Part I

“Development of New Methodologies Using Hypervalent iodine Reagents”
Chapter 1

“Introduction and Literature Survey of Hypervalent Iodine Reagents”
Introduction:

Development of new synthetic methodologies for organic synthesis is a creative function of organic chemistry. Present demands on synthetic methodologies are method should be mild, efficient, robust, selective and environmentally benign. For chemists the challenge of process intensification (PI) lies in creatively developing methodologies capable of performing multiple transformations in one pot. We had carried out methodologies development by means of which intensification is brought into consideration for upgradation of existing methodologies. Focus point of development is cost effectiveness by minimizing the number of steps while increasing the overall efficiency of the method. This gives a good impact on commercialization of synthetic methodologies i.e. process can be made more efficient with the reduction of number of steps. This can be achieved by performing one or more steps of reaction in pot reducing multiple process operation. The methodology is based on the use of hypervalent iodine reagents. Due to ready availability, easy preparative procedures, and mild reactivity with good stability the hypervalent iodine reagents have become regents of interest to organic chemists. Following are some of the factors leading to our interest in hypervalent iodine reagents.

- Chemical properties and reactivity is similar to the heavy metal reagents such as Hg (III), Tl (III), and Pb (IV) but without the toxicity & environmental issues.
- Mild reaction conditions, efficiency of the methods and easy handling.
- Commercial availability and High chemoselective oxidizing properties.
- Stereoselective oxidations.
- Reduced form of the trivalent iodine reagent can be easily recovered and reused after reoxidation.
1.1 Hypervalent Iodine Reagents:

1.1.1 Background and Introduction:

French chemist Bernard Courtois was discovered Iodine in 1811 and it was named by J. L. Gay Lussac in 1813. Its name derives from the Greek word iodes, sense "violet-colored," reflecting both the characteristic lustrous, deep purple colour of resublimed crystalline iodine as well as the colour of its vapours. It can be found in seaweed and brine wells.

**Iodine**

Element number 53

Atomic weight 126.9

Oxidation state

Main I-1

Others I0, I+3, I+5, I+7

Electronic Configuration 1s\(^2\), 2s\(^2\), 2p\(^6\), 3s\(^2\), 3p\(^6\), 3d\(^{10}\), 4s\(^2\), 4p\(^6\), 4d\(^{10}\), 5s\(^2\), 5p\(^5\)

**Hypervalency**

The 15-18 groups’ elements shows higher oxidation states than normal valency in several molecules (Musher, 1969). This capacity of an atom in a molecular entity to develop its valence shell beyond the restrictions of the Lewis octet rule is called as "Hypervalency." An explanation of Hypervalency implies a relocate of the electrons from the central (hypervalent) atom to the nonbonding molecular orbital’s which it forms with (more electronegative) ligands.

Iodine is an important trace element for humans and plays a significant role in many biological organisms. Among the most general everyday uses of iodine is in halogen lamps, in ink pigments and as a topical antiseptic to kill bacteria.

Because iodine is the biggest, least electronegative and generally polarisable of the common halogens, it is able to forming steady Polycoordinated high-valet (with a value of up to 7, IF\(_7\)) compounds.
The most common polyvalent organic iodine compounds are I (III) and I (V) species. The first hypervalent iodine compound, dichloroiodobenzene (C\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2}I) was prepared in 1886 by the German chemist C. Willgerodts by passing chlorine gas through Iodobenzene in a cooled solution of chloroform (Scheme 1.1) (Willgerodts, 1886).

Whereas C. Herman and V. Mayer prepared first hypervalent organo-iodine (V) compound o-Iodoxybenzoic acid (IBX) (Hartmann et al., 1893; Pati, 2010) in 1893, Iodobenzene having 8 valence electros in there valence electron sells as normally, in order to gets oxidized with removal of first 3 electrons and then 5 electrons for getting Hypervalency state. The ligands in turn give electron pairs and form coordinate covalent bonds by adding a total of 6 or 10 electrons back to iodine.

