iodine catalysis using either peracid will be presented together here.

**Carbonyl α-Functionalization.** Some of the first examples of hypervalent iodine(III) catalysis utilized iodobenzene as a catalyst and m-CPBA as the terminal oxidant to achieve the α-oxidation of carbonyl compounds (i.e., conversion of 137 to 138, Figure 28) [117]. Addition boron trifluoride diethyl etherate (BF₃·Et₂O), which was proposed to both induce the enolization of carbonyl starting materials and promote ligand exchange at the in situ generated (diacetoxyiodo)benzenes, was found to be essential for the α-acetoxylation. Following the discovery of α-acetoxylation of ketones by Ochiai and co-workers, several research groups have reported additional examples of α-acetoxylation [118], as well as α-tosyloxylation [119-121], α-phosphoryloxylation [122], and α-fluorination reactions [123, 124].

![Figure 28](image)

**Figure 28.** α-Functionalization of carbonyl compounds is exemplified by catalytic α-acetoxylation of ketones via hypervalent iodine intermediates generated using m-CPBA.

Catalytic enantioselective α-oxidation reactions can be accomplished with chiral iodoarenes and m-CPBA as the terminal oxidant. In 2007, Wirth and co-workers reported the first catalytic, enantioselective α-tosyloxylation of 137 using chiral iodoarene 139 with p-toluenesulfonic acid as the tosylate source to form 141 (Figure 29, condition a) [125]. In contrast to the previously developed method, which used stoichiometric chiral I(III) to accomplish enantioselective α-tosyloxylation and required a reaction temperature of −30 °C for optimum enantioselectivity [126], the catalytic reaction was performed at room temperature to overcome slow reaction kinetics (lower enantioselectivity was observed). The triazole-substituted chiral iodoarene catalyst 140 was later identified to provide similar α-tosyloxylation with higher yields as well as increased enantioselectivity (Figure 29, condition b) [127-131]. Enantioselective α-fluorination of carbonyl compounds has also been accomplished by using chiral iodoarenes and replacing the tosylate nucleophile with triethylamine hydrogen fluoride as fluorine source [132, 133].

![Figure 29](image)

**Figure 29.** Enantioselective α-tosyloxylation of ketones was achieved using iodoarene catalysts bearing chiral o-substituents (139 and 140). Triazole-based catalyst 140 was observed to provide increased enantioselectivity.

**Spirocyclization.** Hypervalent iodine catalysis has also been applied to oxidative spirocyclization chemistry (i.e., the conversion of phenol 142 to spirocycle 143, Figure 30a) [134]. Trifluoroacetic acid was found to improve the yield of spirocylized products, which was attributed to the in situ formation of the stronger oxidant [bis(trifluoroacetoxy)iodo]benzene (15). Enantioselective examples of spirocyclization of phenolic substrates has also been studied [135-137]. Kita and co-workers reported chiral iodoarene 146 bearing an ortho-substituted spirobiindane backbone [135], Ishihara’s group
developed a conformationally flexible C$_2$-symmetric iodoarene catalyst 147 [136], and Ibrahim and co-workers prepared C$_2$-symmetric iodoarene catalyst 148 [137], all of which promote the spirocyclization of substrate 144 to form 145 in good enantioselectivity (Figure 30b). Other catalysts including atropisomeric binaphthyl-based chiral iodides 149 have also been developed for similar spiro lactonization reactions [138-148].

Oxidative C–H Coupling Chemistry. In 2013, Kita and co-workers developed a hypervalent iodine-catalyzed oxidative cross-coupling reaction of aromatic sulfonanilides 150 with aromatic hydrocarbons to give the biaryl products 152 in high yields (Figure 31) [149]. While using iodobenzene as the catalyst resulted in low yields, 2,2$'$-diiodobiphenyl derivative 151 was found to be highly active towards the described C–C coupling chemistry.

Similarly, Gong and co-workers demonstrated intramolecular asymmetric oxidative C–C bond-forming chemistry, in the context of spirooxindole (155) synthesis from 153, using chiral iodoarene 154 as the catalyst (Figure 32) [150]. In 2017, a computational study by Sunoj and co-workers reasoned that the observed enantioselectivity is due to the helical fold of the chiral amide arms on the iodoarene catalyst at ortho-positions [148].
Asymmetric spirocyclization was achieved using chiral iodoarene catalyst 154 and peracetic acid as terminal oxidant.

