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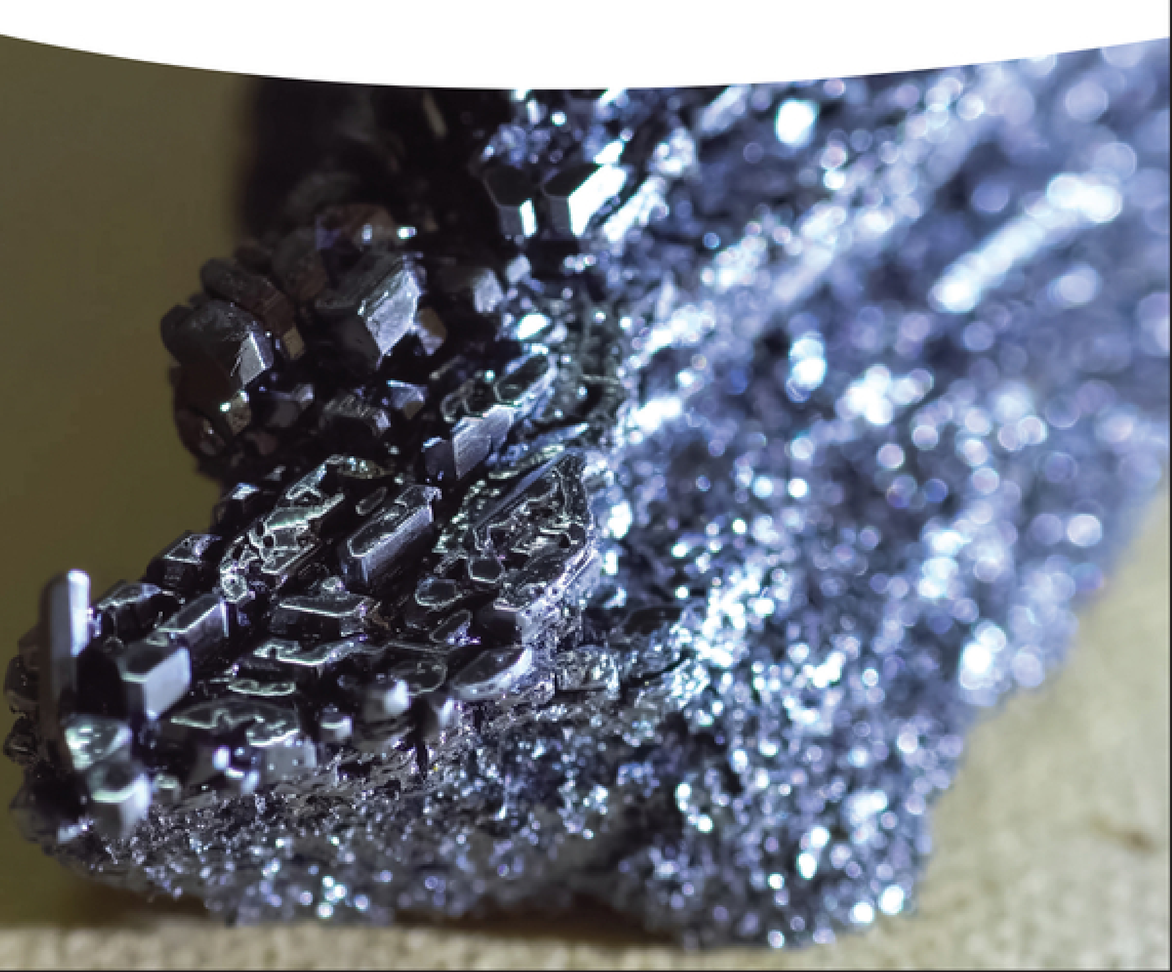
# Iodine Catalysis in Organic Synthesis



# Iodine Catalysis in Organic Synthesis

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**Cover Design:** Wiley
**Cover Image:** © LuYago/Shutterstock

**Library of Congress Card No.:** applied for

**British Library Cataloguing-in-Publication Data**
A catalogue record for this book is available from the British Library.

**Bibliographic information published by the Deutsche Nationalbibliothek**
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

**Print ISBN:** 978-3-527-34829-9
**ePDF ISBN:** 978-3-527-82955-2
**ePub ISBN:** 978-3-527-82957-6
**oBook ISBN:** 978-3-527-82956-9

**Typesetting** Straive, Chennai, India
**Printing and Binding**

Printed on acid-free paper

10 9 8 7 6 5 4 3 2 1

# Contents

# Preface

Iodine (symbol **I** and atomic number 53) is the heaviest of the stable halogens and exists as a lustrous, purplish-black nonmetallic solid under ambient conditions. It was discovered by the French chemist Bernard Courtois in 1811, and was named two years later by Joseph Louis Gay-Lussac, after the Greek *ἰώδης* "violet-colored."