1.1.2 Nomenclature of hypervalent iodine compounds:

Hypervalent iodine compounds are nomenclature on the basis of oxidation states of the central iodine atom. There are huge numbers of compounds are existing having valence from 1 to 5 which are coordinated with 2-4 usually differing ligands (Varvoglis, 1992). Four significant structural types of hypervalent iodine reagents are shown in Fig. 1.1 and 1.2 with general notations for individual iodine reagents.
Trivalent Organo Iodine Reagents

Fig 1.1

Iodosylbenzene

Diacetoxyiodobenzene
Pentavalent Organo Iodine Reagents

IUPAC rules assign $\lambda$ as non-standard bonding; thus, $\text{H}_3\text{I}$ is $\lambda^3$-iodane and $\text{H}_5\text{I}$ is $\lambda^5$-iodane. Most common structure is aryl-$\lambda^3$-iodane ArIL$_2$ ($\text{L} =$ heteroatom) and aryl-$\lambda^5$-iodane ArIL$_4$.

There are four main structural types of hypervalent iodine reagents as shown in Fig.1.1 and 1.2 are important general notations for respective iodine reagents. Martin-Arduengo designation for hypervalent iodine reagents is N-X-L.

Where,
N is number of valence electrons,
X is central iodine atom, and
L is Ligand attached to central iodine atom.

The first two species 8-I-2 and 10-I-3 are called Iodanes and are predictably considered as derivatives of trivalent iodine. The last two 10-I-4 and 12-I-5 periodinane are the most common structural types of pentavalent iodine.
1.1.3 Physical aspects of hypervalent iodine reagents:

Mainly hypervalent iodine reagents are solid (amorphous or crystalline) and are stable to atmospheric oxygen and moisture. Hypervalent iodine reagents like PhI (OMe), PhIO, PhIO₂, IBX, and O-iodylbenzoic acid created explosion when they heated in absence of solvent. In the solid state Iodoxybenzene and (tosyliminoiodo) benzene are polymeric structures terminated by water: HO (PhIO) n H.

1.1.3.1 Properties in terms of reactivity pattern:

Hypervalent iodine chemistry is based on the strongly electrophilic nature of the iodine making it susceptible to nucleophilic attack, in combination with the leaving group ability of phenyliodonio group –IPhX. The useful reduction of the hypervalent iodide to normal valency by reductive elimination of Iodobenzene is the key to its reactivity. Hypervalent iodine Reactivity is depends on the number of carbon and heteroatom ligands (Kirschning, 1998). These reagents’ mainly performs oxidative organic transformation.
All known hypervalent organo iodine derivatives belong to two general types.

1.1.4 Iodine (V) compounds: Also named $\lambda_5$-iodanes. Represented C in Fig. 1.5

1.1.5 Iodine (III) compounds: Also named $\lambda_3$-iodanes according to IUPAC Recommendations

Represented A & B in Fig. 1.4

\[
\begin{align*}
\text{IX}_2 & : \\
\text{RI}^+ & : \\
\text{L} & \\
\end{align*}
\]

where $R = \text{Carbon ligand}$

$X = \text{O or N Ligand}$

Fig 1.4

The iodine atom in $\lambda_3$-iodanes, in Fig. 1.4(A) has a total of 10 electrons having distorted trigonalbipyramid geometry, with two heteroatom ligands X and R with the slightest electronegative carbon and both electron pairs at equatorial positions. Iodonium salts B in (Fig. 1.4) also belong to $\lambda_3$-iodanes, having two carbon ligands and anionic part of the molecule.