Martin and co-workers reported a C(sp²)–O coupling reaction of biphenyl-2-carboxylic acids 156 in the presence of catalytic amounts of iodoarene 134 with peracetic acid as the terminal oxidant to form lactones 157 (Figure 33a) [151]. Previously, similar chemistry had been accomplished under the action of either Pt or Pd catalysts in tandem with stoichiometric hypervalent iodine(III) or Ag(I) terminal oxidants [152-158]. The authors also described formation of 160 via C(sp³)–O coupling of pyrrolobenzoxazinones 158 using 4-bromoiodobenzene (159) as the catalyst (Figure 33b) [151].

Iodoarene-catalyzed (a) C(sp²)–H and (b) C(sp³)–H functionalization of phenyl carboxylic acid derivatives resulted in the formation of corresponding C–O coupled lactone products.

A considerable amount of interest has focused on the development of hypervalent iodine catalysis for oxidative N–H / C–H coupling for both sp² and sp³ C–H amination [115, 159-163]. The Muñiz group reported intermolecular C–H amination (i.e., the conversion of amine 161 to arylated product 162) catalyzed by 1,2-diodobenzene (127), which was identified as an exceptionally efficient catalyst that could be used in as low as 3 mol% loading (Figure 34a) [115]. The high reactivity of the corresponding μ-oxo iodine(III) species 12 was reasoned to be due to the instability of the 5-membered μ-oxo ring. Recently, Kita’s group has also reported such reactivity using the 2,2’-diodo-4,4’,6,6’-tetramethyl-1,1’-biphenyl (163) as catalyst (Figure 34b) [164]. Similar to 12, the μ-oxo structure of the iodine(III) species generated from 163 results in high catalytic activity; catalyst loading as low as 0.5 mol% were found to be effective.

Hypervalent iodine-catalyzed C–H amination was achieved using (a) 1,2-diodobenzene (127) and (b) 2,2’-diodo-4,4’,6,6’-tetramethyl-1,1’-biphenyl (163) as catalysts and peracetic acid as terminal oxidant. These reactions are proposed to proceed through μ-oxo bis-iodine(III) intermediates (e.g. 12).

Difunctionalization of Unsaturated C–C Bonds.
Difunctionalization of olefins is one of the main classes of transformations available to hypervalent iodine compounds [165]. Achieving catalysis using peracid-based oxidants requires that the rate of iodoarene oxidation competes successfully without direct olefin epoxidation chemistry, which can be facile with peracid-based oxidants.

Oxygenation Reactions. Iodomesitylene (165) catalyzed syn-diacetoxylation of alkenes was performed using m-CPBA as terminal oxidant, forming vicinal diacetates (Figure 35a) [166]. These methods complement previous methods that have been developed with transition metal catalysts, including osmium [167], ruthenium [168, 169], manganese [170, 171], iron [172-174], and palladium [175, 176]. Muñiz and co-workers described an enantioselective diacetoxylation of styrenes using chiral iodoarene 168 and peracetic acid (Figure 35b) [177]. While the use of m-CPBA promoted significant epoxidation in this case, little background reaction was observed with peracetic acid as the terminal oxidant. The Muñiz group also demonstrated catalytic olefin diacetoxylation with iodoarene catalyst 171 bearing an o-pyridyl Lewis base, which proved to be kinetically superior to pervious acetoxylation methods (Figure 35c) [178]. In this case, other terminal oxidants including Selectfluor, perborate, and periodate were ineffective; only peracetic acid was found to be effective. Both activated and unactivated olefins were diacetylated in good yields with 171, and the increased reactivity was attributed to the stabilizing effect of pyridyl group on electrophilic iodine centers [179-181].

Fluorination Reactions. In 2016, Jacobsen and co-workers reported the enantioselective 1,2-anti-difluorination of alkenes with iodoarene catalyst 173, m-CPBA as terminal oxidant, and an excess of Py·9HF as fluoride source (Figure 36a) [182]. The developed method is applicable to various substituted alkenes including terminal, internal, and acrylamide olefins. In the case of isolated alkenes, addition of pyridine afforded improved yields, presumably due to reduced acidity and increased nucleophilicity of fluoride ions in the reaction medium. In the same year, the Jacobsen group also reported a method for the catalytic, asymmetric, migratory geminal difluorination of β-substituted styrenes to access products bearing difluoromethylated tertiary or quaternary stereocenters using a chiral iodoarene catalyst 176 (Figure 36b) [183].
Asymmetric (a) vicinal difluorination and (b) gem difluorination of alkenes via chiral hypervalent iodine catalysis were achieved using m-CPBA as the terminal oxidant.

