4

Hypervalent Iodine Catalysis

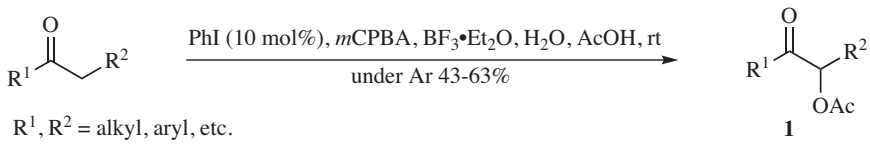
It has been recognized for many years that there are similarities between hypervalent iodine compounds and transition metal organic complexes. The hypervalent bond is highly polarized and it is longer and weaker than a regular covalent bond and the presence of hypervalent bonding leads to special structural features and reactivity pattern characteristic of polyvalent iodine compounds (Chapter 1). The reactions of hypervalent molecules are commonly discussed in terms of oxidative addition, reductive elimination, ligand exchange and ligand coupling, which are typical of transition metal chemistry [1]. However, catalytic reactions, typical of transition metals, remained unknown for hypervalent iodine compounds until the beginning of twenty-first century.

In 2005, Kita and Ochiai independently reported the catalytic use of aryl iodides, in the presence of stoichiometric *m*-chloroperoxybenzoic acid (*m*CPBA), to perform oxidative dearomatization and biarylation of phenolic substrates [2], or α-acetoxylation of carbonyl compounds [3]. These reactions involved selective generation of the highly reactive hypervalent iodine(III) species *in situ* from aryl iodide and terminal oxidant. The first examples of catalytic application of the iodine(V) species in the oxidation of alcohols using Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a stoichiometric oxidant at 70 °C were independently reported by the groups of Vinod [4] in 2005 and Giannis [5] in 2006. These initial reports were quickly followed by the discovery of numerous other reactions based on the iodine(I)/iodine(III), iodine(I)/iodine(V) and iodide anion/hypoiodite catalytic cycles. Several examples of reactions catalyzed by hypervalent iodine species in the presence of a co-catalyst (e.g., TEMPO, ruthenium salts, or metalloporphyrins) have also been reported. While chemical reactions catalyzed by 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, have been known since 1994 (Section 3.1.1) [6]. Reactions catalyzed by hypervalent iodine species have been overviewed in several review articles [7–15].

4.1 Catalytic Cycles Based on Iodine(III) Species

Catalytic reactions of this type usually involve the reoxidation of iodoarene to aryliodine(III) species *in situ* using oxidants such as peroxycarboxylic acids, hydrogen peroxide, sodium perborate, or Oxone at room temperature. The choice of oxidant is critically important; the oxidant must not react with the substrate, as the substrate should only be oxidized by the hypervalent iodine species. The stoichiometric oxidant has to be carefully selected to achieve the re-oxidation of the iodine compound under homogeneous reaction

Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds, First Edition. Viktor V. Zhdankin.



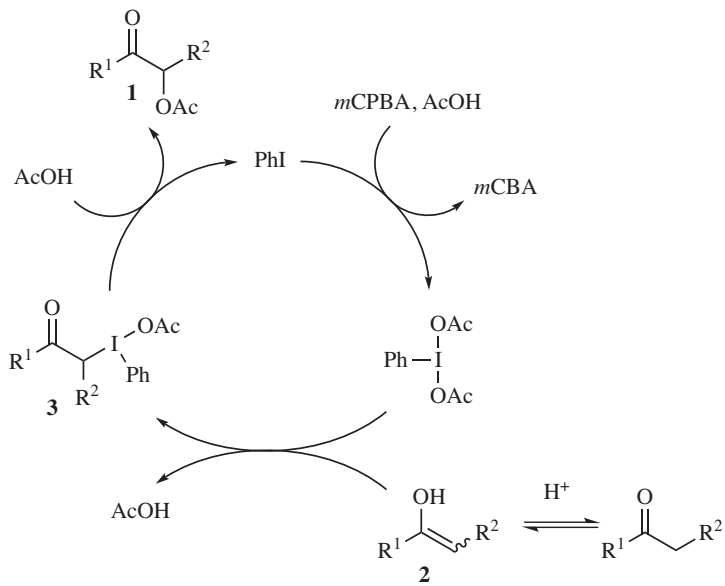
Scheme 4.1

conditions. The nature of the aryl iodide is also important. Most commonly, iodobenzene is used as the catalyst; however, numerous other iodoarenes have also been tested in these reactions. Particularly important are the enantioselective reactions catalyzed by chiral iodoarenes [11, 16].

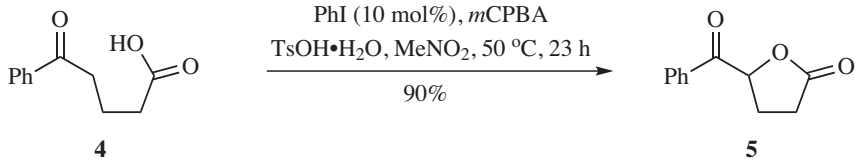
4.1.1 Oxidative α-Functionalization of Carbonyl Compounds

In 2005 Ochiai and coworkers reported the first iodobenzene-catalyzed reaction, a catalytic variant of α-acetoxylation of ketones based on the *in situ* generation of (diacetoxyiodo)benzene from iodobenzene using *m*-chloroperoxybenzoic acid (*m*CPBA) as a terminal oxidant [3]. In a typical example, the oxidation of a ketone with *m*CPBA (2 equiv) in acetic acid in the presence of a catalytic amount of iodobenzene (0.1 equiv), $BF_3{\cdot}OEt_2$ (3 equiv) and water (5 equiv) at room temperature under argon affords the respective α-acetoxy-ketone **1** in a moderate yield (Scheme 4.1). 4-Iodotoluene and 4-chloroiodobenzene can also serve as catalysts in the α-acetoxylation of ketones under these reaction conditions; however, the use of iodobenzene results in the highest yields [3]. The use of at least 10 mol% iodobenzene in this reaction is necessary. When smaller amounts are used, the reaction slows and Baeyer–Villiger oxidation products resulting from a direct reaction of *m*CPBA and the ketone are observed [3].

Scheme 4.2 shows a catalytic cycle for this oxidation. Boron trifluoride etherate accelerates the initial oxidation of iodobenzene to (diacyloxyiodo)benzene by *m*CPBA in the presence of acetic acid. Ligand



Scheme 4.2



Scheme 4.3

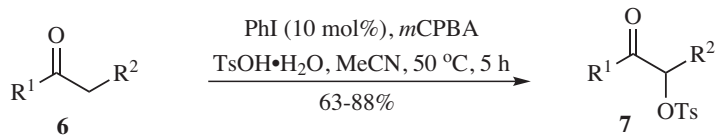
exchange of $PhI(OAc)_2$ with enol **2** derived from a ketone produces an alkyliodonium intermediate (**3**), which on S_N2 displacement by acetic acid affords an α-acetoxy-ketone (**1**) with liberation of iodobenzene [3].

A study of the catalytic α-acetoxylation reaction of acetophenone by electrospray ionization tandem mass spectrometry (ESI-MS/MS) has confirmed the mechanism shown in Scheme 4.2. In particular, the trivalent iodine species was detected when iodobenzene and *m*CPBA in acetic acid were mixed, which indicated the facile oxidation of a catalytic amount of PhI to the iodine(III) species by *m*CPBA. Most importantly, the protonated alkyliodonium intermediate **3** (R^1 = Ph, R^2 = H) was observed at *m/z* 383 from the reaction solution and this ion gave the protonated α-acetoxylation product **1** at *m/z* 179 in MS/MS by an intramolecular reductive elimination of PhI [17].

Based on Ochiai's procedure for α-acetoxylation of ketones, Ishihara and coworkers have developed the hypervalent iodine-catalyzed oxylactonization of ketocarboxylic acids to ketolactones [18]. Optimized reaction conditions consist of the treatment of a ketocarboxylic acid with iodobenzene (10 mol%), *p*-toluenesulfonic acid monohydrate (20 mol%) and *m*CPBA as a stoichiometric oxidant in nitromethane solution; Scheme 4.3 shows as a representative example the cyclization of ketocarboxylic acid **4** to ketolactone **5.**

As a further extension of the Ochiai's procedure for α-acetoxylation, the catalytic procedure for α-tosyloxylation of ketones using *m*CPBA as stoichiometric oxidant and iodoarenes as catalysts in the presence of *p*-toluenesulfonic acid has been developed. Various α-tosyloxyketones **7** can be efficiently prepared in high yields from the reaction of ketones **6** with *m*CPBA (1.1 equiv) and *p*-toluenesulfonic acid (1.1 equiv) in the presence of a catalytic amount of iodobenzene with moderate warming (Scheme 4.4) [19]. The mechanism of this reaction involves initial oxidation of PhI by *m*CPBA in the presence of *p*-toluenesulfonic acid to generate [hydroxy(tosyloxy)iodo]benzene *in situ,* which then reacts with the enol form of ketone to give the α-tosyloxyketone.

Further modification of this reaction (Scheme 4.4) involves the use of polystyrene-supported iodobenzene as a recyclable catalyst, which can be recovered by simple filtration of the reaction mixture and reused (Section 5.5) [20]. Alcohols can be used instead of ketones for the preparation of α-tosyloxyketones **7;** in this case an excess of *m*CPBA (2.1 equiv) is employed in the presence of KBr (0.1 equiv) and PhI or poly(4-iodostyrene)



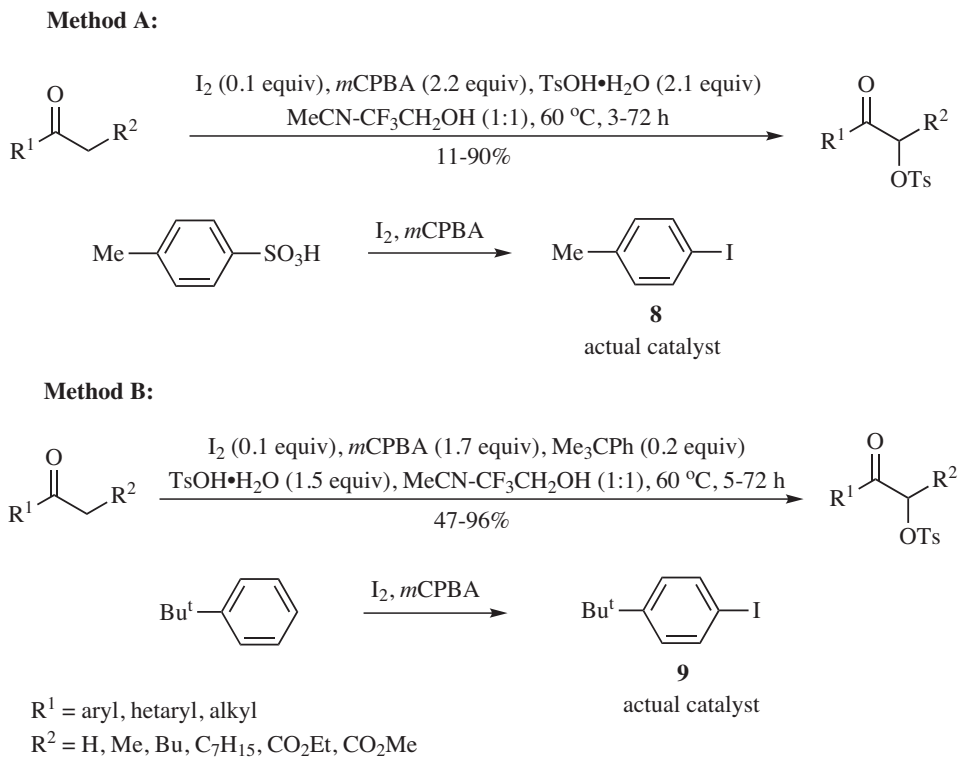
R^1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, Et, C_5H_{11}
R^2 = H, Me, Bu, C_7H_{15}
or $R^1 + R^2 = (CH_2)_5$

Scheme 4.4

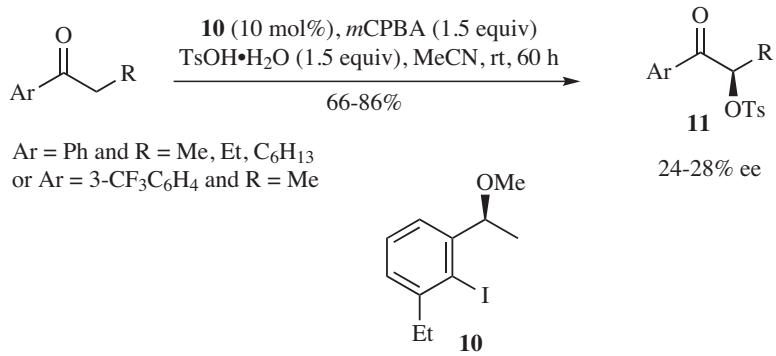
as the catalysts [20]. Recyclable ionic-liquid supported iodoarenes have also been utilized as catalysts in the α-tosyloxylation of ketones with *m*CPBA and *p*-toluenesulfonic acid [21].

Tanaka and Togo investigated the use of Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as terminal oxidant in the iodoarene-mediated α-tosyloxylation of ketones [22]. Various alkyl aryl ketones, dialkyl ketones and cycloheptanone can be converted into the corresponding α-tosyloxyketones in good yields by using Oxone and *p*-toluenesulfonic acid monohydrate in the presence of *p*-iodotoluene in acetonitrile. In these reactions, *p*-iodotoluene, $4\text{-}MeC_6H_4I$, works as the catalyst and *p*-[hydroxy(tosyloxy)iodo]toluene, $4\text{-}MeC_6H_4I(OH)OTs$, is formed *in situ* as the reactive species for the α-tosyloxylation of ketones. However, one equivalent of *p*-iodotoluene was required to obtain α-tosyloxyketones in good yields [22]. The catalytic efficiency of this reaction is low, because *p*-iodotoluene is partially oxidized by Oxone to the iodine(V) species, which are not active in the α-tosyloxylation of ketones.

Togo and coworkers have found that alkyl aryl ketones and dialkyl ketones could be converted into the corresponding α-tosyloxyketones in generally low yields by the reaction with *m*CPBA and *p*-toluenesulfonic acid monohydrate in the presence of a catalytic amount of molecular iodine in a mixture of acetonitrile and 2,2,2-trifluoroethanol (method A, Scheme 4.5) [23]. The same conversion of ketones into the corresponding α-tosyloxyketones could be smoothly carried out by the reaction with *m*CPBA and $TsOH \cdot H_2O$ in the presence of catalytic amounts of iodine and *tert*-butylbenzene in a mixture of acetonitrile and 2,2,2-trifluoroethanol (method B). In these reactions, *p*-iodotoluene **8** (method A) and 4-*tert*-butyl-1-iodobenzene **9** (method B) are formed at first and are then converted into the corresponding [hydroxy(tosyloxy)iodo]arenes, ArI(OH)OTs,



Scheme 4.5



Scheme 4.6

by reaction with *m*CPBA and TsOH·H_2O. [Hydroxy(tosyloxy)iodo]arenes work as the actual reagents for the α-tosyloxylation of ketones in the catalytic cycle. A similar procedure for the α-tosyloxylation of ketones employs Oxone (2 equiv) as the oxidant and I_2 (0.7 equiv) as the catalyst [24].

Several research groups have investigated the enantioselective α-oxytosylation of ketones catalyzed by chiral iodoarenes. The first reaction of this type, catalyzed by the enantiopure iodoarene **10** and resulting in the enantioenriched α-tosyloxyketones **11** (Scheme 4.6), was reported in 2007 by Wirth and coworkers [25]. The authors have tested numerous chiral iodoarenes as catalysts, but in most cases the enantioselectivity of this reaction was very low [25–27].

Higher levels of enantioselectivities in the α-oxytosylation of ketones were achieved in several recent works. Chi Zhang and coworkers have evaluated spirobiindane-based chiral iodoarenes as catalyst and were able to obtain α-tosyloxylated ketones in up to 58% enantiomeric excess using catalyst **12** (Figure 4.1) [28]. Moran and Rodriguez have prepared several chiral aryl iodides (e.g., structures **13** and **14**, Figure 4.1) and

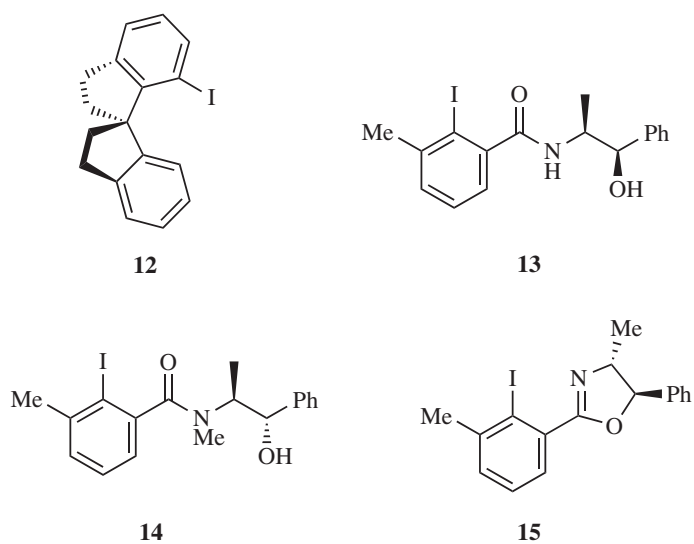
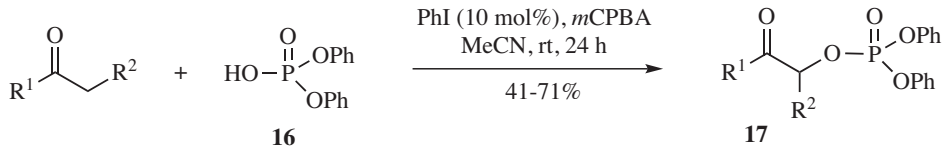


Figure 4.1 *Chiral aryl iodide catalysts for enantioselective α-oxytosylation of ketones.*



16 17

R^1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, Me, Et
R^2 = H, Me

Scheme 4.7

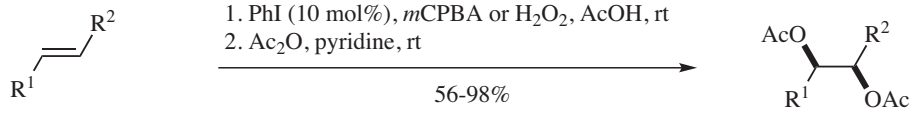
assessed them as catalysts in the enantioselective α-oxytosylation of propiophenone and in the oxidative cyclization of 5-oxo-5-phenylpentanoic acid to 5-benzoyldihydrofuran-2(3*H*)-one (Scheme 4.3) [29]. The highest enantioselectivities obtained were 18% for the α-oxytosylation using catalyst **13** and 51% ee for the oxidative cyclization using catalyst **14.** Legault and coworkers have developed a family of iodooxazoline catalysts (e.g., structure **15,** Figure 4.1) for the iodine(III)-mediated α-tosyloxylation of ketone derivatives [30]. The use of catalyst **15** (10 mol%) in dichloromethane solution allows the best levels of enantioselectivity to be achieved for this reaction (up to 54% ee). A drastic enhancement in catalytic activity was observed due to the introduction of steric hindrance *ortho* to the iodine atom of the catalyst (e.g., methyl group in catalyst **15**) [31].

