Hypervalent Iodine Reagents in the Total Synthesis of Natural Products†

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† Dedicated with deep respect to Prof. Dr. R. A. Pilli.
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1. Introduction

The total synthesis of biologically active natural products has a central role in science.\textsuperscript{1-20} Presently, nearly any highly complex target can be obtained through chemical synthesis, providing enough resources are available. However, many advances are still necessary to furnish the required molecule in the desired quantity and short time without generation of toxic waste.\textsuperscript{2,5-8,11,14,18,21} Hypervalent iodine reagents are particularly important in this scenario, as they, are efficient alternatives to toxic and expensive heavy metals for a large range of transformations.

Iodine(V) reagents, e.g. Dess-Martin periodinane (DMP) and 2-iodoxybenzoic acid (IBX), mediate the oxidation of alcohols to aldehydes under mild conditions, as well as various oxidative transformations of other functional groups (Figure 1). Iodine(III) compounds with two heteroatom ligands, e.g. (diacetoxyiodo)benzene (DIB) and hydroxy(tosyloxy)iodo]benzene (HTIB), react with alkenes and phenols, and are also employed in $\alpha$-functionalization of carbonyl compounds and several rearrangement reactions. Iodine(III) reagents with two carbon ligands, e.g. diaryliodonium salts, are mainly employed in C-C bond formation reactions by transfer of one of the carbon ligands.

\textbf{Hypervalent Iodine(V) Reagents:}

\begin{align*}
\text{Dess-Martin Periodinane (DMP)} & \quad \text{2-Iodoxybenzoic acid (IBX)} \\
\text{(Diacetoxy)iodobenzene (DIB, PIDA, BAIB)} & \quad \text{[Bis(trifluoroacetate)]iodobenzene (BTI, PIFA)} \\
\text{[Hydroxy(tosyloxy)iodo]benzene (HTIB, HTI, Koser's Reagent)} &
\end{align*}

\textbf{Hypervalent Iodine(III) Reagents:}
The chemistry of hypervalent iodine compounds has been reviewed several times in the last years. However, there is no broad and recent review on applications in the total synthesis of natural products. This review aims to illustrate recent applications of hypervalent iodine compounds in the total synthesis of natural products, giving a panorama of the most important reactions in this area. Due to the vast amount of literature available on this topic, the review is not comprehensive, and focuses mainly on syntheses published in 2008-2010.

1.1. Structure and Reactivity of Hypervalent Iodine Reagents

Hypervalent iodine(III) compounds have a T-shaped structure, where the aryl group and the two free electron pairs are in equatorial positions. The two ligands have apical positions (Figure 2a) and share a hypervalent bond (3 center-4 electron bond) with the iodine. Iodine(V) compounds have four ligands and two orthogonal hypervalent bonds (Figure 2b). The non-bonding orbital of the hypervalent bond has a node on iodine (Figure 2c), which distributes the electrons to the ligands and renders the iodine electrophilic.

Thus, hypervalent iodine reagents generally react with various nucleophiles by initial Nu-I bond formation with release of one of the ligands (Scheme 1). Subsequent reductive elimination by ligand coupling, or nucleophilic substitution by the free ligand anion, yields the product Nu-L and...
releases ArI. The mechanism for this process depends on the nucleophile, the nature of the ligand and the reaction conditions. Hypervalent iodine reagents are also good one electron acceptors, and SET mechanisms are observed under certain reaction conditions.

$$\text{Ar}^+ + \text{Nu} \rightarrow \text{ArI} + \text{Nu}^-$$

Scheme 1

Hypervalent iodine reagents are very reactive due to their highly electron deficient nature and the facile reductive transformations involved in their reactions with nucleophiles (Ar-IL$_2$→ArI or Ar-IL$_4$ → Ar-IL$_2$). The leaving group ability of iodine(III) compounds is $10^6$ times higher than that of triflate, and they can be therefore classified as hypernucleofuges.

2. Oxidation of Alcohols

The oxidation of alcohols to aldehydes or ketones is a pivotal transformation in organic chemistry and hypervalent iodine reagents play an important role in this reaction. The iodine(V) reagents DMP and IBX are among the best reagents for this functional group transformation in complex molecules. The combination of the iodine(III) reagent DIB and a nitroxy radical is also a powerful method.

2.1. Oxidations using DMP

DMP is the most common hypervalent reagent for the oxidation of alcohols. It is moisture sensitive and should be handled and stored under anhydrous atmosphere. DMP does not appear to be impact sensitive but explodes violently when heated, thus limiting its use to small scale reactions. The first step in DMP-oxidations is the displacement of an acetate group by the
alcohol. The α-proton of the alcohol is subsequently removed by acetate (internal or external) to form the desired carbonyl compound together with an iodine(III) side product (Scheme 2).

![Scheme 2](image-url)

Oxidations using DMP are typically performed in dichloromethane. NaHCO₃ or pyridine is often added to trap the acid released in the oxidation. This reaction tolerates a wide range of functional and protecting groups (Table 1 and Table 2). During the synthesis of (−)-biyouyanagin A, the oxidation of an alcohol bearing an α-diazo-β-ketoester moiety was reported (Scheme 3).⁷⁵,⁷⁶ Another example is the oxidation of an alcohol possessing an enol ether functionality, as described by Deslomchamps in the total synthesis of (+)-cassaine (Scheme 4).⁷⁷,⁷⁸ The oxidation of a complex substrate bearing a primary alcohol has been described by Hirama and co-workers (Scheme 5).⁷⁹

**Table 1. Examples of Functional Groups in Oxidations with DMP.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Functional Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMP, CH₂Cl₂</td>
<td>alkenes,⁸³,⁸⁶ dienes,⁹¹,92,97,99-102 αkynes,⁸⁷,96,104,105 ethers,⁹⁰,92,94,98,101,106 secondary allylic alcohols,ⁱ¹⁵ tertiary alcohols,⁸³,94,106,116-120 ketones,⁹⁷,¹⁰⁷ esters,⁹⁴,95,101,112,113,117,120-122 carbamates,⁸⁸,123 lactones,⁸⁴,87,109,119,124 α,β-unsaturated ketones,⁹²,125,126 α,β-unsaturated ketones,⁹²,125,126</td>
</tr>
</tbody>
</table>
unsaturated esters, α,β-unsaturated lactones,  α diazo-β-ketoesters, boronic esters, halides (aliphatic, vinylic), azides, tertiary amines, furanes, phosphonates, acetics, epoxides, acetals, and oxazolidinones.