The human body needs iodine because iodine plays an essential role in the biosynthesis of thyroid hormones. The iodine needed by the body must come from the diet. Most food contains very little iodine. However, processed food typically contains more iodine due to the addition of iodized salt. Most of the world's iodine is found in the ocean, where it is concentrated by sea life, especially seaweed, and in certain rocks and sediments. The dominant producers of iodine today are Chile and Japan.

Iodine occurs in many oxidation states, including iodide ($I^-$), iodate ($IO_3^-$), and various periodate anions. Iodine-containing compounds are useful as oxidative reagents and catalysts, due to their oxidative ability and ease of attachment to organic compounds. Furthermore, iodine-containing compounds are useful as Lewis acid catalysts, due to their ability as halogen-bonding(XB) donors. The XB interactions follow the general trend $F < Cl < Br < I$, with iodine normally forming the strongest interactions.

Over the past decade, the expansion of hypoiodite(I)- and organoiodine(III or V)-catalyzed oxidative transformations has been unremitting. Iodine-containing compounds are now some of the most important oxidative catalysts in organic synthesis. Both intramolecular and intermolecular enantioselective oxidative coupling reactions have recently been developed using chiral iodine catalysts. Moreover, iodine-catalyzed oxidative reactions and Lewis acidic reactions are highly attractive from an environmental point of view. Thus, we decided to publish a new book titled "Iodine Catalysis in Organic Synthesis."

This book focuses on different areas of iodine chemistry and catalysis, which have been selected because they have developed significantly, and, in some cases, completely, over the past few years. Each author is very knowledgeable in his/her particular field of chemistry and can provide a valuable perspective.

It is our strong hope that this book will be an invaluable guide for synthetic chemists in both academic and industrial laboratories.

*Kazuaki Ishihara*
Nagoya

*Kilian Muñiz*
Tarragona

PS:
We launched this book project in January 2020. Unfortunately, Prof. Muñiz passed away on 16 March 2020. However, we inherited his spirit and were able to keep pushing until the book was complete. I pray for Kilian's soul.

*Kazuaki Ishihara*

# 1

# Historical Introduction

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## 1.1 Discovery of Iodine and Early Studies

Iodine was originally isolated and recognized as a new element early in the nineteenth century. The French industrial chemist Bernard Courtois had noticed that the addition of concentrated sulfuric acid to seaweed ashes resulted in the emission of a violet vapor that could be condensed to the deep purple solid with the metal-like appearance of the crystals. These observations were first published in November 1813 in the *Annales de Chimie* [1]. In this original paper, the name “iode,” derived from the Greek word *ἰώδης* for violet, was first used for the new substance “due to the beautiful violet color of its vapor.” Soon after, J. L. Gay-Lussac published his initial results on the chemical properties of iodine demonstrating that this was a novel element capable of forming compounds with other elements [2, 3].

Numerous inorganic compounds of polyvalent iodine in the oxidation states +3, +5, and +7 were prepared early in the nineteenth century. In particular, iodine trichloride was first prepared by J. L. Gay-Lussac by reacting iodine or iodine monochloride with an excess of chlorine under gentle heating [4]. In the same 1814 paper [4], the preparation of potassium iodate by the action of iodine on hot potash lye was described. The history of the inorganic chemistry of iodine was summarized in numerous common textbooks and reference sources [5–9]. Iodine history, chemistry, and applications were discussed in detail in the review commemorating two centuries of iodine research [10].

The preparation of first polyvalent organoiodine compound, (dichloroiodo) benzene **1** (Figure 1.1) was reported by the German chemist C. Willgerodt in 1886 in the *Journal fuer Praktische Chemie* [11]. Many other organic iodine(III) and iodine(V) compounds were prepared during the 1890s and at the beginning of the twentieth century. In particular, (diacetoxyiodo)benzene **2**, iodosylbenzene **3**, and iodylbenzene **4** were reported in 1892 [12]; 2-iodoxybenzoic acid (IBX, **5**) in 1893 [13]; and the first example of diaryliodonium salts **6** were reported by C. Hartmann and V. Meyer in 1894 [14].

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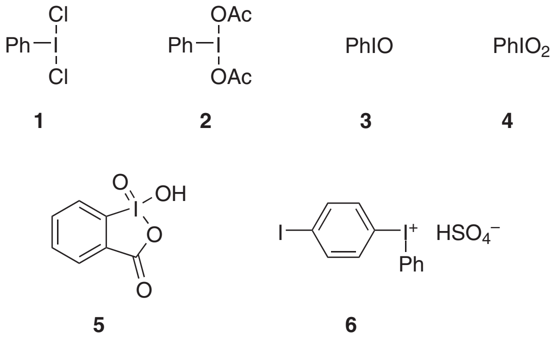


**Figure 1.1** First examples of polyvalent organoiodine compounds reported in 1886–1894.

The early research on organoiodine chemistry was summarized by C. Willgerodt in 1914 in a comprehensive book *Die Organischen Verbindungen mit Mehrwertigen Jod* describing nearly 500 polyvalent organoiodine compounds [15].