**Amination Reactions.** Iodoarene derivatives with modified chiral lactic acid side chains have emerged as effective catalysts for intermolecular diamination reactions [184]. The first hypervalent iodine-catalyzed enantioselective intermolecular diamination (i.e., the conversion of 167 to 179) was reported by the Muñiz group using iodoarene catalyst 178 (Figure 37). Background epoxidation/aminooxygenation reactions of alkenes by m-CPBA were reduced by changing the solvent from ethyl acetate to methyl tert-butyl ether (MTBE) or MTBE/HFIP mixtures, and by lowering the reaction temperature to −5 °C. With a 10 mol % catalyst loading the reaction provided 40-87% yield and up to 98% ee.

**Oxidative Cleavage Reactions.** In 2009, Miyamoto and Ochiai developed an efficient method for iodoarene-catalyzed oxidative cleavage of carbon–carbon multiple bonds as an alternative to ozonolysis [185]. Under these conditions, various unsaturated compounds such as cyclic alkenes, acyclic alkenes, and aryl acetylenes are selectively cleaved to afford carboxylic acids (Figure 38).

**E.3 Catalytic Hypervalent Iodine Reactions Using Oxone**

Although the active oxygen content of Oxone, in which the active oxidant is the peroxymonosulfate anion (HSO₅⁻), is lower than that of O₂ or H₂O₂, it offers several advantages, including stability, ease of transport, simple handling, controllable addition, and is nontoxic [186]. Oxone is prepared from a mixture of H₂SO₄, H₂O₂ and potassium hydroxide (KOH) [187]. Both iodine(III) and iodine(V) species can be generated from iodoarene oxidation with Oxone.
E.3.1 Catalytic Hypervalent Iodine(III) Reactions Using Oxone

Hypervalent iodine-catalyzed oxidation of phenols using Oxone as the terminal oxidant has been widely studied. Yakura and co-workers reported iodoarene (183) catalyzed oxidation of phenolic derivatives to form p-quinones 184 (Figure 39a) [188-190], and p-quinols 186 (Figure 39b) [191, 192], depending on the substituents at para-positions of 182 and 185 respectively. It was hypothesized that the in situ generated I(III) intermediates react with phenolic compounds to form a cationic intermediate, which is then trapped by H2O to form the desired quinols.

![Figure 39. 2-(4-iodophenoxy)acetic acid (183) catalyzed oxidation of phenolic derivatives provided access to (a) p-quinones and (b) p-quinols with Oxone as the terminal oxidant.

Zhdankin and co-workers demonstrated hypervalent iodine-catalyzed Hofmann rearrangements, which had been previously accomplished by Ochiai and co-workers using m-CPBA as the terminal oxidant [114], could also be accomplished using Oxone as the terminal oxidant (Figure 40a) [193]. Using similar reaction conditions with 3,5-dimethyliodobenzene (188) as the catalyst, Zhdankin and co-workers reported cyclization of oxime 187 with alkenes or alkynes to form isoxazolines 190 or isoxazoles 191 (Figure 40b) [194]. In these reactions, in situ generated iodine(III) reagents oxidize oximes into nitrile oxides 189, which then undergo [3+2] cycloaddition with alkenes or alkynes to form the corresponding heterocycles. Synthesis of substituted oxazoles 193 via cycloisomerization-amination reactions of N-propargyl carboxamides 192 was also realized utilizing in situ generated I(III) intermediate by Oxone (Figure 40c) [195].
Oxone is often used as the terminal oxidant for various hypervalent iodine-catalyzed reactions such as (a) Hofmann rearrangement of amides, (b) [3+2] cycloaddition of alkenes or alkynes with in situ generated nitrile oxide, and (c) cycloisomerization-amination reactions of N-propargyl carboxamides.