Table 2. Examples of Protecting Groups in Oxidations with DMP.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Protecting Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMP, CH₂Cl₂</td>
<td>ROTBS, 90-92,117,119,126, α,β-unsaturated lactones, 85,87,89,102,103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROTES, 95,101,104,170,178</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROTBDPS, 78,101,104,114,116,183</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROAc, 95,113,115,138,173,184</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROBz, 90,94,123,170</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROMOM, 78,105,107,169,183,187</td>
</tr>
<tr>
<td>2</td>
<td>DMP, CH₂Cl₂, NaHCO₃</td>
<td>alkynes, 143-145, aldehydes, 92, α,β-unsaturated ketones, 92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-hydroxy esters, 168, amides, 166, lactones, 161, α,β-unsaturated lactones, 92, macro lactones, 114, lactams, 168, carbamates, 98, amines, 168, alkyl halides, 84, phosphates, 165, azides, 165, acetals, 81, 88, 106, 160, and sulfides, 81, and epoxides, 84</td>
</tr>
</tbody>
</table>
Bec: 2-bromoethyl carbonate, EE: ethoxyethyl acetal

**Scheme 3**
Although DMP tolerates several functional groups, Grieco and Piñeiro-Nuñez reported that the oxidation of a hydroxy carboxylate intermediate (formed by ring opening the corresponding lactone) was best performed with the less popular fluorinated iodine(V) compound. This IBX analogue generates only water during the oxidation, while DMP releases acetic acid. When DMP was applied the required keto ester was obtained in only 60%, with 40% of the starting lactone recovered (Scheme 6).
In the inspiring review by Nicolaou and Baran about the synthesis of CP molecules, examples of DMP oxidations are discussed. A key issue in this synthesis was the preparation of a γ-hydroxylactol, which could only be performed under relatively harsh conditions, i.e. with 5 equiv of DMP in benzene at 80 °C (Scheme 7).
An important feature of DMP oxidations using is the possibility to prepare aldehydes and ketones bearing an α-stereocenter without epimerization or racemization (DMP/CH$_2$Cl$_2$)\(^{91,93,97,98,103,114,121,123,132,137,156,174,184,185,188,192,195,198}\). This was exemplified in the oxidation of a diol to the corresponding dicarbonylic derivative in the synthesis of (+)-peloruside A (Scheme 8).\(^{212}\) Another example was reported by Dai and co-workers, who formed a ketone bearing stereocenters on both α-carbonyl positions in the synthesis of amphidinolide T2 (Scheme 9).\(^{147}\) Analogous examples have been reported in the synthesis of (−)-callystatin A\(^{102}\) and nakiterpiosin. In the latter case the reaction was performed in the presence of H$_2$O (Scheme 10).\(^{213,214}\) Water has also been used in other total syntheses using DMP in CH$_2$Cl$_2$,\(^{97,121,122,215}\) because it accelerates the reaction.\(^{73}\)
Scheme 8

Scheme 9
Treatment of diols with excess DMP leads to the corresponding dicarbonylic derivatives, as reported in the synthesis of (+)-clavolonine (3 equiv DMP, CH₂Cl₂, rt, 2 h), auripyrones A and B (4 equiv DMP, CH₂Cl₂, rt, 20 min), echinopines A and B (4 equiv DMP, 16 equiv NaHCO₃, CH₂Cl₂, 25 °C, 2 h), and cylindrocyclophane A (5 equiv DMP, 10 equiv NaHCO₃, CH₂Cl₂, 23 °C, 1 h). However, the oxidation of substrates bearing two or more alcohol moieties can be performed chemoselectively. Some recent examples reported in the context of total synthesis are shown herein. In one of the last steps of the total synthesis of (+)-azaspiracid-1, the chemoselective oxidation of a primary alcohol in the presence of a secondary was performed at 0 °C with a large excess of oxidant (Scheme 11). The low temperature is critical in this transformation, because at room temperature the C20 secondary alcohol is also oxidized. Another selective oxidation of a primary alcohol is given in studies toward the synthesis of azithromycin (Scheme 12). During the synthesis of (−)-englerin A, the chemoselective oxidation of a secondary alcohol was achieved in the presence of a more hindered one (Scheme 13).
Scheme 11

1) TBAF, THF, 0 °C
2) 20 equiv DMP, CH₂Cl₂, pyr
0 °C, 3 h
3) NaIO₄, NaH₂PO₄·H₂O
2-methoxyethanol, t-BuOH

84%

(+)-Azaspiracid-1
Scheme 12

1.2 equiv DMP
5 equiv ppy
CH3Cl, 0 °C, 2 h
yield for the single step not reported

Scheme 13

0.9 equiv DMP
3 equiv NaHCO3
CH2Cl2, 0 °C to rt.

(8)-Englerin A
2.2. Oxidations using IBX

IBX is another hypervalent iodine reagent highly used in the oxidation of alcohols.\textsuperscript{66} The first step in these oxidation reactions is a fast pre-equilibrium, which can be formally considered as a ligand exchange process (hydroxy \pm alklyoxy) on the iodine atom. A hypervalent twist, which is considered the rate limiting step, then takes place. Finally, the intermediate disproportionates to the carbonyl derivative and the iodosoarene IBA (Scheme 14).\textsuperscript{67,216} The preparation and application of polymer-supported IBX in oxidation reactions has been described.\textsuperscript{217,218} IBX immobilized in the ionic liquid [bmim][Br] was used in the oxidation of alcohols and in the dehydrogenation of ketones (cf. section 4.1).\textsuperscript{219}

![Scheme 14](image)

Although IBX was first synthesized in 1893, its use in synthetic organic chemistry has intensified only in the last two decades.\textsuperscript{220-223} IBX is cheaper and more stable than DMP, but it is explosive (on heating > 200 °C and on impact)\textsuperscript{66,224} and light-sensitive.\textsuperscript{225} Several functional and protecting groups are tolerated in IBX oxidations (Table 3). However, during the total synthesis of baconipyrene C, the elimination of a pivaloate protecting group and hydrolysis of an acetal has been observed (cf. Scheme 80).\textsuperscript{226}

Table 3. Examples of Functional and Protecting Groups in IBX-Oxidations.
IBX is not soluble in many organic solvents and the typical oxidation takes place in DMSO at room temperature. However, the oxidation of alcohols with IBX has been described using other procedures. Some examples in the total synthesis of natural products are:

i) The oxidation of a chiral primary alcohol with IBX in DMSO in the presence of 4Å molecular sieves at room temperature gave an aldehyde bearing an α-stereocenter.

ii) Ethyl acetate is an alternative solvent for IBX oxidations when reactions are performed at reflux. The oxidation of a primary alcohol has been described using 2 equivalents of IBX in EtOAc at reflux for 2 h. In the synthesis of pluraflavin A by Danishefsky and his group, a secondary alcohol was also oxidized with 3.5 equivalents of IBX in EtOAc; the mixture was capped under argon and heated at 90 ºC for 6 h. The preparation of a dialdehyde was achieved by the reaction of a bis-benzylic alcohol with 8.5 equivalents of IBX in EtOAc at reflux. In the synthesis of all stereoisomers of phenatic acid B, the oxidation of a secondary alcohol was accomplished with 2 equivalents of IBX in refluxing EtOAc for 20 h. In the formal synthesis of palmerolide A, primary alcohols were oxidized to the corresponding aldehydes using 1.3 to 1.5 equiv of IBX at reflux in EtOAc for 6 h. The crude aldehydes were used in Wittig or Horner-Wadsworth-Emmons
The oxidation of a primary allylic alcohol was reported using 2.5 equiv of IBX in refluxing EtOAc for 4 h during the total synthesis of (−)-englerin A.\textsuperscript{151}

iii) A mixture of DMSO with another solvent was used in some examples. A 1:1 mixture of DMSO/THF was employed in the synthesis of (−)-amphidinolide K (Scheme 15).\textsuperscript{171} Another possible mixture is DMSO/CH\textsubscript{2}Cl\textsubscript{2} (1:1), which was used in the oxidation of a secondary alcohol in the synthesis of ciguatoxin.\textsuperscript{231} In the synthesis of (−)-erinacine E, a 1:4 mixture of DMSO/CH\textsubscript{2}Cl\textsubscript{2} was employed.\textsuperscript{227} The oxidation of an allylic alcohol to the corresponding enone was performed with IBX in a 2:1 mixture of toluene/DMSO during the synthesis of (+)-chamaecyparosin C by Porco.\textsuperscript{230}

iv) The oxidation of an alcohol with IBX has been performed in refluxing benzene in a sealed pressure tube. In this case, an intramolecular conjugate addition took place after the formation of the enone moiety (Scheme 16).\textsuperscript{240}

v) The transformation of a diol into the corresponding dialdehyde has been performed using 2.4 equiv of IBX in MeCN at 80 °C in the total synthesis of baconipyrone A, baconipyrone C, and siphonarin B (Scheme 16).\textsuperscript{226}