## 1.2 Iodine Research in the Twentieth Century

During the period between 1914 and 1970s, research activity in the area of organic chemistry of iodine compounds was relatively low and represented mainly by valuable contributions from the laboratories of I. Masson, R. B. Sandin, F. M. Beringer, K. H. Pausacker, A. N. Nesmeyanov, and O. Neilands. This research, dealing mostly with various iodonium compounds, was summarized in the reviews of R. B. Sandin [16] and D. F. Banks [17] published in 1943 and 1966, respectively. A comprehensive list of known at that time iodine(III) and iodine(V) compounds with their physical properties was published by F. M. Beringer and E. M. Gindler in *Iodine Abstracts and Reviews* in 1956 [18].

Starting from the 1970s, the interest in the chemistry of iodine compounds had significantly increased. At that time, numerous new classes of polyvalent organoiodine compounds were discovered and many useful synthetic applications of these compounds were developed. The concept of hypervalent molecules was originally proposed by J. I. Musher in 1969 [19], and shortly after, the terminologies "hypervalent iodine," "hypervalent iodine reagents," "hypervalent iodine compounds," and "organohypervalent iodine reagents" were broadly introduced in the works of J. C. Martin, R. M. Moriarty, and several other researchers. During the 1980s, polyvalent iodine compounds have achieved the status of valuable synthetic reagents known under the common name of hypervalent iodine reagents.

The foundation of modern hypervalent iodine chemistry was established in the 1980s in the groundbreaking works of G. F. Koser, J. C. Martin, R. M. Moriarty, P. J. Stang, A. Varvoglis, Y. Kita, M. Ochiai, and N. S. Zefirov. The twentieth-century iodine research was summarized in two books published by A. Varvoglis in 1992 and 1997: a comprehensive monograph *The Organic Chemistry of Polycoordinated Iodine* [20] and a book on the applications of hypervalent iodine compounds in organic synthesis [21]. Numerous general reviews [22–27], book chapters [28–33], and specialized reviews on phenyliodine(III) carboxylates [34, 35], [hydroxy(tosyloxy)iodo]benzene [36], the chemistry of alkynyliodonium salts [37], electrophilic perfluoroalkylations [38], application of hypervalent iodine in the carbohydrate chemistry [39], carbon–carbon bond formation via hypervalent iodine [40], hypervalent iodine oxidations [41, 42], hypervalent iodine compounds as free radical precursors [43], synthesis of heterocyclic compounds using organohypervalent iodine reagents [44], and the chemistry of benziodoxoles [45] were also published during the 1980s and 1990s.

## 1.3 Iodine Research in the Twenty-first Century

During the first two decades of the twenty-first century, iodine chemistry has experienced explosive development. Six books [46–51] and hundreds of reviews summarizing various aspects of iodine chemistry and applications have been published between 2001 and 2020. Thousands of research works utilizing iodine reagents in organic and inorganic synthesis are currently published every year. Starting from the beginning of the twenty-first century, the International Conference on Hypervalent Iodine Chemistry (ICHIC) is regularly convened in different countries, the Society of Iodine Science (SIS) holds annual meetings in Japan, and the American Chemical Society presents the National Award for Creative Research and Applications of Iodine Chemistry biennially. The World Iodine Association (www.worldiodineassociation.com) was officially registered in 2017 as an international nonprofit organization established with the main goal of providing information about the purposes, uses, and applications of iodine and its derivatives.

Current surging interest in iodine chemistry is mainly explained by the very useful oxidizing properties of hypervalent iodine reagents, combined with their benign environmental character and commercial availability. Iodine(III) and iodine(V) derivatives are now routinely used in organic synthesis as reagents for various selective oxidative transformations of complex organic molecules. The discovery and utilization of similarities between the transition metal chemistry and the hypervalent iodine chemistry, and in particular, the development of the highly efficient and enantioselective catalytic systems based on the iodine redox chemistry, has added a new dimension to the field of hypervalent iodine chemistry and initiated a major surge of research activity, which is expected to continue in the future.