Analogously to the α-oxytosylation, an effective catalytic method for the α-phosphoryloxylation of ketones has been developed [32]. When ketones are treated with phosphates **16** in the presence of iodobenzene as the catalyst and *m*CPBA as the terminal oxidant in acetonitrile at room temperature, the α-phosphoryloxylation of ketones takes place easily and the corresponding keto phosphates **17** are obtained in moderate to good yields (Scheme 4.7) [32].

4.1.2 Oxidative Functionalization of Alkenes and Alkynes

Several examples of hypervalent iodine-catalyzed reactions of unsaturated compounds have been reported. A method for the organocatalytic *syn* diacetoxylation of alkenes has been developed using aryl iodides as efficient catalysts and hydrogen peroxide or *m*CPBA as terminal oxidants (Scheme 4.8) [33]. A broad range of substrates, including electron-rich as well as electron-deficient alkenes, are smoothly transformed by this procedure, furnishing diacetoxylation products **18** in good to excellent yields with high diastereoselectivity (up to >19 : 1 dr). Iodobenzene or 4-iodotoluene can be used as catalysts in this reaction.

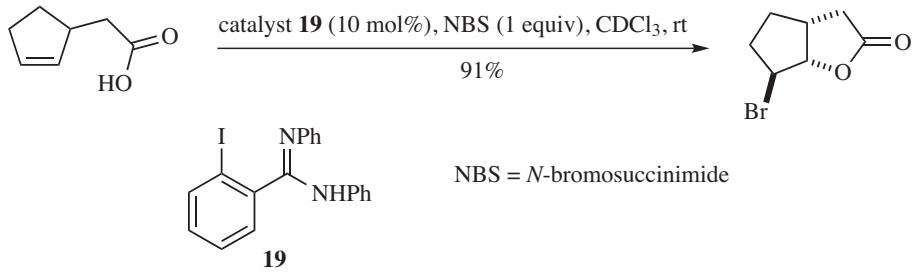
Braddock and coworkers have demonstrated that suitably *ortho*-substituted iodobenzenes act as organocatalysts for the transfer of electrophilic bromine from *N*-bromosuccinimide to alkenes via the intermediacy of bromoiodinanes [34]. Particularly active catalyst is the *ortho*-substituted iodoarene **19,** as illustrated by a bromolactonization reaction shown in Scheme 4.9. An alternative procedure for the bromolactonization of



R^1 and R^2 = alkyl, aryl

18

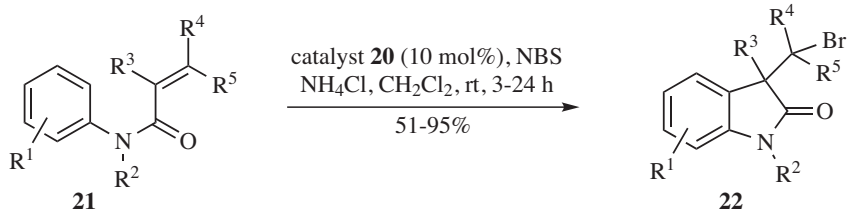
Scheme 4.8



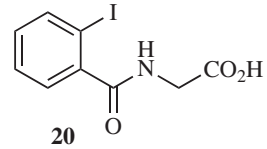
Scheme 4.9

alkenoic acids employs iodobenzene as a catalyst, sodium bromide as the source of bromine and Oxone as the terminal oxidant in CF_3CH_2OH at room temperature [35].

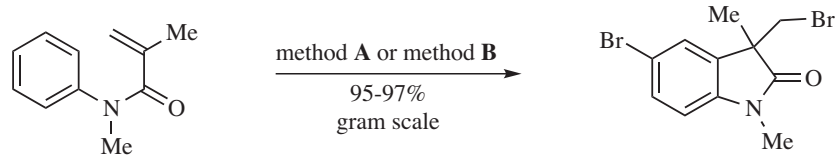
Based on the hypervalent iodine-catalyzed bromocarbocyclization of appropriate alkenoic precursors **21,** Gulder and coworkers have developed an efficient synthetic approach to 3,3-disubstituted oxoindoles **22** (Scheme 4.10) [36]. These cyclizations are catalyzed by 2-iodobenzamide **20** at room temperature using NBS as the source of electrophilic bromine. Alternatively, KBr can be used as the source of bromine in the presence of Oxone as a terminal oxidant. The synthetic utility of this cyclization has been demonstrated by the



R^3 = Me, R^4 and R^5 = H; R^2 = Me or Bn; R^1 = H, Me, OMe, F, Br, I, etc

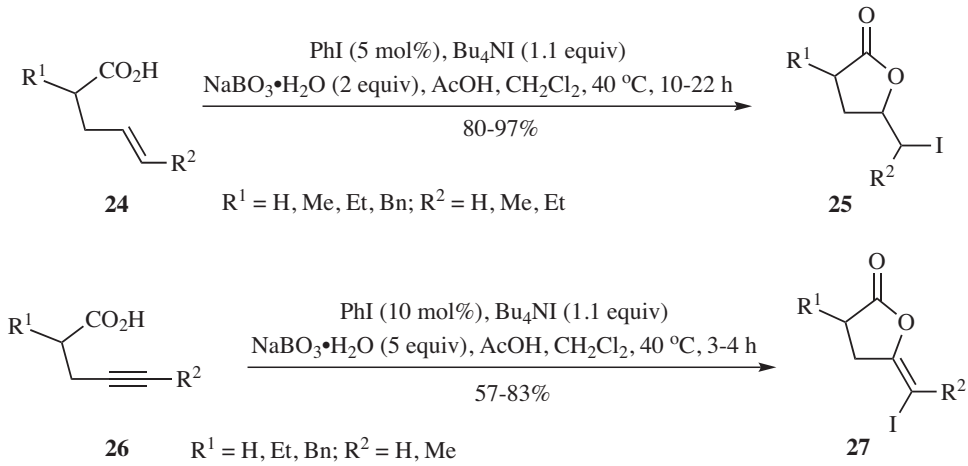


NBS = *N*-bromosuccinimide



A: catalyst **20** (10 mol%), NBS (2.4 equiv), NH_4Cl (10 mol%), CH_2Cl_2, rt, 12 h
B: catalyst **20** (10 mol%), KBr (2.4 equiv), Oxone (2.4 equiv), CH_2Cl_2, rt, 12 h

Scheme 4.10



Scheme 4.11

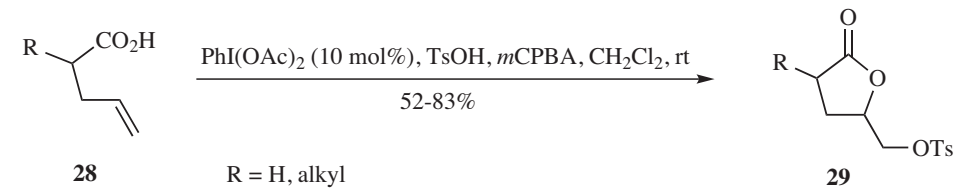
preparation of product **23,** which is the key intermediate in the formal synthesis of the acetylcholinesterase inhibitor physostigmine [36].

A catalytic procedure for the (diacetoxyiodo)benzene-promoted oxidative iodolactonization of pentenoic, pentynoic and hexynoic acids in the presence of tetrabutylammonium iodide has been reported [37]. In this procedure, (diacetoxyiodo)benzene is generated *in situ* using a catalytic amount of iodobenzene with sodium perborate monohydrate as the stoichiometric oxidant. Various unsaturated acids, including δ-pentenoic acids **24,** δ-pentynoic acids **26** and δ-hexynoic acid, gave high yields of the respective lactones (e.g., **25** and **27**) using this organocatalytic methodology (Scheme 4.11) [37].

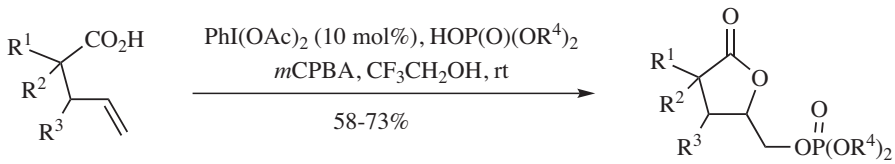
An efficient catalytic method for sulfonyloxylactonization of alkenoic acids using (diacetoxyiodo)benzene as a recyclable catalyst in combination with *m*-chloroperoxybenzoic acid as an oxidant in the presence of a sulfonic acid has been reported [38]. This reaction effects the cyclization of alkenoic acids **28** in dichloromethane at room temperature, giving tosyloxylactones **29** in good yields (Scheme 4.12).

A similar catalytic phosphoryloxylactonization of pentenoic acids has been reported. In particular, the cyclization of 4-pentenoic acids **30** with phosphates using (diacetoxyiodo)benzene as a catalyst in combination with *m*CPBA as the terminal oxidant in CF_3CH_2OH at room temperature affords phosphoryloxylactones **31** in good yields (Scheme 4.13) [39].

Iodobenzene has been shown to catalyze the 5-*exo-dig* cyclization of δ-alkynyl β-ketoesters **32** under oxidative conditions that generate hypervalent iodine species *in situ* (Scheme 4.14) [29]. The cyclopentane

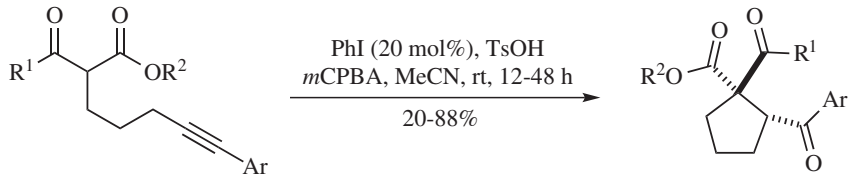


Scheme 4.12



30 $R^1 - R^3$ = H or alkyl; R^4 = Ph, Bn, 4-$NO_2C_6H_4$ **31**

Scheme 4.13



32 **33**

R^1 = Me or Et
R^2 = Me, Et, Pr^i
Ar = Ph, 4-$Bu^tC_6H_4$, 4-BuC_6H_4, 4-ClC_6H_4

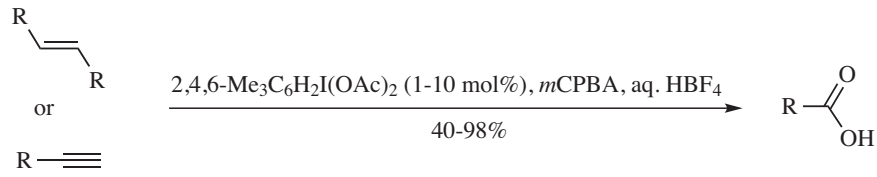
Scheme 4.14

products **33** contain adjacent quaternary and tertiary stereocenters, which are generated with excellent diastereoselectivity (up to over 20 : 1 dr).

Ochiai and coworkers have developed an efficient iodoarene-catalyzed oxidative cleavage of alkenes and alkynes using *m*CPBA as a terminal oxidant [40]. Various cyclic and acyclic alkenes as well as aliphatic and aromatic alkynes are smoothly cleaved to carboxylic acids under these organocatalytic conditions (Scheme 4.15) [40].

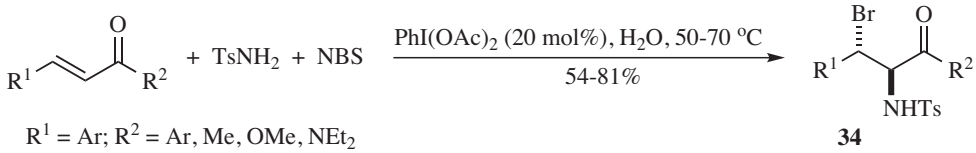
A convenient procedure for the aminobromination of electron-deficient olefins using *N*-bromosuccinimide/tosylamide (Scheme 4.16) or Bromamine-T promoted by (diacetoxyiodo)benzene has been reported [41, 42]. This efficient metal-free protocol affords the vicinal bromamines **34** with excellent stereoselectivities. A similar (diacetoxyiodo)benzene-catalyzed aminochlorination can be performed by using Chloramine-T as nitrogen and chlorine source [43].

Wirth and coworkers published in 2007 a detailed study of the aziridination of alkenes with the $PhI(OAc)_2$/N-substituted hydrazine system (Scheme 4.17) and, in particular, reported tentative evidence that this reaction proceeds through the formation of an aminoiodane that reacts directly with the alkene [44].



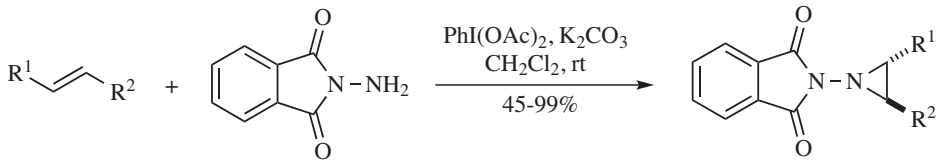
R = alkyl or aryl

Scheme 4.15



R^1 = Ar; R^2 = Ar, Me, OMe, NEt_2 **34**

Scheme 4.16



R^1/R^2 = Ph/H, 4-$CF_3C_6H_4$/H, 4-FC_6H_4/H, 4-MeC_6H_4/H, Ph/Me, Ph/CO_2Me, etc.

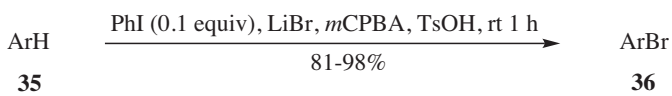
Scheme 4.17

Furthermore, the authors of this publication have analyzed the requirements to make this reaction catalytic in iodoarene. This reaction requires an oxidant that will oxidize iodoarenes but that does not oxidize alkenes and it is possible that no such oxidant actually exists [44]. However, the catalytic variant of this aziridination has been developed more recently employing an iodide–hypoiodite catalytic cycle (Section 4.4) [45].

4.1.3 Oxidative Bromination of Aromatic Compounds

Oxidative bromination of arenes can be achieved by the reaction with a source of bromide anion and an appropriate oxidant, possibly via intermediate formation of electrophilic bromoiodanes. In particular, an efficient and regioselective monobromination of electron-rich aromatic compounds has been developed, in which iodobenzene is used as the catalyst in combination with *m*CPBA as the terminal oxidant. The bromination of arenes **35** with lithium bromide is fast in THF at room temperature, providing regioselective monobrominated products **36** in good yields (Scheme 4.18) [46].

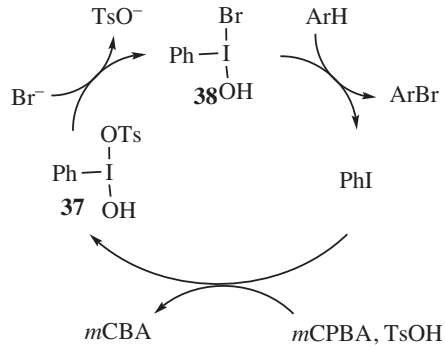
The proposed catalytic cycle for this reaction includes initial formation of [hydroxyl(tosyloxy)iodo]benzene **37** by oxidation of iodobenzene in the presence of toluenesulfonic acid followed by its conversion into the bromoiodane **38** via ligand exchange and then the bromination of arene to form the aryl bromide (Scheme 4.19). The reduced by-product, iodobenzene, is again transformed into the hypervalent iodine reagent by oxidation with *m*CPBA [46].