Scheme 15
Like DMP, IBX has been used in the oxidation of chiral primary alcohols, which delivered aldehydes bearing an \( \alpha \)-stereocenter without epimerization problems\(^{171,194,220,235,244}\) (Scheme 15 and Scheme 18).\(^{234}\)
The oxidation of a secondary alcohol and an anisole moiety to the desired keto quinolide derivative has been described in 66% yield by Nicolaou, Chen and co-workers using excess of IBX in DMSO during the synthesis of (-)-hopeahainol A and (-)-hopeanol (Scheme 19).\textsuperscript{232,247} Reagents unable to perform this transformation included DMP, PCC, SO\textsubscript{3}-py, DDQ, and CAN.\textsuperscript{247}
A popular way to prepare carboxylic acids from primary alcohols is the oxidation with DMP\cite{189} or IBX\cite{171,172,233} to the corresponding aldehyde, which is then oxidized to the acid using NaClO$_2$ (Pinnick oxidation), as exemplified in the synthesis of (+)-azaspiracid-1 (Scheme 11) and (−)-penifulvin A (Scheme 20).\cite{235}
The oxidation of alcohols with IBX can be chemoselective. For example, after deprotection of an acetonide, an allylic alcohol was selectively oxidized with the unactivated alcohol untouched, giving the corresponding enone as product (Scheme 21).

The oxidation of a diol to the corresponding diketone can be difficult. One recent example of this transformation has been described by Nicolaou and his group in studies toward the synthesis of vannusals A and B (cf. Scheme 25). Among the oxidants tested under different conditions (PCC, DMP and TPAP-NMO), only IBX in DMSO promoted the desired oxidation (Scheme 22).
The handling of IBX and of DMP requires caution, because these compounds and their derivatives may explode. Quideau and co-workers developed a formulation consisting of benzoic acid (22%), isophtalic acid (29%), and IBX (49%). This non-explosive white power formulation was denominated SIBX (Stabilized IBX) and is a safe alternative to IBX. During the total synthesis of wasabienone B₁ (cf. Scheme 40), the same research group applied this commercially available reagent in the oxidation of a secondary alcohol, affording the desired optically active ketone without epimerization (Scheme 23).

In the presence of oxygen nucleophiles, the oxidation of primary alcohols with IBX can go until the carboxylic acid oxidation level. This reaction has been performed with an benzaldehyde derivative and IBX in the presence of \(N\)-hydroxysuccinimide as nucleophile. However, this protocol was not successful in the synthesis of erythronolide A.

2.3. Oxidations using DIB/nitroxy radical
Besides the highly popular iodine(V) reagents DMP and IBX, the combination of the iodine(III) reagent DIB and a nitroxyl radical is a powerful method for the oxidation of alcohols.\textsuperscript{256-258} In the total synthesis of natural products, the most common nitroxyl radical is TEMPO,\textsuperscript{228,257,259-262} but AZADO\textsuperscript{258} and 1-Me-AZADO\textsuperscript{258} have also been employed (Figure 3). The function of DIB in this transformation is to oxidize the nitroxyl radical to the more reactive oxoammonium salt, which is the species that oxidizes the alcohol moiety. Additionally, DIB regenerates the \textit{N}-hydroxylamine formed in the reaction back to the oxoammonium salt (Scheme 24).\textsuperscript{258}

Figure 3. Structure of \textit{N}-Oxides used in Oxidations with DIB.

Scheme 24

Considering that the main actor in the oxidation of DIB/TEMPO is the \textit{N}-oxide, only a few examples of this reaction will be discussed herein. In the total synthesis of natural products, the most important application of the combination DIB/nitroxyl radical is the chemoselective oxidation of a primary alcohol in the presence of a secondary. This transformation was performed by the
Nicolaou group in the synthesis and structure revision of vannusals A and B.\textsuperscript{248,263} The oxidation was performed with DIB and three different nitroxy radicals: a) 2 equiv of DIB, 0.1 equiv of AZADO, \( \text{CH}_2\text{Cl}_2 \); b) 2 equiv of DIB, 0.2 equiv of 1-Me-AZADO, \( \text{CH}_2\text{Cl}_2 \) (Scheme 25); c) 4 equiv of DIB, 2.0 equiv of TEMPO, \( \text{CH}_2\text{Cl}_2 \).\textsuperscript{264,265} Other recent examples of chemoselective oxidations using DIB/TEMPO were reported in the total synthesis of neopeltolide,\textsuperscript{266} brevetoxin A,\textsuperscript{90,267} spirastrellolide A methyl ester,\textsuperscript{159} (+)-branimycin,\textsuperscript{268} monorhizopodin,\textsuperscript{101} pteridic acids A and B,\textsuperscript{269} and studies toward maitotoxin.\textsuperscript{104}

\textbf{Scheme 25}

A chemoselective oxidation of three secondary alcohols to the corresponding keto diol has been performed using DIB/TEMPO in the synthesis of baflomycin A\textsubscript{1} reported by Kleinbeck and Carreira\textsuperscript{270} (Scheme 26). According to the authors, this is the first example of such remarkable transformation.
The combination DIB/TEMPO is efficient in the transformation of diols into the corresponding lactones,\textsuperscript{271} as illustrated in the total synthesis of brevetoxin A by Crimmins.\textsuperscript{90,267} The diol moiety is oxidized to the lactone, an aldehyde is formed from a primary alcohol, and the secondary alcohol is kept untouched (Scheme 27). Another example was reported during studies toward maitotoxin by Nicolaou.\textsuperscript{104,110} Furthermore, the oxidation system TEMPO/DIB was employed in the oxidative cyclization of a pair of diol epimers to the corresponding lactones in the synthesis of (−)-cyclopamine (Scheme 28).\textsuperscript{272}
Scheme 27
The combination of TEMPO/DIB has been used in the transformation of a primary alcohol to the corresponding carboxylic acid during the total synthesis of tryprostatins A and B (Scheme 29). TEMPO/DIB can also be employed in the oxidation of aldehydes to carboxylic acids (cf. Scheme 104).
3. Reactions of Phenols and Phenol Ethers

3.1. Oxidative Dearomatization of Phenols

Oxidative dearomatization of phenols is a powerful strategy in the synthesis of natural products, and hypervalent iodine reagents are frequently employed in this transformation. The reaction of 2- or 4-substituted phenols with DIB or PIFA in the presence of a nucleophile gives cyclohexadienones. Depending on the substitution pattern of the phenol and whether the nucleophilic attack occurs intra- or intermolecularly, 2,4- and 2,5-cyclohexadienones can be selectively obtained. The mechanistic possibilities for this transformation are depicted in Scheme 30, starting with the electrophilic attack of the iodine(III) on the phenolic oxygen. The intermediate iodane can either undergo dissociative formation of a stabilized cation before nucleophilic attack (a), be directly attacked by the nucleophilic (b) or have the nucleophile internally delivered via ligand exchange and subsequent reductive elimination (c). Both substrate and reaction conditions will influence which of these paths will operate.
There is a detailed review by Quideau and co-workers dedicated to the use of hypervalent iodine reagents in oxidative dearomatization of phenols in natural product synthesis,\textsuperscript{28} and this topic is also covered in other articles.\textsuperscript{37,250,274-276} Thus, only a few recent applications illustrating the rich chemistry available, with intra- and intermolecular nucleophilic attack by heteroatom (O, N) and carbon (olefinic and aromatic) nucleophiles, will be given here.