In the hypervalent model, bonding in RIX$_2$ uses the non-hybridized 5p orbital of iodine in the linear X-I-X bond. Such a linear three-centre, four-electron bond is highly polarized and is longer and weaker compared to a regular covalent bond. This bond is hypervalent, and the existence of this bond in $\lambda_3$-iodanes is liable for their high electrophilic reactivity.
Organic (C) in Fig. 1.5(C) of λ5-iodanes have a distorted octahedral structure having group R and the electron pair in the vertical positions and four heteroatom ligands X in basal positions. All ligands X are accommodating by 3C-4e bonds, while group R at the top is linked to iodine by a normal covalent bond using a 5sp-hybridized orbital. The stable aryl-substituted λ3- and λ5-iodanes acquire high chemical reactivity and are extensively used in oxidants and electrophilic agents in organic synthesis, which are commonly referred to as hypervalent iodine reagents.

1.1.4 Iodine (V) Reagents (λ5-iodanes):

The chemistry of iodine (V) compounds (λ5-iodanes) has also involved substantial awareness in recent years. Pentavalent iodine reagents also played important role in new organic conversion development. There are two types’ i.e. cyclic and acyclic pentavalent iodine reagents.

a) Acyclic Pentavalent Iodine Reagents:

Acyclic Pentavalent iodine reagents having low stability that’s, why they are use rarely in organic transformation in chemistry. Moreover, the aryl derivatives, ArIO₂, can form moderately stable compounds; iodylalkanes are extremely unstable and can exist only at very low temperatures.
Even with their low solubility and explosive character, iodylarenes have found some practical application like allylic oxidation. For Stereoselective synthesis of tetrodotoxim used as dehydrogenating agent in steroidal compounds and Oxidation-dehydrogenation of 3α-hydroxy-5β-bile acid formyl esters to give oxodienes. Among various ArIO₂, iodylbenzene PhIO₂ is the most popular reagent.

b) Cyclic Pentavalent Iodine Reagents:

2-iodobenzoic acid (IBX) is the important repetitive of thirds class of reagents, was first synthesized by Harman and Mayer in 1893. IBX has the structure of the cyclic benziodoxole oxide as determined by X-ray structural analysis. Until the 1980s IBX was infrequently used in organic synthesis, because of its insolubility in most organic solvents (Dess and Martin, 1983). IBX transformed to the soluble triacetoxybenziodoxole by treating IBX with acetic anhydride at 100 °C. In the subsequent years, the triacetate has used as the reagent of choice for the oxidation of alcohols to the respective carbonyl compounds, and now it is commonly referred to as Dess-Martin periodinane (DMP).

c) Some of the derivatives of IBX and other cyclic pentavalent reagents:

The synthetic efficiency of IBX in general is extensively restricted by its low solubility in most organic solvents with the exception of DMSO. Several analogs of IBX have reported in literature, which overcome the solubility problem and solubility of IBX also improved by derivatisation and complexation of IBX.

Some of the Examples of hypervalent iodine (IV) regents, derivatives of IBX and other cyclic pentavalent reagents are shown bellow (Fig 1.6).
In spite of these derivatives and analogs of IBX, various groups have reported the immobilization of IBX into solid or soluble polymeric supports (Mülbaier et al., 2001; 2003; Sutherland et al., 2003). These supported IBX reagents are non-explosive...
and can be used in common solvents like THF or dichloromethane. These Reagents used for various transformations as oxidising agents for primary, secondary, benzylic, allylic, terpene alcohols, and the Carbamate protected amino alcohols to afford the respective aldehydes or ketones in exceptional yields and purities.

d) Polymer supported Hypervalent (IV) reagents:

1.1.4.1 Applications of IBX:

IBX become precious oxidizing agent in developing various organic transformations. Its mildness proved to be an outstanding and selective oxidizing agent in total synthesis of natural products as well as in multistep synthesis of APIs and its intermediates (Fischer et al., 1999; Paintner et al., 2001; Fallis et al., 2001; Chiar et al., 2000; Welzel et al., 1999; Guillemin et al., 1998; Showalter et al., 1996; Wenbao et al., 2000; Shioiri et al., 2002; Corey et al., 1995; Santagostin et al., 1996; Kirsch et al., 2003).
I] Different Organic transformations developed by IBX:

- Oxidative cleavage of vicinal 1, 2-diols.
- Oxidative transformation of threonines, which proceeded with oxidation of a secondary alcohol to the ketone and subsequent α-hydroxylation (Harding, 2009).
- Dehydrogenation of tetrahydro-carbolines to their aromatic forms.
- Oxidative Transformation of Primary Carboxamides to One-Carbon Dehomologated Nitriles
- Synthesis of α-β Unsaturated Systems from Alcohols and Ketones
- Oxidation of primary alcohol to carboxylic acid
- Oxidation of secondary alcohol to ketone.
- α-Hydroxylation of Alkynyl Carbonyl Systems
- Oxidation of various phenols to α-quinones.
- Key step of the total synthesis of the streptomycin maritimus metabolite, wailupemycin B.
- Oxidation of primary alcohols or aldehydes to N-hydroxysuccinimide esters.
- Oxidation of alcohols, ketones, and aldehydes to the corresponding α-β unsaturated species.
- Oxidation of alkyl-substituted aromatic compounds at the benzylic position to the corresponding carbonyl derivatives.
- Oxidation of alcohols, secondary amines can be oxidized with IBX in DMSO to yield the corresponding imines.
- A variety of new heterocycles can be synthesized by the treatment of unsaturated aryl amides, carbamates, thiocarbamates, and urea’s with IBX.
- Conversion of acylated Alkoxyamines in to isoxazolidines and oxazinanes.
- Three-component synthesis of R-iminonitriles by Strecker reaction.
- Synthesis of p-quinones from 4-substituted anilides.
- Construction of N-Containing Quinones and Derivatives.
- Rearrangement of five- and six-membered cyclic tertiary allylic alcohols to β disubstituted α-β unsaturated ketones.
Introduction

Chapter 1

Novel Synthetic Methodologies for Bioactive Molecules

- Oxidative Conversion of \(\alpha,\alpha\)-Disubstituted Acetamides to Corresponding One-Carbon-Shorter Ketones.
- Iodohydroxylation of Olefins and Iodination of Aromatics.
- Synthesis of key precursor to the antifungal agent GM222712
- Synthesis of key step in carbohydrate like moenomycin a disaccharide analogues.
- Benzylic, allylic and propargylic alcohol as well as diols, can be oxidised in to \(\alpha, \beta\) unsaturated esters in presence of witting ylide.

1.1.4.2 Applications of DMP:

Exclusive oxidizing properties and convenience of use advance DMP to be broadly in use in the synthesis of biologically important natural products (Ottenheijm et al., 1997; Wipf et al., 1998; Martin et al., 1997; Paterson et al., 2001; Fuchs et al., 1999; Tueckmantel et al., 1999; Kita et al., 2001; Comins et al., 1997; Meinke et al., 1998; Larsen et al., 1996; Miller et al., 1996; Tadano et al., 1996; Nicolaou et al., 2002; 2002; 1999). In recent times DMP was used in the key oxidation steps in the total syntheses of cyclotheonamide B, tricyclic \(\beta\)-lactam antibiotics, erythromycin B, (+)-discodermolide, (+)-cephalostatin, (+)-ritterazine K, fredericamycin A, 1,19-aza-1,19-desoxy-avermectin B, angucyclcline antibiotics and the platelet aggregation-inhibiting \(\gamma\)-lactam PI-091. The unique oxidizing properties of DMP can be best illustrated by its application in the total synthesis of the CP-molecules, lead structures for cardiovascular and anticancer drugs published by Nikolaou and co-workers.