35 **36**

Ar = 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-MeO-naphthyl, 2-MeO-5-IC_6H_3, 2,5-$(MeO)_2C_6H_3$, 2,4,6-$Me_3C_6H_2$, 4-$Me_2NC_6H_4$, 4-Me-thienyl

Scheme 4.18

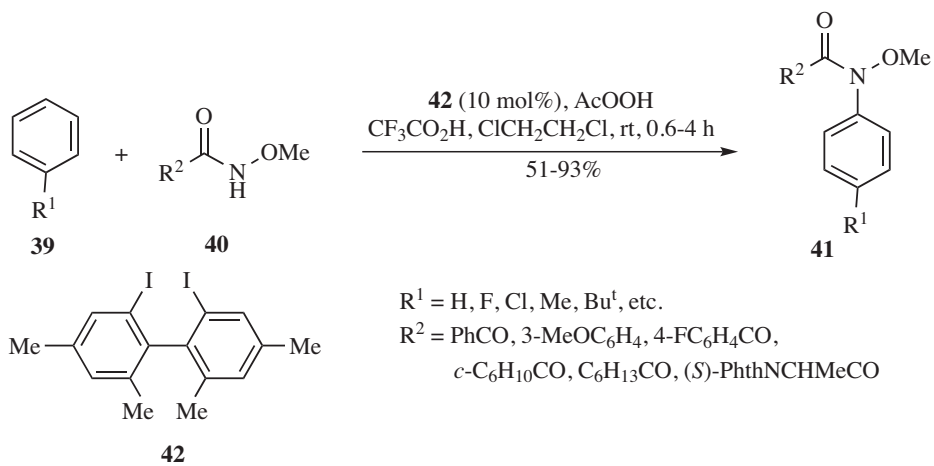


Scheme 4.19

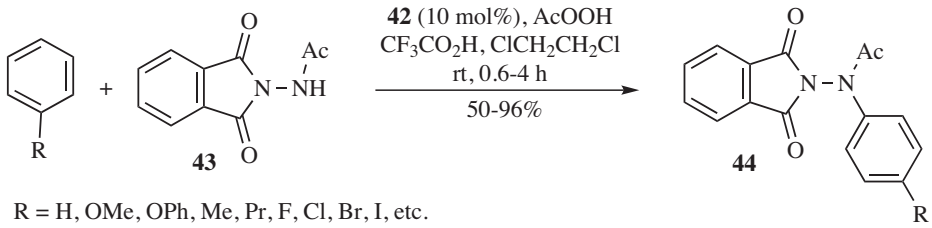
4.1.4 Oxidative Amination of Aromatic Compounds

Aromatic C–H bonds can be aminated in intermolecular or intramolecular mode using amides as the nitrogen source, catalytic iodoarene and an appropriate oxidant, such as peroxycarboxylic acid. An atom-economical, environmentally friendly, direct oxidative intermolecular procedure for the amination and hydrazination of non-functionalized arenes has been developed by Antonchick and coworkers [47]. A wide range of arenes (e.g., **39**), including simple benzene, can be aminated using *N*-methoxybenzamides **40** as amination reagent in the presence of peracetic and trifluoroacetic acids to give products **41** (Scheme 4.20). Even electron-poor arenes like chlorobenzene and fluorobenzene can be selectively functionalized in the *para*-position using this mild method. The reactions of electron-rich arenes afford products of amination in up to 93% yield. Out of several iodoarenes tested, 2,2′-diiodo-4,4′,6,6′-tetramethylbiphenyl (**42**) has shown the highest catalytic activity in this reaction.

This procedure was further extended to organocatalytic hydrazination of non-functionalized arenes to products **44** using *N*-(1,3-dioxoisoindolin-2-yl)acetamide (**43**) as the nitrogen source (Scheme 4.21) [47].



Scheme 4.20

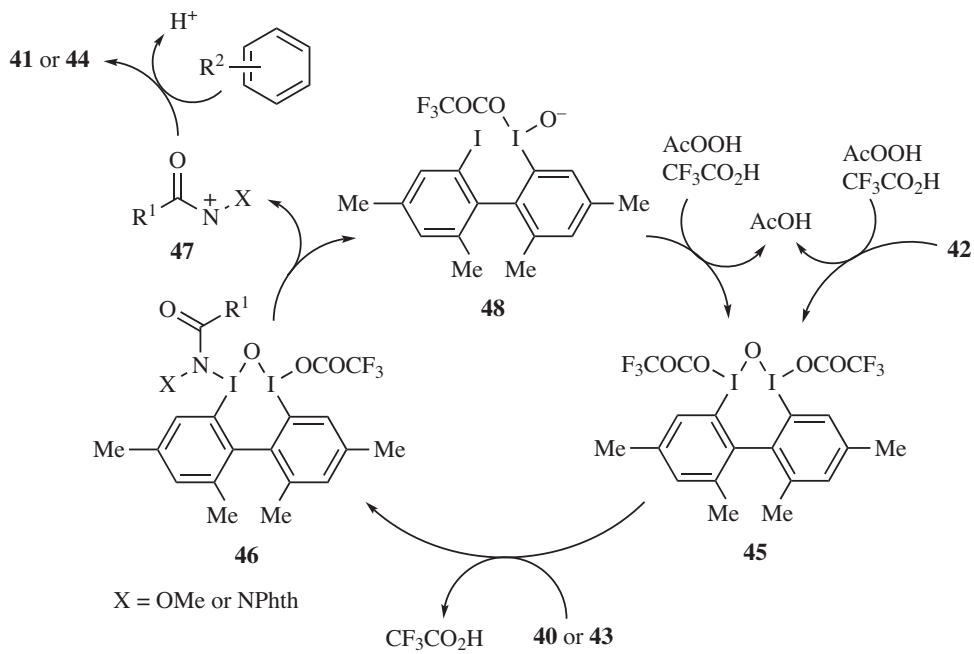


Scheme 4.21

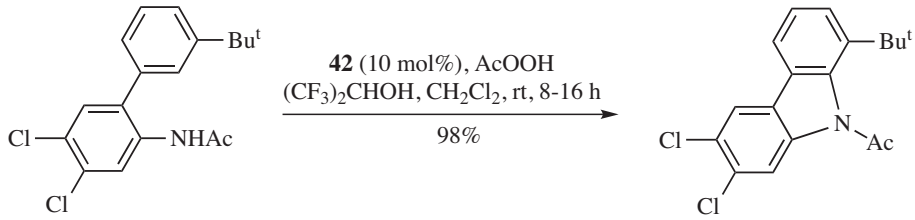
The mechanism of this reaction involves initial oxidation of aryl iodide **42** by peracetic acid to the active hypervalent iodine species **45,** followed by ligand substitution at iodine(III) by **40** or **43** to generate species **46,** which undergo oxidative fragmentation to form nitrenium ions **47.** Reaction of an arene with the electron-deficient nitrenium ion **47** affords the final products of amination and the reduced intermediate **48,** which is reoxidized to the species **45** (Scheme 4.22) [47].

Several examples of cyclizations through intramolecular C–N bond formation catalyzed by hypervalent iodine species have been reported. Antonchick and coworkers developed an efficient organocatalytic method for the preparation of carbazoles through catalytic oxidative C–N bond formation [48]. The best yields of products were obtained in hexafluoro-2-propanol using 2,2′-diiodo-4,4′,6,6′-tetramethylbiphenyl (**42**) as the catalyst and peracetic acid as the oxidant, as illustrated by a representative example shown in Scheme 4.23.

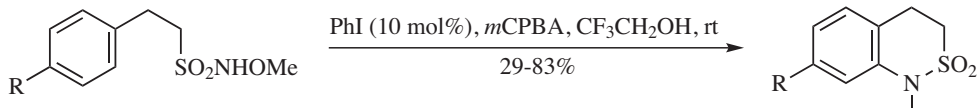
Togo and Moroda have reported a (diacetoxyiodo)benzene-mediated cyclization reaction of 2-aryl-*N*-methoxyethanesulfonamides **49** using iodobenzene as a pre-catalyst (5–10 mol%) and *m*-chloroperoxybenzoic



Scheme 4.22



Scheme 4.23



49 R = Me, F, Cl, Br, $ClCH_2$

Scheme 4.24

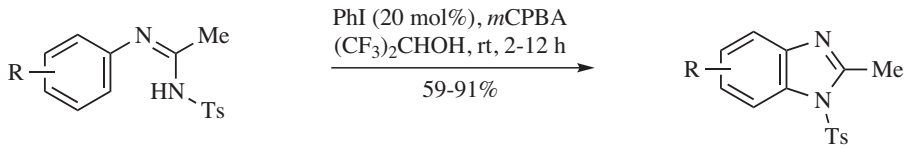
acid (*m*CPBA) as the stoichiometric oxidant (Scheme 4.24) [49]. A similar catalytic cyclization has also been achieved using Oxone in acetonitrile [50].

Likewise, the oxidative C–H amination of *N*″-aryl-*N*′-tosyl/*N*′-methylsulfonylamidines and *N*,*N*′-bis(aryl)amidines has been accomplished using iodobenzene as a catalyst to furnish 1,2-disubstituted benzimidazoles in the presence of *m*CPBA as a terminal oxidant at room temperature (Scheme 4.25) [51]. The reaction is general and the target benzimidazoles can be obtained in moderate to high yields.

4.1.5 Oxidation of Phenolic Substrates to Quinones and Quinols

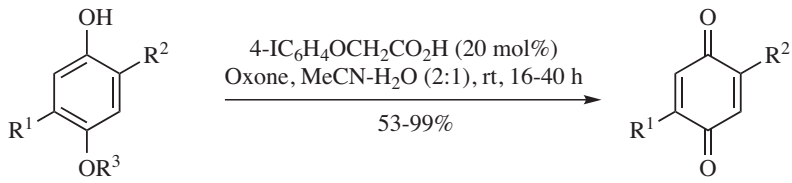
The oxidation of phenols or *o*- and *p*-hydroquinones with stoichiometric [bis(acyloxy)iodo]arenes to the corresponding benzoquinones is one of the most typical synthetic applications of hypervalent iodine reagents (Section 3.1.11). The catalytic version of this reaction was first reported by Yakura and Konishi in 2007 [52]. The reaction of *p*-alkoxyphenols **50** with a catalytic amount of 4-iodophenoxyacetic acid in the presence of Oxone as the terminal oxidant in aqueous acetonitrile at room temperature affords *p*-quinones **51** in high yields (Scheme 4.26) [52]. 4-Iodophenoxyacetic acid is a readily available and water-soluble aromatic iodide that has a particularly high catalytic activity in this reaction.

In the initial publication [52], a catalytic cycle based on the iodine(V) species was proposed for this reaction (Scheme 4.26); however, more recent studies (Section 4.2) have demonstrated that the oxidation of



R = Me, F, Cl, Br in different ring positions

Scheme 4.25



50 **51**

R^1 = H or $MeCH_2CH_2CMe_2$
R^2 = H, Bu^t, $MeCH_2CH_2CMe_2$, $Bu^tPh_2SiOCH_2$, N_3CH_2, phthalimide
R^3 = Me or Et

Scheme 4.26

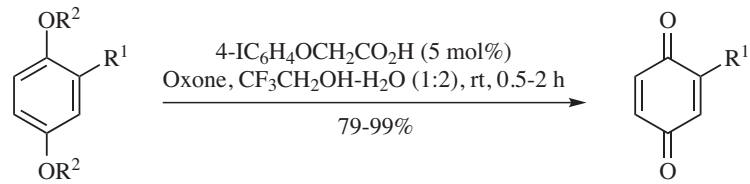
iodoarenes with Oxone at room temperature generates active iodine(III) species and heating to about 70 °C or the presence of a ruthenium catalyst is required to oxidize ArI to $ArIO_2$ [53].

Several modifications of the original procedure shown in Scheme 4.26 have been reported [54–56]. In particular, the reaction of *p*-dialkoxybenzenes **52** with a catalytic amount of 4-iodophenoxyacetic acid in the presence of Oxone as a co-oxidant in 2,2,2-trifluoroethanol–water (1 : 2) gives the corresponding *p*-quinones **53** in excellent yields (Scheme 4.27) [54, 56]. The same solvent system, 2,2,2-trifluoroethanol–water (1 : 2), can also be used for the efficient oxidation of *p*-alkoxyphenols to *p*-quinones [55].

A similar catalytic oxidation of *p*-substituted phenols bearing an alkyl or aryl group in the *para* position affords the corresponding *p*-quinols. In particular, the reaction of *p*-substituted phenols **54** with a catalytic amount of 4-iodophenoxyacetic acid and Oxone (4 equiv) at room temperature in an aqueous tetrahydrofuran or 1,4-dioxane solution gave *p*-quinols **55** in generally high yields (Scheme 4.28) [55, 57].

4.1.6 Oxidative Spirocyclization of Aromatic Substrates

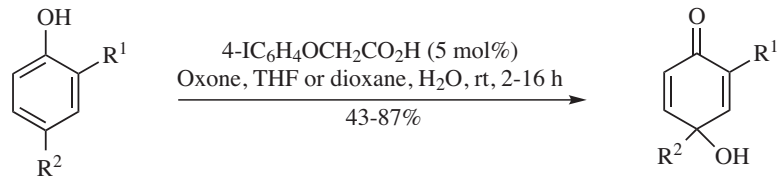
The oxidative dearomatization of appropriately substituted phenolic substrates resulting in intramolecular cyclization with the formation of spirocyclic products represents one of the most powerful synthetic tools in modern organic synthesis (Section 3.1.11). Kita and coworkers were the first to report a catalytic variant of the oxidative spirocyclization reaction based on the *in situ* regeneration of a [bis(trifluoroacetoxy)iodo]arene from iodoarene using *m*CPBA as a terminal oxidant [2]. In a representative example, the oxidation of



52 **53**

R^1 = H, Me, Bu^t, $CH_2CH_2CO_2Me$, etc.
R^2 = Me, Et, Bu^tMe_2Si

Scheme 4.27



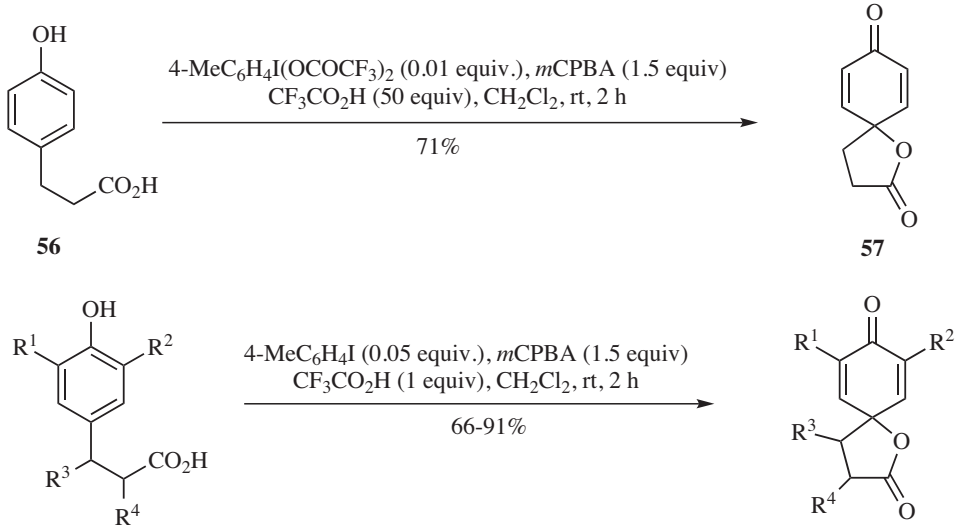
54 **55**

R^1 = H, Me, Pr, Ph, Br, etc.
R^2 = Me, Et, Bu^tCOOCH_2, Br, CN

Scheme 4.28

the phenolic substrate **56** with *m*CPBA in dichloromethane in the presence of a catalytic amount of *p*-[bis(trifluoroacetoxy)iodo]toluene (1 mol%) and trifluoroacetic acid at room temperature affords the respective spirolactone **57** in good yield (Scheme 4.29). Various other [bis(trifluoroacetoxy)iodo]arenes [e.g., $PhI(OCOCF_3)_2$, 4-$MeOC_6H_4I(OCOCF_3)_2$ and 2,4-$F_2C_6H_3I(OCOCF_3)_2$] and different acidic additives (acetic acid, $BF_3{\cdot}OEt_2$, TMSOTf, molecular sieves) can be used as catalysts in this reaction; however, the 4-$MeC_6H_4I(OCOCF_3)_2$/trifluoroacetic acid system generally provides the best catalytic efficiency. Under optimized conditions, various phenolic substrates **58** were oxidized to spirolactones **59** in the presence of catalytic amounts of *p*-iodotoluene (Scheme 4.29) [2]. Further modification of this catalytic procedure involved the use of peracetic acid as the terminal oxidant in fluoroalcohol solvents [58].

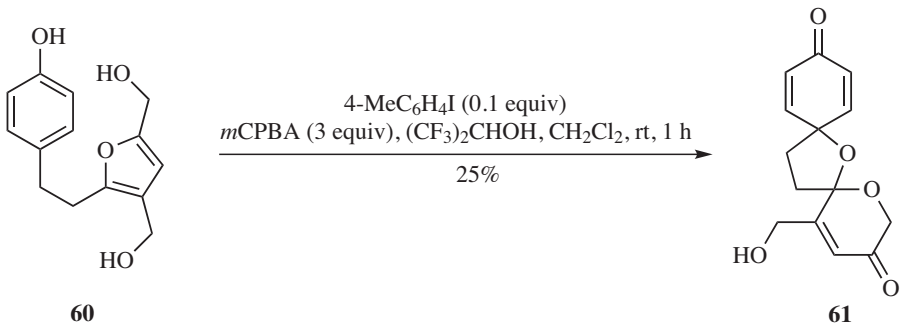
More recently, the Kita's catalytic spirocyclization has been tested in the synthesis of bioactive polyspirocyclohexa-2,5-dienones, as illustrated by Scheme 4.30 [59]. The target product **61** was isolated



56 **57**

58 R^1, R^2, R^3, R^4 = H, Me, Br
or R^1, R^2 = H, $R^3 + R^4$ = (=CH-CH=CH-CH=) **59**

Scheme 4.29

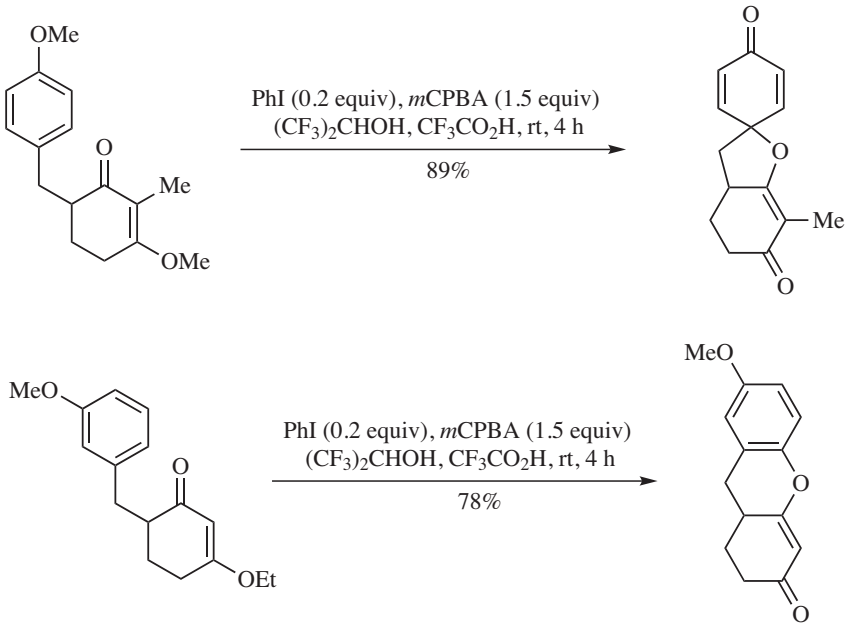


60 **61**

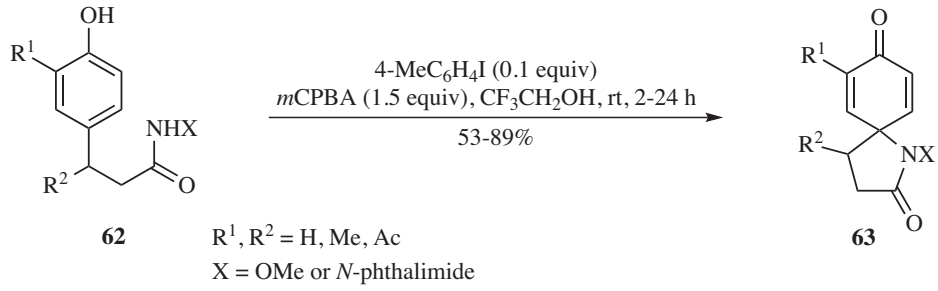
Scheme 4.30

in a low yield, probably due to the competitive oxidation of substrate **60** directly by *m*CPBA to give unwanted side products.