In the synthesis of isotarins E and F, Pettus and co-workers utilized a PIFA-mediated spirocyclization to reach the requested lactone intermediate with modest diastereoselectivity, which could be improved to 12:1 by treatment with DBU (Scheme 31).\textsuperscript{277} The same group also described the oxidative ipso-cyclization of a nitro group toward the synthesis of spironitrates,\textsuperscript{278} and scyphostatin analogues.\textsuperscript{279}

Myers and co-workers recently reported the synthesis of cortistatins A, J, K, and L (cf. Scheme 53) from a common precursor, the oxabicyclic core of which was prepared by PIFA-mediated oxidative dearomatization of a phenol derivative. In this one-pot three-step process, an internal hydroxyl group acted as nucleophile (Scheme 32).\textsuperscript{112} This strategy has previously been
employed in synthetic efforts towards the cortistatin family\textsuperscript{28,275} (cf. Scheme 69 for another example).

\textbf{Scheme 32}

In studies toward the lomaiviticins A and B, the Nicloaou group synthesized the monomeric aglycon unit of the lomaivictins using two hypervalent iodine oxidation steps. First, a phenol moiety was oxidized with PIFA to the corresponding $p$-quinone. Then, three oxidations were performed in a single step using DMP: the secondary alcohol was oxidized to the corresponding ketone, the hydrazone was transformed into a diazo derivative, and the bis-(SEM)-protected aromatic system gave the quinine moiety (Scheme 33).\textsuperscript{280} The same group has employed PIFA with PMBOH as external nucleophile in an oxidative dearomatization toward (+)-sporolide B.\textsuperscript{190} The preparation of 4-hydroxy dienones with DIB in MeCN/water has been reported in the synthesis of cleroidincins C, D, F\textsuperscript{281} and in the formal synthesis of cortistatin.\textsuperscript{282} Another example with an external oxygen nucleophile is given in Scheme 54, where a naphthol is transformed to the corresponding naphthoquinone ketal.\textsuperscript{283} A paraquinone is also formed as an intermediate in the synthesis of rubioncolin B reported by Trauner and co-workers.\textsuperscript{284} The use of DIB or PIFA in methanol results in formation of a 4,4-dimethoxycyclohexa-2,5-dienone. This transformation was utilized in the synthesis of starting material towards (−)-harveynone\textsuperscript{285} and the core structure of maoecrystal V.\textsuperscript{238}
Oxidative dearomatization with nitrogen nucleophiles has been more difficult to realize.\textsuperscript{37} Ciufolini and co-workers found that sulfonamides and oxazolines could be employed in this transformation, which has been applied to the total synthesis of several natural products.\textsuperscript{286,287} A tandem oxidative amidation/intramolecular Diels-Alder reaction was devised for an approach to the himandrine core (Scheme 34).\textsuperscript{288}
Kita and co-workers have developed the intramolecular PIFA-mediated spirocyclization with carbon nucleophiles and applied it to several syntheses of the discorhabdin natural product family.\textsuperscript{289,290} A recent application is shown in Scheme 35, where PIFA is activated by montmorillonite K10 and the reaction is performed in 2,2,2-trifluoroethanol (TFE). The obtained spirocyclohexadienones were converted to oxa analogues of discorhabdin A.\textsuperscript{291}

![Scheme 34](image)

Scheme 34

Solid-supported iodine(III) reagents have been developed to simplify removal of the PhI formed as a side product.\textsuperscript{31,56} In an elegant total synthesis of both enantiomers of plicamine, Ley and co-workers used solid-supported reagents in all the steps.\textsuperscript{292,293} Polymer-supported DIB (PS-DIB) in TFE was employed in the oxidative coupling of a phenol using an internal aryl nucleophile (Scheme 36).\textsuperscript{293,294}
A formal total synthesis of (−)-platensimycin was described by Canesi’s group, where the key transformation is a tandem Prins-pinacol process. This reaction took place upon treatment of an unsaturated phenol with DIB, and the oxonium intermediate was captured with H₂O₂ to yield the hydroperoxyketal shown in Scheme 37. Another oxidative Prins transformation was reported with an alkyne substituent, leading to the core structure of hispidospermidin.

The use of an external carbon nucleophile in dearomatization of phenols was developed by Quideau’s group; both allyl silanes and silyl enol ethers could be employed. This reaction has
been applied in the total synthesis of (±)-aspidospermidine, and an intramolecular version was utilized in the synthesis of platensimycin.

Oxidative functionalization of phenols in the ortho position leads to 2,4-cyclohexadienones, which are often employed in subsequent Diels-Alder reactions. In the racemic synthesis of subereamollines A and B, Ley and co-workers used DIB to create a spiroisoxazoline from the corresponding oxime, as depicted in Scheme 38. An intramolecular ortho-functionalization was achieved with PIFA in TFE in Moon’s racemic synthesis of the cripowellin skeleton.

![Scheme 38](image)

Phenols can be oxidized to the corresponding o-quinones using IBX, and phenols carrying an o-methoxy substituent deliver o-quinones by oxidative demethylation. This reaction has been employed in Lee’s synthesis of kendomycin (Scheme 39), and later also in Multzer’s synthesis of the same target.
When the phenol is otherwise ortho-substituted, treatment with IBX leads to hydroxylative dearomatization. This is exemplified using SIBX (see section 2.2) in the synthesis of wasabidienone B₁ (Scheme 40).²⁵⁰

In the synthesis of azaphilones, Porco and co-workers developed an elegant cycloisomerization-oxidation sequence of o-alkynylbenzaldehydes. Gold(III) acetate was employed as Lewis acid in a very fast cyclization to the intermediate 2-benzopyrylium salt, which was oxidized

Scheme 39

Scheme 40
with IBX under phase-transfer conditions to the azaphilone (Scheme 41). This methodology was later employed in Böger’s synthesis of clorofusin and its seven chromophore diastereomers.

Scheme 41

3.2. Oxidative Coupling Reactions

The reactions discussed in this section are mechanistically similar to the oxidative dearomatization of phenols. When the nucleophilic attack on the iodine(III) intermediate occurs at an unsubstituted carbon of the phenol moiety (Scheme 30) subsequent prototropic rearomatization takes place and the deariomatization is thus only temporary.