I] Different methodologies developed by DMP are shown below:

- Baylis-Hillman adducts of allylic aldehydes and alkyl acetylates are efficiently oxidised to corresponding \(\alpha\)-methylene-\(\beta\)-keto esters.
- Synthesis of Cyclic enecarbamates from oxidation of \(\alpha\)-hydroxy carbamates.
- Synthesis of cyclic acetoxy acetals from 1, 4 diols.
- Polyfluorinated alcohols can be oxidised to respective aldehydes.
- Primary alcohol can be oxidised to \(\alpha, \beta\) unsaturated esters in presence of witting ylide.
- Deoximation of aldoximes as well as ketoximes to respective ketones.
Oxidation of n-acyl hydroxylamine’s to acyl nitroso compounds
Intramolecular Cycloaddition reactions.
Application in the total synthesis of the CP-molecules, lead structures for cardiovascular and anticancer drugs.
Synthesis of 2-substituted benzothiazoles via oxidative cyclization of thioformanilides.
Synthesis of thioesters from the corresponding aldehydes and thioles under mild conditions.
Synthesis of imides N-acyl vinylogous carbamates and urea’s, and nitriles by the oxidation of amides and amines.
α- bromination of α-β unsaturated ketones.
α- tosylation of secondary alcohol.
α- bromination of 1, 3 diketones.

1.1.5 Iodine (III) Reagents (λ3-iodanes):

Iodine (III) Compounds to the IUPAC nomenclature are commonly classified according to the type of the ligand attached to the iodine atom. Wide work has been carried out using trivalent iodine reagents useful in variety of chemical transformations (Varvoglis et al., 1992; 1997; Zhdankin et al., 2002; 2005; 1996; 2006; Wirth et al., 2005; 2003; Skulski et al., 2000). Well recognized trivalent iodine reagents are shown below in (Fig. 1.8; 1.9) and new trivalent iodine reagents shown in (Fig. 1.10). Acyclic trivalent iodine reagents are ordinary and have widely studied and useful for various transformations. Cyclic trivalent iodine reagents like IBA are less studied and have incomplete applications in the organic chemical transformations.
The heterocyclic iodanes

2-Iodosylbenzoic acid (IBA)

IBA Derivatives

X = CF₂, Me
Y = OAc, N₃, OH, CN etc

Y = OH, Oac, N₃, CN etc
Z = H, Ac etc

Fig 1.9

Fig 1.8

(dichloroiodo)arenes
(difluoro)arenes
(diacetoxy)benzene

(Bis(trifluoroacetoxy) iodo) benzene

Iodosylarenes

(Hydroxy) (tosyloxy) iodo) benzene

Koser's Reagent

BTI

IOB

HTI

aryliodine(III) organosulfonates

4,4-bis(dichloroiodo) biphenyl

Fig 1.8
1.1.5.1 General Structural Features of Organic Iodine (III) Compounds:

The following general classes of iodine (III) compounds have found broad applications in organic synthesis (Zhdankin, 2009).

(Difluoriodo) arenes and (Dichloriodo) arenes are effective fluorinating and chlorinating reagents, respectively. Iodosylarenes (IOD), aryl iodine (III) carboxylates and organosulfonates are strong oxidizing agents have found extensive application as reagents for oxygenation and oxidative functionalization of organic substrates. The most significant and commercially available representatives of aryl iodine (III) carboxylates are (diacetoxyiodo)benzene PhI(OAc)$_2$ which has several commonly used abbreviations such as DIB, PIDA (phenyliodine diacetate), IBD or IBDA (Iodosobenzene diacetate) and [bis(trifluoroacetoxy)iodo]benzene PhI(OCOCF$_3$)$_2$ abbreviated as BTI or PIFA [(phenyliodine bis(trifluoroacetate)].

Some researchers have prepared derivatives of trivalent iodine reagents containing heterocyclic rings. Aliphatic alkyl iodides are also oxidized to aliphatic Koser’s reagent and also some heterocyclic ring containing iodine substituent are also synthesized and used as reagents.
1.1.6 Preparation of trivalent reagents:

a) (Difluoroido) arenes

This is a very powerful fluorinating reagent can be prepared by the fluorination of iodoarenes with powerful fluorinating reagents such as $\text{F}_2$, $\text{ClF}$, $\text{BrF}_3$ and $\text{XeF}_2$ etc. Previously there is one procedure in which mercuric oxide and aqueous HF react with (Dichloroiodo) arenes in MDC. Inconvenience of this method is these of large quantity of harmful HgO for removal of Chloride ion from reaction mixture. A convenient modified procedure without use of HgO consists of the treatment of Iodosylarenes with 40-46% aqueous hydrofluoric acid followed by crystallization of resulting (Dichloroiodo) arenes from hexane (Hara et al., 2002; Wirt et al., 2005; DiMagno et al., 2008). It is important that the freshly prepared Iodosylarenes are used in this procedure.