Hutt, Lupton and coworkers have further investigated the synthetic utility of the catalytic spirocyclization reaction and developed a procedure for the iodobenzene-catalyzed synthesis of spirofurans and benzopyrans by oxidative cyclization of vinylogous esters [60]. In particular, vinylogous esters bearing *para* or *meta* methoxy benzyl groups undergo oxidative cyclization with 5–20 mol% iodobenzene and *m*CPBA to give spirofuran- or benzopyran-containing heterocycles as illustrated by two specific examples shown in Scheme 4.31. Both of these reactions proceed via radical–cation intermediates (Section 3.1.12). These cyclizations allow rapid generation of skeletally complex products in good to excellent yields [60].



Scheme 4.31

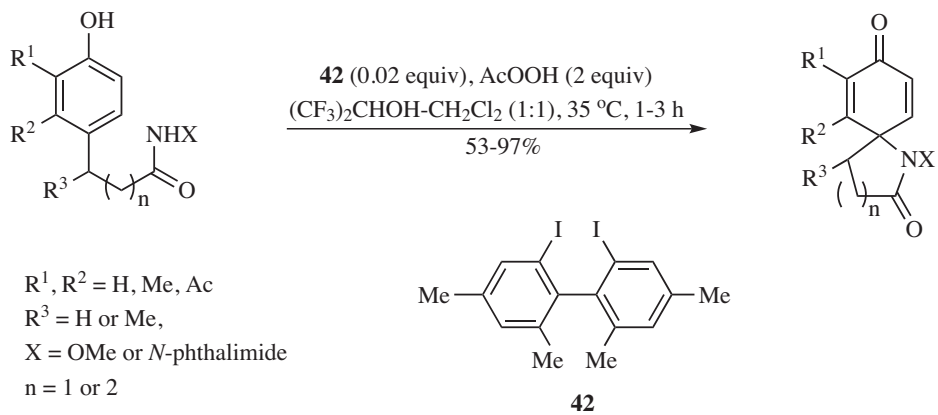


Scheme 4.32

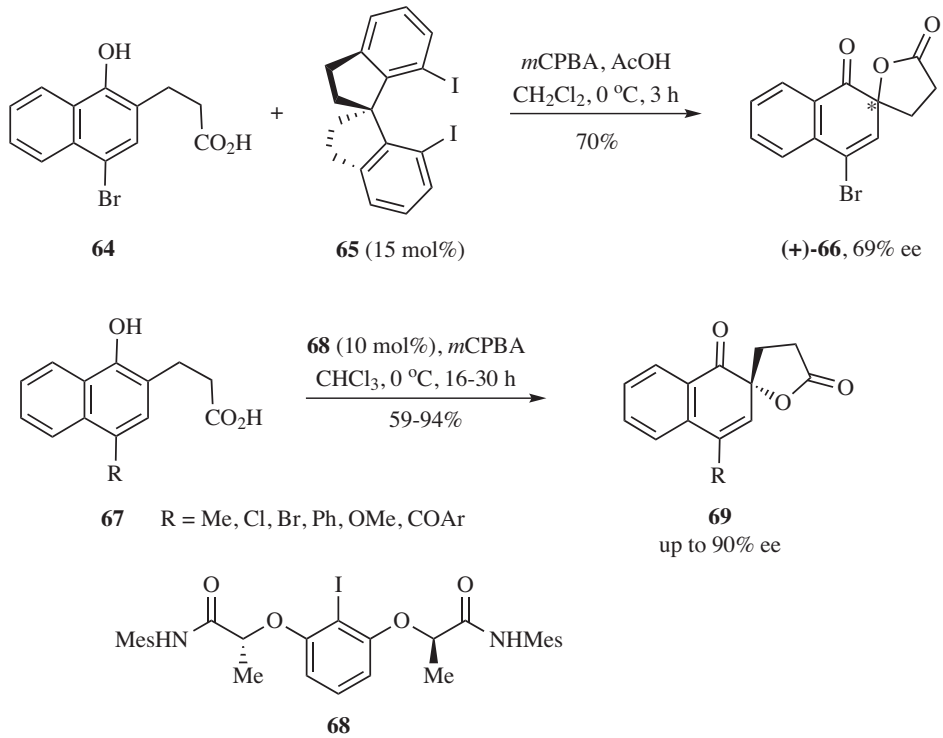
In a similar procedure, the amide derivatives of phenolic substrates **62** can be catalytically oxidized to the respective N-fused spirolactams **63** using catalytic amounts of *p*-iodotoluene and *m*CPBA as the terminal oxidant (Scheme 4.32) [61].

The catalytic spirocyclization procedure has been further improved by using 2,2′-diiodo-4,4′,6,6′-tetramethylbiphenyl (**42,** Section 4.1.4) as the catalyst instead of *p*-iodotoluene. Diiodide **42** has shown high catalytic activity in this reaction in the presence of peracetic acid as the terminal oxidant (Scheme 4.33) [62]. It is assumed that *in situ* generated μ-oxo-bridged hypervalent iodine(III) species (similar to species **45,** see Scheme 4.22) are the actual active species in this catalytic cycle [62].

The catalytic oxidative spirocyclization of phenolic substrates can be performed as an enantioselective reaction using chiral organic iodides as the catalysts [63–65]. In particular, the chiral iodoarene **65** with a rigid spirobiindane backbone has been found to enantioselectively dearomatize naphtholic substrates **64** in a highly selective manner to give optically active products **66** with up to 69% ee (Scheme 4.34) [63]. Ishihara and coworkers have designed a conformationally flexible C_2-symmetric iodoarene catalyst (**68**) for a similar enantioselective oxidative spirolactonization [64, 66, 67]. In a specific example, hydroxynaphthalenyl propanoic acid derivatives **67** undergo dearomatization and spirocyclization in the presence of catalyst **68** to afford the corresponding spirolactones **69** in yields of up to 94% with enantioselectivity up to 90% (Scheme 4.34) [64].



Scheme 4.33

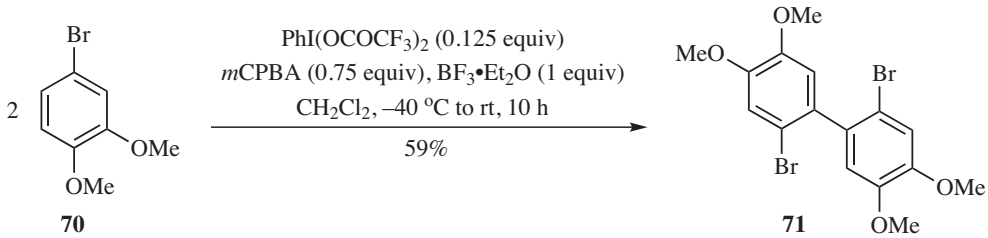


Scheme 4.34

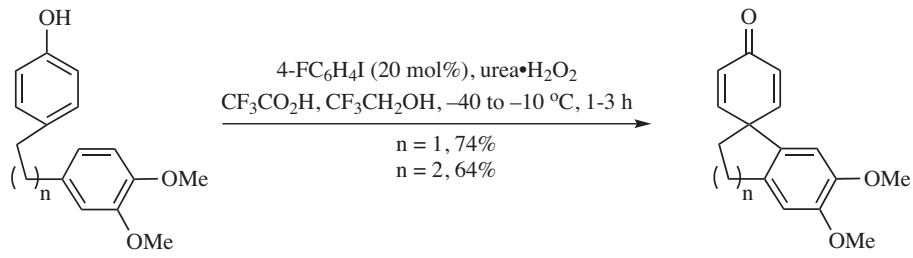
4.1.7 Carbon–Carbon Bond-Forming Reactions

Only a few examples of hypervalent iodine-catalyzed reactions leading to the formation of new C–C bonds have been reported. In seminal work, Kita and coworkers reported in the 2005 a single example of an intermolecular C–C bond formation reaction catalyzed by an iodoarene [2]. Specifically, the oxidative coupling of phenolic ether **70** using [bis(trifluoroacetoxy)iodo]benzene as a catalyst and *m*CPBA as a terminal oxidant afforded product **71** in moderate yield (Scheme 4.35).

Kita and coworkers have also developed a new H_2O_2/acid anhydride system for the iodoarene-catalyzed intramolecular C–C cyclization of phenolic derivatives; Scheme 4.36 shows a representative example of this catalytic cyclization [68].



Scheme 4.35



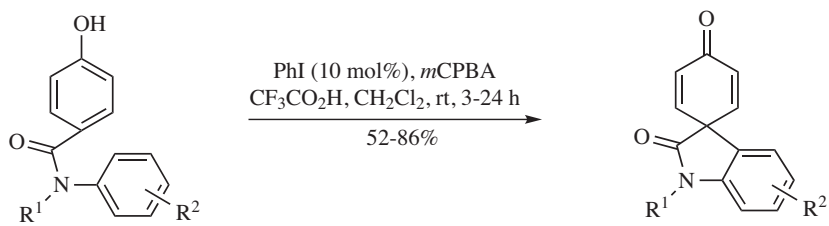
Scheme 4.36

Likewise, the intramolecular oxidative coupling of substituted 4-hydroxyphenyl-*N*-phenylbenzamides **72** has been realized in a catalytic manner by using iodobenzene as catalyst and *m*CPBA or urea–H_2O_2 as terminal oxidant (Scheme 4.37). This reaction constitutes an efficient method for the synthesis of spirooxindoles **73** [69].

4.1.8 Hofmann Rearrangement of Carboxamides

Hypervalent iodine reagents have been employed in numerous synthetic works as oxidants for Hofmann-type rearrangements (Section 3.1.13.3). Synthetic procedures for Hofmann rearrangement using stoichiometric organohypervalent iodine species generated *in situ* from iodoarenes and appropriate oxidants have also been reported [70, 71]. In particular, alkylcarboxamides can be converted into the respective amines by Hofmann rearrangement using hypervalent iodine species generated *in situ* from stoichiometric amounts of iodobenzene and Oxone in aqueous acetonitrile [70]. Likewise, the Hofmann-type rearrangement of aromatic and aliphatic imides using a hypervalent iodine(III) reagent generated *in situ* from PhI, *m*CPBA and TsOH·H_2O has been reported [71].

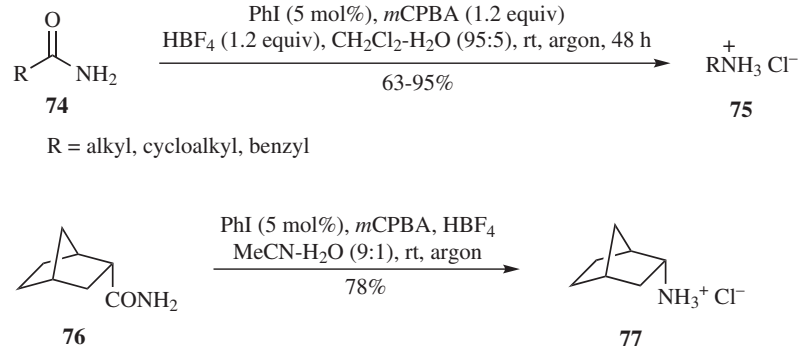
The first catalytic version of the Hofmann rearrangement using aryl iodides as catalysts and *m*CPBA as terminal oxidant was reported by Ochiai and coworkers in 2012 [72]. A study of the catalytic efficiency of substituted iodobenzenes and some aliphatic alkyl iodides in the iodane(III) catalyzed Hofmann rearrangement of benzylic carboxamides has demonstrated that iodobenzene is the best catalyst. The introduction of both electron-donating (4-methyl, 3,5-dimethyl and 2,4,6-trimethyl) and electron-withdrawing groups (4-Cl and 4-CF_3) into iodobenzene decreased the yield of rearranged products. Aliphatic iodides such as methyl, trifluoroethyl and 1-adamantyl iodides showed no catalytic efficiency. Under optimized reaction conditions,



72 **73**

R^1 = Me, $PhCH_2$, CH_2=$CHCH_2$
R^2 = H, Me, OMe, OEt, Cl, F in *o*- or *p*-position to N

Scheme 4.37

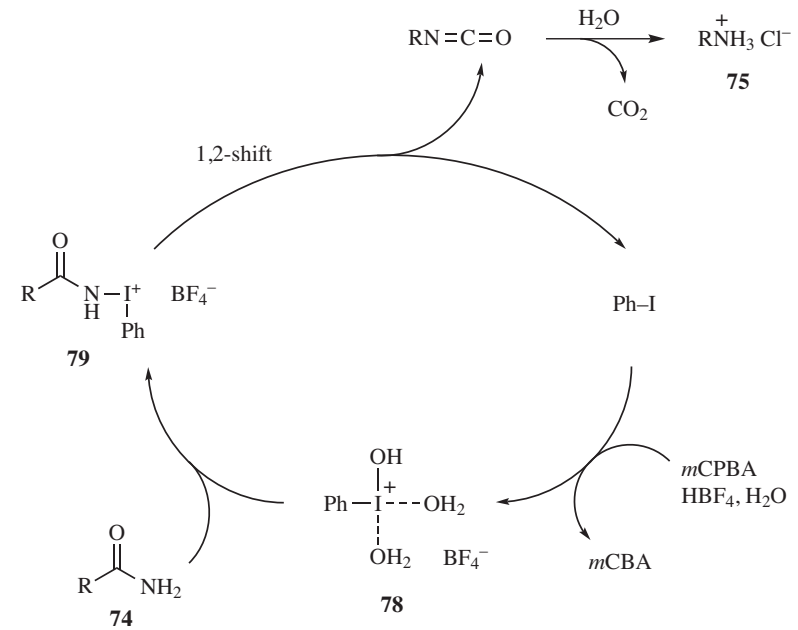


74 **75** **76** **77**

Scheme 4.38

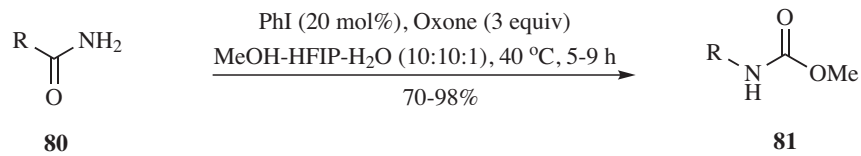
various linear, branched and cyclic aliphatic carboxamides **74** afford alkylammonium chlorides **75** in high yields (Scheme 4.38). The catalytic conditions are compatible with the presence of various functionalities such as halogens (F, Cl, Br), sulfonamides, amines and methoxy and nitro groups. Bicyclic amide **76** affords *endo*-ammonium chloride **77** stereoselectively in a good yield, which suggests retention of the stereochemistry of the migrating groups in the catalytic λ^3-iodane-promoted rearrangement of carboxamides – as observed in the classical Hofmann rearrangement.

The catalytic cycle for this reaction probably involves the *in situ* generation of a tetracoordinated square-planar bis(aqua)(hydroxy)phenyl-λ^3-iodane complex **78** as an active oxidant from a catalytic amount of iodobenzene by the reaction with *m*CPBA in the presence of aqueous HBF_4 (Scheme 4.39).



79 **74** **78** **75**

Scheme 4.39



80 **81**

R = $PhCH_2$, 4-$MeC_6H_4CH_2$, 4-$FC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 3-$ClC_6H_4CH_2$, 2-$ClC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 4-$CF_3C_6H_4CH_2$, Ph(Et)CH, C_5H_{11}, $PhCH_2CH_2$, C_6H_{13}, $BuMe_2C$, cyclopentyl, cyclohexyl, 1-adamantyl, etc.

Scheme 4.40

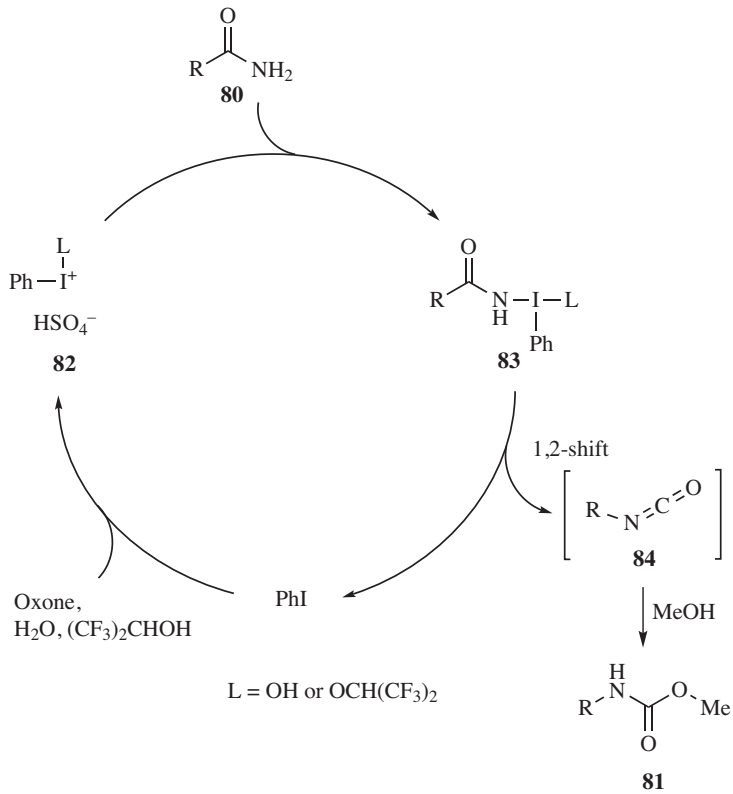
(Hydroxy)phenyl-λ^3-iodane complex **78** promotes the Hofmann rearrangement of carboxamides **74,** probably via intermediate formation of *N*-(phenyliodanyl)carboxamides **79** [72].