Harran and co-workers employed this type of transformation as key step in their synthesis of (−)-diazonamide A. The advanced intermediate depicted in Scheme 42, containing both a phenol and an indole moiety, was cyclized by treatment with DIB and LiOAc in TFE. Following reaction of the phenol with DIB, intramolecular attack by the indole gave an iminium ion that subsequently acted as electrophile in the final oxacyclization to give the product in moderate yield as a 3:1 diastereomeric mixture.
Nicolaou and Chen performed an intermolecular version of this type of coupling with PIFA in the synthesis of (+)-haplophytine (Scheme 43).\textsuperscript{307,308} Although the reaction was low-yielding, excellent diastereoselectivity was observed and the starting material could be recycled and successively transformed into product. This type of indole coupling was also studied towards the synthesis of phalarine,\textsuperscript{309} and a similar indole-aniline coupling was investigated with HTIB in the synthesis of psychotrimine, although other reagents were chosen to complete the synthesis.\textsuperscript{310}
In the formal synthesis of both enantiomers of phalarine, Chen and co-workers developed an oxidative double cyclization with PIFA. In this reaction, the phenol oxygen reacts with PIFA in the usual manner, followed by attack by the alkene onto the oxygen to form the cationic intermediate depicted in Scheme 44, and subsequent cyclization by the amide leads to the product.\(^{311}\)

**Scheme 43**

**Scheme 44**
3.3. Oxidative Transformations of Phenol Ethers

Iodine(III) reagents are good single electron transfer (SET) oxidants for electron-rich arenes in fluoroalcoholic solvents like TFE and HFIP (1,1,1,3,3,3-hexafluoro-2-propanol). Kita and co-workers studied the ortho-substitution of para-substituted phenol ethers with a range of nucleophiles, the mechanism of which proceeds via cation radicals (Scheme 45).

PIFA was employed to dihydroxylate a phenol ether in the total synthesis of hypocrellin A (Scheme 46). An analogous procedure was used in the synthesis of related natural products, where the authors pointed out that the reaction was sensitive to changes in the oxidation potential, thereby needing reoptimization for each substrate.
Arenes can also act as nucleophiles in this reaction, resulting in an oxidative biaryl coupling. This was demonstrated in the synthesis of \(N\)-acetylcolchinol by Kocienski and co-workers, where the coupling was followed by TBS deprotection in the workup (Scheme 47). The reaction mechanism was thus suggested to proceed via a cation radical rather than through the oxidative coupling mechanism described in Section 2.4. In a synthesis of 1-dearyllamellarin D, Iwao and co-workers reported that a key PIFA-mediated cyclization of a pyrrole-containing phenol ether failed, and instead resulted in a decarbonylative cyclization.
4. Transformation of Carbonyl Compounds

4.1. Dehydrogenation of Ketones

Nicolaou and co-workers described that IBX can be used in the formation of α,β-unsaturated carbonyl compounds by dehydrogenation of the corresponding carbonyl derivatives,\textsuperscript{318,319} probably through a single electron transfer (SET) mechanism.\textsuperscript{319} This transformation has been applied in the total synthesis of many natural products, such as (+)-lepadin B (Scheme 48),\textsuperscript{320} (−)-minfiensine (Scheme 49),\textsuperscript{86} oildiodendrolides,\textsuperscript{119} alkaloids (−)-GB 13 and (+)-GB 16,\textsuperscript{148} and (−)-mersicarpine.\textsuperscript{321} The reaction is usually performed with an excess of IBX in a mixture of toluene and DMSO, and is selective for ketones in the presence of lactones.\textsuperscript{148}
Toward the synthesis of pallavicinolide A, Dong and Wong performed the oxidation of a ketone to the corresponding enone using IBX in DMSO in the presence of PPTS. The enone thus formed participated in a Diels-Alder reaction giving the tetracyclic structure of the target molecule (Scheme 50). In the synthesis of (−)-anominine, Tosic acid was used with IBX in DMSO to promote the dehydrogenation of a cyclohexanone derivative. A dehydrogenation has been described using IBX in MeCN in the presence of triflic acid in the route toward baconipyrone A, baconipyrone C, and siphonarin B.
During the total synthesis of ceratamines A and B, Coleman and his group described the application of IBX in the presence of pyridine for a double dehydrogenation, which led to the formation of an \( \alpha,\beta \)-unsaturated lactam (Scheme 51).\textsuperscript{323} Treatment of tetrahydro-\( \beta \)-carbolines with IBX in the presence of tetrabutylammonium bromide at room temperature resulted in aromatization. This reaction was applied in the total synthesis of eudistomin U.\textsuperscript{324}

The reactivity of IBX can be enhanced by complexation with \( N \)-oxides such as MPO (4-methoxypyridine-\( N \)-oxide) and, consequently, the dehydrogenation of carbonyl compounds can be performed at room temperature.\textsuperscript{225} Moreover, the same transformation can be achieved through a two step procedure, where a silyl enol ether is first obtained and subsequently oxidized with the
complex IBX-MPO (Scheme 52).\textsuperscript{325} An example of this reaction in an architecturally complex substrate has been reported in the total synthesis of (\textpm-)cortistatin A (Scheme 53).\textsuperscript{155,157} Additionally, this methodology was applied in studies toward platensimycin,\textsuperscript{283,326,327} platencin,\textsuperscript{237} and cylindramide.\textsuperscript{237} When two isomeric \(\alpha,\beta\)-unsaturated compounds can be formed, a mixture of isomers is usually obtained (Scheme 54 and Scheme 55).\textsuperscript{219,237,283} Furthermore, there are reports describing that this reaction did not afford the desired unsaturated product.\textsuperscript{118,328}
4.2. α-Functionalization of Carbonyl Compounds

A series of papers from Moriarty and co-workers\textsuperscript{47,62,329-331} described that ketones can be converted into the corresponding α-hydroxy derivative by iodine(III). This transformation is sometimes called Moriarty’s α-hydroxylation, and the most used conditions are DIB in KOH/MeOH.\textsuperscript{47,62,329} The mechanism is illustrated in Scheme 56. The reaction occurs by attack of an enolate to (dimethoxyiodo)benzene, which is formed \textit{in situ} from DIB and MeOH, giving a hypervalent iodine intermediate. This reacts with methoxide, followed by intramolecular displacement of the iodine(III) to give an oxirane and PhI. Finally, ring opening by methoxide delivers an α-hydroxy ketal, which can be isolated or treated with acid to yield an α-hydroxy-ketone.
Examples include the synthesis of (+)-bakkenolide A (Scheme 73)\textsuperscript{332} and rubrolone aglycon.\textsuperscript{333} This $\alpha$-hydroxylation can be stereoselective, as described in the synthesis of nakiterpiosinone (Scheme 57),\textsuperscript{214} seragakinone A,\textsuperscript{334} (--)-$\gamma$-deoxydaunomycinone,\textsuperscript{335} and formal total synthesis of (--)-cephalotaxine (Scheme 58).\textsuperscript{336}
During the total synthesis of (±)-gelsemine, Overman and his group tried to α-oxidize a ketone using DIB under basic conditions, but the reaction led to unidentifiable products.\textsuperscript{337,338} Instead, they utilized a two step protocol also developed by Moriarty and co-workers,\textsuperscript{339,340} where a silyl enol ether was prepared and treated with iodine(III) in the presence of a Lewis acid in methanol to give the α-oxidized product (Scheme 59). An analogous protocol can be used to promote a α-sulfonyloxylation,\textsuperscript{341} as reported in the synthesis of (+)-duloxetine.\textsuperscript{342}
Nagasawa and co-workers have developed an IBX-mediated α-hydroxylation of α-amino carbonyl compounds, which proceeds through formation of an enol-IBX intermediate that delivers the hydroxyl group intramolecularly, assisted by the nitrogen (Scheme 60). When this reaction was applied as the key step in the synthesis of (−)-decarbamoyloxysaxitoxin, preparation of the starting ketone was performed by Swern oxidation, as a one-pot reaction with 4 equiv IBX gave the dehydrogenated ketone as by-product. The methodology was later applied also in the synthesis of (+)-dibromophakellin (Scheme 61).
Scheme 61

5. Transformation of Other Functional Groups

5.1. Transformations of Nitrogen-containing Compounds

Aziridinations and C-H aminations have been used in the total synthesis of several natural products.\textsuperscript{345,346} Although this reaction can be performed in several ways using iodine(III),\textsuperscript{51,347-349} the most used protocol in recent total synthesis is with a Rh(II) catalyst and the iodine(III) reagent DIB as oxidant. Under these conditions, a nitrene intermediate is formed.