E.3.2 Catalytic Hypervalent Iodine(V) Reactions Using Oxone

The first example of I(V) catalysis was reported by Vinod and co-workers in 2005, who reported oxidation of primary and secondary alcohols to carboxylic acids and ketones, respectively, by the in situ generation of IBX (89) from 2-iodobenzoic acid (88) using Oxone as the terminal oxidant (Figure 41) [196]. 1,2-Diols were also cleanly oxidized to corresponding dicarbonyls without oxidative C–C cleavage. Control reactions in the absence of catalyst resulted in no product formation.

The Ishihara group reported oxidation of primary and secondary alcohols with iodosylphenylsulfonate 194 as the catalyst (Figure 42a) [197]. It is noteworthy that a significantly lower catalyst loading (as low as 1 mol%) was achievable with sodium 2-iodobenzenesulfonate (194) to generate 2-iodoxysulfonic acid (IBS), which is an analogue of IBX. It was proposed that IBS might have had greater catalytic activity since the iodine(V) center has higher Lewis acidity than that of IBX due to a strong electron withdrawing sulfonate group in the ortho-position. Also, the oxidative rearrangement of tertiary alcohols with sodium 5-methyl-2-iodobenzenesulfonate (196) as catalyst was accomplished to form enones with Oxone as the terminal oxidant (Figure 42b) [198].
Iodoarene-catalyzed (a) oxidation of primary and secondary alcohols and (b) rearrangement of tertiary alcohols were performed using Oxone as the terminal oxidant. Selective oxidation of primary alcohols to aldehydes was observed. In contrast to the I(III)-mediated oxidation of phenolic derivatives in presence of Oxone, which gave rise to 1,4-quinones (section E.3.1) [188-190], 5-methyl-2-iodobenzenesulfonate (196) catalyzed oxidation of phenols leads to selective ortho-oxidation to form 1,2-quinones via corresponding I(V) intermediate (Figure 43a) [199]. Although the reason for the selectivity remained unclear, a mechanism was proposed where the phenol-iodine(V) adduct underwent [2,3]-sigmatropic rearrangement to give the resulting 1,2-quinones. This reaction was further expanded to effect the formation of o-quinols (202 and 203) catalyzed by sodium 4,5-dimethyl-2-iodobenzenesulfonate 201 from ortho-substituted phenols 200 (Figure 43b) [200]. The introduction of a trialkylsilylethyl substituent at the 2-position in this case further improved the reaction rate and selectivity for monomeric quinol product 202 over the dimerized product 203.

E.4 Catalytic Hypervalent Iodine Reactions Using Electrophilic Halides

Electrophilic halogen-based reagents, such as Selectfluor and N-bromosuccinimide (NBS), can act as terminal oxidants in hypervalent iodine catalysis. While Selectfluor oxidation generates (difluoroiodo)arenes, which are stable to isolation [201], NBS oxidation affords (dibromoiodo)arenes, which are not generally stable to isolation (the presence of ortho-substituents that are Lewis basic can stabilize cyclic bromo-I(III) reagents) [202]. Among the oxidants discussed here, electrophilic halides are the least atom economical; the reduced
products of Selectfluor and NBS are 1-chloromethyl-1,4-diazabicyclo[2.2.2]octane and succinimide, respectively.

E.4.1 Catalytic Hypervalent Iodine(III) Reactions Using Electrophilic Halides

(Difluoroiodo)arenes, generated in situ by the combined action of Selectfluor and hydrofluoric acid, have been applied in fluorination reactions. Moran and co-workers described the hypervalent iodine-catalyzed cyclization of N-allylamides to the corresponding oxazoline compounds with five- to seven-membered rings using o-iodoanisole (205) as catalyst (Figure 44a) [203]. Saito and co-workers demonstrated metal-free and catalytic fluorinative cyclization of N-propargyl amides to form substituted oxazoles with a similar catalysis strategy (Figure 44b) [204].

![Figure 44](image)

Figure 44. (a) Cyclization of N-allylamides in presence of Selectfluor and o-iodoanisole (205) furnished corresponding hydroxy substituted oxazoline compounds. (b) Addition of fluoride source such as pyridine hydrogen fluoride to the previous reaction condition leads fluorocyclized products 208.