Hypervalent-iodine-catalyzed Hofmann rearrangement of carboxamides to carbamates using Oxone as the oxidant has been reported [73]. This reaction involves hypervalent iodine species generated *in situ* from catalytic amounts of PhI and Oxone in the presence of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in aqueous methanol solutions. Under these conditions, Hofmann rearrangement of various carboxamides **80** affords the corresponding carbamates **81** in high yields (Scheme 4.40). The addition of small amount of water is required to dissolve Oxone in the reaction mixture and the presence of HFIP in the mixture dramatically improves the yield of carbamates **81.** Iodobenzene has the most pronounced catalytic effect; the use of other iodine-containing pre-catalysts (2,4,6-$Me_3C_6H_2I$, 4-MeC_6H_4I, 4-$CF_3C_6H_4I$, 3-$HO_2CC_6H_4I$, Bu_4NI) instead of PhI gives poor results. In general, all benzylcarboxamides with either electron-donating or electron-withdrawing substituents afford corresponding carbamates **81** in good yields. Various aliphatic amides, including primary, secondly, tertiary and cyclic alkylcarboxamides, also smoothly react under the same conditions. Compared to the previous method of Hofmann rearrangement with the stoichiometric hypervalent iodine species generated *in situ* [70], the catalytic method affords carbamates **81** in similar yields.

The proposed reaction catalytic cycle involves the reactive species **82** [hydroxy(phenyl)iodonium ion possibly activated by HFIP] generated from PhI and Oxone in aqueous HFIP, which further react with carboxamide **80** to give the hypervalent amidoiodane **83** via ligand exchange (Scheme 4.41). Amidoiodane **83** then undergoes the reductive elimination of iodobenzene and a 1,2-shift at the electron-deficient nitrenium nitrogen atom to give isocyanate **84.** Subsequently, the addition of methanol to isocyanate **84** gives the final carbamate **81.** The regenerated PhI continues the catalytic cycle. The presence of HFIP may help to generate more electron-deficient active species **82** and **83** via ligand exchange with hydroxy(phenyl)iodonium ion or hypervalent aminoiodine, which help to accelerate further steps of the catalytic cycle, such as ligand exchange and 1,2-shift.

4.1.9 Oxidation of Anilines

Anilines can be oxidized to azobenzenes under hypervalent iodine catalysis using peracetic acid as the terminal oxidant (Scheme 4.42) [74]. 2-Iodobenzoic acid has shown the most pronounced catalytic effect compared to other aryl iodides (PhI, 4-$MeOC_6H_4I$, 4-$NO_2C_6H_4I$, 3-$IC_6H_4CO_2H$, 4-$IC_6H_4CO_2H$). This metal-free oxidation system demonstrates wide substituent tolerance: alkyls, halogens and several versatile functional groups, such as amino, ethynyl and carboxyl substituents, are readily compatible and the corresponding products are formed with good to excellent yields. The large-scale preparation of azo compounds could also be carried out successfully by this method.

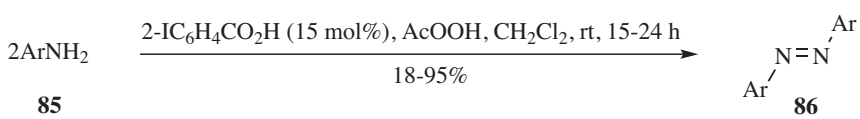


Scheme 4.41

The asymmetrical azo compounds **88** have also been prepared under these conditions in reasonable yields by coupling 3-ethynylaniline (**87**) with a twofold excess of less reactive aniline (Scheme 4.43) [74].

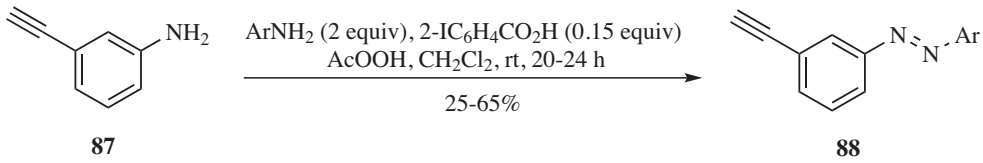
4.2 Catalytic Cycles Based on Iodine(V) Species

Hypervalent iodine(V) reagents, such as IBX (2-iodoxybenzoic acid) and DMP, have found widespread synthetic application as stoichiometric oxidants for the facile and selective oxidation of primary alcohols and secondary alcohols to the respective carbonyl compounds and for other important oxidative transformations



Ar = H, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 3,5-Me$_2$C$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NH$_2$C$_6$H$_4$, 2-HO$_2$CC$_6$H$_4$, 4-(4'-NH$_2$-3'-MeC$_6$H$_3$)-2-MeC$_6$H$_3$, 3-HC≡CC$_6$H$_4$

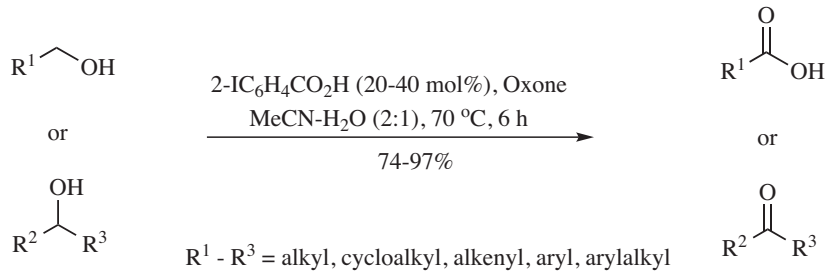
Scheme 4.42



87 **88**

Ar = 3-ClC_6H_4, 4-ClC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$

Scheme 4.43

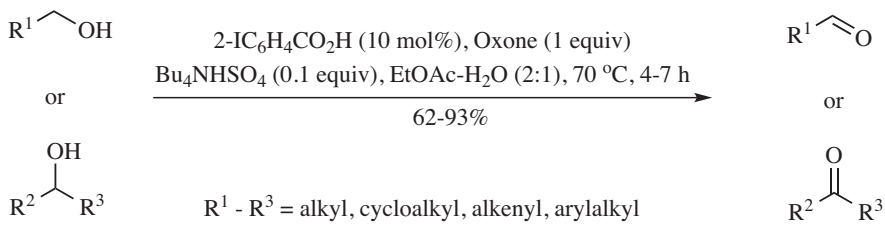


Scheme 4.44

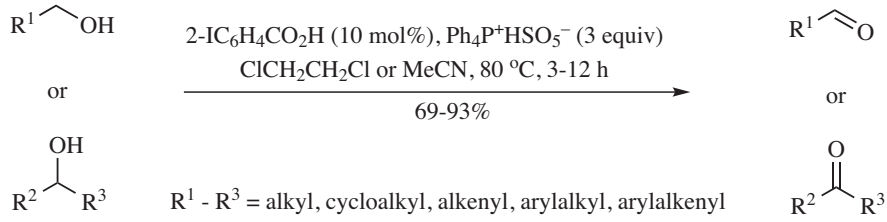
(Section 3.2). Catalytic application of the iodine(V) species in the oxidation of alcohols has been reviewed by Uyanik and Ishihara [10, 75]. The first examples of a catalytic application of an iodine(V) species (i.e., IBX) in the oxidation of alcohols using Oxone as a stoichiometric oxidant were independently reported by the groups of Vinod [4] in 2005 and Giannis [5] in 2006. Vinod's group employed 20–40 mol% of 2-iodobenzoic acid in a water–acetonitrile biphasic solvent system, in which primary and secondary alcohols were oxidized to carboxylic acids and ketones, respectively (Scheme 4.44) [4].

For a similar catalytic oxidation, Giannis' group utilized a water–ethyl acetate biphasic solvent system in the presence of 10 mol% of 2-iodobenzoic acid and tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst. Under these conditions, primary benzylic alcohols were oxidized to the corresponding aldehydes, which, in contrast to the Vinod's procedure, did not undergo further oxidation (Scheme 4.45) [5].

Page and coworkers have demonstrated that primary and secondary alcohols can be oxidized to the respective aldehydes and ketones under reflux conditions in acetonitrile or dichloroethane in the presence of a catalytic amount of 2-iodobenzoic acid and using tetraphenylphosphonium monoperoxysulfate, $Ph_4P^+HSO_5^-$,



Scheme 4.45

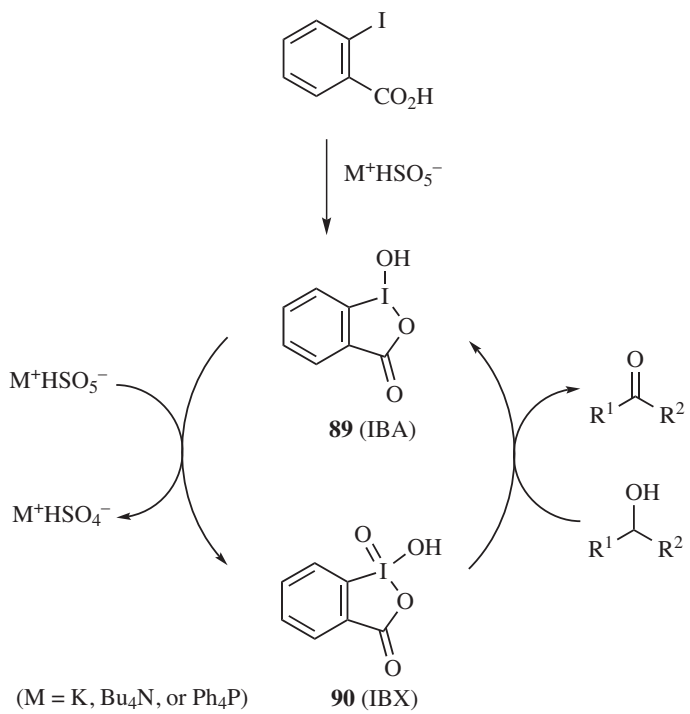


Scheme 4.46

as the terminal oxidant (Scheme 4.46) [76]. Tetraphenylphosphonium monoperoxysulfate is prepared from Oxone by simple counterion exchange with tetraphenylphosphonium chloride. This catalytic system enables the oxidation of primary alcohols to the corresponding aldehydes without further oxidation to the carboxylic acids.

All these catalytic oxidations (Schemes 4.44–4.46) utilize a catalytic cycle involving IBX (**90**) as the reactive species generated *in situ* from 2-iodosylbenzoic acid (IBA, **89**) and monoperoxysulfate salts as terminal oxidants (Scheme 4.47) [75]. The synthetic value of this iodine(V)-based catalytic cycle is limited by the reoxidation step of IBA to IBX, which proceeds relatively slowly even at temperatures above 70 °C.

Several modified catalysts for the iodine(V)-mediated oxidation of alcohols have been developed based on IBX derivatives and analogues (Figure 4.2). In particular, the "fluorous IBX" **91** works efficiently as a catalyst for the oxidation of various alcohols to the corresponding carbonyl compounds in good to high yields



Scheme 4.47

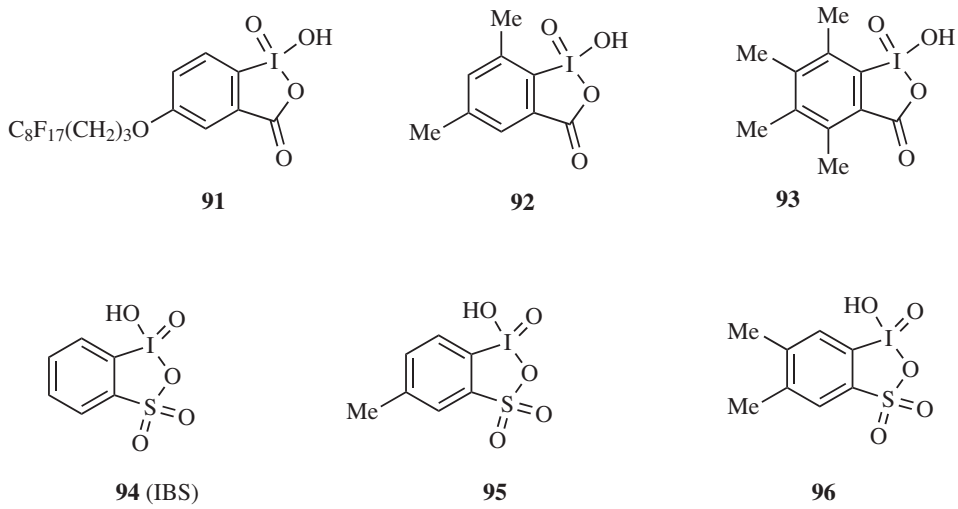
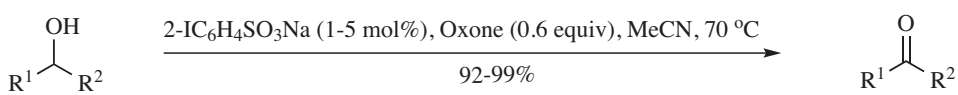


Figure 4.2 *IBX derivatives and analogues used as catalysts for the iodine(V)-mediated oxidation of alcohols.*

[77]. Fluorous IBX **91** can be regenerated from "fluorous IBA," which is readily recovered from the reaction mixture by simple filtration. The recovered reagent **91,** without further purification, retains its catalytic activity for at least five cycles.

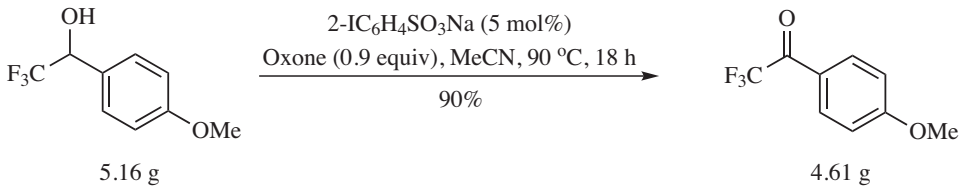
The "twisted" dimethyl-IBX **92** and tetramethyl-IBX **93** have especially high catalytic activity and can catalyze the oxidations of alcohols and sulfides with Oxone at room temperature in common organic solvents [78]. The *ortho*-methyl groups in reagents **92** and **93** lower the activation energy corresponding to the rate-determining hypervalent twisting (Section 1.4.2) and also the steric relay between successive methyl groups twists the structure, which manifests itself in significant solubility in common organic solvents.

Ishihara and coworkers have found that 2-iodylbenzenesulfonic acid (IBS **94** [79], see Section 2.2.3) is an extremely active catalyst in the oxidations of alcohols with Oxone as the terminal oxidant [80]. Methyl substituted IBS derivatives **95** and **96** have even slightly higher catalytic activity. Catalysts **94–96** can be conveniently generated *in situ* by using sodium or potassium salts of the respective 2-iodylbenzenesulfonic acids and Oxone in such solvents as acetonitrile, ethyl acetate, or nitromethane. Scheme 4.48 illustrates the catalytic oxidation of alcohols using IBS and Oxone. Primary alcohols are oxidized to aldehydes, when a smaller quantity of Oxone (0.6–0.8 equiv) is used, or to carboxylic acids in the presence of excess Oxone (1.2 equiv) [80]. This reaction (Scheme 4.48) has been used for a selective larger scale oxidation of 4-bromobenzyl alcohol (6 g) to the corresponding aldehyde or carboxylic acid in excellent yields by controlling the amount of Oxone added in the presence of 1 mol% of the pre-catalyst, potassium 2-iodo-5-methylbenzenesulfonate [75].