In the synthesis of (−)-agelastatin by Wehn and Du Bois, the key aziridination step was performed with a dimeric Rh(II) catalyst (bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)], Rh\textsubscript{2}(esp)\textsubscript{2}) in the presence of DIB (Scheme 62).\textsuperscript{350} Similar conditions have been used in the enantioselective synthesis of the core of banyaside, suomilide, and spumigin HKVV.\textsuperscript{351} In the latter case, the aziridination was followed by ring opening mediated by a sulfonamide to construct the oxazolidinone ring (Scheme 63).\textsuperscript{351} An analogous sequence was reported by Wardrop and coworkers in the synthesis of (+)-castanospermine, where a piperidine ring was obtained by the cyclization of an unsaturated amide promoted by PIFA in TFE/CHCl\textsubscript{3}.\textsuperscript{352} In the synthesis of (−)-oseltamivir,\textsuperscript{353,354} which is used in the treatment of influenza, Trost and Zhang\textsuperscript{355,356} used an aziridination step that was investigated in detail. The catalyst used was also Rh\textsubscript{2}(esp)\textsubscript{2}, however the best yield was obtained using PhI(OCOt-Bu)\textsubscript{2} as oxidant in chlorobenzene (Scheme 64).
The amination of a pyrrole derivative under conditions analogous to those utilized in the aziridination allowed the construction of the cyclic guanidine moiety of (+)-gonyautoxin 3 (Scheme 65). The enantioselective amination of silyl enol ethers using a chiral rhodium(II) catalyst has
been developed\textsuperscript{357} and applied in the formal total synthesis of (−)-metazocine\textsuperscript{358} and in the synthesis of (−)-ritodrine\textsuperscript{359} by Hashimoto and co-workers.

Scheme 65

The stereospecific C-H insertion of guanidines using DIB and Rh(II) has been investigated by Du Bois and co-workers,\textsuperscript{360-362} including the application in the total synthesis of (−)-manzacidin A,\textsuperscript{363} (−)-manzacidin C,\textsuperscript{363} and (−)-tetradotoxin.\textsuperscript{364} The key step in the synthesis of (+)-phakellin and (+)-monobromophakelin is a C-H insertion of a guanidine derivative, which was performed also using DIB and MgO. However, the best result was obtained without the presence of a Rh(II) catalyst.\textsuperscript{365} An important feature in the mechanism suggested by Wang and Romo is the generation of an acyliminium ion, which is intramolecularly attacked by guanidine (Scheme 66).
Feldman’s group has developed an oxidative cyclization of an imidazole derivative using PhI(CN)OTf. The suggested mechanism is an extension of the Pummerer reaction, with initial oxidation of the sulfide followed by two cyclizations (Scheme 67). The reaction, which did not work with DIB or PIFA, was employed in the synthesis of \((\pm)\text{-dibromophakellstatin}\) and \((\pm)\text{-dibromophakellin}\). In a different approach to the same target molecule, Austin and co-workers used hypervalent iodine in a diazidation reaction to introduce the vicinal nitrogen moiety as a diazide.
Another reaction involving an N-oxidized intermediate is the intramolecular cyclization of N-alkoxyamides. Upon treatment with PIFA, an N-acylnitrenium species is obtained, which attacks the neighbouring arene to yield pyrrolobenzodiazepines. This reaction was applied in the synthesis of the antitumor antibiotic DC-81 (Scheme 68). When the amide lacks an alkoxy substituent, the reaction gives an imidate intermediate that cyclizes in a similar fashion to give carbazoles, as demonstrated in the synthesis of glycozoline using an electrochemically generated iodine(III) reagent.
Ciufolini and co-workers recently developed the DIB-mediated oxidation of oximes to nitrile oxides, which were trapped in situ by alkenes.\textsuperscript{371} This enabled a tandem oxidative phenol dearomatization (see section 3.1) and cycloaddition sequence,\textsuperscript{371} which was applied in Sorensen’s synthesis of the cortistatin core structure. The sequence started by intramolecular oxidative ether formation followed by oxidation to the nitrile oxide and [3+2] dipolar cycloaddition (Scheme 69).\textsuperscript{372}
One of the key steps in the synthesis of (+)-caphalostatin involves a selective allylic oxidation, where a methyl group is oxidized in the presence of three other allylic hydrogens. The reaction sequence starts by treatment with 4-phenyl-1,2,4-triazoline-3,5-dione, which selectively functionalizes the methyl group with the substituent shown in blue (Scheme 70). This group is oxidatively removed with DIB via N=N formation, tautomerization and hydrolysis, yielding the aldehyde. 373

Scheme 69

Scheme 70

5.2. Deprotection of Dithianes
Dithianes are highly used protecting groups for carbonyl compounds. In addition, these sulfur-containing compounds can be used in alkylation reactions. For many years, the deprotection of dithianes relied on the use of mercury(II) reagents. However, in 1989 Stork and Zhao reported that PIFA can be used in this transformation. This iodine(III) reagent has been used in an efficient manner during the total synthesis of several natural products, including cembranes (Scheme 71), (±)-uleine (Scheme 72), lyngbouilloside macrolactone core, peribysin E, (+)-bakkenolide A (Scheme 73), and rapamycin. The deprotection using PIFA can also be performed using an alcohol as solvent, directly delivering an acetal. This protocol has been used in studies toward brevetoxin A, using MeOH as solvent (Scheme 74).

Scheme 71

Scheme 72
In the total synthesis of (+)-aculeatin D, several reactions took place in the same operation using PIFA: oxidative dearomatization of the phenol, deprotection of the dithiane, and cyclization (Scheme 74). \(^{378}\)
In complex substrates, the acidic medium of the reaction using PIFA can lead to additional transformations. For example, in the synthesis of (−)-2-epi-peloruside A, the deprotection using PIFA led to the hydrolysis of the 1,3-dithiane, as well as deprotection of the isopropylidene group, giving eventually a hemiketal as final product (Scheme 76). In addition, the dethioacetalization mediated by PIFA gave low yield of the desired products in the synthesis of (+)-tedanolide (Scheme 77) and on studies toward hexacyclinic acid (Scheme 78). In the latter case, the transformation was accomplished using Mel/Ag$_2$CO$_3$ instead.