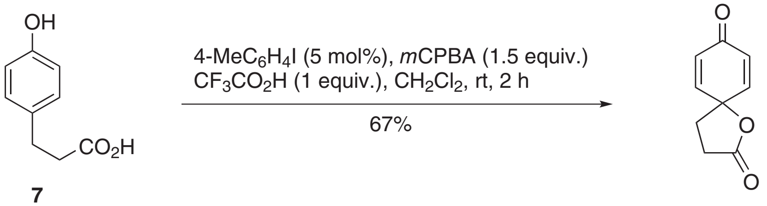
## 1.4 Brief History of Iodine Catalysis

A quick SciFinder search on the concept “iodine catalysts” reveals over 10 000 papers published between 1890 and 2020, including about 300 older papers published during the first half of the twentieth century. The first reliable observations of inorganic and organic reactions catalyzed by iodine date back to the early 1900s. For example, J. Brode [52] and J. H. Walton [53] reported in 1904 the catalytic decomposition of hydrogen peroxide in the presence of iodine involving hypoiodite as a key intermediate. L. Bruner in 1902 published a mechanistic study of the catalytic action of iodine on the bromination of benzene, in which the catalytic effect of iodine is explained by the formation of iodine bromide, IBr, as active species [54].

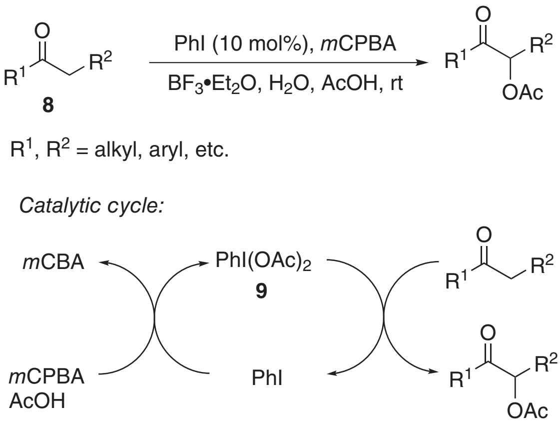
The vast majority of papers on iodine catalysis published between 1900 and 2005 did not involve the oxidation of iodine to the hypoiodite or hypervalent iodine-active species. These papers almost exclusively deal with the catalytic application of iodine as a Lewis acid or as a radical initiator. In some catalytic reactions, iodide anion is utilized as a strong nucleophile, generating organic iodides RI as intermediate species incorporating the excellent iodide-leaving group. Such catalysis involving the generation of organic iodides has been employed in the important Monsanto–Cativa industrial process for the production of acetic acid. In this process, the catalytic hydroiodic acid converts the methanol feedstock into methyl iodide, which undergoes Rh- or Ir-catalyzed carbonylation. Hydrolysis of the resulting acetyl iodide regenerates hydroiodic acid and gives acetic acid [55]. The carbonylation of methanol, catalyzed by rhodium in the presence of hydroiodic acid, was originally invented by Monsanto company in the 1960s. In the 1990s, Eastman Chemical Company developed a modification of this industrial process based on the use of lithium iodide as the cocatalyst [56].

A new era in iodine catalysis was opened in 2005 by the discovery of reactions catalyzed by hypervalent iodine species. The similarities between hypervalent iodine species and transition metal-organic complexes had been widely recognized in the works of many researchers since the end of the twentieth century. At that time, the terminologies "oxidative addition," "reductive elimination," "ligand exchange," and "ligand coupling" became common in mechanistic discussions of the reactions of hypervalent molecules [57]. However, catalytic reactions, typical of transition metals, remained unknown for hypervalent iodine compounds until the beginning of the twenty-first century.

In 2005, Kita and Ochiai independently reported the catalytic use of aryl iodides, in the presence of stoichiometric *m*-chloroperoxybenzoic acid, to perform oxidative dearomatization of phenolic substrates **7** (Scheme 1.1) [58], or α-acetoxylation of carbonyl compounds **8** (Scheme 1.2) [59], respectively. These reactions involved selective generation of the highly reactive hypervalent iodine(III) species (e.g. **9** in Scheme 1.2) *in situ* from aryl iodide and terminal oxidant.



**Scheme 1.1** Catalytic oxidative spirocyclization reaction of a phenolic substrate in the presence of 4-iodotoluene.



**Scheme 1.2** Catalytic α-acetoxylation of carbonyl compounds in the presence of iodobenzene.

First examples of the catalytic application of the iodine(V) species in the oxidation of alcohols using Oxone® ($2KHSO_5•KHSO_4•K_2SO_4$) as a stoichiometric oxidant at 70 °C were independently reported by the groups of Vinod [60] in 2005 and Giannis [61] in 2006. A few years later, Ishihara and coworkers discovered that 2-iodoxybenzenesulfonic acid (IBS) can act as an extremely active catalyst for the selective oxidation of alcohols to aldehydes, ketones, carboxylic acids, and enones with Oxone [62]. While chemical reactions catalyzed by hypervalent iodine species were discovered only in 2005, the electrochemical generation of iodine(III) species *in situ* from catalytic amounts of iodoarenes (0.05–0.2 equiv), and the use of these species as the in-cell mediators in electrochemical fluorination reactions, had been known since 1994 [63].