R^1 = alkyl, cycloalkyl, alkenyl, aryl
R^2 = H or alkyl

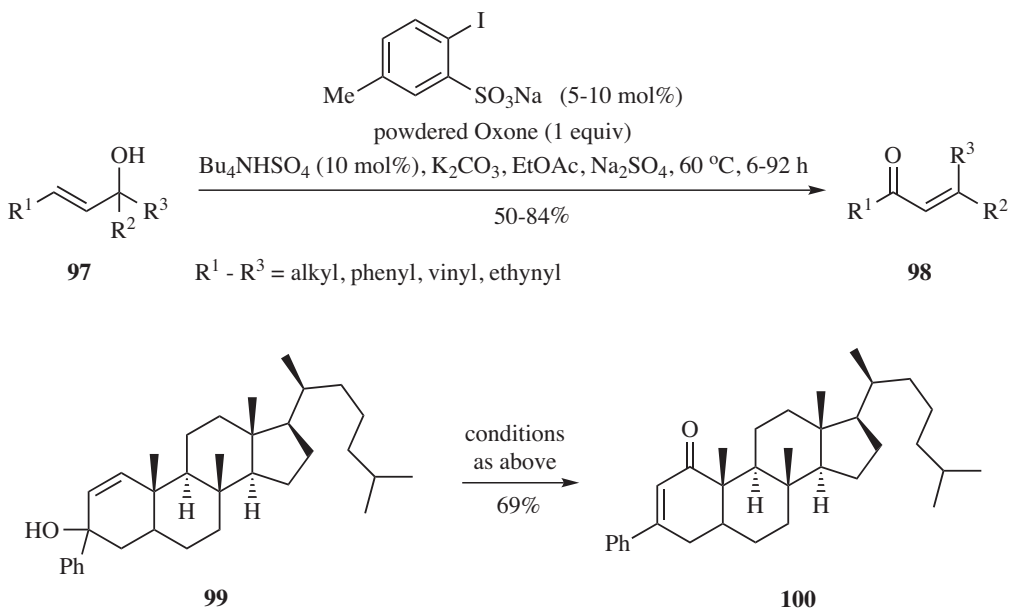
Scheme 4.48



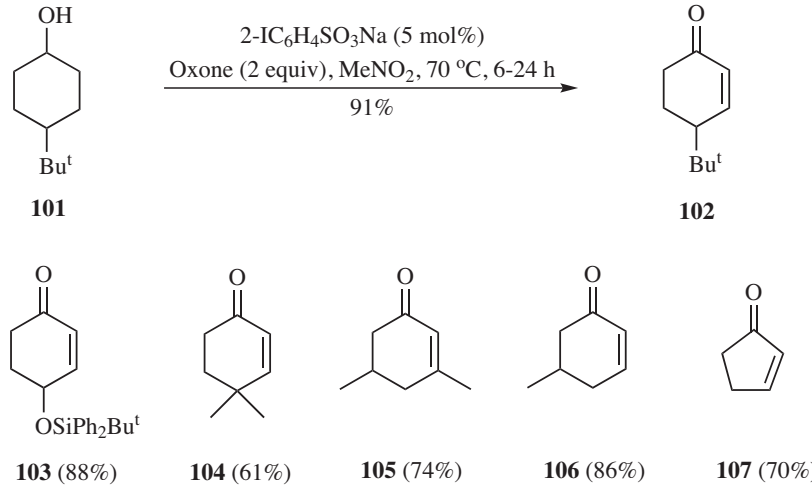
Scheme 4.49

Konno and coworkers investigated in detail the oxidation of various fluoroalkyl-substituted alcohols in the presence of a catalytic amount of sodium 2-iodobenzenesulfonate and Oxone in acetonitrile or nitromethane [81]. The efficiency of this oxidation was also evaluated by comparison to other oxidations, such as the Dess–Martin, pyridinium dichromate and Swern oxidations. It was demonstrated that the hypervalent iodine(V)-catalyzed oxidation could be applied for almost all types of fluorinated alcohols and it was comparable to Dess–Martin oxidation, while pyridinium dichromate and Swern oxidations could not be employed for allylic and propargylic alcohols as well as the alcohols having an aliphatic side chain. Additionally, the hypervalent iodine-catalyzed oxidation could be applied for a larger scale reaction (Scheme 4.49) without any decrease in reaction efficiency [81].

Ishihara and coworkers have developed an oxidative rearrangement of tertiary allylic alcohols **97** to enones **98** with Oxone promoted by catalytic quantities of sodium 2-iodobenzenesulfonate (Scheme 4.50) [82]. Under these conditions, 5-methyl-IBS **95** is generated *in situ* and serves as the actual catalyst for the oxidation. Cyclic and acyclic substrates afford the corresponding enones in moderate to high yields. Notably, sterically demanding steroidal alcohol **99** has been converted into enone **100** in high yield [82].



Scheme 4.50

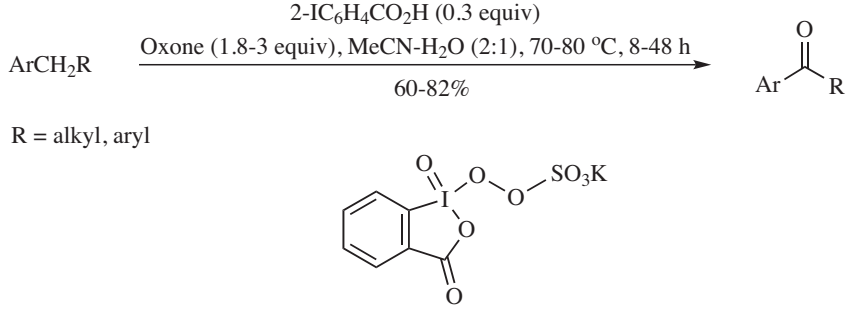


Scheme 4.51

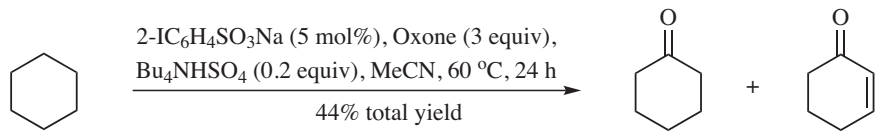
During research into the oxidation of cycloalkanols, Ishihara and coworkers also found that the selective oxidation of 4-*tert*-butylcyclohexanol (**101**) to 4-*tert*-butyl-2-cyclohexenone (**102**) can be achieved in excellent yield in the presence of a catalytic amount of sodium 2-iodobenzenesulfonate and two equivalents of Oxone (Scheme 4.51) [80]. Using this procedure, five- and six-membered cycloalkanols can be transformed into the corresponding enones **103–107** in good yields [80].

Vinod and coworkers were the first to develop a selective procedure for the oxidation of benzylic C–H bonds to the corresponding carbonyl functionalities using a catalytic amount of 2-iodobenzoic acid and Oxone as a stoichiometric oxidant in aqueous acetonitrile under reflux conditions (Scheme 4.52) [83]. The authors hypothesized that the active hypervalent iodine oxidant generated *in situ* might not be IBX (**90**) (Scheme 4.47) but, instead, a soluble derivative of IBX (**108**) that incorporates a peroxysulfate ligand. This intermediate is believed to oxidize a benzylic C–H bond via a single-electron transfer (SET) mechanism [83].

Zhang and coworkers have further improved the procedure for catalytic oxidation of benzylic C–H bonds using IBS as a catalyst, which is generated *in situ* by the oxidation of sodium 2-iodobenzenesulfonate



Scheme 4.52



Scheme 4.53

(5 mol%) by Oxone in the presence of a phase-transfer catalyst, tetrabutylammonium hydrogen sulfate, in anhydrous acetonitrile at 60 °C [84]. Various alkylbenzenes, including methyl- and ethylarenes, substituted alkylbenzenes containing acetoxy or cyclic acetal functionalities and a cyclic benzyl ether, could be efficiently oxidized. The same catalytic system can also be applied to the oxidation of alkanes (Scheme 4.53) [84].

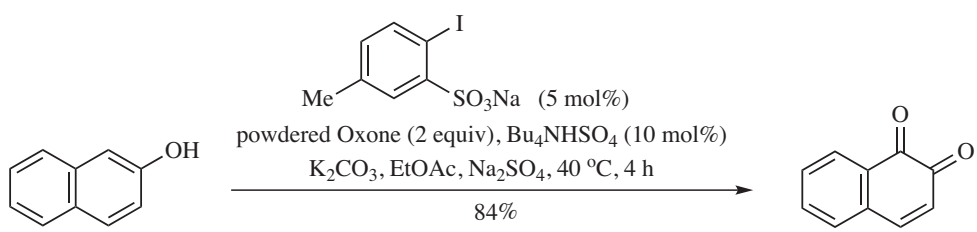
Ishihara and coworkers have reported the first example of hypervalent iodine(V)-catalyzed regioselective oxidation of phenols to *o*-quinones [85]. Various phenols could be oxidized to the corresponding *o*-quinones in good to excellent yields using catalytic amounts of sodium 2-iodo-5-methylbenzenesulfonate and stoichiometric amounts of Oxone as a co-oxidant under mild conditions; Scheme 4.54 shows a representative example [85].

4.3 Tandem Catalytic Systems Involving Hypervalent Iodine and other Co-catalysts

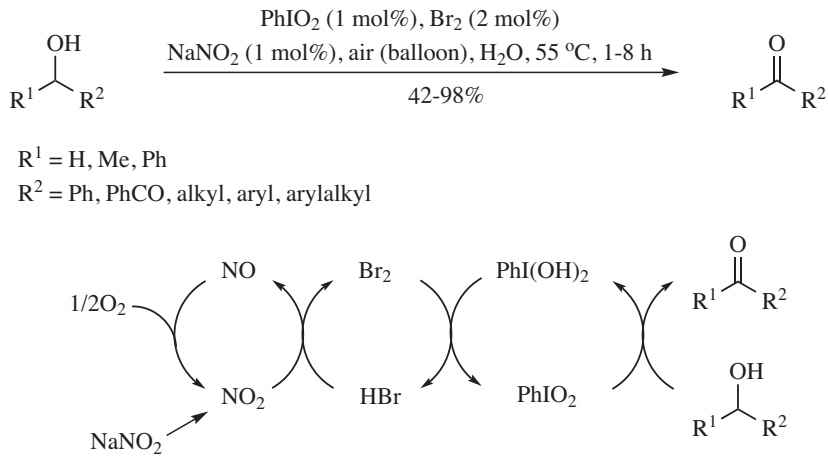
Several catalytic systems involving two or more sequential catalytic cycles and utilizing hypervalent iodine species as catalysts have been developed. An efficient, catalytic aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones by using catalytic amounts of iodylbenzene, bromine and sodium nitrite in water (Scheme 4.55) has been reported by Liu and coworkers [86].

The proposed reaction mechanism includes three redox cycles (Scheme 4.55). In the first redox cycle, $PhIO_2$ is the active species that oxidizes the alcohol to the corresponding carbonyl compound and is reduced to (dihydroxyiodo)benzene, $PhI(OH)_2$. In the second cycle, $PhI(OH)_2$ is reoxidized to $PhIO_2$ with Br_2, which is reduced to HBr. In the third and final cycle, the oxidation of NO with O_2 produces NO_2, which reoxidizes HBr to Br_2 [86]. Notably, however, Ishihara's group was unable to reproduce the oxidation of alcohols under Liu's conditions and it was suggested, on the basis of several control experiments, that the actual oxidant of the alcohols in this case is Br_2 rather than $PhIO_2$ [87].

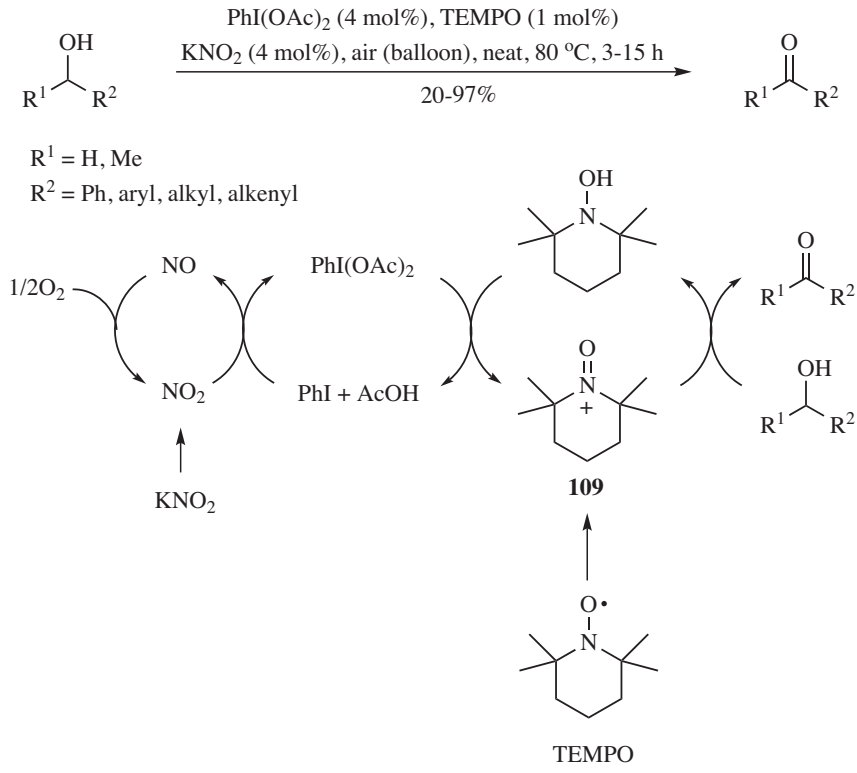
Li and coworkers developed an effective system for the oxidation of alcohols under an atmosphere of oxygen, without the need for any additional solvent or transition metal catalyst, by using catalytic amounts of (diacetoxyiodo)benzene, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and potassium nitrate (Scheme 4.56) [88]. A tentative mechanism for this catalytic oxidation involves the oxoammonium cation **109,** which



Scheme 4.54



Scheme 4.55



Scheme 4.56

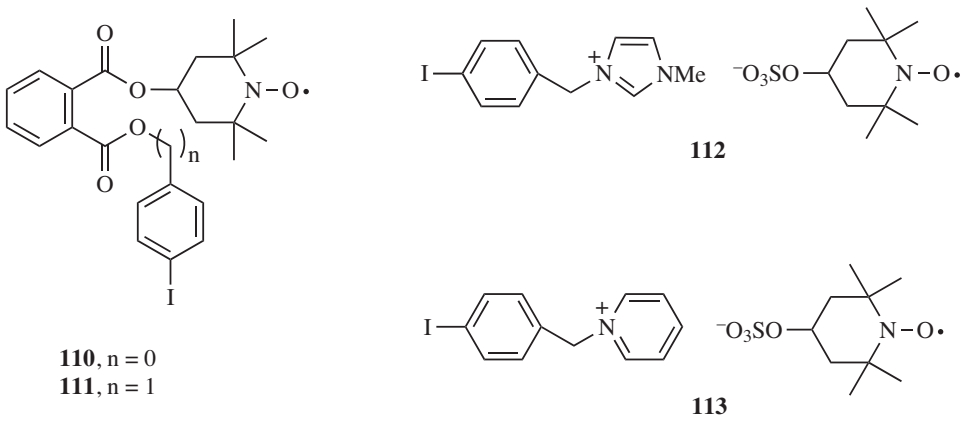


Figure 4.3 *Bifunctional catalysts bearing TEMPO and iodoarene moieties.*

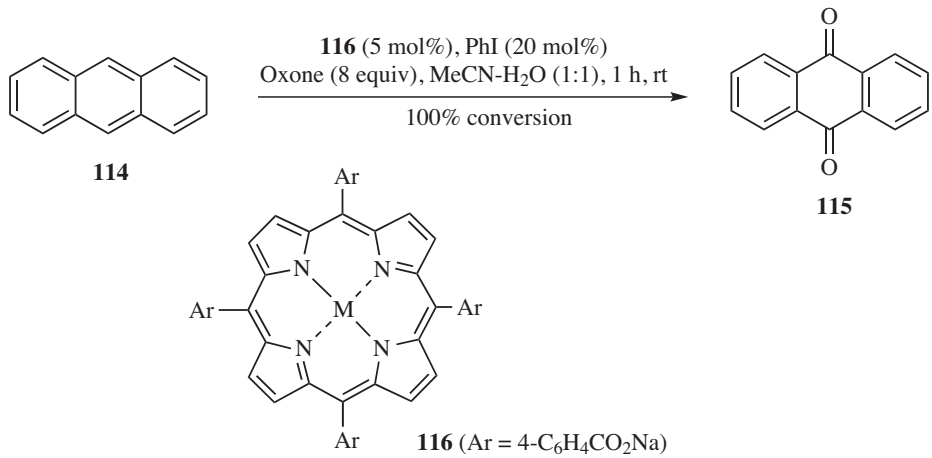
serves as the active oxidant in this reaction, responsible for the oxidation of alcohols to the corresponding carbonyl compounds [88].

An efficient, mild oxidation of alcohols to the corresponding aldehydes or ketones with potassium peroxodisulfate and TEMPO in the presence of catalytic amounts of iodobenzene has been reported [89]. The oxidation proceeds in aqueous acetonitrile at 40 °C to afford carbonyl compounds in high yields. Likewise, the oxidation of alcohols with *m*-chloroperoxybenzoic acid and *N*-hydroxyphthalimide (NHPI) in the presence of catalytic iodobenzene proceeds in aqueous acetonitrile at room temperature to afford the respective carbonyl compounds in excellent yields [90]. The mechanism of these oxidations is similar to the TEMPO-promoted reaction shown in Scheme 4.56 and involves the oxidation of iodobenzene by *m*CPBA or $K_2S_2O_8$ *in situ* to form a λ^3-iodane species, which act as reoxidant of NHPI or TEMPOH.

Yakura and coworkers have developed bifunctional catalysts bearing TEMPO and iodobenzene moieties (structures **110** and **111**, Figure 4.3), which are useful for the environmentally benign oxidation of primary alcohols to carboxylic acids. Reaction of primary alcohols with a catalytic amount of catalyst **111** in the presence of peracetic acid as the terminal oxidant under mild conditions affords the corresponding carboxylic acids in excellent yields [91].

Likewise, efficient recyclable bifunctional catalysts **112** and **113** (Figure 4.3) bearing ionic liquid-supported TEMPO and iodoarene moieties have been developed and used for the environmentally benign catalytic oxidation of alcohols [92]. Compounds **112** and **113** have been tested as catalysts for the oxidation of alcohols to the corresponding carbonyl compounds using peracetic acid as a green and practical oxidant. Ion-supported catalysts **112** and **113** can be conveniently recovered from the reaction mixture and reused without any loss of catalytic activity (Section 5.5).

Hypervalent iodine species were demonstrated to have a pronounced catalytic effect on the metalloporphyrin-mediated oxygenations of aromatic hydrocarbons [93]. In particular, the oxidation of anthracene (**114**) to anthraquinone (**115**) with Oxone readily occurs at room temperature in aqueous acetonitrile in the presence of 5–20 mol% of iodobenzene and 5 mol% of a water-soluble iron(III)-porphyrin complex (**116**) (Scheme 4.57) [93]. 2-*tert*-Butylanthracene and phenanthrene also can be oxygenated under similar conditions in the presence of 50 mol% of iodobenzene. The oxidation of styrene in the presence of 20 mol% of iodobenzene leads to a mixture of products of epoxidation and cleavage of the double bond. Partially hydrogenated aromatic hydrocarbons (e.g., 9,10-dihydroanthracene, 1,2,3,4-tetrahydronaphthalene



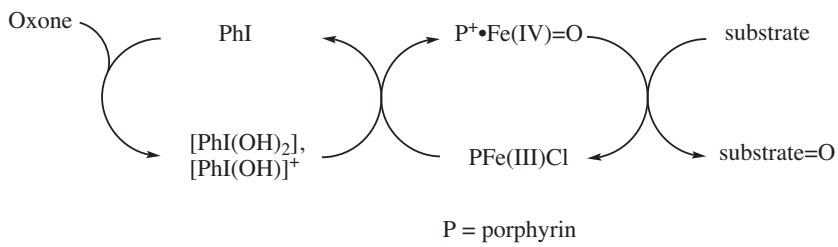
Scheme 4.57

and 2,3-dihydro-1*H*-indene) afford under these conditions the products of oxidation at the benzylic position in moderate yields.