Scheme 75

Scheme 76

Scheme 77

Scheme 78
In the early 2000’s, Wu\textsuperscript{380} and Panek\textsuperscript{381} described, respectively, that the iodine(V) reagents IBX and DMP can be used for the deprotection of dithianes. The IBX reaction was latter investigated in detail by Nicolaou,\textsuperscript{382,383} including an application in the synthesis of cortistatins.\textsuperscript{155,157} Using these reagents, the reaction medium is less acidic, which can be advantageous in certain
applications. For example, in the total synthesis of leucascandrolide A, Panek and co-workers observed the formation of alkene isomerization using PIFA, which did not take place using DMP (Scheme 79). However, in studies toward (+)-rimocidin, these iodine(V) reagents were not effective in the deprotection of dithianes. During the total synthesis of baconipyronone C, a mixture of aldol products was oxidized with IBX in DMSO, giving the corresponding diketone derivative. This was again treated with IBX, but in MeCN and in the presence of triflic acid to remove the dithiane and promote the formation of the pyrone ring. However, the undesired elimination of the pivaloate and hydrolysis of the acetal group was also observed (Scheme 80).

Scheme 79

Scheme 80
For the IBX-mediated deprotection of dithianes, a mechanism has been suggested by Nicolaou and co-workers. The first step would be the reaction of the dithiane with IBX, leading to a sulfonium intermediate. From this intermediate, two pathways were proposed according to the structure of the sulfonium intermediate. For those without an α-hydrogen adjacent to the sulfonium cation, formation of a mixed thioacetal leads to the desired unmasked carbonyl compound. Alternatively, tautomerization could take place in the sulfonium intermediate when an α-hydrogen adjacent is present, subsequently giving the free carbonyl compound (Scheme 81). A different mechanism has been proposed for hindered dithianes lacking α-hydrogen.

Scheme 81

5.3. Oxidations via Oxygen Radicals

Suárez and co-workers have developed several hypervalent iodine-mediated transformations of carbohydrates and other compounds that proceed via alkoxy radicals. Treatment of an alcohol with DIB and iodine or bromine under irradiation yields an alkyl hypohalite
intermediate, which upon homolysis gives an alkoxy radical (Scheme 82). Subsequent 1,5-hydrogen transfer delivers a carbon radical that is trapped to yield the halogenated alcohol or the corresponding ether.\textsuperscript{389}

![Scheme 82](image)

The DIB/iodine reaction was applied to construct a tetrahydrofuranyl ether in the synthesis of theopederin D by Floreancig and co-workers.\textsuperscript{390} The bromination methodology has been applied as the key step in the synthesis of (+)-cortistatin A (cf. Scheme 53) by Baran and co-workers.\textsuperscript{391} This impressive reaction, which is the first example of an alcohol-directed geminal dibromination of an unactivated methyl group, delivered the product in 57% yield after trapping the alcohol with TMSCl to avoid ether formation (Scheme 83).

![Scheme 83](image)

Amino acids can be decarboxylated by treatment with DIB and iodine via a radical mechanism similar to that in Scheme 82. After formation of a carboxyl radical, carbon dioxide is lost
and the corresponding carbon radical is oxidized to an N-acyliminium ion, which can be trapped by various nucleophiles.\(^{392}\) A decarboxylation step in Danishefsky’s synthesis of (-)-phalarine proved challenging, and several variants of radical-based decarboxylation were attempted. The most successful conditions employed DIB/I\(_2\) with reduction of the N-acyliminium intermediate with NaCNBH\(_3\) (Scheme 84).\(^{393}\)

![Scheme 84](image)

**Scheme 84**

5.4. Oxidation of Benzyl Bromides

IBX in DMSO promotes the oxidation of benzyl bromides to the corresponding carbonyl compound.\(^{394}\) According to the proposed mechanism, this transformation resembles the oxidation of alcohols. The first step is a nucleophilic substitution that releases HBr and a hypervalent intermediate (Scheme 85), which subsequently gives IBA and the desired carbonyl compound, as previously discussed (Scheme 14).

![Scheme 85](image)

**Scheme 85**
This transformation was not successful in the synthesis of cyclo-mumbaistatin. However, Trauner and co-workers described the oxidation of an allylic bromide to the corresponding aldehyde upon heating with IBX in DMSO during the biomimetic synthesis of (+)-shimalactone A (Scheme 86).

![Scheme 86]

6. Rearrangements and Fragmentations

6.1. Hofmann-Type Rearrangement

The treatment of aliphatic amides with iodine(III) gives the corresponding amines in a Hofmann-type rearrangement. This transformation has been described with DIB, PIFA, and HTIB. An important feature of this rearrangement is the retention of configuration of the migrating carbon. An analogous reaction was also reported for aromatic amides using DIB. The procedure described by Loudon and co-workers using PIFA in aqueous acetonitrile appears to be the most commonly employed in total synthesis of natural products. Examples of applications are (±)-2-epi-validamine (Scheme 87), pantocin B, and (−)-platensimide A (Scheme 88). An
application of this rearrangement in large scale has been reported using DIB. A lower yield was obtained when PIFA/pyridine was used (Scheme 89).

The following mechanism has been suggested for the PIFA-mediated Hofmann-type rearrangement. The first step is the formation of a dimer of PIFA (although the reaction could also take place by PIFA itself), on which the amide displaces one of the ligands to give a mixed dimer. Migration of the R group to the electron-deficient nitrogen then delivers an isocyanate, which gives the amine as a salt after hydrolysis (Scheme 90).
Moriarty and co-workers developed a protocol where the amide is treated with DIB and KOH in methanol. Under these conditions, the intermediate isocyanate reacts with methanol, giving a methyl carbamate. This procedure has been applied in the total synthesis of (−)-epinephrine and of isoprekinamycin (Scheme 91). The reaction can also be performed in the presence of other alcohols than methanol. For example, allyl alcohol was used in the synthesis of (−)-oseltamivir phosphate (Tamiflu®) (Scheme 92). Furthermore, the intermediate isocyanate can be trapped by an internal hydroxyl group giving an oxazolidinone ring, as described in the synthesis of (−)-myriocin.