Diffucionalization of olefins can also be achieved with Selectfluor as the terminal oxidant. In 2016, Muñiz and co-workers developed an enantioselective styrene diacetoxylation reaction using chiral iodoarene 209 as catalyst (Figure 45a) [205]. The use of Selectfluor as the terminal oxidant avoided background reactions, such as epoxidation, that were observed with peracid-based oxidants. In addition, oxidation by Selectfluor generates aryfluoriodonium species that have a more electrophilic iodine(III) center and is highly reactive towards olefins compared to other hypervalent iodine reagents like PhI(OAc). Gilmour and co-workers elaborated on the developed method to achieve vicinal dichlorination of alkenes (i.e., the conversion of 164 to 210) by in situ generation of 4-(dichloriodo)toluene (32) from the I(III) fluoride species via ligand exchange reaction with cesium chloride (CsCl) (Figure 45b) [206].

![Figure 45](image)

Figure 45. Selectfluor is used as a terminal oxidant for iodoarene-catalyzed (a) diacetoxylation and (b) vicinal dichlorination of alkenes.

NBS has been used for in situ generation of (dibromoiodo)arenes, which are efficient in bromine transfer to alkenes or arenes. Braddock and co-workers reported the in situ synthesis of cyclic brominated hypervalent iodine intermediates from a variety of ortho-substituted iodoarenes (e.g. 213-217), and found that amidine 213 was superior in the synthesis of bromolactones 212 from alkenecarboxylic acids 211 (Figure 46) [202]. Although molecular bromine has better atom economy, it failed to give rise to the formation of the expected bromoiodinane species. Instead, NBS was found to be a suitable reagent for such
transformation in good yields. Increased reaction rate and yields were obtained by increasing the nucleophilicity of the ortho-substituents of the iodoarene.

Figure 46. Bromocyclization of alkenecarboxylic acids to bromolactones was realized using (E)-2-iodo-N,N'-diphenylbenzimidamide (213) as catalyst and Selectfluor as terminal oxidant.

Gulder and co-workers expanded the utility of olefin functionalization catalyzed by iodoarenes using NBS as the terminal oxidant to access bromination reactions with 2-iodobenzamide derivatives 219 and 222 as the catalysts. Specifically, 1,2-dibromination of alkenes (i.e., the conversion of 218 to 220, Figure 47a) [207] and bromocyclization of methacrylamide derivatives (i.e., the conversion of 221 to 223, Figure 47b) [208] were accomplished by the iodoarene catalysts 219 and 222, respectively. In a similar fashion, iodoarene-catalyzed bromination followed by rearrangement of N-alkyl derivatives 224 was performed to access \( \alpha, \alpha \)-dialkylated \( \alpha \)-alkanoate carboxylamides 225 (Figure 47c) [209] as well as the cascade bromination/rearrangement/cyclization reaction to generate \( \beta \)-lactams 227 from 226 (Figure 46d) [210]. The generation of bromobenziodoxolone 228, from 2-iodobenzamide 222 and NBS, was observed by NMR spectroscopy and ESI-MS experiments, and was proposed to be the active brominating reagent in these transformations.

Figure 47. Hypervalent iodine-catalyzed substrate functionalizations with NBS as the terminal oxidant are exemplified in the context of (a) 1,2-dibromination of alkenes, (b) bromocyclization of methacrylamide derivatives, (c) bromination/rearrangement, and (d) cascade bromination/rearrangement/cyclization of N-alkyl imide derivatives. Formation of brominated hypervalent iodine intermediates is proposed in these transformations.
**E.5 Hypervalent Iodine Electro catalysis**

As discussed in the context of electrochemical synthesis of hypervalent iodine reagents, *ex cell* methods require the stoichiometric generation of hypervalent iodine species, which obviates many of the potential advantages of electrochemistry vis-à-vis sustainability. *In cell* electrocatalytic methods, in which hypervalent iodine species are generated *in situ* during substrate functionalization, can be limited by the significant overpotential that is often required to anodically oxidize many iodoarenes, however, strategies to enable electrocatalysis have begun to emerge.

**E.5.1 Catalytic Hypervalent Iodine(III) Electro catalysis**

In 1994, Fuchigami and co-workers reported *in cell* utilization of hypervalent iodine intermediates to accomplish 1,1-difluorination of dithioketals (*i.e.*, the conversion of 229 to 230, Figure 48) [56]. As discussed in section C.1, Fuchigami and co-workers were only able to electrosynthesize 4-(difluoroiodo)nitrobenzene upon anodic oxidation of 4-iodonitrobenzene in Et₃N·5HF (Figure 11). Since the oxidation peak potential of 4-iodonitrobenzene (2.3 V vs SCE) was higher than the potential required for the oxidation of dithioketals (2.1-2.2 V vs SCE), 4-iodoanisole was used as an electrocatalyst (1.9 V vs SCE), and resulted in selective iodoarene oxidation to form the reactive 4-(difluoroiodo)anisole (231) *in situ*.