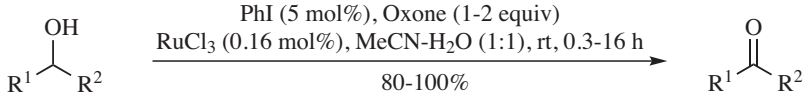
The proposed mechanism for these catalytic oxidations includes two catalytic redox cycles: (i) initial oxidation of iodobenzene with Oxone, producing hydroxy(phenyl)iodonium ion and hydrated iodosylbenzene and (ii) the oxidation of iron(III)-porphyrin to the oxoiron(IV)-porphyrin cation-radical complex by the intermediate iodine(III) species (Scheme 4.58) [93]. The oxoiron(IV)-porphyrin cation-radical complex acts as the actual oxygenating agent toward aromatic hydrocarbons. The presence of the $[PhI(OH)]^+$ and $PhI(OH)_2$ species in solutions containing PhI and Oxone has been confirmed by ESI mass spectrometry [93].

Based on studies of the $RuCl_3$-catalyzed disproportionation of iodine(III) species to iodobenzene and iodylbenzene [53, 94–96], a mild and efficient tandem catalytic system for the oxidation of alcohols and hydrocarbons via a Ru(III)-catalyzed reoxidation of ArIO to $ArIO_2$ using Oxone as a stoichiometric oxidant has been developed [53, 96, 97]. In particular, various alcohols are smoothly oxidized in the presence of catalytic PhI and $RuCl_3$ in aqueous acetonitrile at room temperature to afford the respective ketones from secondary alcohols, or carboxylic acids from primary alcohols, in excellent isolated yields (Scheme 4.59) [97].

Likewise, various alkylbenzenes are selectively oxidized under these mild catalytic conditions to respective aromatic ketones in high yield; Scheme 4.60 shows a representative example [97]. Compared to the

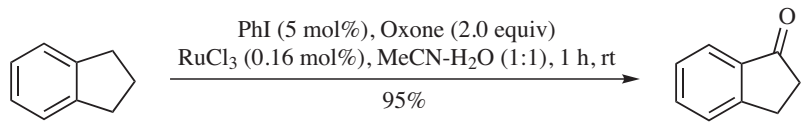


Scheme 4.58



R^1 = alkyl, cycloalkyl, aryl; R^2 = H, alkyl, aryl

Scheme 4.59



Scheme 4.60

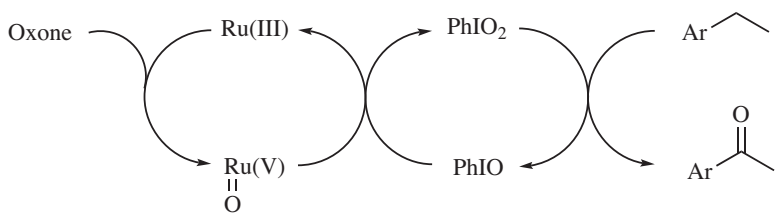
high-temperature IBX/Oxone procedure (Section 4.2) [83], this protocol is much more selective and generally does not afford products of C–C bond cleavage and carboxylic acids.

A plausible, simplified mechanism for these catalytic oxidations includes two catalytic redox cycles (Scheme 4.61). The reaction starts with the initial oxidation of PhI to PhIO and then to $PhIO_2$ by the Oxone/Ru(III,V) system. The *in situ* generated highly active monomeric $PhIO_2$ species is responsible for the actual oxidation of organic substrates by known mechanisms [98, 99].

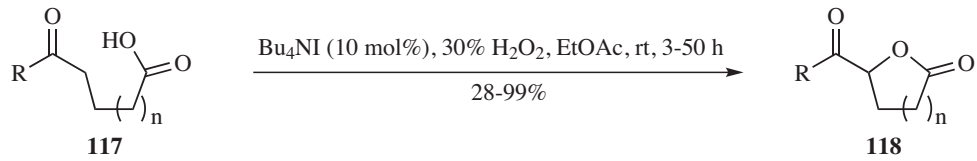
Efficient and recyclable bifunctional catalysts bearing silica-supported $RuCl_3$ and iodoarene moieties have been developed and used for the environmentally benign oxidation of alcohols or alkylarenes at the benzylic position. In the presence of these catalysts, the oxidation of alcohols or alkylbenzenes by Oxone as the stoichiometric oxidant affords the corresponding carbonyl compounds in high yields under mild conditions and convenient work-up. Furthermore, these SiO_2-supported bifunctional catalysts can be recovered by simple filtration and directly reused (Section 5.5) [100].

4.4 Catalytic Cycles Involving Iodide Anion or Elemental Iodine as Pre-catalysts

Catalytic reactions, utilizing iodide anion or elemental iodine as the pre-catalysts, may involve the iodine cation, hypoiodic acid, or inorganic hypervalent iodine(III) species as active oxidants. Numerous examples of such reactions have been reported since 2010; however, no systematic mechanistic studies have been published. The oxidative catalytic reactions utilizing iodide anion or elemental iodine as a catalyst or pre-catalyst have been summarized in several reviews [15, 101, 102].



Scheme 4.61



117 **118**

R = aryl, hetaryl, alkyl
n = 1 or 2

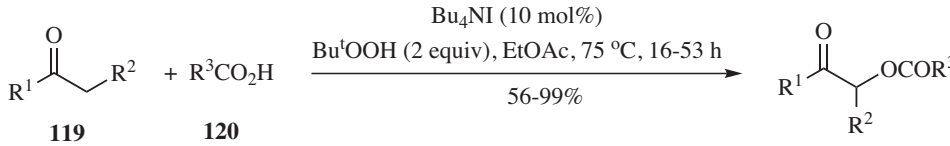
Scheme 4.62

Ishihara and coworkers first found that tetrabutylammonium iodide can be used as a highly effective pre-catalyst for the oxylactonization of oxocarboxylic acids **117** with aqueous hydrogen peroxide even at room temperature (Scheme 4.62) [103]. These results are comparable with the procedure using iodobenzene with *m*CPBA (Section 4.1.1). Importantly, no Baeyer–Villiger products were obtained under these reaction conditions. Both γ-aryl- and γ-heteroarylcarbonyl-γ-butyrolactones **118** (R = aryl or heteroaryl, $n = 1$) were obtained in excellent yields and γ-alkylcarbonyl-γ-butyrolactones **118** (R = alkyl, $n = 1$) and δ-valerolactones **118** ($n = 2$) in moderate yields.

This catalytic procedure has been further extended to the oxidative coupling of ketones as well as 1,3-dicarbonyl compounds with carboxylic acids using a catalytic amount of Bu_4NI and *tert*-butyl hydroperoxide (TBHP) as the terminal oxidant [103]. Hydrogen peroxide is not an effective oxidant for this reaction; however, the use of a commercially available solution of TBHP in anhydrous nonane or decane at moderate heating gives excellent results. Various ketones (**119**) as well as 1,3-dicarbonyl compounds as substrates react with carboxylic acids **120** under these conditions to give the corresponding α-acyloxy ketones **121** in good to excellent yields (Scheme 4.63) [103]. A similar TBAI-catalyzed oxidative coupling of β-ketoesters with carboxylic acid has been reported in more recent work of Li, Zhou and Xu [104].

The α-oxyacylation of aldehydes can also be achieved under similar conditions in the presence of a catalytic amount of piperidine [103]. Thus, equimolar amounts of aldehydes **122** and acids **123** react upon mild heating in the presence of catalytic amounts of Bu_4NI and piperidine and TBHP as the terminal oxidant, in ethyl acetate to give α-acyloxy aldehydes **124** in high yields (Scheme 4.64). Several functional groups such as terminal or internal alkenyl, benzyloxy, silyloxy, acetal, halogen and ester are tolerated under these conditions.

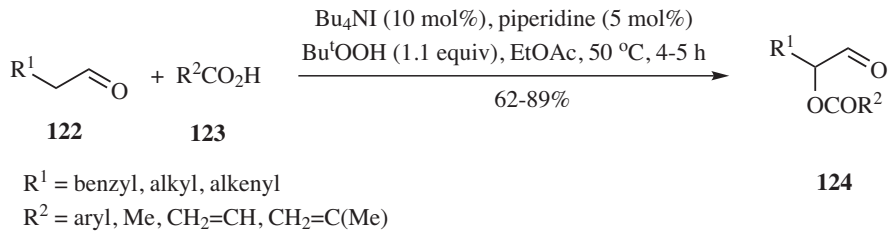
The same Bu_4NI/TBHP catalytic system has also been applied towards the α-oxyacylation of ethers with carboxylic acids in ethyl acetate at 80 °C [105], which possibly occurs via a radical mechanism.



119 **120** **121**

R^1 = aryl, hetaryl, alkyl
R^2 = H, alkyl, COMe, COPh, etc.
R^3 = aryl, Me, CH_2=CH, CH_2=C(Me)

Scheme 4.63



Scheme 4.64

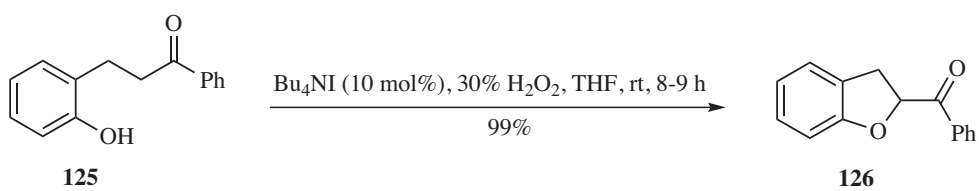
During studies on the oxylactonization of oxocarboxylic acids **117** (Scheme 4.62), Ishihara and coworkers found that the catalytic oxidative system Bu_4NI/H_2O_2 could be applied for the oxidative cycloetherification of oxo-substituted phenols [101]. Thus, the oxidation of phenolic substrate **125** with two equivalents of 30% aqueous H_2O_2 in the presence of a catalytic amount of Bu_4NI in THF or diethyl ether at room temperature gave the corresponding 2-acyldihydrobenzofuran **126** in quantitative yield (Scheme 4.65). Notably, excellent chemoselectivity has been observed in this reaction (Scheme 4.65) with no phenol oxidation products detected.

Based on this reaction (Scheme 4.65), Ishihara and coworkers have developed a highly enantioselective oxidative cycloetherification of substrates **127** using hydrogen peroxide as the stoichiometric oxidant in the presence of the chiral quaternary ammonium iodide catalyst **128** (Scheme 4.66) [106]. The optically active 2-acyl-2,3-dihydrobenzofuran skeleton **129,** created in this cycloetherification, is a key structural unit in several biologically active compounds, such as entremirol and entremiridol.

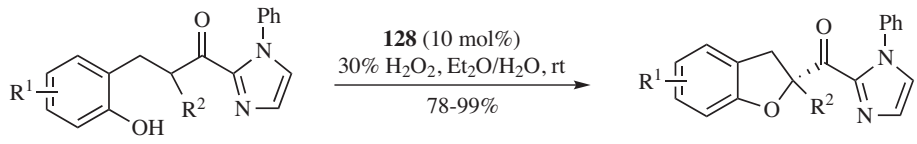
In the later works by Li, Xue and coworkers, the Ishihara's hypoiodite-catalytic cycloetherification has been employed for the synthesis of bis-benzannelated spiro[5.5]ketals [107] and as a key step in a new synthesis of γ-rubromycin [108].

The results of several control experiments suggested that either tetrabutylammonium hypoiodite ($Bu_4N^+IO^-$) or iodite ($Bu_4N^+IO_2^-$), which should be generated *in situ* from tetrabutylammonium iodide and a co-oxidant, might be the active species in all these oxidations (Schemes 4.62–4.66) [103]. The presence of highly unstable iodite anions (IO_2^-) in reaction mixtures containing Bu_4NI/H_2O_2 was confirmed by means of negative ion ESI-MS analysis [109]. Although hypoiodite (IO^-) species were also detected, this species disappeared too quickly to obtain a reliable measurement.

A one-pot procedure for the α-tosyloxylation of ketones by the reaction of ketones with *m*CPBA and $TsOH{\cdot}H_2O$ in the presence of catalytic amounts of NH_4I and benzene in a mixture of MeCN and trifluoroethanol (8 : 2) has been reported (Scheme 4.67) [110]. This method has some advantages, such as mild reaction conditions with a simple procedure and it is suitable for preparing not only α-tosyloxy ketones but also other α-sulfonyloxy ketones. It has been suggested that [hydroxyl(tosyloxy)iodo]benzene, generated by the reaction of iodide anion with *m*CPBA, benzene and TsOH, serves as the active species in this reaction [110].



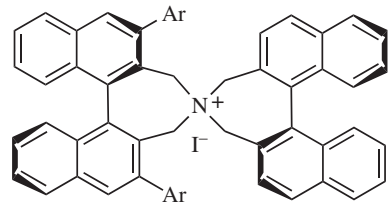
Scheme 4.65



127

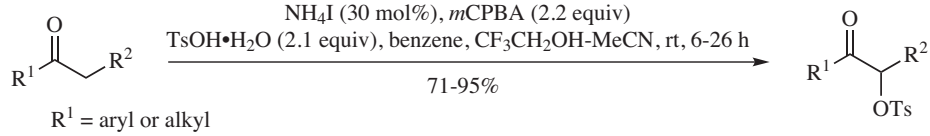
129
up to 96% ee

R^1 = 4-Cl, 4-F, 4-OR, 3,5-$(OMe)_2$, etc.
R^2 = H or Me



128, Ar = 3, 5-[3, 5-$(CF_3)_2C_6H_3$]C_6H_3

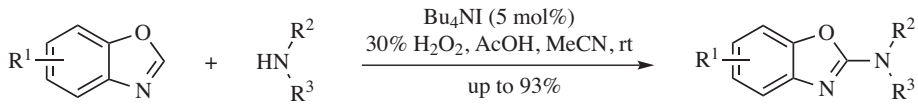
Scheme 4.66



R^1 = aryl or alkyl
R^2 = H or alkyl

Scheme 4.67

The first examples of a hypoiodite-catalyzed oxidative C–N coupling reaction were independently reported by Nachtsheim's group [111] and Yu and Han's group [112] in 2011. Nachtsheim and coworkers found that the reaction of benzoxazoles **130** with various amines in the presence of a catalytic amount of Bu_4NI and 30% aqueous H_2O_2 or 70% aqueous TBHP as a terminal oxidant gave the corresponding C–N coupling products **131** in moderate to high yields (Scheme 4.68) [111]. The reaction was generally faster and the chemical yield of the products was higher if TBHP was used as an oxidant. The authors suggested that the *in situ* generated acetyl hypoiodite is the actual oxidant in this reaction [111].

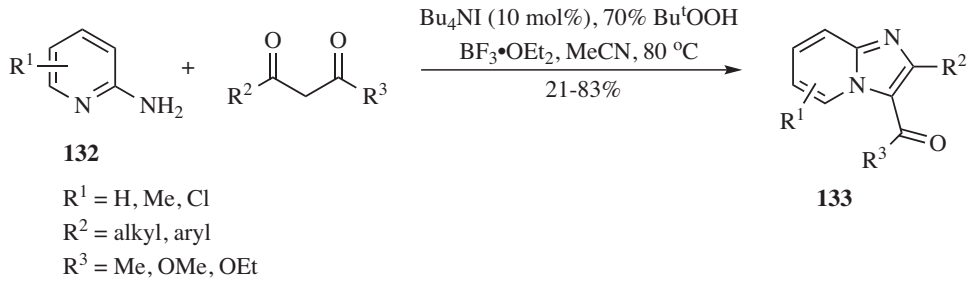


130

131

R^1 = H, alkyl, Cl, NO_2
R^2 = H, alkyl
R^3 = alkyl

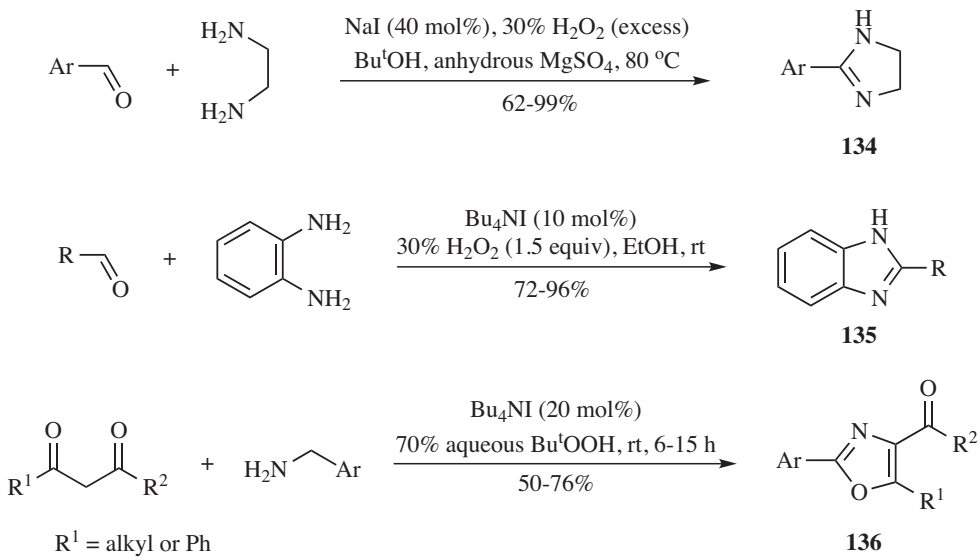
Scheme 4.68



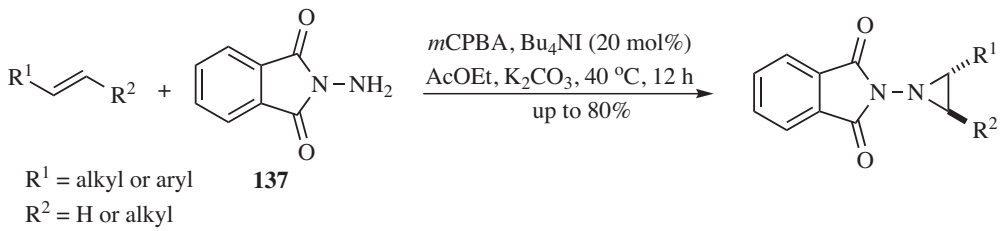
Scheme 4.69

Yu, Han and coworkers reported the oxidative coupling of 2-aminopyridines **132** with β-ketoesters or 1,3-diones in the presence of 10 mol% of Bu_4NI, BF_3-etherate and two equivalents of 70% aqueous TBHP in acetonitrile (Scheme 4.69) [112]. The corresponding imidazo[1,2-*a*]pyridines **133** were obtained in moderate to high yields. The *in situ* generated hypoiodite or iodite species were suggested to be the actual oxidants under these conditions.