First examples of enantioselective reactions catalyzed by chiral aryl iodides [64–69] or chiral ammonium iodides [70] were reported by several research groups in 2007–2010. These groundbreaking initial reports were followed by a huge wave of publications describing various enantioselective oxidative transformations catalyzed by hypervalent iodine species. A brief historical overview of enantioselective iodine catalysis can be found in the 2019 review of Muñiz and coauthors [71].

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## 2

## Concepts in Iodine Catalysis

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### 2.1 Introduction

Iodine can form inorganic and organic derivatives in various oxidation states (−1, 0, +1, +3, +5, +7), and the structural features and reactivity patterns of these iodine compounds are, in many respects, similar to those of the derivatives of heavy transition metals. However, in contrast to heavy metals, iodine is both environmentally friendly and relatively inexpensive. About 30 000 tons of iodine are produced annually, and the world's total reserves are estimated to be 15 million metric tons, located mainly in Chile and Japan [1].

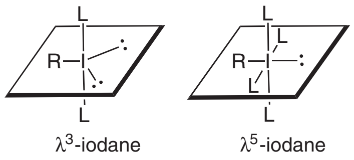
Iodine readily disproportionates into iodide and hypoiodites as well as other iodine–oxygen species in basic aqueous solutions according to the Latimer diagrams in Scheme 2.1 [2, 3]. In contrast, iodine is stable against disproportionation in acidic solutions, near pH 0. For neutral solutions around pH 7, which are probably closest to most experimental conditions, a very unfavorable equilibrium constant of $2.0 \times 10^{-13}$ has been determined for the reaction between water and iodine [3]. Therefore, water and alcohols can react with molecular iodine to give hydroiodic acid (HI).

Iodine compounds are used in industry. About 16% of the global production of iodine is utilized in industrial catalysis [4]. Hydroiodic acid is used as a cocatalyst for the production of acetic acid by the Monsanto process using rhodium catalyst and the Cativa process using iridium catalyst, which are the main industrial processes for the production of acetic acid. In the Cativa process (Scheme 2.2), hydroiodic acid converts the methanol feedstock into methyl iodide, which then undergoes iridium-catalyzed carbonylation [5]. Hydrolysis of the resulting acetyl iodide regenerates hydroiodic acid and gives acetic acid. The role of iodine as a cocatalyst for the Monsanto and Cativa processes is based on the strong nucleophilicity of the iodide anion and the high reactivity as a leaving group of intermediates. Please refer to Chapter 13 for the industrial application of iodine catalysis.

In recent years, hypervalent organoiodine derivatives and hypoiodite salts have attracted significant attention as versatile and environmentally benign catalysts for

*Iodine Catalysis in Organic Synthesis*, First Edition. Edited by Kazuaki Ishihara and Kilian Muñiz.

| | | |
|---|---|---|
| I(0) | $I_2$: iodine | $I^-$: iodide |
| I(I) | I–OH: hypoiodous acid | $I{-}O^-$: hypoiodite |
| I(III) | O=I–OH: iodous acid | $O{=}I{-}O^-$: iodite |
| I(V) | $(O{=})_2I{-}OH$: iodic acid | $(O{=})_2I{-}O^-$: iodate |
| I(VII) | $(O{=})_3I{-}OH$: periodic acid | $(O{=})_3I{-}O^-$: periodate |



**Latimer diagrams summarizing the standard potentials for iodine**

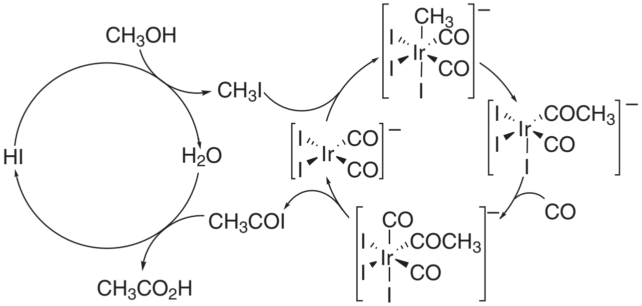
Basic solution (pH 14)

$$(O{=})I(OH)_3(O^-)_2 \xrightarrow{0.65\ V} (O{=})_2I{-}O^- \xrightarrow{0.15\ V} I{-}O^- \xrightarrow{0.42\ V} I_2 \xrightarrow{0.54\ V} I^-$$