b) Koser’s reagent

[Hydroxy (tosyloxy) iodo] arenes are typically prepared by a ligand exchange reaction of (diacetoxyiodo) arenes with p-toluenesulfonic acid monohydrate in acetonitrile (Scheme 1.2) (Zhdankin et al., 2008; Zhang et al., 2005; Wirth et al., 2001; 2005 Katzenellenbogen et al., 2007; Togo et al., 2002; 2005; 2001; Kita et al., 2004; 2005).

![Scheme 1.2](image-url)
A convenient modified procedure for the preparation of various [hydroxy (sulfonyloxy) iodo] arenes consists of the one-pot reaction of iodoarenes and mCPBA in the presence of sulfonic acids in a small amount of chloroform at room temperature. This modified procedure was recently used for the preparation of new biphenyl- and terphenyl-based recyclable organic trivalent iodine reagents.

1.1.6.1 (Diacetoxyiodo) benzene preparations:

(DIB) is one of the first reagent of this family to be investigated, and is the synthetic precursor to several related compounds; among these derivatives, [Bis (trifluoroacetoxy) iodo] benzene (BTI) plays a key role by offering several interesting applications in modern organic synthesis.

It has been observed that trivalent iodine compounds synthetic properties are frequently similar to those of lead and thallium derivatives, somehow with better yields and improved toxicity, which make them more compatible in a pharmaceutical production environment.

![Diagram](image.png)

**Fig 1.11**

a) From Iodoarenes:

Oxidation, diacetoxylation of iodoarenes in acetic or trifluoroacetic acid using suitable oxidants, such as periodates potassium peroxodisulfate, 3g H₂O₂-urea and sodium perborate (Kraszkiewicz et al., 2001). The reaction with peracetic acid is exothermic, and can be considered dangerous if not carefully controlled. This method may be used for toluenic and xylenic derivatives. Sodium perborate in acetic acid is also a useful reagent for the synthesis of DIB.
The oxidation of iodoarenes with sodium perborate in acetic acid at 40 °C is the most easy and universal procedure that has been used for a small scale preparation of numerous (diacetoxyiodo)-substituted arenes and hetarenes. This method has been better by performing the perborate oxidation in the presence of trifluoro methanesulfonic acid. A further convenient modification of this approach employs the interaction of arenes with iodine and potassium peroxodisulfate in acetic acid.

**b) From Dichloriodobenzene:**

Another route, known as the safest process for the synthesis of DIB was investigated by Alcock starting from dichloriodobenzene in presence of silver salts. Karele performed an analogous synthesis in two steps from Iodobenzene using thionylchloride to yield dichloriodobenzene, then aqueous acetic acid in pyridine to convert it to DIB.
1.1.7 Applications of hypervalent iodine (III) reagent:

Different methodologies developed by hypervalent iodine (III) iodine are:

- Oxygenation at carbon (example: preparation of allylic aldehydes from allylsilanes).
- Dehydrogenation i.e. synthesis of C=C double bonded from C-C single bond in cyclic compounds.
- Addition to the alkenes and dienes.
- Oxidation of alcohols to carbonyl compounds.
- Phenolic oxidation (phenolic oxidation).
- Intramolecular cyclization.
- α-substitution to ketone.
- Rearrangements of ketone.
- Decarboxylative bromination.
- Decarboxylative azidation reaction.
- Hoffman rearrangement in modern vision.
- Synthesis of urethanes from amide.
- Transformation of carbohydrates.
- Nucleophilic aromatic substitution.
- Oxidation of alcohol to carboxylic acid.
- Sulphur to Sulfoxides synthesis.
- α-fluorination of β-ketoesters.
- Deportation of dithianes to formation of ketones.
- Bromo decarboxylation of carboxylic acid.
- Cleavage of N, N-dimethylhydrazides in to carboxylic acid.
- Conversion of N-substituted amidines in to corresponding tosylates.
- Synthesis of α-tosyloxyketones directly from alcohol.
- Transformation of aryl aldehydes to aroyl azides.
- Generation of reactive intermediates like carbenes, nitrene, arynes etc.
I. Lactonization:

Electrophilic lactonization by addition of DIB to the double bond of substrate (1) followed by migration leading to the final rearranged lactones (2) (Wirth et al., 2003)

II. Oxidative Functionalization of Carbonyl Derivatives and Unsaturated comp.

[Bis (acetoxy) iodo] arenes can be used as the oxidants in organocatalytic. Asymmetric epoxidation of α-β-unsaturated aldehydes using imidazolidinone catalyst (A) (Pettus et al., 2004) example, the reaction of aldehyde (3) with DIB affords epoxide (4) with good enantioselectivity (Scheme 1.6). Synthesis of aromatic aldehydes (6) from isopropenylbenzenes (5) and zeolite-supported DIB under microwave irradiation (Scheme 1.6) has been reported. This method was used for a spotless and reproducible preparation of piperonal, vanillin, and p-anisaldehyde with high yields and selectivity (Antune et al., 2006). A multicomponent reaction of allenes (7), diaryl diselenides, DIB and alcohols or acids formed substituted allyl derivatives (8) in moderate yields (Huang et al., 2007).
III. Synthesis of lactols via an oxidative rearrangement reaction:

Kita and co-workers developed a facile and efficient synthesis of lactols (10) via an oxidative rearrangement reaction of (9) with BTI (Scheme 1.7) (Kita et al.,...
2005). This BTI-induced oxidative transformation used in asymmetric synthesis of the marine γ-lactone metabolite (+)-tanikolide (Fujioka et al., 2007; Kita et al., 2005).

IV. Iodination and cyanation of a wide range of electron-rich heteroaromatic compounds:

Substituted pyrazoles (11) can be iodinated to the corresponding 4-iodopyrazole derivatives (12) by treatment with iodine and DIB or polymer-supported DIB at room temperature (Scheme 1.8) (Chen et al., 2003). While N-tosylpyrroles (13) are selectively cyanated at the 2-position using PIFA and TMSN₃ to afford products (14) in good yields (Kita et al., 2007).

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Ph</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td></td>
</tr>
</tbody>
</table>
|     | Me | Ph etc

V. Oxidative transformations of steroidal substrates:

In case of steroidal substrate (15) with DIB and boron trifluoride etherate in acetic acid led to the introduction of an axial acetoxy group at position C-23 of the side chain, (Iglesias-Arteaga et al., 2006; 2007) (Scheme 1.9). While a similar reaction of
the same substrate (17) with DIB and BF$_3$•OEt$_2$ in formic acid unexpectedly produced the equatorial formate (18) (Scheme 1.10).

VI. Hofmann rearrangement, by the conversion of amide to the respective amine

DIB is a better reagent for the Hofmann rearrangement of protected asparagines (Zhang et al., 1997). This procedure was used for the preparation of optically pure NR-n-Boc-L,-diaminopropionic acid (20) from asparagines (19) in hundred kilogram quantities (Scheme 1.11) Oxidative rearrangement of anthranilamides or salicylamides (21) to the respective heterocycles (22) (Om Prakash et al., 2001).
VII. Oxidative Cationic Cyclization, Rearrangements, and Fragmentations:

Recent representative examples include the preparation of indoline derivatives (24) from anilides (23) (Tellitu et al., 2006) and also indazol-3-ones (26) from anthranilamides (25) (Scheme 1.12) (Tellitu et al., 2006; Dominguez et al., 2005, 2006, 2007). Synthesis of pyrrolidinones (28) from alkynylamides (27) has been done with the help of PIFA.
VIII. Oxidation of primary and secondary alcohols:

\[
R\text{OH} \xrightarrow{\text{DIB, TEMPO}} R\text{CHO}
\]

where \( R = \text{aryl, alkyl etc} \)  

\[
R\text{OH} \xrightarrow{\text{DIB, Alumina, MW}} R\text{C}CH_3
\]

where \( R = \text{aryl, alkyl etc} \)
IX. Oxidative phenolic cyclization:

In particular, the oxidative cyclization of phenolic oxazolines (33) affords synthetically useful spirolactams (34) (Ciufolini et al., 2000) (Scheme 1.14).

And the spirocyclic product (36) has been prepared by a BTI-induced oxidation of catechol (35) in a key step of the total synthesis of the marine sesquiterpene quinone (+)-puupehenone (Quideau et al., 2002).

![Scheme 1.14](image)

X. Oxidative Coupling of Electron-Rich Aromatic Substrates:

This is simple oxidative cyclization of 3, 4-dimethoxyphenyl 3, 4-dimethoxyphenylacetate (37) and leading to the seven-membered lactone (38) (Pyne et al., 2007) (Scheme 1.15)
Kita and co-workers reported a facile and efficient oxidative coupling reaction of alkylarenes (39) for the formation of alkylbiaryls (40) using a combination of BTI and BF3•OEt2 (Scheme 1.16) (Kita et al., 2002).

XI. Radical Cyclizations, Rearrangements, and Fragmentations:

Cyclization or rearrangement of the nitrogen-centered radicals generated in the reaction of the appropriate amides with DIB in the presence of iodine (Suarez et al., 2005; Fan et al., 2007). Examples are illustrated by the synthesis of bicyclic spirolactams (42) from amides (41), fragmentation of carbohydrate anomeric alkoxy radicals generated from (43) the respective carbohydrates (Scheme 1.17)
Other few Applications of DIB and PIFA

- Synthesis of aldehydes and ketones from oximes.
- Oxidation of benzylic position.
- Synthesis of disulfides to thioles.
- N-acylation of thioamide.
- Transformation of 1,4-diols to lactols.
- Alpha hydroxylation of ketones.
- Desulfuration reaction of thioamide to synthesis of nitrile.
- Ring breaking of ortho phenylene diamine to corresponding nitriles.
- Synthesis of quinone from 1,4 diamino benzenes.
- Benzylic C-H oxidation for formation of ketones.
- Aziridination of alkenes.
By using this system of DIB/NaN₃ novel methods have been developed in our laboratory these are presented in (Fig 9.12)

1.1.7.1 Application of BTI (Koser’s reagent)

- Oxidative rearrangements and fragmentations.
- Total synthesis of indatraline.
- Oxidative rearrangement of alkenes can be effectively used in ring expansion reactions.
- Conversion of benzocycloalkenones by Wittig olefination to the homologous benzocycloalkenones.
- Oxidative substitution reactions of polycyclic aromatic hydrocarbons.
- Iodination reactions in presence of Iodinating reagents.
- Conversion of ketones in to carboxylic acid.
- Synthesis of p-nitro aniline from p-nitrobenzamide.
- Azidation of N, N-dimethylarylamines.
- Synthesis of heterocycles by cyclization.
- Chalcones rearranged to acetals.
- α- tosylation of ketones
- Secondary alcohol undergoes to alpha tosylation.
- Cleavage of hydrazine ester to alpha kito ester.
- Synthesis of imides from secondary amides.
- Deoximation of aldoximes and ketaloximes.
- Oxidation of phenol to synthesis of quinones.
- Intramolecular cyclization of enamines.
- Arylalkenes with HTIB in 95% methanol affording the corresponding α-aryl ketones.
- ring expansion reactions