Scheme 90

Scheme 91

Scheme 92
6.2. Rearrangement of Alkenes

Ring contraction is an important method to increase molecular complexity in a single step. Although the number of carbon-carbon bonds remain the same in these rearrangements, the reorganization of the bonds may occur with a high level of selectivity, affording products not easily accessible by other approaches. Ring contraction reactions can be effected by acids, bases, oxidants or by photochemical means. The ring contraction of 1-alkyl-1,2-dihydronaphthalenes mediated by iodine(III) is an efficient method to obtain trans-1,3-disubstituted indanes, representing an alternative to the analogous transformation mediated by thallium(III). The exclusive formation of trans-1,3-disubstituted indanes in the ring contractions in methanol can be explained by the mechanism detailed in Scheme 93. The electrophilic addition of HTIB to the double bond leads to an iodine(III) intermediate through a cyclic organoiodine. The approach of the electrophile occurs opposite to the remote methyl group, explaining the stereoselectivity of this ring contraction. The iodine(III) intermediate equilibrates to its more stable conformation, in which the required anti-periplanarity for the rearrangement is achieved. Migration of the aryl group (carbon 8a) displaces PhI to give an oxonium ion, which furnishes the trans-indane after addition of MeOH.
This reaction has been applied in the total synthesis of (−)- and (+)-mutisianthol (Scheme 94)\textsuperscript{420} and (±)-indatraline (Scheme 95).\textsuperscript{413} The synthesis of the latter target also features a Hofmann-type rearrangement. Iodine(III) was tested without success in the ring contraction step of the synthesis (±)-trans-trikentrin A. Eventually, the required the rearrangement was performed using thallium(III).\textsuperscript{421} Although in low yield and diastereoselectivity, an iodine(III)-promoted ring contraction of an optically octalone was mentioned in the total synthesis of (+)-bakkenolide A (cf. Scheme 73).\textsuperscript{332}
Chalcones can undergo oxidative rearrangement in the presence of iodine(III) reagents. The reaction starts by addition of HTIB and MeOH to the alkene, followed by 1,2-aryl migration (Scheme 96). This transformation has been employed as key step in the synthesis of (±)-pterocarpin, wighteone and other isoflavone natural products, and using unprotected carbohydrate-substituted chalcones in the synthesis of genistein and orobol (Scheme 97).
Kita’s group has reported a PIFA-mediated domino reaction of 2,3-epoxy alcohols, which leads to lactols by oxidative fragmentation and subsequent ring closure (Scheme 98). This reaction was applied in the synthesis of (+)-tanikolide.
Kita and co-workers have developed an efficient synthesis of $N,O$-acetals by oxidative fragmentation of $\alpha$-amino acids or $\beta$-amino alcohols. The reaction is believed to proceed via a five membered ring intermediate that fragments into an iminium ion. This methodology was applied in the total synthesis of both enantiomers of discorhabdin A, which also involved a PIFA-mediated spirodiene formation (Scheme 99).

Oxidative fragmentations have also been used in the synthesis of medium ring lactones, as demonstrated by Posner in the synthesis of $(-)$-phoracantholide J (Scheme 72).
Iodonium salts are iodine(III) compounds with two carbon ligands, one of which is a vinyl, alkynyl or aryl moiety and the other is usually a phenyl group (Figure 1). In reactions with nucleophiles, they transfer one of the carbon ligands through mechanisms that vary both with the type of salt and with the nucleophile.\textsuperscript{25,33,63}

7.1. $\alpha$-Arylation with Diaryliodonium Salts

$\alpha$-Arylated carbonyl subunits are commonly occurring in biologically active molecules. Introduction of aryl moieties to the $\alpha$-position of carbonyl compounds usually involves Pd-catalyzed couplings at elevated temperature for prolonged reaction times, whereas methodology for asymmetric $\alpha$-arylation is scarce.\textsuperscript{33} Diaryliodonium salts have successfully been used in metal-free or metal-mediated $\alpha$-arylations of various carbonyl compounds, including asymmetric transformations.\textsuperscript{33,432} The reaction entails nucleophilic attack of an enolate onto the iodonium salt, with subsequent transfer of one aryl moiety and elimination of PhI. The mechanistic studies of this reaction have recently been reviewed.\textsuperscript{25}

Gao and Portoghese utilized this methodology in the synthesis of 7-arylmorphinans to be tested on opioid receptors.\textsuperscript{433} Arylation of a highly substituted ketone using diphenyliodonium iodide
and LiHMDS diastereoselectively delivered the monophenylated product without scrambling of the existing α-stereocenter (Scheme 101).\textsuperscript{433,434}

Scheme 101

In the synthesis of tabersonine, Kozmin and Rawal arylated a silylenol ether in excellent yield using (2-nitrophenyl)phenyliodonium fluoride (Scheme 102).\textsuperscript{435} The electron deficient 2-nitrophenyl group was chemoselectively transferred in this mild and base-free arylation.

Scheme 102

In the first total synthesis employing an asymmetric α-arylation with diaryliodonium salts. Aggarwal and Olofsson used a chiral base to desymmetrize a 4-substituted cyclohexanone prior to arylation in a short synthesis of (─)-epibatidine (Scheme 103).\textsuperscript{436}
MacMillan and co workers recently combined the use of organocatalysis and diaryliodonium salts to obtain a highly enantioselective $\alpha$-arylation of aldehydes. The efficiency of this transformation was demonstrated in the rapid synthesis of (S)-ketoprofen, which also involved the TEMPO/DIB oxidation of the aldehyde to the corresponding carboxylic acid (Scheme 104).

### Scheme 104

#### 7.2. Arylation of Phenols with Diaryliodonium Salts
Diaryl ethers are common structures in natural products, and there are several methods available for their synthesis. Diaryliodonium salts are powerful electrophiles for a variety of heteroatom nucleophiles, including phenoxides. The application to natural product synthesis has been hampered by harsh reaction conditions, but it was recently demonstrated that the reaction can be performed at room temperature without racemization of sensitive α-amino acid derivatives.

Couladouros and co-workers have employed diaryliodonium salts in the synthesis of several bastadins. Both diaryl ether moieties in the target molecules were created using the same iodonium salt, and the couplings proceeded in good to excellent yields (Scheme 105). Similar diaryliodonium salts have been used in the synthesis of glycopeptide antibiotics.

\[
\begin{align*}
\text{Scheme 105}
\end{align*}
\]

7.3. Transformations with Alkynyliodonium Salts

Alkyny(aryl)iodonium salts are structurally related to diaryliodonium salts, but are less stable and react with nucleophiles through different mechanisms, usually with formation of an alkylidenecarbene intermediate that undergoes further transformations. Cossy’s group
alkynylated an amide by sequential treatment with KHMDS and an alkynyliodonium triflate in the synthesis of (±)-lennoxamine (Scheme 103).

Scheme 106

Wardrop and Fritz generated an alkynyliodonium salt from the corresponding alkynyl stannane and PhI(CN)OTf, which was directly treated with sodium benzene sulfinate to generate an alkylidenecarbene. This intermediate underwent [1,5] C-H insertion to form a dihydrofuran, which was transformed into (±)-magnoefgesin (Scheme 107).

Scheme 107
Feldman et al have utilized alkynyliodonium salts in the synthesis of $(-)$-agelastatin A, B\(^{444}\) and pareitropone.\(^{445}\) In the latter synthesis, an unusual addition of the carbene to an aromatic ring leads to a ring-expanded product (Scheme 108).

8. Conclusions

The examples described in this review show that hypervalent iodine compounds have been used intensively in the total synthesis of natural products. Good isolated yields and chemoselective reactions can be achieved even for highly functionalized molecules. Additionally, tandem transformations could be accomplished in many circumstances. Based on these features, hypervalent iodine reagents have become an essential tool in synthetic organic chemistry.

Many outstanding reactions mediated by hypervalent iodine have recently been developed. They will probably be used in the near future in stereoselective key steps of the total synthesis of...
complex natural products, more often including transformations involving carbon-carbon bond formations.

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References and Notes

(1) This theme was discussed in the editorial of the JACS virtue issue regarding the total synthesis of natural products: W. R. Roush, *J. Am. Chem. Soc.*, 2008, 130, 6654.
Different acronyms are used in the literature for iodine(III) reagents. Unfortunately, there is no consensus even among the specialists. The most employed in the literature (DIB, PIFA, and HTIB) are used in the review.


(69) The chapter "Synthetic Applications (Total Synthesis and Natural Product Synthesis)" by Tohma and Kita in ref. 23 published in 2003 describes several applications. Reference 28 describes applications of the phenol dearomatization in the total synthesis of natural products. Reference 49 does the same for the oxidation of alcohols.


(253) A. Schulze and A. Giannis, Synthesis, 2006, 257.