![Figure 48](image)

*Figure 48.* The first example of hypervalent iodine electrocatalysis was reported in the context of the difluorination of propane-1,3-dithiol protected carbonyl compounds 229 under constant potential conditions.

In 2019, Ackermann and co-workers reported an electrochemical co-catalytic system based on iodobenzene (1) and Ru-compound 233, for the directed C–H hydroxylation of 232 to give 234 (Figure 49) [211]. The iodine(III)/ruthenium(II)-electrocatalyzed C–H functionalization was enabled by the electrochemical generation of hypervalent iodine(III) reagents. Complementary computational work indicated that the oxidation potential of iodobenzene is 200 mV lower than that of the ruthenium(II/IV) manifold, and most likely goes through anodically generated hypervalent iodine intermediates [212]. Replacement of applied potential with other oxidants, like *m*-CPBA or Oxone, under these reaction conditions, resulted in considerably inferior yield (15% and 32% respectively).

![Figure 49](image)

*Figure 49.* Iodoarene and Ru co-catalyzed C–H hydroxylation of benzamide derivatives.

In 2020, Powers and co-workers developed hypervalent iodine electrocatalysis for intra- and intermolecular C–N bond-forming reactions [213]. In the intramolecular carbazole formation, either iodoarene catalyst 134 or 163 was used depending on the substrate (Figure 50a). 4-
Iodoanisole was selected for its low onset potential and was successfully used as an electrocatalyst for electron-neutral or slightly electron-poor substrates. For more electron-poor substrates, bearing nitro- or carbonyl substituents, the more oxidizing iodoarene 163 was employed as catalyst in potentiostatic electrolysis at 1.9 V vs Ag⁺/Ag. Electron-rich substrates with methyl or methoxy substituents underwent unselective anodic oxidative degradation due to lower onset potentials compared to iodoarene catalyst. Intermolecular C–H amination was also achieved between N-(1,3-dioxoisindolin-2-yl)acetamide 161 and arenes using iodoarene 163 as catalyst (Figure 50b). The absence of an oxidation peak in the cyclic voltammogram (CV) for amine 161 at the high potentials required to oxidize iodoarene 163 allowed for its in cell utilization. Control experiments in the absence of iodoarene, acetate, or HFIP resulted in no desired products. Titration of increasing acetate concentration to iodoarene resulted in CVs with decreased reversibility and increased current response, which is indicative of trapping anodically generated I(II) intermediate by acetate ion and subsequent oxidation to I(III) intermediate (Figure 50c).

![Figure 50](image)

Figure 50. Anodically generated hypervalent iodine intermediates were used in (a) inter- and (b) intramolecular C–H amination reactions. (c) Stabilization of in situ generated I(II) intermediate (237) by acetate anion was proposed to enable hypervalent iodine electrocatalysis.

**F. Conclusion**

Hypervalent iodine compounds are an important class of oxidants in synthetic chemistry. Use of hypervalent iodine reagents is often not highly atom economical due to the low active oxygen content of these species. Advances in the sustainable synthesis of these reagents promise to impact the sustainability of the substrate functionalization reactions that can be affected by these compounds. Here, we have discussed advances in the use of environmentally benign oxidants such as O₂ and H₂O₂ in the preparation of hypervalent iodine species. In addition, significant progress has been made towards the electrochemical oxidation of iodoarenes, which avoids the need for stoichiometric terminal chemical oxidants. Polymer-supported and fluorous hypervalent iodine compounds have emerged as recyclable platforms that could reduce the waste associated with stoichiometric application of these reagents. More recently, the development of hypervalent iodine catalysis promises to significantly impact the sustainability of reaction chemistry effected at the hypervalent iodine center by enabling use of substoichiometric iodoarene loading. To fully realize the potential of hypervalent iodine catalysis, new approaches to achieving selective oxidation of iodoarenes in the presence of oxidatively labile substrates is critical. Ongoing efforts to better define the mechanistic
alternatives available for the synthesis of these species promises to impact the ongoing development of aerobic and electrochemical strategies to hypervalent iodine compounds and catalysis.

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