The catalytic oxidative system I^-/oxidant has also been applied for the synthesis of the following heterocyclic systems: 2-imidazolines **134** by the oxidative coupling of benzaldehydes with ethylenediamines [113], benzimidazoles **135** by a similar oxidative coupling reaction of phenylenediamines with aromatic or aliphatic aldehydes [109] and oxazole derivatives **136** by the oxidative coupling of β-ketoesters with benzylamines (Scheme 4.70) [114].



Scheme 4.70

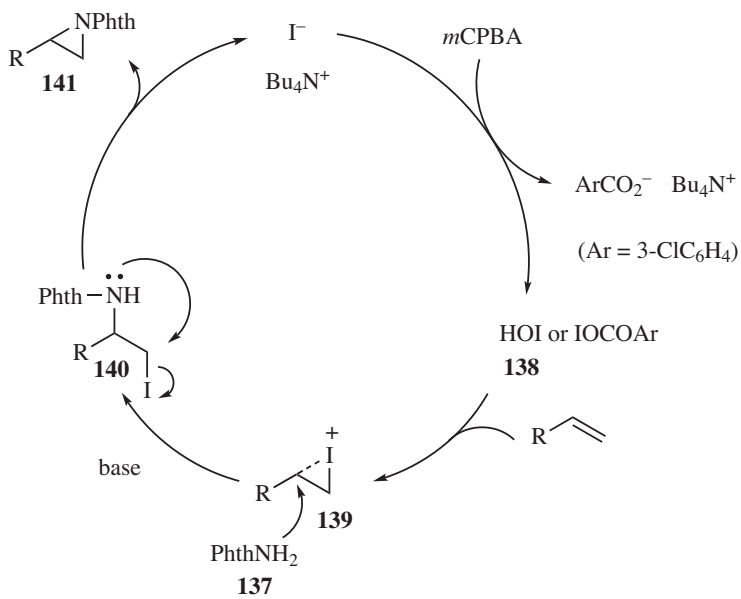


Scheme 4.71

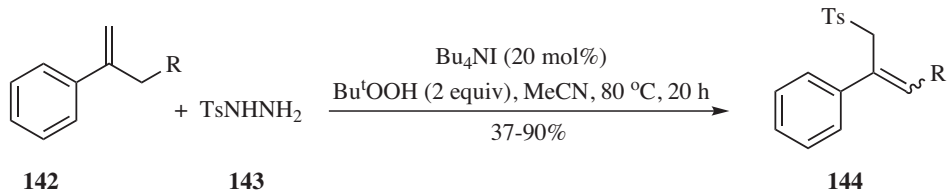
An efficient metal-free catalytic procedure for aziridination of alkenes using tetrabutylammonium iodide as a catalyst, *m*-chloroperoxybenzoic acid as the terminal oxidant and *N*-aminophthalimide (**137**) as a nitrenium precursor has been developed (Scheme 4.71) [45].

The proposed mechanism of this catalytic aziridination is outlined in Scheme 4.72 [45]. The active species, hypoiodous acid (**138**) (or iodine 3-chlorobenzoate, IOCOAr), generated from Bu_4NI and *m*CPBA, further reacts with alkene to give the iodonium ion **139,** which is then opened at the benzylic position by *N*-aminophthalimide (**137**) (or the corresponding potassium salt, PhthNHK, formed from **137** in the presence of K_2CO_3). This sequence of reactions gives β-iodo-*N*-aminophthalimide **140,** cyclization of which affords the aziridine product **141** and iodide anion. The regenerated iodide anion continues the catalytic cycle [45].

Li and coworkers have reported Bu_4NI-catalyzed allylic sulfonylation of α-methyl styrene derivatives with sulfonyl hydrazides **143** using TBHP (Bu^tOOH) as the terminal oxidant (Scheme 4.73) [115]. The mechanism of this reaction involves the generation of sulfonyl radicals, $Ts^•$, from sulfonyl hydrazides **143** by the Bu_4NI/TBHP catalytic system, followed by the addition of $Ts^•$ to α-methyl styrene derivatives **142** to give the corresponding allylic sulfones **144.**



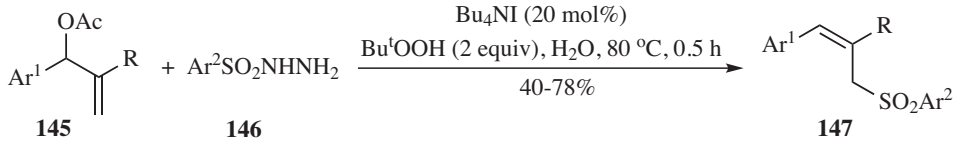
Scheme 4.72



142 **143** **144**

R = alkyl or Ph

Scheme 4.73



145 **146** **147**

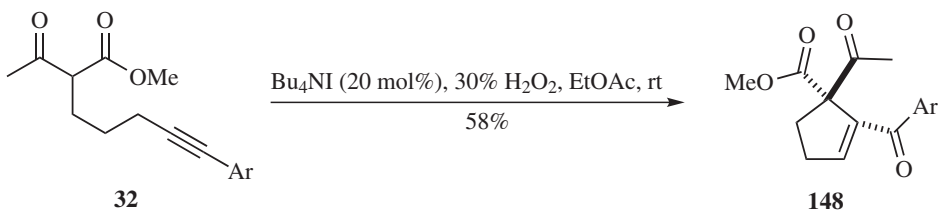
R = CO_2Me, CO_2Et, CO_2Bu, CN
Ar^1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$Pr^iC_6H_4$, 2-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 2-thienyl, etc.
Ar^2 = Ph, 4-MeC_6H_4, 4-BrC_6H_4

Scheme 4.74

This reaction has been further extended to a catalytic procedure for the synthesis of allyl aryl sulfone derivatives**147** from Baylis–Hillman acetates **145** and sulfonyl hydrazides **146** using Bu_4NI as the catalyst and TBHP as an oxidation agent in water (Scheme 4.74) [116].

Only two examples of the C–C bond-forming Bu_4NI-catalyzed reactions have been reported. In 2011, during their studies on the hypervalent iodine-catalyzed oxidative cyclization of δ-alkynyl β-ketoesters with *m*CPBA (see Scheme 4.14 in Section 4.1.2), Moran and coworkers found that treatment of starting material **32** with a catalytic amount of Bu_4NI and 30% aqueous H_2O_2 gave product **148** in moderate yield (Scheme 4.75) [117]. Although the mechanism is not clear, this is the first example of a hypoiodite-catalyzed C–C coupling reaction.

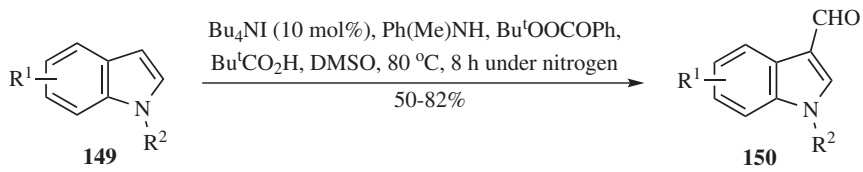
The second example of the hypoiodite-catalyzed C–C coupling reaction is represented by the C3-selective formylation of indoles **149** to products **150** by using *N*-methylaniline as a formylating reagent in the presence of catalytic Bu_4NI and *tert*-butyl peroxybenzoate as the terminal oxidant (Scheme 4.76) [118]. Pivalic acid is



32 **148**

Ar = 4-ClC_6H_4

Scheme 4.75



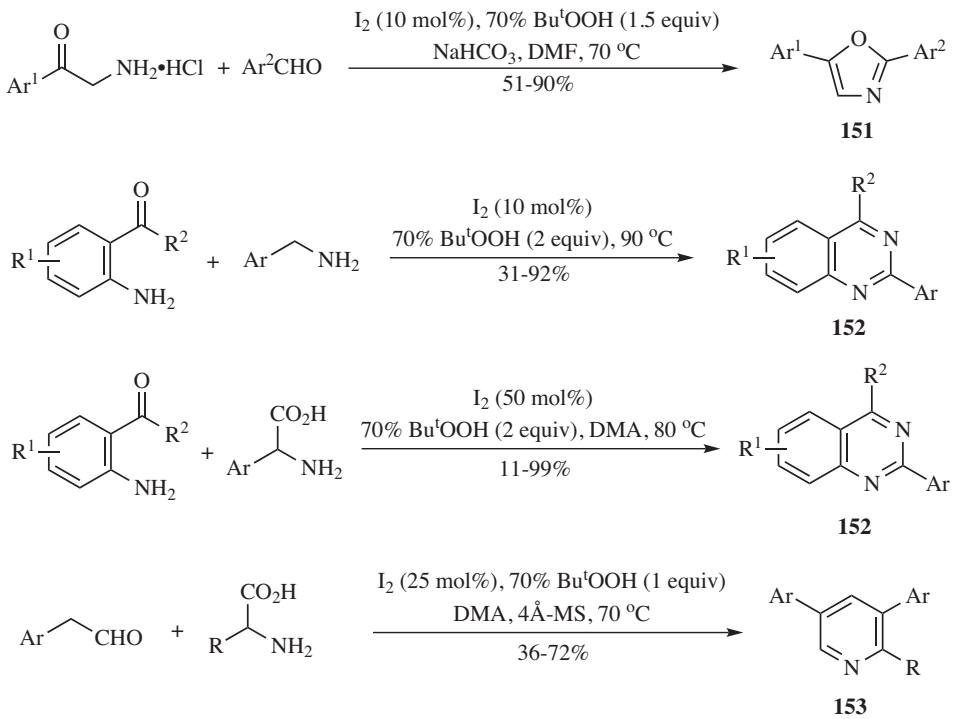
R^1 = H, F, Cl, Et, Br, I, OCH_2Ph, OMe, CN, Me, CO_2Me in different ring positions
R^2 = H, Me, CH_2Ph, Ph

Scheme 4.76

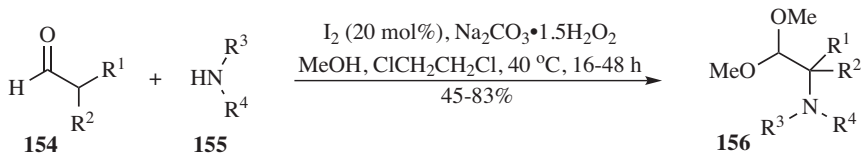
used as an additive since it has been shown to suppress decomposition of indoles under oxidative conditions. This reaction probably proceeds via a free radical process [118].

Several oxidative catalytic systems utilizing elemental iodine as the catalyst have been developed. Wang and colleagues have reported several tandem oxidative cyclization reactions using I_2 as a catalyst and 70% aqueous TBHP (Bu^tOOH) as a stoichiometric oxidant (Scheme 4.77) [119–122]. Heteroaromatic compounds such as oxazoles **151,** quinazolines **152** and pyridine derivatives **153** were synthesized in moderate to high yields under these catalytic conditions. The authors suggested that the I_2/I^- catalytic cycle might play an important role in the radical mechanism under these conditions [122].

A highly efficient α-amination of sterically divergent aldehydes **154** using secondary amines **155** as nitrogen source, iodine as the pre-catalyst and sodium percarbonate as an environmentally benign co-oxidant has been



Scheme 4.77

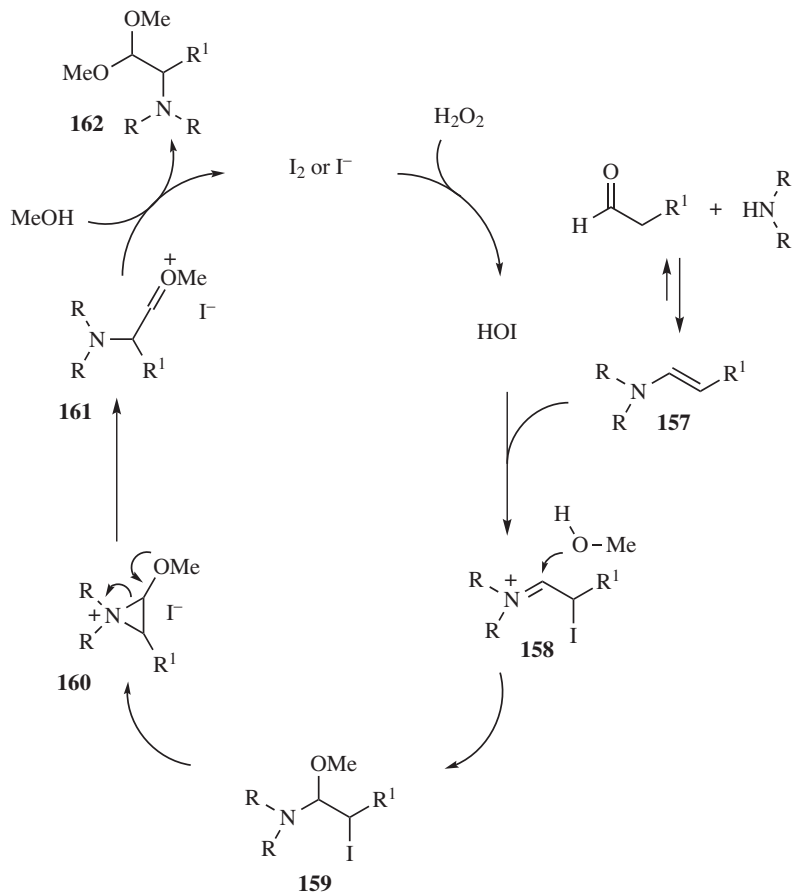


R^1 = aryl, alkyl and R^2 = H or $R^1 + R^2 = (CH_2)_5$
R^3 and R^4 = CH_2Ph, allyl, CH_2CO_2Me, Me, CH(Me)Ph

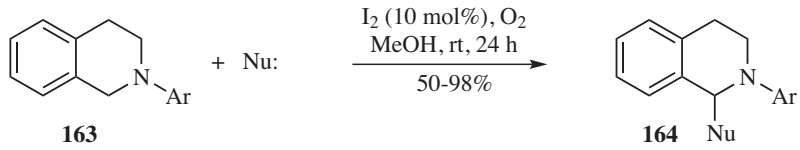
Scheme 4.78

reported (Scheme 4.78) [123]. The reaction affords synthetically useful α-amino acetals **156** in good yields and tolerates a wide range of functionalities, such as benzyl, allyl, or ester groups, as well as bulky aldehydes and secondary amine derivatives.

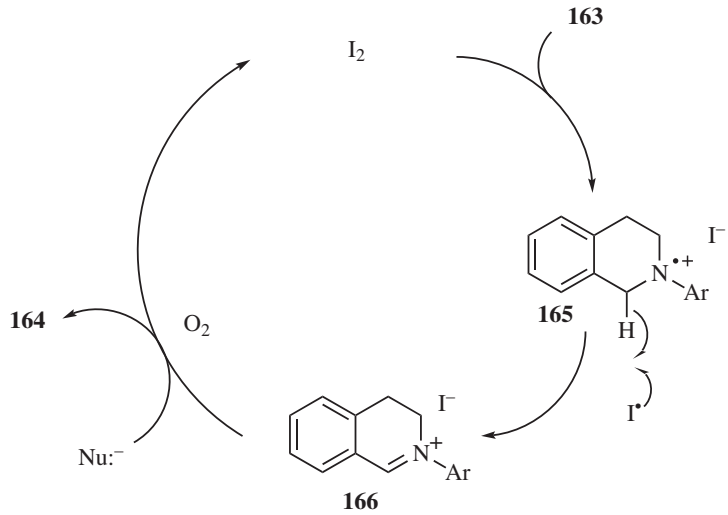
On the basis of control experiments a mechanism for the α-amination of aldehydes catalyzed by *in situ* generated hypoiodite has been proposed (Scheme 4.79) [123]. In the first step, the active cationic iodine species, hypoiodite acid, which is thought to function as a one-electron oxidizing reagent or electrophilic



Scheme 4.79



Nu: = coumarin, nitroalkane, phosphite, TMSCN, phenol, indole, ketone, active methylene compounds, imide, amide, etc.



Scheme 4.80

reagent, is formed by oxidation of iodine (I_2) or iodide (I^-) with hydrogen peroxide. In the second step, hypoiodite reacts with enamine **157** to provide iminium ion **158,** the existence of which was confirmed by a control experiment; hydrolysis of the intermediate **158** led to the corresponding α-iodoaldehyde. In the third step, methanol attacks iminium ion **158** to give the iodo-substituted intermediate **159,** which undergoes intramolecular cyclization to afford aziridinium ion **160.** Finally, an additional methanol molecule captures the ring-opened intermediate **161** to afford the final product **162.**

A versatile iodine-based aerobic catalytic system (I_2 and O_2) for C–H functionalization of tetrahydroisoquinolines **163** using various nucleophiles (Nu:) has been developed by Prabhu and coworkers (Scheme 4.80) [124]. This cross-dehydrogenative coupling reaction is compatible with a large number of nucleophiles and is performed under ambient reaction conditions. A tentative reaction mechanism includes the generation of iminium iodide **166** by the reaction of tetrahydroisoquinoline **163** with molecular I_2 through a radical–cation intermediate **165,** followed by the reaction of **166** with the nucleophile and O_2 furnishing the coupled product **164** and regenerating I_2 (Scheme 4.80) [124].

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