Acidic solution (pH 0)

$$(O{=})I(OH)_5 \xrightarrow{1.60\ V} (O{=})_2I{-}O^- \xrightarrow{1.13\ V} I{-}OH \xrightarrow{1.44\ V} I_2 \xrightarrow{0.54\ V} I^-$$

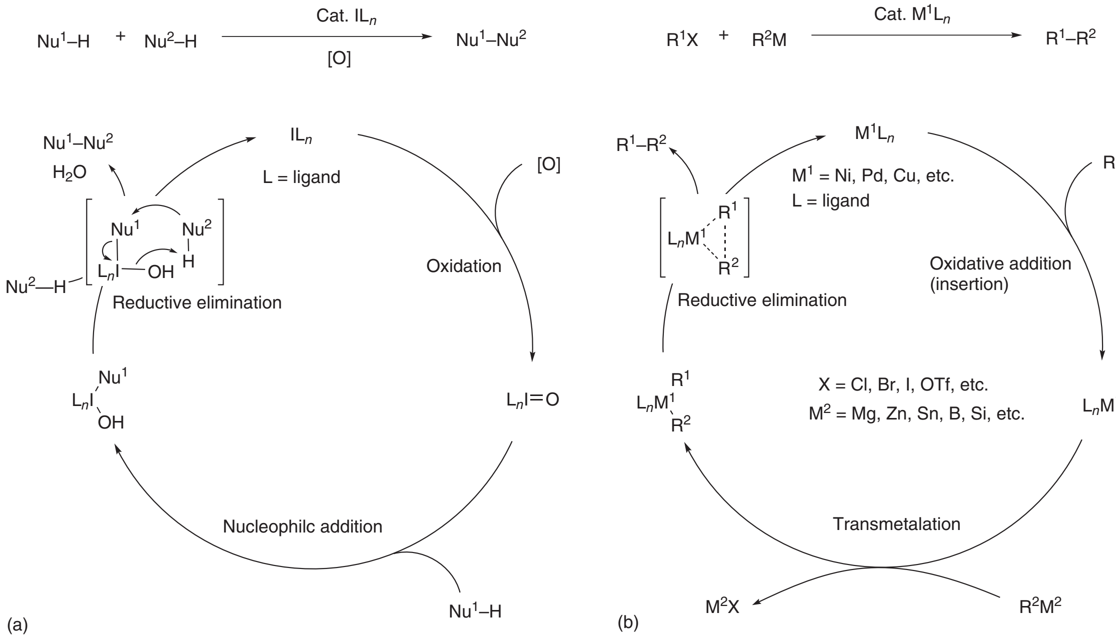
**Scheme 2.1** Iodine compounds.



**Scheme 2.2** Production of acetic acid by the Cativa process.

organic synthesis [6–8]. One of the most impressive recent achievements in this area has been the discovery of the catalytic activity of iodine derivatives in numerous oxidative transformations leading to the formation of new C–O, C–N, and C–C bonds in organic compounds, as shown in Scheme 2.3a. These transformations involving (i) oxidation to hypoiodites, (ii) nucleophilic addition of $Nu^1$–H to hypoiodites, and (iii) reductive elimination are similar to the transition-metal-catalyzed coupling reactions involving (i) oxidative addition, (ii) transmetalation, and (iii) reductive elimination steps, as shown in Scheme 2.3b. However, the reductive elimination step of iodine intermediates is mechanistically different from that of transition metal intermediates. In the former case, umpolung of $Nu^1$ due to the electron-deficient iodine atom of the I–$Nu^1$ bond is a driving force for the $Nu^1$–$Nu^2$ coupling step (reductive elimination).

The choice of stoichiometric cooxidants [O] is very important to achieve the catalytic use of hypervalent organoiodine derivatives or hypoiodite salts for oxidative transformations (Scheme 2.3a). Oxygen gas, hydrogen peroxide, alkyl hydroperoxides such as *tert*-butyl hydroperoxide (TBHP) and cumene hydroperoxide (CHP), peracids such as *m*-chloroperbenzoic acid (*m*-CPBA) and Oxone®, and electrophilic



**Scheme 2.3** (a) Iodine-catalyzed coupling reaction. (b) Transition-metal-catalyzed coupling reaction.

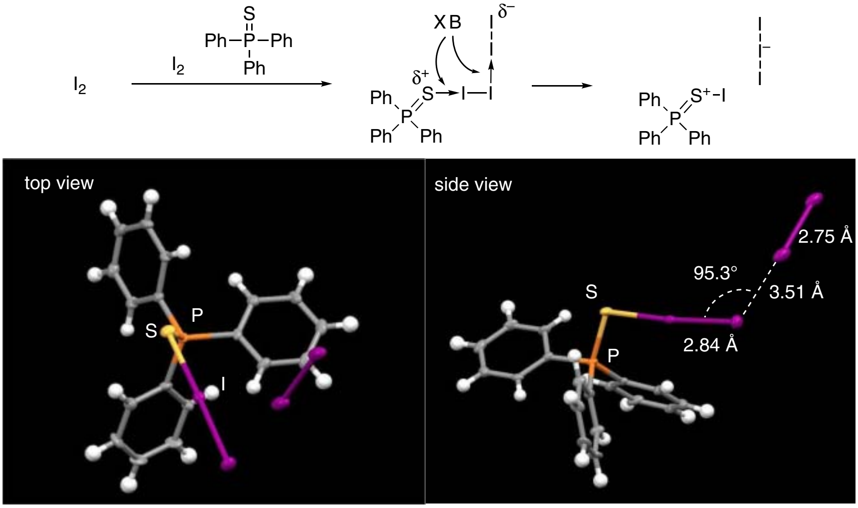
halides such as Selectfluor® and *N*-bromosuccinimide (NBS) have been used as cooxidants for the *in situ* generation of active iodine species. More recently, electrochemical methods have also been developed. Please refer to Chapter 12 for cooxidants in iodine catalysis.

Halogen-bonding (XB) interactions of electron-deficient iodine derivatives as soft Lewis acid catalysts have also attracted significant research activity. Dihalogens ($X_2$) and organohalides (X–L) are capable of acting as XB donors and follow the general trend: F < Cl < Br < I, with iodine normally forming the strongest interactions.

This chapter focuses on iodine catalysis for organic reactions. Please refer to Chapter 1 for historical aspects of iodine catalysis.

## 2.2 Halogen-bonding Catalysis

Dihalogens ($X_2$) tend to form strong halogen bonds (XBs) [9]. If the halogen (X) is bonded to an electron-withdrawing group (L), it is more likely to form stronger XBs. For example, iodoperfluoroalkanes are well-designed for XB in crystal engineering. XBs are strong, specific, and directional interactions that give rise to well-defined structures. XB strengths range from 5 to 180 kJ mol$^{-1}$. The strength of XB allows it to compete with hydrogen bonds (HBs), which are slightly weaker. XBs tend to form at 180° angles. Another factor that contributes to the strength of an XB comes from the short distance between the halogen (Lewis acid, XB donor) and Lewis base (XB acceptor). The attractive nature of XBs makes the distance between the donor and acceptor shorter than the sum of their van der Waals radii. The halogen-bonding interaction becomes stronger as the distance between the halogen and Lewis base decreases. For example, the crystal structure of molecular iodine and triphenylphosphine sulfide is shown in Scheme 2.4 [10]. Molecular iodine is activated by double

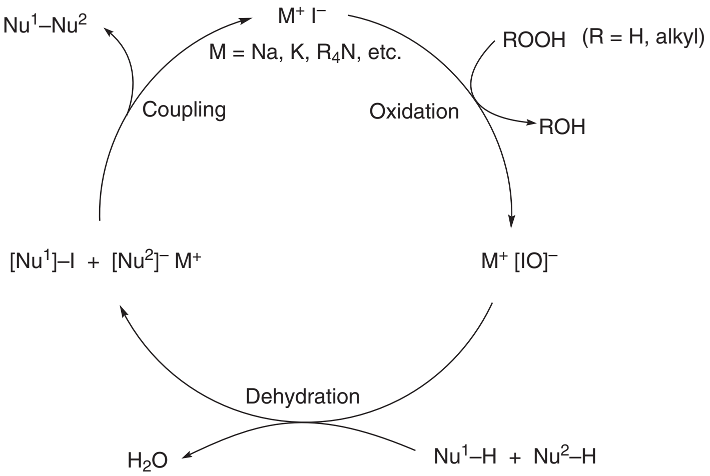


Scheme 2.4 Activation of molecular iodine through double halogen-bonding interaction.

halogen-bonding interaction of Lewis acidic another molecular iodine and Lewis basic triphenylphosphine sulfide. This method for the activation of iodine is highly effective for enantioselective iodocyclization using chiral Lewis base catalyst and halosuccinimide [10, 11]. Please refer to Chapter 3 for details on catalysis by XB based on iodine.

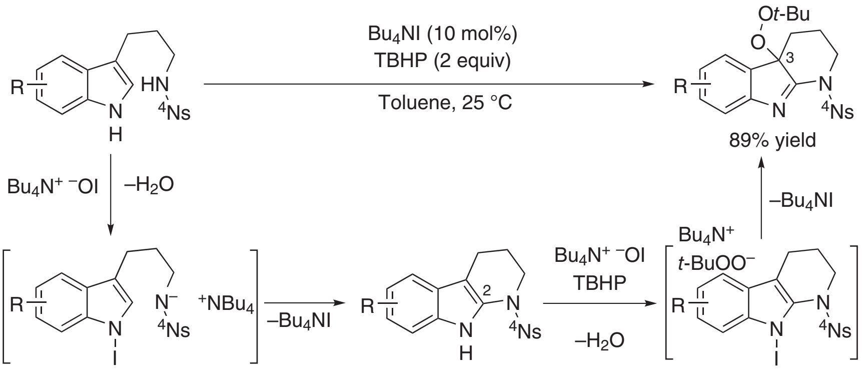
## 2.3 Iodine(I) Catalysis

Iodide salts are often used as precatalysts in the presence of appropriate cooxidants such as hydrogen peroxide, alkyl hydroperoxides, sodium percarbonate, Oxone, potassium persulfate, and *m*-CPBA. Depending on the coupling partners, oxidants, and reaction conditions, these reactions may proceed *via* an ionic or radical mechanism. In 2010, Ishihara et al. developed a quaternary ammonium hypoiodite catalysis for the oxidative coupling reactions [12, 13]. Hypoiodite salts, the catalytic active species, are generated *in situ* from the corresponding iodides in the presence of relatively inexpensive and mild oxidants such as hydrogen peroxide or alkyl hydroperoxides (Scheme 2.5) [14]. This catalytic oxidation system proceeds under milder conditions, and water or alcohol is the only side product derived from the oxidant used.



**Scheme 2.5** General catalytic cycle of hypoiodite catalysis for oxidative coupling.

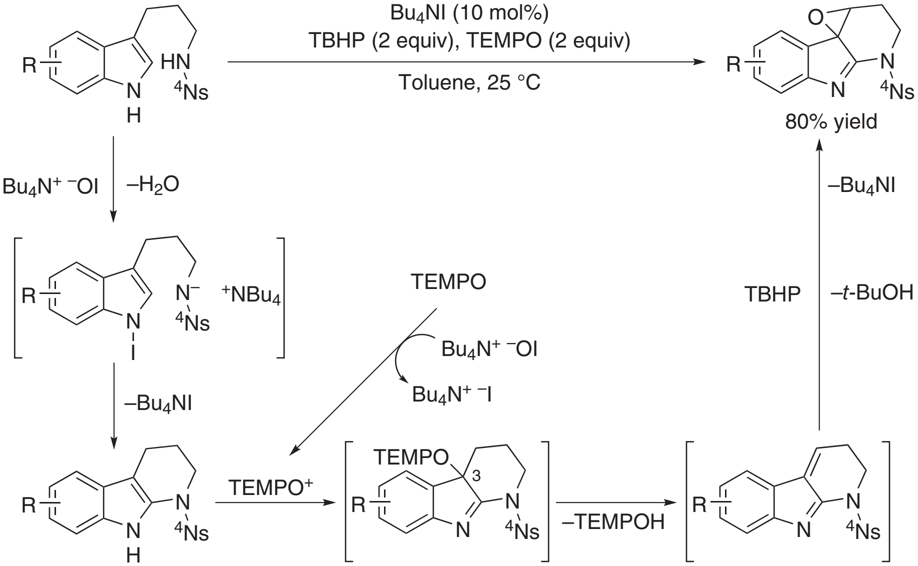
As an example, in 2020, Ishihara et al. reported the hypoiodite-catalyzed dearomative peroxycyclization of homotryptamine derivatives to peroxytetrahydropyridoindolenines under mild conditions (Scheme 2.6) [15]. This is the tandem reaction of the intramolecular oxidative aminocyclization of homotryptamines at the C-2 position and the subsequent oxidative coupling of tetrahydropyridoindoles with TBHP at the C-3 position.



Scheme 2.6 Hypoiodite-catalyzed tandem oxidative cyclization/coupling reactions of homotryptamine derivatives.

Interestingly, a tandem oxidative cyclization/epoxidation proceeds in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as an additive to give epoxyindolenines (Scheme 2.7). In the latter case, a preferential electrophilic addition of TEMPO$^+$ to tetrahydropyridoindole, a common intermediate, is generated *in situ* by the hypoiodite-catalyzed oxidation of TEMPO, at the C-3 position followed by elimination and epoxidation.

In contrast, the tandem oxidative cyclization of indole derivatives tethered to aniline sulfonamides using a catalytic amount of tetrabutylammonium iodide (TBAI) and TBHP as an oxidant gives the corresponding indolo[2,3-*b*]quinolines as



Scheme 2.7 Hypoiodite-catalyzed tandem oxidative cyclization/epoxidation reactions of homotryptamine derivatives (ionic pathway).